2021 Annual Report

Cancer Is Our Cause

EXELIXIS®

2021 Highlights

$1.43 billion in total revenues, including, for the first time, more than $1 billion in U.S. net product revenue for the cabozantinib franchise

2 new FDA approvals for CABOMETYX® (cabozantinib) in forms of kidney and thyroid cancer, markedly expanding the opportunity for our flagship product to help patients

4 additional promising clinical-stage compounds with diverse mechanisms and significant potential

8 new or amended business development transactions, including two clinical trial collaboration and supply agreements focused on XL092, our next-generation oral tyrosine kinase inhibitor (TKI)

10+ discovery programs across internal and collaborative efforts, with the potential for five new development candidates to enter preclinical testing in 2022

A team of more than **950** full-time employees committed to the Exelixis mission, an increase of 23% for the year

~$1.9 billion in year-end cash and investments* to support our future growth through the buildout of our pipeline and infrastructure, including our campus in Alameda and East Coast expansion

* Includes cash and cash equivalents, restricted cash equivalents and investments

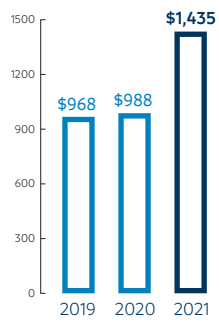
To Our Stockholders

2021 was a year marked by transition. As the world navigated its second year of COVID-19, the global biopharmaceutical community rose to the challenges at hand, delivering vaccines and therapeutics that changed the pandemic's trajectory and made it possible to contemplate a more normal future.

At Exelixis, we made important progress on our discovery, development and commercial priorities, while at the same time witnessing members of our community face cancer on the most personal and emotional level. In particular, at the end of last summer, we mourned the loss of two amazing friends and colleagues – Dr. Gisela Schwab, our longtime President of Product Development & Medical Affairs and Chief Medical Officer, and Jon Berndt, our Senior Vice President of Sales. Losing Gisela and Jon to cancer in the same week struck our team to its core. As we move forward, we are keeping their memories close and honoring their legacies as incredible people and talented biopharma professionals each and every day. For all of us at Exelixis, the experience of last summer served as a poignant, personal reminder of why cancer is our cause, and reinforced, yet again, just how critical our mission is.

Progress throughout 2021 set Exelixis on a clear path toward becoming a multi-product oncology company. More than six years after its first approval, the continued and growing commercial success of CABOMETYX is the fuel for driving rapid expansion of our differentiated pipeline. Supported by the global cabozantinib franchise, we now have the financial and human resources necessary to advance a wave of new programs, establish potential new product franchises and make an even greater impact on the treatment of cancer than we do now. To get there, we are prioritizing clinical assets that include highly promising small molecules and our first antibody-drug conjugate (ADC). We are also accelerating earlier-stage discovery and development activities through internal efforts and our network of collaborations. With so many promising opportunities in front of us, Exelixis is well positioned to further advance our mission to help cancer patients recover stronger and live longer in 2022 and beyond.

As we accelerate the development of our pipeline portfolio, we remain committed to maximizing near-term, high-value opportunities for cabozantinib. The U.S. and European Union approvals of CABOMETYX in combination with OPDIVO® (nivolumab) as a first-line therapy for patients with advanced renal cell carcinoma (RCC) in early 2021 were major milestones, and we're excited about the potential for multiple ongoing clinical trials to serve as the basis for regulatory filings that could further grow the cabozantinib franchise. Data from COSMIC-313, the phase 3 pivotal trial evaluating the combination of cabozantinib, nivolumab and ipilimumab (YERVOY®) for previously untreated poor- and intermediate-risk RCC, are expected this year. In 2022, we're also anticipating interim data from CONTACT-01 and CONTACT-03, the phase 3 pivotal trials evaluating cabozantinib in combination with atezolizumab (TECENTRIQ®) in forms of non-small cell lung cancer (NSCLC) and RCC. CONTACT-02, the phase 3 pivotal trial evaluating the same combination in a form of metastatic prostate cancer, is continuing to enroll patients globally.



Total Revenues
(in millions)

Supported by the global cabozantinib franchise, we now have the resources to advance a wave of new programs, establish potential new product franchises, and make an even greater impact.

Cabozantinib is just the starting point of our journey to play a continuous, leading role in transforming outcomes for patients. In 2021, we rapidly advanced our clinical pipeline, including XL092, our next-generation oral TKI. We intend to develop XL092 in a broad array of potential indications in which cabozantinib has demonstrated anti-tumor activity. To that end, in 2021 we initiated the dose-escalation stage of STELLAR-002, one of two ongoing phase 1b trials evaluating XL092 in combination with immuno-oncology (IO) therapies in advanced solid tumors, and made plans to launch the compound's pivotal trial program in the first half of 2022. The first phase 3 pivotal study, STELLAR-303, will evaluate XL092 in combination with atezolizumab in a metastatic colorectal cancer (CRC) setting, an indication supported both by robust preclinical data for XL092 and clinical results for cabozantinib in CRC.

Our other pipeline programs include XB002, an ADC targeting tissue factor (TF) and our first biotherapeutic, as well as XL102, a potent, selective and orally bioavailable small molecule cyclin dependent kinase 7 (CDK7) inhibitor. We're working towards expanding the phase 1 clinical development programs for both compounds, pairing them in combination with other therapies and opening expansion cohorts in new tumor types. In April 2022, we also initiated a phase 1 trial of a third compound, XL114, a small molecule inhibitor of the CARD11-BCL10-MALT1 (CBM) complex, in non-Hodgkin's lymphoma (NHL).

XB002 is the first of what we expect will be a growing portfolio of biotherapeutics to enter clinical development. Over the past several years, we've increased our internal expertise and collaborated with external partners to roll out an ADC platform that can identify and optimize these molecules with excellent activity *in vitro* and *in vivo*. At the end of 2021, we designated our first development candidate (DC) to emerge from that platform, XB010. To create this promising molecule, we sourced antibodies from Invenra and worked with partners at Catalent to design a novel ADC with broad applicability, a proprietary payload and a next-generation linker. We believe integrating cutting-edge technologies across our network in this way has created a powerful biologics discovery and development engine that can yield transformative cancer therapies and help drive our long-term growth. In total, across both the small molecule and biotherapeutics spheres, we are advancing more than ten discovery programs through internal and collaborative efforts, and we expect to take up to five new DCs into preclinical development in 2022.

To support our rapidly growing pipeline and commercial opportunities, we're expanding our campus, technology infrastructure and team. In June 2021, we opened a new state-of-the-art laboratory building, effectively tripling our available lab space. Less than a year later, in April 2022, we opened our new corporate headquarters building, the heart of our campus in Alameda, CA. And at the beginning of 2022, we welcomed Vicki L. Goodman, M.D., as our Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, who will be integral not only to moving our clinical pipeline forward, but also to the buildout of our Exelixis East expansion in the Greater Philadelphia area. We intend to complement our existing development efforts, take advantage of the East Coast biopharmaceutical talent pool and, with global ambitions, lay groundwork for future growth outside the U.S.

To support our rapidly growing pipeline and commercial opportunities, we're expanding our campus, technology infrastructure and team.

As we move through 2022, there's a companywide sense of excitement about everything that lies before us here at Exelixis. The entire team is energized and highly focused on our work to expand the cabozantinib franchise, advance our other clinical programs and drive innovation in our preclinical portfolio. After more than a decade of intense focus on cabozantinib – a tactic necessary to bring the company to this point in its evolution – it's gratifying to see our pipeline mature and, with it, to know we have so many opportunities on deck to realize our vision of improving outcomes for many more patients with cancer. Thank you for your continued interest in Exelixis. We are moving forward with urgency and momentum, and we look forward to sharing our achievements with you in the months and years ahead.

Michael M. Morrissey, Ph.D.
President and Chief Executive Officer
Exelixis, Inc.

Continued Momentum for Cabozantinib: Our Fuel for Growth

As we execute toward our vision of becoming a global, multi-product oncology company, we remain committed to our mission to help cancer patients recover stronger and live longer. To that end, our goal has always been to maximize the forms of cancer and therapy settings that cabozantinib can positively impact to ensure as many patients as possible benefit from our medicines at some point in their treatment journey.

CABOZANTINIB

Cabozantinib has been the key driver of growth for our business for the past decade, and 2021 was no exception. For the first time, the compound received two U.S. regulatory approvals within the same calendar year, including as a first-line therapy in combination with nivolumab for patients with advanced RCC, and as a monotherapy in the second-line setting and beyond for patients with differentiated thyroid cancer. These approvals are the latest in a line of cabozantinib product development milestones that stretch back to 2005, when cabozantinib entered phase 1 clinical development and soon afterwards began to demonstrate the robust anti-tumor activity that would define its potential across multiple tumor types.

Following its initial FDA approval in November 2012 as a treatment for progressive, metastatic medullary thyroid cancer, a rare form of thyroid cancer for which new U.S. diagnoses number in the hundreds each year, cabozantinib has evolved into a global oncology franchise and has seen its label expanded to encompass multiple opportunities to treat forms of advanced kidney, liver and thyroid cancer in the U.S. and many other countries. In 2022, Exelixis and our partners in the worldwide clinical development and commercialization of cabozantinib are sponsoring multiple ongoing phase 3 pivotal trials. These studies have the potential to even further expand the population of patients that may be able to benefit from our flagship therapy.

COSMIC 313

Cabozantinib + nivolumab + ipilimumab
First-line advanced intermediate- or poor-risk RCC

Top-line results expected in 1H 2022

CONTACT-01

Cabozantinib + atezolizumab
Metastatic NSCLC

Enrollment complete; interim data expected in 2H 2022

CONTACT-02

Cabozantinib + atezolizumab
Metastatic castration-resistant prostate cancer

Patient enrollment ongoing

CONTACT-03

Cabozantinib + atezolizumab
Advanced or metastatic RCC

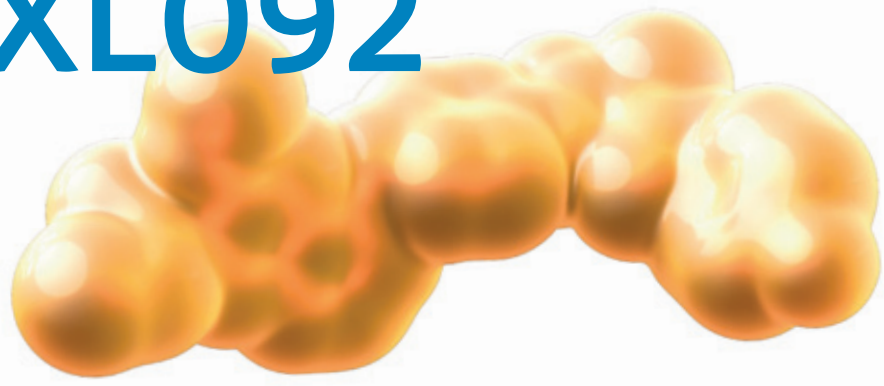
Enrollment complete; interim data expected in 2H 2022

Building a Diverse and Differentiated Product Pipeline

Supported by revenues from the growing cabozantinib franchise, Exelixis resumed drug discovery activities in 2017. Over the past five years, we've combined our deep expertise in medicinal chemistry and biology to assemble a diverse pipeline of innovative small molecules, ADCs and other biotherapeutics addressing highly promising targets. By coupling our robust internal discovery capabilities with our ability to identify, establish and execute productive collaborations, we've created a powerful engine for advancing and expanding our next-generation product portfolio. In particular, we are increasingly excited about our rapidly evolving ADC pipeline, a testament to our ability to combine multiple technologies from our collaboration partners into novel molecules optimized for efficacy and safety.

We are currently advancing more than 10 discovery programs and expect to bring up to five candidates into preclinical development in 2022. These promising candidates utilize diverse mechanisms of action and modes of therapy, providing multiple pathways for us to improve outcomes for a larger number of patients with cancer.

XL092



XL092

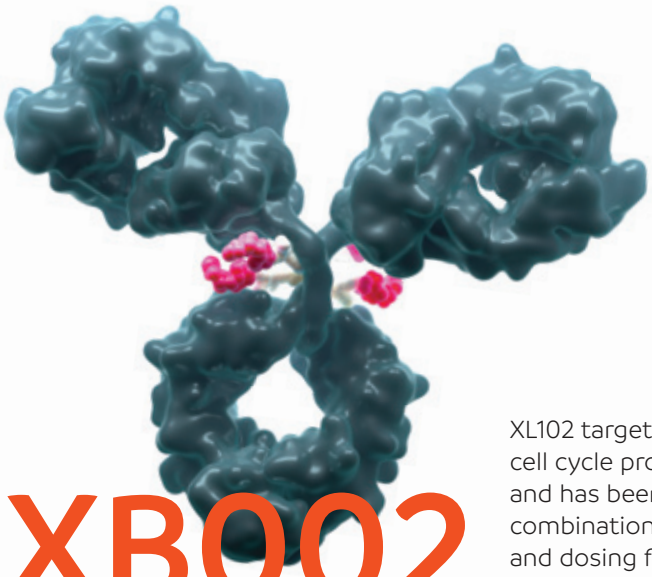
Next-generation oral TKI

Discovered by Exelixis in 2018

Phase 1b; Initiation of pivotal trial program expected in 1H 2022

XL092 is a next-generation oral TKI with a targeted multi-kinase inhibition profile similar to cabozantinib, but engineered to have a shorter clinical half-life with the potential for an improved safety profile. XL092's carefully selected characteristics may enable the use of this multi-targeted TKI therapy in a broad array of indications and regimens. We intend to leverage our clinical experience with cabozantinib to expand our TKI footprint into new indications and expanded treatment settings beyond where cabozantinib is already indicated, potentially including neoadjuvant, adjuvant and maintenance regimens.

Throughout 2022, we expect to expand the ongoing phase 1b STELLAR-001 and STELLAR-002 studies, which are evaluating XL092 in combination with several IO therapies, and may initiate additional studies in potential new tumor types and combination regimens (IO and otherwise). We are also on track to initiate STELLAR-303, a global phase 3 pivotal trial of XL092 in combination with atezolizumab as a third-line therapy in patients with microsatellite stable metastatic CRC in the first half of 2022. Multiple other phase 3 studies will follow.



XB002
ADC targeting TF
In-licensed from Iconic Therapeutics, Inc. in 2020
Phase 1

XB002

Tissue factor is a clinically validated target in cervical cancer and has broad potential in diverse cancer indications. A growing body of preclinical and clinical data suggest that XB002 may have significant advantages over first-generation TF-targeted therapies. Our ongoing phase 1 clinical study is designed to evaluate XB002 as a monotherapy in multiple solid tumor indications. Early data from the trial support a potentially differentiated and best-in-class profile for XB002, which increases our confidence in its potential to serve as the foundation for an Exelixis TF-targeting oncology franchise. In 2022, we plan to expand the clinical development program for XB002, as a monotherapy and in combination regimens, across a wide range of tumor types. In the second half of the year, we also expect to report clinical updates from the ongoing phase 1 trial.

XL102

XL102 targets CDK7, a key regulator of cell cycle progression and transcription, and has been designed to offer a combination of selectivity, potency and dosing flexibility that provides best-in-class potential. Preclinical data suggest that XL102 may have activity in a variety of solid tumors as a monotherapy and in combination with other targeted therapies. Our ongoing phase 1 trial is evaluating XL102 as a monotherapy, and in two combination regimens, in multiple solid tumors. We are working towards initiating the trial's cohort expansion phase, with planned cohorts in forms of ovarian, breast, prostate and colorectal cancer. We expect to provide clinical updates from the ongoing phase 1 study of XL102 in the second half of 2022.

XL102
Small molecule inhibitor of CDK7
In-licensed from Aurigene, Inc. in 2020
Phase 1

XL114
Small molecule inhibitor of the CBM complex
In-licensed from Aurigene, Inc. in 2021
Phase 1

XL114

XL114 inhibits the CBM complex, a key component of signaling downstream of B- and T-cell receptors which promotes B- and T-cell lymphoma survival and proliferation. In preclinical studies, the compound was shown to have activity in lymphoma models that are resistant to BTK inhibitor therapy, and in subsets of B-cell lymphomas in which BTK inhibitors are not active. In April 2022, we also initiated a phase 1 trial of XL114 in patients with NHL.

Our Fully Integrated Biopharmaceutical Continuum

Program Name	Mechanism	Discovery/ Preclinical	IND	Phase 1a	Phase 1b	Phase 2/3
XL092	Next-generation TKI targeting MET/VEGFR/AXL/MER					
XB002	Next-generation TF-targeting ADC					
XL102	Potent, selective, orally bioavailable CDK7 inhibitor					
XL114	CBM pathway inhibitor					
XB010	Next-generation 5T4-targeting ADC					
Aurigene Collaboration Programs	CDK12 and MALT1 inhibitors					
Invenra Collaboration Programs	PD-L1 + CD47 and PD-L1 + NKG2A					
StemSynergy Collaboration Programs	CK1α activators and selective Notch inhibitors					
STORM Therapeutics Collaboration Program	ADAR1					
Exelixis Discovery Programs	G9a inhibitors					
Biologics Programs Invenra, NBE Therapeutics, Catalent, WuXi, GamaMabs & Adagene Collaborations	AMHR2, ROR1/2, TF, DLL3					

TKI = tyrosine kinase inhibitor
CDK7 = cyclin-dependent kinase 7
CK1α = casein kinase 1 alpha

TF = tissue factor
ADC = antibody-drug conjugate
IND = Investigational New Drug application

CDK12 = cyclin-dependent kinase 12
NKG2A = natural killer cell receptor group 2A
ADAR1 = adenosine deaminase 1

CBM = CARD11-BCL10-MALT1

For more information on the programs highlighted above, please see Form 10-K in our Annual Report on the following pages.

Our validated discovery and development capabilities, along with our robust commercial organization, have yielded a $1 billion per year product franchise on a global basis since 2019. With cabozantinib now a mainstay in the treatment of multiple forms of cancer, we are similarly focused on expediting the flow of innovative and potentially best-in-class therapeutic candidates in oncology successfully through clinical trials and ultimately to the patients who need them most. To do this, we are leveraging synergies across Exelixis' internal disciplines and drawing on a growing body of expertise available through our multiple collaboration programs.

With our internal and collaborative research and development capabilities, we have the resources and knowledge to continue our leadership in discovering and developing multi-targeted TKIs while expanding our portfolio into additional small molecules and biotherapeutics that incorporate the latest advanced technologies. At each step of the process, we benefit from our commercial team's key market insights and perspectives informed by the experience representing cabozantinib for nearly a decade. This comprehensive approach allows us to leverage our existing discovery and development expertise and commercial infrastructure, while strategically investing in and combining cutting-edge targets and technologies from our partners to enable wholly new therapeutic approaches with the potential to raise the bar for standard of care for cancer patients.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2021

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission File Number: 000-30235

EXELIXIS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**04-3257395**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

1851 Harbor Bay Parkway
Alameda, CA 94502
(650) 837-7000

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock $.001 Par Value per Share	**EXEL**	**The Nasdaq Stock Market LLC**

Securities registered pursuant to Section 12(g) of the Act:
None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

State the aggregate market value of the voting and non-voting common equity held by non-affiliates computed by reference to the price at which the common equity was last sold, or the average bid and asked price of such common equity, as of the last business day of the registrant's most recently completed second fiscal quarter: $5,680,065,864. Excludes shares of the registrant's common stock held by persons who were directors and/or executive officers of the registrant at July 2, 2021 on the basis that such persons may be deemed to have been affiliates of the registrant at such date. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

Number shares of the registrant's common stock outstanding as of February 7, 2022: 319,448,174

DOCUMENTS INCORPORATED BY REFERENCE

Certain portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A, not later than April 30, 2022, in connection with the registrant's 2022 Annual Meeting of Stockholders are incorporated herein by reference into Part III of this Annual Report on Form 10-K.

EXELIXIS, INC.
ANNUAL REPORT ON FORM 10-K
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PART I

SPECIAL NOTE REGARDING FORWARD LOOKING STATEMENTS

Some of the statements under the captions "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business" and elsewhere in this Annual Report on Form 10-K are forward-looking statements. These statements are based on our current expectations, assumptions, estimates and projections about our business and our industry and involve known and unknown risks, uncertainties and other factors that may cause our company's or our industry's results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied in, or contemplated by, the forward-looking statements. Our actual results and the timing of events may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include those discussed under the heading "Item 1A. Risk Factors" as well as those discussed elsewhere in this Annual Report on Form 10-K.

These and many other factors could affect our future financial and operating results. We undertake no obligation to update any forward-looking statement to reflect events after the date of this report.

RISK FACTOR SUMMARY

Investing in our securities involves a high degree of risk. Below is a summary of material factors that make an investment in our securities speculative or risky. Importantly, this summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, as well as other risks that we face, can be found under the heading "Item 1A. Risk Factors" below.

- *Our ability to grow our company is dependent upon the commercial success of CABOMETYX in its approved indications and the continued clinical development, regulatory approval, clinical acceptance and commercial success of the cabozantinib franchise in additional indications.*
- *If we are unable to obtain or maintain coverage and reimbursement for our products from third-party payers, our business will suffer.*
- *Pricing for pharmaceutical products, both in the U.S. and in foreign countries, has come under increasing attention and scrutiny by federal, state and foreign national governments, legislative bodies and enforcement agencies. These activities may result in actions that have the effect of reducing our revenue or harming our business or reputation.*
- *The entrance of generic competitors and legislative and regulatory action designed to reduce the barriers to the development, approval and adoption of generic drugs in the U.S. could limit the revenue we derive from our products, most notably CABOMETYX, which could have a material adverse impact on our business, financial condition and results of operations.*
- *We are subject to healthcare laws, regulations and enforcement, as well as laws and regulations relating to privacy, data collection and processing of personal data; our failure to comply with those laws could have a material adverse impact on our business, financial condition and results of operations.*
- *Clinical testing of cabozantinib for new indications, or of new product candidates, is a lengthy, costly, complex and uncertain process that may fail ultimately to demonstrate safety and efficacy data for those products sufficiently differentiated to compete in our highly competitive market environment.*
- *The regulatory approval processes of the U.S. Food and Drug Administration and comparable foreign regulatory authorities are lengthy, uncertain and subject to change, and may not result in regulatory approvals for additional cabozantinib indications or for our other product candidates, which could have a material adverse impact on our business, financial condition and results of operations.*
- *We may be unable to expand our discovery and development pipeline, which could limit our growth and revenue potential.*
- *Our profitability could be negatively impacted if expenses associated with our extensive clinical development, business development and commercialization activities, both for the cabozantinib franchise and our earlier-stage product candidates, grow more quickly than the revenues we generate.*

- *Our clinical, regulatory and commercial collaborations with major companies make us reliant on those companies for their continued performance and investments, which subjects us to a number of risks. For example, we rely on Ipsen and Takeda for the commercial success of CABOMETYX in its approved indications outside of the U.S., and we are unable to control the amount or timing of resources expended by these collaboration partners in the commercialization of CABOMETYX in its approved indications outside of the U.S. In addition, our growth potential is dependent in part upon companies with which we have entered into research collaborations, in-licensing arrangements and similar business development relationships.*
- *Data breaches, cyber attacks and other failures in our information technology operations and infrastructure could compromise our intellectual property or other sensitive information, damage our operations and cause significant harm to our business and reputation.*
- *If we are unable to adequately protect our intellectual property, third parties may be able to use our technology, which could adversely affect our ability to compete in the market.*
- *If the COVID-19 pandemic is further prolonged or becomes more severe, our business operations and corresponding financial results could suffer, which could have a material adverse impact on our financial condition and prospects for growth.*
- *The loss of key personnel or the inability to retain and, where necessary, attract additional personnel could impair our ability to operate and expand our operations.*

BASIS OF PRESENTATION

We have adopted a 52- or 53-week fiscal year policy that ends on the Friday closest to December 31st. Fiscal year 2021, which was a 52-week year, ended December 31, 2021, fiscal year 2020, which was a 52-week fiscal year, ended on January 1, 2021 and fiscal year 2019, which was a 53-week fiscal year, ended on January 3, 2020. For convenience, references in this report as of and for the fiscal years ended January 1, 2021 and January 3, 2020 are indicated as being as of and for the years ended December 31, 2020 and 2019, respectively.

Item 1. Business

Overview

Exelixis, Inc. (Exelixis, we, our or us) is an oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Using our considerable drug discovery, development and commercialization resources and capabilities, we have invented and brought to market innovative therapies that appropriately balance patient benefits and risks; we will continue to build on this foundation as we strive to provide cancer patients with new treatment options that improve upon current standards of care.

Today, four products that originated in Exelixis laboratories are available to be prescribed to patients. Sales related to our flagship molecule, cabozantinib, account for the large majority of our revenues. Cabozantinib is an inhibitor of multiple tyrosine kinases including MET, AXL, VEGF receptors and RET and has been approved by the U.S. Food and Drug Administration (FDA) and in 61 other countries as: CABOMETYX® (cabozantinib) tablets approved for advanced renal cell carcinoma (RCC), both alone and in combination with Bristol-Myers Squibb Company's (BMS) OPDIVO® (nivolumab), for previously treated hepatocellular carcinoma (HCC) and, currently by the FDA, for previously treated, radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC); and COMETRIQ® (cabozantinib) capsules approved for progressive, metastatic medullary thyroid cancer (MTC). For physicians treating these types of cancer, cabozantinib has become or is becoming an important drug in their selection of effective therapies.

The other two products resulting from our discovery efforts are: COTELLIC® (cobimetinib), an inhibitor of MEK approved as part of multiple combination regimens to treat specific forms of advanced melanoma and marketed under a collaboration with Genentech, Inc. (a member of the Roche Group) (Genentech); and MINNEBRO® (esaxerenone), an oral, non-steroidal, selective blocker of the mineralocorticoid receptor (MR) approved for the treatment of hypertension in Japan and licensed to Daiichi Sankyo Company, Limited (Daiichi Sankyo). For additional information about these products, see "—Collaborations and Business Development Activities—Other Collaborations."

The year 2021 was our fifth year of profitability. Our total revenues grew by approximately 45% as a result of markedly increased sales of our cabozantinib products by our commercial organization in the U.S. and increased royalties and milestones earned pursuant to collaboration agreements with our ex-U.S. partners. Our plan is to utilize our operating cash flows and cash and investments to expand the cabozantinib franchise by potentially adding new indications in areas of unmet medical need. We will also leverage our operating cash flows to continue advancing our diverse small molecule and

biotherapeutics programs, exploring multiple modalities and mechanisms of action to discover new oncology drugs. So far, these drug discovery and preclinical activities have resulted in four clinical-stage compounds: XL092, a next-generation oral tyrosine kinase inhibitor (TKI); XB002, an antibody drug conjugate (ADC) that targets tissue factor (TF); XL102, a potent, selective and orally bioavailable covalent inhibitor of cyclin-dependent kinase 7 (CDK7); and XL114, a novel anti-cancer compound that inhibits the CARD11-BCL10-MALT1 (CBM) complex.

Exelixis Marketed Products: CABOMETYX and COMETRIQ

As detailed below, CABOMETYX and COMETRIQ have been approved to treat patients with various forms of cancer by the FDA for the U.S. market, the European Commission (EC) for the European Union (EU) markets and the Japanese Ministry of Health, Labour and Welfare (MHLW), as well as by comparable regulatory authorities across other markets worldwide.

Product	Indication	Approval Date	Regimen	Major Markets
CABOMETYX® (cabozantinib)	**Renal Cell Carcinoma (RCC)**			
	Patients with advanced RCC who have received prior anti-angiogenic therapy	April 25, 2016	Monotherapy	U.S.
	Advanced RCC in adults following prior VEGF-targeted therapy	September 9, 2016	Monotherapy	EU
	Patients with advanced RCC	December 19, 2017	Monotherapy	U.S.
	First-line treatment of adults with intermediate- or poor-risk advanced RCC	May 17, 2018	Monotherapy	EU
	Patients with curatively unresectable or metastatic RCC	March 25, 2020	Monotherapy	Japan
	First-line treatment of patients with advanced RCC	January 22, 2021	Combination with OPDIVO® (nivolumab)	U.S.
	First-line treatment for patients with advanced RCC	March 31, 2021	Combination with OPDIVO	EU
	Patients with unresectable or metastatic RCC	August 25, 2021	Combination with OPDIVO	Japan
	Hepatocellular Carcinoma (HCC)			
	HCC in adults who have previously been treated with sorafenib	November 15, 2018	Monotherapy	EU
	Patients with HCC who have been previously treated with sorafenib	January 14, 2019	Monotherapy	U.S.
	Patients with unresectable HCC that has progressed after cancer chemotherapy	November 27, 2020	Monotherapy	Japan
	Differentiated Thyroid Cancer (DTC)			
	Adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGF receptor-targeted therapy and who are RAI-refractory or ineligible	September 17, 2021	Monotherapy	U.S.

COMETRIQ® (cabozantinib)	**Medullary Thyroid Cancer (MTC)**			
	Patients with progressive, metastatic MTC	November 29, 2012	Monotherapy	U.S.
	Adult patients with progressive, unresectable locally advanced or metastatic MTC	March 25, 2014	Monotherapy	EU

In 2021, 2020 and 2019, our U.S. commercial organization generated $1,077.3 million, $741.6 million and $760.0 million, respectively, in net product revenues from sales of CABOMETYX and COMETRIQ. Outside the U.S., we rely on collaboration partners for the commercialization of CABOMETYX and COMETRIQ; Ipsen Pharma SAS (Ipsen) is responsible for all territories outside of the U.S. and Japan, and Takeda Pharmaceutical Company Limited (Takeda) is responsible for the Japanese market. In 2021, 2020 and 2019, we earned $105.2 million, $78.4 million and $62.4 million, respectively, of royalties on net sales of cabozantinib products outside of the U.S. For additional information on the terms of our collaboration agreements with Ipsen and Takeda, see "—Collaborations and Business Development Activities—Cabozantinib Commercial Collaborations."

Renal Cell Carcinoma - CABOMETYX is a Leading TKI Treatment Option for Patients with Advanced RCC

CABOMETYX has become a standard of care for the treatment of patients suffering from advanced RCC, and a growing number of these patients have been or will be treated with CABOMETYX. Kidney cancer is among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S. Estimates suggest that approximately 33,000 patients in the U.S. and over 71,000 worldwide will require systemic treatment for kidney cancer in 2022, with over 15,000 patients in need of a first-line treatment in the U.S.

Since CABOMETYX was first approved, we have deployed our promotional and medical affairs teams to educate physicians about CABOMETYX, and we believe that the product's success is attributable to the strength of the clinical data reflected in its FDA-approved labeling for advanced RCC. The CABOMETYX label incorporates the results of the METEOR, CABOSUN and CheckMate -9ER clinical trials. In July 2015, we announced positive results of METEOR, a phase 3 pivotal trial comparing CABOMETYX to everolimus in patients with advanced RCC who have experienced disease progression following treatment with at least one prior VEGF receptor inhibitor. These results formed the basis for the FDA's approval in April 2016, following which CABOMETYX became the first and only single-agent therapy approved in the U.S. for previously treated advanced RCC to demonstrate statistically significant and clinically meaningful improvements in three key efficacy parameters in a global pivotal trial: overall survival (OS); progression-free survival (PFS); and objective response rate (ORR). Subsequently, in October 2016, we announced positive results from CABOSUN, a randomized, open-label, active-controlled phase 2 trial conducted by the Alliance for Clinical Trials in Oncology, comparing cabozantinib with sunitinib in patients with previously untreated advanced RCC with intermediate- or poor-risk disease. These results formed the basis for the FDA's approval in December 2017 of CABOMETYX for previously untreated patients with advanced RCC, and for this patient population, CABOMETYX is the only approved single-agent therapy to demonstrate improved PFS compared with sunitinib, a first-generation TKI that was the previous standard of care.

CABOMETYX has also demonstrated positive clinical results in combination with immune checkpoint inhibitors (ICIs), most notably in CheckMate -9ER, an open-label, randomized, multinational phase 3 pivotal trial evaluating OPDIVO, an ICI developed by BMS, in combination with CABOMETYX versus sunitinib in patients with previously untreated, advanced or metastatic RCC. Results from CheckMate -9ER demonstrated that the combination of CABOMETYX and OPDIVO doubled PFS and ORR and reduced the risk of disease progression or death by 40% compared with sunitinib, and formed the basis for the FDA's approval of the combination in January 2021 as a first-line treatment of patients with advanced RCC. The National Comprehensive Cancer Network (NCCN), the nation's foremost non-profit alliance of leading cancer centers, has included the combination of CABOMETYX with OPDIVO in its Clinical Practice Guidelines for Kidney Cancer as a Category 1 option for the first-line treatment of patients with clear cell RCC. The NCCN also lists single-agent CABOMETYX as a category 1 preferred regimen in subsequent treatments for patients with clear cell RCC, and as a preferred systemic therapy regimen for non-clear cell RCC, supporting CABOMETYX's position in the RCC treatment landscape.

In markets outside the U.S. in 2021, we continued to work closely with our collaboration partner Ipsen in support of its regulatory strategy and commercialization efforts for CABOMETYX as a treatment for advanced RCC, both as a single

agent and in combination with OPDIVO, as well as in preparation for submission of applications for approvals of CABOMETYX in combination with other therapies, and similarly with our collaboration partner Takeda with respect to the Japanese market. As a result of the approvals of CABOMETYX and/or the combination of CABOMETYX with OPDIVO for RCC indications in 61 countries outside of the U.S., including the Member States of the EU, Japan, the U.K., Canada, Brazil, Taiwan, South Korea and Australia, CABOMETYX has continued to grow markedly outside the U.S. both in sales revenue and the number of RCC patients benefiting from its clinical effect.

Hepatocellular Carcinoma - CABOMETYX Offers an Important Alternative for Patients with Previously Treated HCC

According to published studies, liver cancer is a leading cause of cancer death worldwide, accounting for more than 800,000 deaths and 900,000 new cases each year. Although HCC is the most common form of liver cancer, making up about three-fourths of the more than 41,000 cases of liver cancer estimated to be diagnosed in the U.S. during 2022, this patient population has long been underserved. Prior to 2017, there was only one approved systemic therapy for the treatment of HCC. Since that time, multiple new therapies were approved in the U.S. for HCC, both for previously untreated patients and for patients previously treated with sorafenib. Given the introduction of new and demonstrably more effective therapies, including ICI combination therapies, we believe the second- and later-line market for HCC therapies has the potential to grow significantly in coming years, as these new treatment options are expected to improve longer-term outcomes, thereby resulting in a greater number of patients receiving multiple lines of therapy. With the approval of CABOMETYX in January 2019 for HCC patients previously treated with sorafenib, we expect to continue to play a key role in the treatment landscape for these patients.

The FDA's approval of CABOMETYX's HCC indication was based on our phase 3 pivotal study, CELESTIAL. The CELESTIAL study met its primary endpoint, demonstrating that cabozantinib significantly improved OS, as compared to placebo. The NCCN has included CABOMETYX in its Clinical Practice Guidelines for Hepatobiliary Cancers as a Category 1 option for the treatment of patients with HCC (Child-Pugh Class A only) who have been previously treated with sorafenib, providing further support for CABOMETYX as an important treatment option for eligible HCC patients.

Outside the U.S., the EC's approval of CABOMETYX provided physicians in the EU with a second approved therapy for the second-line treatment of this aggressive and difficult-to-treat cancer, and approvals from Health Canada and the Japanese MHLW brought a much-needed therapy to HCC patients in those countries. In addition to the Member States of the EU, Japan, the U.K. and Canada, CABOMETYX is also approved for previously treated HCC indications in Brazil, Taiwan, South Korea, Australia and Hong Kong, among other countries.

Differentiated Thyroid Cancer - a New Opportunity for CABOMETYX to Help an Underserved Patient Population

Published studies indicate that approximately 44,000 new cases of thyroid cancer will be diagnosed in the U.S. in 2022. Differentiated thyroid tumors, which make up about 90% of all thyroid cancers, are typically treated with surgery followed by ablation of the remaining thyroid with radioiodine (RAI). Approximately 5% to 15% of differentiated thyroid tumors are resistant to RAI treatment. With limited treatment options, these patients have a life expectancy of only three to six years from the time metastatic lesions are detected. New treatment options are therefore urgently needed. In December 2020, we announced that COSMIC-311, our phase 3 pivotal trial evaluating cabozantinib in patients with RAI-refractory DTC who have progressed after up to two prior VEGF receptor-targeted therapies, met its co-primary endpoint of demonstrating significant improvement in PFS as compared with placebo. These results formed the basis for the FDA's approval in September 2021 of CABOMETYX for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGF receptor-targeted therapy and who are RAI-refractory or ineligible. We commenced the commercial launch of CABOMETYX in this patient group upon the FDA's approval, and we have seen a strong uptake in prescriptions for CABOMETYX in previously treated DTC during the months that followed.

Outside the U.S., our collaboration partner Ipsen submitted a variation application to the European Medicines Agency (EMA) seeking approval of CABOMETYX as a treatment for patients with previously treated, RAI-refractory DTC, with the EMA validating the variation application and beginning its centralized review process in August 2021.

Medullary Thyroid Cancer - COMETRIQ, the First Commercial Approval of Cabozantinib

Estimates suggest that there will be approximately 940 MTC cases diagnosed in the U.S. in 2022, and COMETRIQ has served as an important treatment option for these patients since January 2013. The FDA's approval of COMETRIQ for progressive, metastatic MTC was based on our phase 3 trial, EXAM. The EXAM trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful prolongation in PFS for cabozantinib, as compared to placebo. In connection with the approval of COMETRIQ for the treatment of progressive, metastatic MTC, we were subject to post-marketing requirements, including a requirement to conduct the EXAMINER clinical study, comparing a lower 60mg dose of cabozantinib with the labeled dose of 140 mg. Although EXAMINER did not meet the prespecified statistical noninferiority criterion for PFS (per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1. as assessed by independent review) in the cabozantinib 60 mg arm compared with the 140 mg arm, it provided another rich data set of cabozantinib experience in MTC. In the meantime, we will continue to market COMETRIQ capsules for MTC patients at the labeled dose of 140 mg.

Exelixis Development Programs

We have extensive expertise in the clinical development of oncology products, which we leverage when exploring additional clinical uses of cabozantinib in combination with other therapies and advancing that effort to new regulatory approvals. Those activities comprise the broad cabozantinib development program described below. In addition, we also apply that expertise to advancing our company's next generation of cancer treatments: new, innovative therapies that have the potential to help future cancer patients recover stronger and live longer. Accordingly, we are initiating clinical studies for our small molecule drug candidates—XL092, XL102 and XL114—as well as for our first biotherapeutics product candidate, XB002, and these activities are described under "—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates."

A summary of our cabozantinib and other development programs is provided below.

Cabozantinib Development Program

Cabozantinib inhibits the activity of tyrosine kinases, including MET, AXL, VEGF receptors, and RET. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance and maintenance of the tumor microenvironment. Objective tumor responses have been observed in patients treated with cabozantinib in multiple individual tumor types investigated in phase 1, 2 and 3 clinical trials to date, reflecting the medicine's broad clinical potential. We continue to evaluate cabozantinib, both as a single agent and in combination with ICIs, in a broad development program comprising over 100 ongoing or planned clinical trials across multiple tumor types. We, along with our collaboration partners, sponsor some of those trials, and independent investigators conduct the remaining trials through our Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI-CTEP) or our investigator sponsored trial (IST) program. In addition to co-funding select trials with us, our collaboration partners Ipsen and Takeda also conduct trials in their respective territories through similar independently-sponsored programs.

The following two tables summarize select cabozantinib clinical development activities, one describing studies that evaluate the potential of cabozantinib as a single-agent, and the other describing studies that evaluate the potential of cabozantinib in combination with other therapies, including ICIs:

CLINICAL DEVELOPMENT PROGRAM FOR CABOZANTINIB, SINGLE-AGENT	
Indication	**Status Update**
Thyroid Cancer	
Progressive, metastatic medullary thyroid cancer	Approved in U.S. and EU (EXAM)
Second-line differentiated thyroid cancer (DTC) after prior VEGF receptor-targeted therapy	Approved in U.S. (COSMIC-311)
Renal Cell Carcinoma (RCC)	
Advanced RCC	Approved in U.S., EU and Japan (METEOR and CABOSUN)
First- or second-line papillary RCC	Randomized phase 2† (PAPMET/SWOG S1500)
Metastatic variant histology RCC	Phase 2* (CABOSUN II)
Locally advanced non-metastatic clear cell RCC	Phase 2*
Clear cell or non-clear cell metastatic RCC	Phase 2*

Hepatocellular Carcinoma (HCC)	
Second- and later-line HCC after prior sorafenib	Approved in U.S., EU and Japan (CELESTIAL)
Advanced HCC with Child-Pugh class B cirrhosis after first-line therapy	Phase 2*
Non-Small Cell Lung Cancer (NSCLC)	
Molecular alterations in RET, ROS1, MET, AXL, or NTRK1	Phase 2*
Additional Trials	
High-risk prostate cancer	Phase 2* (SPARC)
Metastatic castration-resistant prostate cancer (mCRPC) with genomic alterations	Phase 2*
Metastatic urothelial carcinoma (UC)	Phase 2* (ATLANTIS)
Advanced or metastatic UC	Phase 2†
Colorectal cancer (CRC)	Phase 2*
High-grade uterine sarcomas	Phase 2§
Pancreatic neuroendocrine tumors and carcinoid tumors	Phase 2* and Phase 3† (CABINET)
Metastatic adrenocortical carcinoma	Phase 2*
Metastatic pheochromocytomas and paragangliomas	Phase 2*
Plexiform neurofibromas (pediatric and adult cohorts)	Phase 2*
Neuroendocrine neoplasms	Phase 2*
Soft-tissue sarcomas	Phase 2†
Refractory germ cell tumors	Phase 2*
High-risk pediatric solid tumors	Phase 2* (CaboMain)
Pediatric refractory sarcoma, Wilms tumor and other rare tumors	Phase 2†
High-grade pediatric glioma	Phase 2*

* Trial conducted through our IST program.
† Trial conducted through collaboration with NCI-CTEP.
§ Trial sponsored by the European Organization for Research and Treatment of Cancer.

CLINICAL DEVELOPMENT PROGRAM FOR CABOZANTINIB, IN COMBINATION WITH OTHER THERAPIES		
Indication	**Combination Regimen**	**Status Update**
Genitourinary Cancers		
First-line advanced RCC	+ nivolumab	Approved in U.S., EU and Japan (CheckMate -9ER)
First-line advanced or metastatic RCC	+ nivolumab + ipilimumab	Phase 3 pivotal trial (COSMIC-313)
mCRPC that progressed during or following treatment with one novel hormonal therapy (NHT)	+ atezolizumab	Phase 3 pivotal trial (CONTACT-02)
Advanced RCC that progressed during or following treatment with an immune checkpoint inhibitor (ICI)	+ atezolizumab	Phase 3 pivotal trial (CONTACT-03)
First-line metastatic RCC	+ nivolumab vs. nivolumab after 4 cycles of nivolumab + ipilimumab	Phase 3† randomized (PDIGREE)
Advanced or metastatic non-clear cell RCC	+ nivolumab	Phase 2*
Advanced RCC with bone metastasis	+ radium-223 dichloride	Phase 2† (RadiCaL)

Cisplatin-Ineligible advanced UC	+ pembrolizumab	Phase 2* (PemCab)
Neoadjuvant muscle-invasive UC	+ atezolizumab	Phase 2* (ABATE)
Genitourinary tumors	+ nivolumab ± ipilimumab	Phase 1b†
Genitourinary tumors	+ nivolumab + ipilimumab	Phase 2† (ICONIC)
Advanced non-clear cell RCC	+ nivolumab + ipilimumab	Phase 2*
Metastatic RCC	+ nivolumab after cytoreductive surgery	Phase 2* (Cyto-KIK)
Metastatic RCC	+ avelumab	Phase 1b*
Locally advanced or metastatic UC	+ enfortumab vedotin	Phase 1*
Metastatic hormone-sensitive prostate cancer	+ abiraterone + nivolumab	Phase 1* (CABIOS)
Metastatic RCC	+ nivolumab ± CBM 588	Phase 1*
Gastrointestinal Cancers		
First-line advanced HCC	+ atezolizumab	Phase 3 pivotal trial (COSMIC-312), including a single-agent cabozantinib arm
First- and later-line advanced HCC	+ nivolumab ± ipilimumab	Phase 1/2 (CheckMate 040)
Neoadjuvant locally advanced HCC	± nivolumab	Phase 1b*
HCC who are not candidates for curative intent treatment	+ nivolumab + ipilimumab + transarterial chemoembolization	Phase 2*
Advanced HCC	+ pembrolizumab	Phase 2*
Refractory metastatic microsatellite stable CRC	+nivolumab	Phase 2*
Metastatic, refractory pancreatic cancer	+ atezolizumab	Phase 2*
Metastatic pancreatic adenocarcinoma	+pembrolizumab	Phase 2*
Metastatic colorectal adenocarcinoma	+trifluridine/tipiracil	Phase 1*
Thyroid Cancers		
Advanced DTC	+ nivolumab + ipilimumab	Phase 2†
Lung Cancers		
Metastatic NSCLC previously treated with an ICI and platinum-containing chemotherapy	+ atezolizumab	Phase 3 pivotal trial (CONTACT-01)
Previously treated non-squamous NSCLC	+ nivolumab	Randomized phase 2†
Gynecologic Cancers		
Advanced or metastatic endometrial cancer	+ nivolumab	Phase 2†
Neuroendocrine Tumors (NET) and Carcinoid		
Advanced carcinoid tumors	+ nivolumab	Phase 2*
Poorly differentiated neuroendocrine carcinomas	+ nivolumab + ipilimumab	Phase 2†
Head and Neck Cancers		

Recurrent, metastatic squamous cell carcinoma	+ cetuximab	Phase 1*
Recurrent, metastatic squamous cell carcinoma	+ pembrolizumab	Phase 2*
Melanoma		
Unresectable, advanced melanoma	+ nivolumab + ipilimumab	Phase 2*
Advanced, metastatic melanoma	+ pembrolizumab	Phase 2*
Sarcoma		
Unresectable or metastatic leiomyosarcoma and other soft tissue sarcomas	+ temozolomide	Phase 2*
Sarcomas of the extremities	+ radiation therapy	Phase 2*
Metastatic soft tissue sarcomas	+ PD-1 + CTLA-4 inhibition	Phase 2*
Angiosarcoma pre-treated with taxane	+ nivolumab	Phase 2†
Additional Trials in Multiple Tumor Types		
Advanced solid tumors	+ atezolizumab	Phase 1b (COSMIC-012) with 20 cabozantinib and atezolizumab expansion cohorts, including mCRPC, RCC, UC, HCC, colorectal adenocarcinoma, DTC, NSCLC, endometrial cancer, ovarian cancer, breast cancer, gastric or gastroesophageal junction adenocarcinoma and head and neck cancer, and two single-agent cabozantinib exploratory cohorts (NSCLC and mCRPC), and one single-agent atezolizumab exploratory cohort (mCRPC)
Advanced CRC, HCC, gastric, gastroesophageal or esophageal adenocarcinoma	+ durvalumab	Phase 1* (CAMILLA)
Metastatic or recurrent gastric or gastro-esophageal adenocarcinoma	+ pembrolizumab	Phase 2*
Advanced non-squamous NSCLC, UC and advanced malignant mesothelioma	+ pemetrexed	Phase 1*
Multiple solid tumor types and HIV	+ nivolumab	Phase 1†
Advanced solid tumors	+ pamiparib	Phase 1*
Pediatric multiple tumor types	+ retinoic acid	Phase 1*

* Trial conducted through our IST program.

† Trial conducted through collaboration with NCI-CTEP.

§ Trial sponsored by the European Organization for Research and Treatment of Cancer.

Trials Conducted Under our Clinical Collaboration Agreements

We continue to invest significantly in the exploration of additional clinical uses of cabozantinib in combination with other therapies. In particular, given that clinical observations from clinical trials evaluating cabozantinib in combination with ICIs have shown promising activity across a diverse range of tumors, and that patients have been able to tolerate these drug combinations, we are focused on the potential of cabozantinib in combination with ICIs in additional late-stage or other potentially label-enabling trials.

Combination Studies with BMS

In February 2017, we entered into a clinical collaboration agreement with BMS for the purpose of conducting clinical studies combining cabozantinib with BMS' PD-1 ICI, nivolumab, both with or without BMS' CTLA-4 ICI, ipilimumab. Based on the data from CheckMate -9ER, the first clinical trial conducted under this collaboration, the FDA approved CABOMETYX in combination with OPDIVO on January 22, 2021 as a first-line treatment of patients with advanced RCC. We continue to evaluate these combinations in COSMIC-313, a phase 3 pivotal trial in previously untreated advanced RCC. Pursuant to our agreements with BMS, each party is responsible for supplying finished drug product for the applicable clinical trial, and responsibility for the payment of costs for each trial is determined on a trial-by-trial basis. For additional information on the terms of the clinical trial collaboration agreement, see "—Collaborations and Business Development Activities—Cabozantinib Development Collaborations—BMS."

RCC - COSMIC-313. In May 2019, we initiated COSMIC-313, a multicenter, randomized, double-blinded, controlled phase 3 pivotal trial evaluating the triplet combination of cabozantinib, nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab in patients with previously untreated advanced intermediate- or poor-risk RCC. Patients were randomized 1:1 to the experimental arm of the triplet combination of cabozantinib, nivolumab and ipilimumab or to the control arm of nivolumab and ipilimumab in combination with matched placebo. The primary endpoint for the trial is PFS, and secondary endpoints include OS and ORR. Based on long-term follow-up results for CheckMate 214, in which the combination of nivolumab and ipilimumab showed a longer median OS compared to original assumptions, we expanded the enrollment target for COSMIC-313 to provide additional power to assess the secondary endpoint of OS for COSMIC-313. We completed the expanded enrollment of 855 patients in March 2021 and expect to report top-line results of the event-driven analyses from the trial in the first half of 2022. We are sponsoring COSMIC-313, and BMS is providing nivolumab and ipilimumab for the study free of charge.

Combination Studies with Roche

Diversifying our exploration of cabozantinib combinations with ICIs, in February 2017, we entered into a master clinical supply agreement with F. Hoffmann-La Roche Ltd. (Roche) for the purpose of evaluating cabozantinib and Roche's anti-PD-L1 ICI, atezolizumab, in locally advanced or metastatic solid tumors. As part of the clinical supply agreement, we are evaluating this combination in a phase 1b trial in locally advanced or metastatic tumors, COSMIC-021, and a phase 3 pivotal trial in previously untreated advanced HCC. Informed by the data generated from COSMIC-021, we also entered into a joint clinical research agreement with Roche in December 2019, pursuant to which we are evaluating this combination in three late-stage clinical trials: the first, CONTACT-01, focuses on patients with metastatic non-small cell lung cancer (NSCLC) who have been previously treated with an ICI and platinum-containing chemotherapy; the second, CONTACT-02, focuses on patients with metastatic castration-resistant prostate cancer (mCRPC) who have been previously treated with one novel hormonal therapy (NHT); and the third, CONTACT-03, focuses on patients with inoperable, locally advanced or metastatic RCC who have progressed during or following treatment with an ICI as the immediate preceding therapy. For additional information on the terms of the joint clinical research agreement, see "—Collaborations and Business Development Activities—Cabozantinib Development Collaborations—Roche."

Locally Advanced or Metastatic Solid Tumors - COSMIC-021. In June 2017, we initiated COSMIC-021, a phase 1b dose escalation study that is evaluating the safety and tolerability of cabozantinib in combination with Roche's atezolizumab in patients with locally advanced or metastatic solid tumors. We are the trial sponsor of COSMIC-021, and Roche is providing atezolizumab free of charge. The study is divided into two parts: a dose-escalation phase, which was completed in 2018; and an expansion cohort phase, which is ongoing.

Enrollment in the expansion phase of this study includes 20 combination therapy tumor expansion cohorts in NSCLC, mCRPC, RCC and various other tumor types. Encouraging efficacy and safety data has emerged from the trial and has been instrumental in guiding our clinical development strategy for cabozantinib in combination with ICIs, including supporting the initiation of COSMIC-312, CONTACT-01, CONTACT-02 and CONTACT-03. Moreover, certain cohorts have been expanded, including a cohort of patients with mCRPC who have been previously treated with enzalutamide and/or abiraterone acetate and experienced radiographic disease progression in soft tissue (Cohort 6) and a cohort of patients with NSCLC who have been previously treated with an ICI. Data from Cohort 6, announced in May 2021 and presented at the European Society for Medical Oncology (ESMO) 2021 Congress in September 2021, resulted in an investigator assessed ORR per RECIST v. 1.1 of 23% and a blinded independent radiology committee (BIRC) assessed ORR per RECIST v. 1.1 of 15%. Other more detailed results from Cohort 6 were also presented at the ESMO 2021 Congress, including investigator assessed PFS per RECIST v. 1.1 of 5.5 months and BIRC assessed PFS per RECIST v. 1.1 of 5.7 months. While these results show promise, following discussions with the FDA, we will not pursue a regulatory submission for the combination regimen based

solely on the Cohort 6 results; however, we will continue to evaluate the combination regimen in patients with previously treated mCRPC in the CONTACT-02 phase 3 pivotal trial.

HCC - COSMIC-312. In December 2018, we initiated COSMIC-312, a multicenter, randomized, controlled phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus sorafenib in previously untreated advanced HCC. The trial also includes a third arm evaluating cabozantinib monotherapy in this first-line setting in order to address the contribution of components for the combination therapy. We are sponsoring COSMIC-312, and Ipsen is co-funding the trial. Ipsen will have access to the results to support potential future regulatory submissions outside of the U.S. and Japan. Roche is providing atezolizumab free of charge. In August 2020, we announced the completion of patient enrollment in COSMIC-312, providing the requisite patient population to conduct the event-driven analyses of the trial's two primary endpoints of PFS and OS. Separately, patient enrollment remains open in mainland China in order to enroll a sufficient number of patients to enable local registration, if supported by the clinical data. Patients are being randomized to one of three arms: cabozantinib (40 mg) in combination with atezolizumab; sorafenib; or cabozantinib monotherapy (60 mg). In June and November 2021, we announced results from COSMIC-312, which were presented at the ESMO Asia Virtual Oncology Week in November 2021. The trial met one of the primary endpoints, demonstrating significant improvement in BIRC assessed PFS at the planned primary analysis, reducing the risk of disease progression or death by 37% compared with sorafenib (hazard ration [HR]: 0.63; 99% confidence interval [CI]: 0.44-0.91; P=0.0012; pre-specified critical P-value of 0.01). Median PFS was 6.8 months for cabozantinib in combination with atezolizumab versus 4.2 months for sorafenib. The interim OS analysis performed at the same time did not reach statistical significance (HR: 0.90; 96% CI: 0.69-1.18; P=0.438). Median OS was 15.4 months for cabozantinib in combination with atezolizumab versus 15.5 months for sorafenib. The trial is continuing as planned to the final analysis of OS, anticipated during the first quarter of 2022, and we intend to submit an sNDA to the FDA for the combination regimen if supported by the final OS analysis.

NSCLC - CONTACT-01. Lung cancer is the second most common type of cancer in the U.S., with more than 236,000 new cases expected to be diagnosed in 2022. The disease is the leading cause of cancer-related mortality in both men and women, causing 25% of all cancer-related deaths. The majority (84%) of lung cancer cases are NSCLC, which mainly comprise adenocarcinoma, squamous cell carcinoma and large cell carcinoma. The five-year survival rate for patients with NSCLC is 25%, but that rate falls to just 7% for those with advanced or metastatic disease. Due to the urgent need for treatment options for patients with NSCLC and based on positive early-stage results from COSMIC-021, in June 2020, we and Roche initiated CONTACT-01, a global, multicenter, randomized, open-label phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus docetaxel in patients with metastatic NSCLC who have been previously treated with an ICI and platinum-containing chemotherapy. Patients are randomized 1:1 to the experimental arm of cabozantinib in combination with atezolizumab or to the control arm of docetaxel. The primary endpoint for the trial is OS, and secondary endpoints include PFS, ORR and DOR, in each case per RECIST v. 1.1. In November 2021, we announced the completion of enrollment of 366 patients at 117 sites globally. Based on current event rates, we anticipate announcing results of the interim OS analysis in the second half of 2022. CONTACT-01 is sponsored by Roche and co-funded by us. In addition, both Ipsen and Takeda have opted into and are co-funding the trial, and both companies will have access to the results to support potential future regulatory submissions in their respective territories outside of the U.S.

mCRPC - CONTACT-02. According to the American Cancer Society, in 2022, approximately 268,500 new cases of prostate cancer will be diagnosed, and 34,500 people will die from the disease. Prostate cancer that has spread beyond the prostate and does not respond to androgen-suppression therapies—a common treatment for prostate cancer—is known as mCRPC. Researchers estimate that in 2020, 43,000 men were diagnosed with mCRPC, which has a median survival of less than two years. In response to this significant unmet need and based on positive early-stage results from Cohort 6 of COSMIC-021, in June 2020, we and Roche initiated CONTACT-02, a global, multicenter, randomized, open-label phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab in patients with mCRPC who have been previously treated with one NHT. The trial aims to enroll approximately 580 patients at approximately 280 sites globally, and we expect to complete enrollment in the second half of 2022. Patients are being randomized 1:1 to the experimental arm of cabozantinib in combination with atezolizumab or to the control arm of a second NHT (either abiraterone and prednisone or enzalutamide). The two primary endpoints for the trial are PFS per RECIST v. 1.1 as assessed by BIRC and OS, and secondary endpoints include ORR, prostate-specific antigen response rate and DOR. CONTACT-02 is sponsored by us and co-funded by Roche. In addition, both Ipsen and Takeda have opted into and are co-funding the trial, and both companies will have access to the results to support potential future regulatory submissions in their respective territories outside of the U.S.

RCC - CONTACT-03. Taking into account the rapidly evolving treatment landscape for RCC and based on positive early-stage results from COSMIC-021, in July 2020, we and Roche initiated CONTACT-03, a global, multicenter, randomized, open-label phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus cabozantinib alone in

patients with inoperable, locally advanced or metastatic RCC who progressed during or following treatment with an ICI as the immediate preceding therapy. Patients are randomized 1:1 to the experimental arm of cabozantinib in combination with atezolizumab or to the control arm of cabozantinib alone. The two primary endpoints for the trial are PFS per RECIST v. 1.1 as assessed by BIRC and OS, and secondary endpoints include PFS, ORR and DOR as assessed by the investigators. CONTACT-03 is sponsored by Roche and co-funded by us. In addition, both Ipsen and Takeda have the right to opt in and co-fund the trial and if doing so, they will have access to the results to support potential future regulatory submissions in their respective territories outside of the U.S. In January 2022, we announced the completion of enrollment of 523 patients at 168 sites globally. Based on current event rates, we anticipate announcing results of PFS and the first interim OS analysis in the second half of 2022. We intend to use the data from CONTACT-03 to further study the therapeutic potential of cabozantinib in this patient population, both as a single agent and in combination with ICIs.

Other Trials Evaluating Cabozantinib in Combination with other Therapies

RCC - CANTATA: In January 2021 Calithera Biosciences, Inc. (Calithera) announced that the CANTATA trial did not meet its primary endpoint of improving PFS per independent review for Calithera's teleaglenastat (also known as CB-839) plus cabozantinib as compared with cabozantinib alone in previously treated advanced or metastatic RCC. The HR was 0.94 (p=0.65), and median PFS was 9.2 months among patients treated with telaglenastat and cabozantinib as compared to 9.3 months for patients treated with cabozantinib and placebo. We provided cabozantinib for the trial through a material supply agreement with Calithera.

Trials Conducted through our CRADA with NCI-CTEP and our IST Program

In October 2011, we entered into a CRADA with NCI-CTEP for the clinical development of cabozantinib. The CRADA and our IST program have enabled further expansion of the cabozantinib development program with less burden on our internal development resources. This CRADA reflects a major commitment by NCI-CTEP to support the broad exploration of cabozantinib's potential in a wide variety of cancers, each representing a substantial unmet medical need. Through this mechanism, NCI-CTEP provides funding for as many as 20 active clinical trials of cabozantinib each year for a five-year period. We and NCI-CTEP have extended the term of the CRADA through October 2026, provided that both parties maintain the right to terminate the CRADA for any reason upon sixty days' notice, for an uncured material breach upon thirty days' notice and immediately for safety concerns. Investigational New Drug (IND) applications for trials under the CRADA are held by NCI-CTEP. NCI-CTEP also retains rights to any inventions made in whole or in part by NCI-CTEP investigators. However, for inventions that claim the use and/or the composition of cabozantinib, we have an automatic option to elect a worldwide, non-exclusive license to cabozantinib inventions for commercial purposes, with the right to sublicense to affiliates or collaborators working on our behalf, as well as an additional, separate option to negotiate an exclusive license to cabozantinib inventions. Further, before any trial proposed under the CRADA may commence, the protocol is subject to our review and approval, and the satisfaction of certain other conditions. As reflected by the results from completed trials and given the numerous ongoing and planned clinical trials, we believe our CRADA with NCI-CTEP has and will enable us to continue to expand the cabozantinib development program broadly in a cost-efficient manner. A summary of key trials under this collaboration is provided below.

Advanced Genitourinary Tumors

PDIGREE is a phase 3 trial led by The Alliance that is enrolling 1,046 intermediate- or poor-risk advanced RCC patients who have a clear cell component in their tumors. All patients are initially treated with up to 4 cycles of induction ipilimumab combined with nivolumab. Subsequently, patients are treated based on their response to the induction therapy. Patients achieving a complete response (CR) continue on maintenance nivolumab, while patients with progressive disease (PD) are switched to cabozantinib monotherapy. Patients who neither achieve a CR nor develop PD during induction are randomized 1:1 to either maintenance nivolumab or nivolumab in combination with cabozantinib 40 mg daily. The primary endpoint is OS, while PFS, CR rate, ORR and safety are among the secondary endpoints.

In February 2021, positive initial results were announced from PAPMET (also known as SWOG S1500), a randomized phase 2 trial conducted by the Southwest Oncology Group evaluating cabozantinib versus sunitinib in patients with metastatic papillary RCC. PAPMET met its primary endpoint, demonstrating a statistically significant and clinically meaningful prolongation of PFS, with a median PFS of 9.0 months for cabozantinib (95% CI: 6-12) versus 5.6 months for sunitinib (95% CI: 3-7) (HR: 0.60; 95% CI: 0.37-0.97; P=0.019). Detailed results from PAPMET were presented at the virtual American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium in February 2021 and published in *The Lancet.*

RADICAL is a randomized phase 2 trial being conducted by The Alliance that plans to enroll up to 210 patients with advanced RCC. All patients must have at least 2 sites of bone metastases and may have received up to 2 prior lines of systemic therapy. Patients are randomized 1:1 to be treated with cabozantinib in combination with radium-223 dichloride or cabozantinib as a single agent. The primary endpoint is symptomatic skeletal event-free survival, while secondary endpoints include PFS, OS, ORR and safety.

Neuroendocrine Tumors

The Alliance is leading the CABINET study that treats patients with well- or moderately-differentiated neuroendocrine tumors (NETs). CABINET includes 2 separate randomized studies, one for patients with pancreatic NETs and the other for patients with carcinoid tumors. The planned enrollment for the pancreatic NET study is 185 patients and for the carcinoid study is 210 patients. Both studies randomize previously treated patients 2:1 to cabozantinib 60 mg daily or placebo. The primary endpoint for both studies is PFS per Response Evaluation Criteria in Solid Tumors 1.1 as determined by a blinded IRRC.

Other Cancer Indications

Overall, there are 66 ongoing and 26 planned externally sponsored trials evaluating the therapeutic potential of cabozantinib, including those administered through our CRADA with NCI-CTEP and our IST program. Like our CRADA with NCI-CTEP, our IST program helps us to continue to evaluate cabozantinib across a broad range of tumor types.

These externally sponsored trials include signal seeking studies of single-agent cabozantinib, novel combinations, and randomized trials. The monotherapy trials are focused on solid tumors including genitourinary neoplasms, gastrointestinal malignancies, lung cancer and a variety of less common tumor types. The combination studies include trials combining cabozantinib with several different ICIs, as well as studies adding cabozantinib to various other anti-cancer therapies, including monoclonal antibodies (mAbs), chemotherapeutic agents, small molecules which target specific cellular pathways, or radiation. In addition to the various trials described above, our CRADA includes an ongoing randomized phase 2 study in NSCLC, also in combination with an ICI.

A complete listing of all ongoing cabozantinib trials can be found at www.ClinicalTrials.gov.

Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates

We have advanced several other product candidates into clinical trials during recent years, including both small molecules and biotherapeutics that we have discovered or in-licensed and believe may have the potential to benefit patients with a variety of cancers. The following table summarizes our current and planned clinical development activities outside of the cabozantinib franchise:

CLINICAL DEVELOPMENT PROGRAM FOR PIPELINE			
Product	**Mechanism of Action**	**Setting**	**Status Update**
XL092	Next-generation tyrosine kinase inhibitor (TKI) targeting MET/VEGFR/AXL/MER	Advanced or metastatic solid tumors	Phase 1b trials evaluating single-agent and immune checkpoint inhibitor (ICI) combination regimens ongoing • In combination with atezolizumab and with avelumab (STELLAR-001) • In combination with nivolumab, with nivolumab and ipilimumab and with nivolumab and bempegaldesleukin (STELLAR-002) Potential to initiate late-stage trials in 2022 (including STELLAR-303)

XB002	Next-generation tissue factor (TF)-targeting antibody-drug conjugate (ADC)	Advanced solid tumors	Phase 1 trial evaluating single-agent ongoing Potential to add combination regimens with ICIs and other targeted therapies in 2022
XL102	Potent, selective, orally bioavailable cyclin-dependent kinase 7 (CDK7) inhibitor	Advanced or metastatic solid tumors	Phase 1 trial evaluating single-agent and combination regimens ongoing • In combination with fulvestrant, with abiraterone and prednisone and potentially with other anti-cancer regimens
XL114	CARD11-BCL10-MALT1 (CBM) complex inhibitor	Non-Hodgkin's lymphoma (NHL)	Phase 1 trial evaluating single-agent planned for first half of 2022

XL092 Development Program

The first compound discovered at Exelixis to enter the clinic following our re-initiation of drug discovery activities in 2017 was XL092, a next-generation oral TKI that targets VEGF receptors, MET, AXL, MER and other kinases implicated in cancer's growth and spread. In designing XL092, we sought to build upon our experience with cabozantinib, retaining a similar target profile while improving key characteristics, including the pharmacokinetic half-life. We are evaluating XL092 in a growing clinical development program across various tumor types.

Advanced Solid Tumors - STELLAR-001. Following the FDA's acceptance of our IND for XL092, in February 2019, we initiated STELLAR-001, a multicenter phase 1b clinical trial evaluating the pharmacokinetics, safety, tolerability and preliminary anti-tumor activity of XL092. STELLAR-001 is divided into dose-escalation and expansion phases. In October 2020, we presented data at the 32nd EORTC-NCI-AACR (ENA) Symposium that suggest XL092 has a desirable therapeutic profile. We believe it pairs the potential for significant anti-tumor activity with a much shorter clinical pharmacokinetic half-life than cabozantinib, and also presents the potential for synergistic effects in combination with ICIs. In consideration of these data, we amended the phase 1 study protocol in October 2020 to include dose-escalation and expansion cohorts for XL092 in combination with atezolizumab, and again in March 2021 to include dose-escalation and expansion cohorts for XL092 in combination avelumab, an ICI developed by Merck KGaA, Darmstadt, Germany (Merck KGaA) and Pfizer Inc. (Pfizer). We are continuing to enroll patients into the dose-escalation cohorts of the combination part of the trial, and we expect that once recommended doses are established for single-agent XL092, XL092 in combination with atezolizumab and XL092 in combination with avelumab, the trial will begin to enroll expansion cohorts for patients with clear cell and non-clear cell RCC, colorectal cancer (CRC), hormone-receptor positive breast cancer mCRPC and urothelial carcinoma (UC). The primary efficacy endpoints for the expansion phase may include ORR per RECIST v. 1.1 and PFS per RECIST v. 1.1.

Advanced Solid Tumors - STELLAR-002. In December 2021, we initiated STELLAR-002, a multicenter phase 1 clinical trial evaluating the safety, tolerability and efficacy of XL092 in combination with either nivolumab, nivolumab and ipilimumab, or nivolumab and bempegaldesleukin, an investigational CD122-preferential IL-2–pathway agonist developed by Nektar Therapeutics (Nektar). STELLAR-002 is divided into dose-escalation and expansion phases. The dose-escalation phase of the trial is enrolling patients with advanced solid tumors and will determine the recommended dose in patients for each of the XL092 combination regimens. Depending on the dose-escalation results, STELLAR-002 may enroll expansion cohorts for patients with clear cell and non-clear cell RCC, mCRPC and UC. The primary efficacy endpoint of the expansion phase will be ORR, except for the cohort of patients with mCRPC, for which the primary efficacy endpoint will be duration of radiographic PFS. To better understand the individual contribution of the therapies, treatment arms in the expansion cohorts may include XL092 as a single agent in addition to the ICI combination regimens.

In addition to clinical updates for XL092 expected in 2022, we plan to initiate the first global phase 3 pivotal trial for the compound in the first half of the year, and other pivotal trials may follow throughout the year. This first planned trial, STELLAR-303, will evaluate XL092 in combination with atezolizumab versus regorafenib in patients with metastatic microsatellite stable CRC who have progressed after or are intolerant to the current standard of care. Preclinical data and emerging results from STELLAR-001 for XL092, both alone and in combination with ICIs, reinforce our belief in the

opportunity for XL092, which pairs a target profile similar to cabozantinib with a potentially significantly improved safety profile. The decision to initiate STELLAR-303 is also supported by data from a CRC cohort of COSMIC-021, our phase 1b study evaluating cabozantinib in combination with atezolizumab, and from CAMILLA, a phase 1 IST evaluating cabozantinib in combination with durvalumab or with durvalumab and tremelimumab. Results from both of these trials were presented at the ASCO Gastrointestinal Cancers Symposium in January 2022. We intend to develop XL092 in novel combination regimens in a broad array of future potential indications where cabozantinib has demonstrated RECIST v. 1.1 anti-tumor activity.

XB002 Development Program

XB002 (formerly ICON-2) is our lead TF-targeting ADC program, which we in-licensed from Iconic, Inc. (Iconic). XB002 is an ADC composed of human mAb against TF that is conjugated to a cytotoxic agent. TF is highly expressed on tumor cells and in the tumor microenvironment, and TF overexpression, while not oncogenic itself, facilitates angiogenesis, metastasis and other processes important to tumor development and progression. After binding to TF on tumor cells, XB002 is internalized, and the cytotoxic agent is released, resulting in targeted tumor cell death. XB002 is a rationally designed next-generation ADC that leverages proprietary linker-payload technology. Based on promising preclinical data, we exercised our exclusive option to license XB002 in December 2020, resulting in our assuming responsibility for all subsequent clinical development of XB002. For additional information on our business development activities with Iconic, see "—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities—Iconic." Following the FDA's acceptance of our IND for XB002, in June 2021, we initiated a multicenter phase 1, open-label clinical trial designed to evaluate its safety, tolerability, pharmacokinetics and preliminary anti-tumor activity in patients with advanced solid tumors. The trial is divided into dose-escalation and cohort-expansion phases. The dose-escalation phase of the trial is enrolling patients with advanced solid tumors, with the primary objective of determining the maximum tolerated dose or recommended dose levels for intravenous infusion of XB002 as a single agent. Assuming positive data from the initial phase of the trial, the cohort-expansion phase is designed to further explore the selected dose of XB002 in individual tumor cohorts, which may include forms of NSCLC, cervical cancer, ovarian cancer, UC, squamous cell head and neck cancers, pancreatic cancer, esophageal cancer, mCRPC, triple negative breast cancer and hormone-receptor positive breast cancer, and will evaluate ORR per RECIST v. 1.1 as a primary endpoint as well as XB002's safety, tolerability and pharmacokinetic profile. We expect to provide clinical updates from the ongoing phase 1 study of XB002 during 2022. We also intend to initiate additional dose-escalation and expansion cohorts to evaluate the potential of XB002 in combination with ICIs and other targeted therapies across a wide range of tumor types, including indications other than those currently addressed by commercially available TF-targeted therapies. Since initiating the XB002 phase 1 trial, we amended our exclusive option and license agreement with Iconic in December 2021 to acquire broad rights to use the anti-TF antibody used in XB002 for any application, including conjugated to other payloads, as well as rights within oncology to a number of other anti-TF antibodies developed by Iconic, including for use in ADCs and multispecific biotherapeutics. For additional information on our business development activities with Iconic, see "—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities—Iconic."

XL102 Development Program

XL102 (formerly AUR102) is the lead compound under our research collaboration with Aurigene Discovery Technologies Limited (Aurigene). It is a potent, selective and orally bioavailable covalent inhibitor of CDK7, which is an important regulator of the cellular transcriptional and cell cycle machinery. Based on encouraging preclinical data for XL102, which we and Aurigene presented at the 32nd ENA Symposium in October 2020, we exercised our exclusive option to license XL102 in December 2020, resulting in our assuming responsibility for all subsequent clinical development of XL102. For additional information on our collaboration with Aurigene, see "—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities—Aurigene."

Following the FDA's acceptance of our IND for XL102, in January 2021, we initiated a multicenter phase 1, open-label clinical trial designed to evaluate its safety, tolerability, pharmacokinetics and preliminary anti-tumor activity, both as a single agent and in combination with other anti-cancer therapies, in up to 298 patients with inoperable, locally advanced or metastatic solid tumors. The trial is divided into dose-escalation and cohort-expansion phases. The dose-escalation phase of the trial is enrolling patients with advanced solid tumors, with the primary objective of determining the maximum tolerated dose or recommended dose levels for daily oral administration of XL102 as a single agent, as well as in combination with fulvestrant for patients with hormone-receptor positive breast cancer and with abiraterone and prednisone for patients with mCRPC. Combinations with other agents may also be evaluated. Assuming positive data from the initial phase of the trial, the cohort-expansion phase is designed to further explore the selected dose of XL102 as a

single agent and in combination regimens in individual tumor cohorts, including ovarian cancer, triple-negative breast cancer, hormone-receptor positive breast cancer and mCRPC, and will evaluate ORR per RECIST v. 1.1, as well as XL102's safety, tolerability and pharmacokinetic profile. We expect to provide clinical updates from the ongoing phase 1 study of XL102 during 2022.

XL114 Development Program

XL114 (formerly AUR104) is a novel anti-cancer compound that inhibits activation of the CBM complex, a key component of signaling downstream of B- and T-cell receptors, which promotes B- and T-cell lymphoma survival and proliferation. Constitutive activation of B- or T-cell receptor signaling is a common feature of B-cell and T-cell lymphomas, and therefore we believe CBM is an attractive target for the development of new anti-cancer therapies with the potential to treat lymphoid malignancies. Notably, the CBM complex is downstream of BTK, inhibitors of which are approved therapies for certain B-cell lymphomas. Inhibitors of CBM complex activation may therefore provide options for patients who develop resistance to BTK inhibitors. At the American Association of Cancer Research Annual Meeting in April 2021, Aurigene presented preclinical data (Abstract 1266) demonstrating that XL114 exhibited potent anti-proliferative activity in a large panel of cancer cell lines ranging from hematological cancers to solid tumors with excellent selectivity over normal cells. We exercised our exclusive option to in-license XL114 in October 2021, resulting in our assuming responsibility for all subsequent clinical development, manufacturing and commercialization of XL114. For additional information on our collaboration with Aurigene, see "—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities —Aurigene."

The FDA accepted our IND application for XL114 in October 2021, and we plan to initiate a phase 1 clinical trial evaluating the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of the compound as a monotherapy in patients with non-Hodgkin's lymphoma (NHL) in the first half of 2022. The trial will be divided into dose-escalation and cohort-expansion phases and will aim to enroll approximately 144 patients with advanced NHL. The dose-escalation phase of the trial will determine the maximum tolerated dose or recommended dose levels for daily oral administration of XL114 as a monotherapy. Assuming positive data from the initial phase of the trial, the cohort-expansion phase will enroll subjects in cohorts with diffuse large cell B-cell lymphoma, chronic lymphocytic leukemia or small lymphocytic lymphoma, and mantle cell lymphoma, and will evaluate ORR based on lymphoma-specific response criteria.

Expansion of the Exelixis Pipeline

We are working to expand our oncology product pipeline through drug discovery efforts, which encompass our diverse small molecule and biotherapeutics programs exploring multiple modalities and mechanisms of action. This approach provides a high degree of flexibility with respect to target selection and allows us to prioritize those targets that we believe have the greatest chance of yielding impactful therapeutics. As part of our strategy, our drug discovery activities include research collaborations, in-licensing arrangements and other strategic transactions that serve to increase our discovery bandwidth and allow us to access a wide range of technology platforms. We also opened a new laboratory building on our Alameda campus in 2021, effectively tripling our available lab space and significantly enhancing the capacity and capability of our small molecule discovery efforts. As of the date of this Annual Report, we are currently advancing more than 10 discovery programs and expect to progress up to five new development candidates into preclinical development during 2022. In addition, we will continue to engage in business development initiatives with the goal of acquiring and in-licensing promising oncology platforms and assets and then further characterize and develop them utilizing our established preclinical and clinical development infrastructure.

Small Molecule Programs

Our small molecule discovery programs are supported by a robust and expanding infrastructure, including a library of 4.6 million compounds. We have extensive experience in the identification and optimization of drug candidates against multiple target classes for oncology, inflammation and metabolic diseases.

Since our inception in 1994, our drug discovery group has advanced 25 compounds to the IND stage, either independently or with collaboration partners, and today we deploy our drug discovery expertise in medicinal chemistry, tumor biology and pharmacology to advance small molecule drug candidates toward and through preclinical development. These efforts are led by our experienced scientists, including some of the same scientists that led the efforts to discover cabozantinib, cobimetinib and esaxerenone, each of which are now commercially distributed drug products. In pursuit of new drug discoveries, we concentrate our in-house work on the most demanding and time-sensitive aspects of lead optimization and use contract research organizations to support more routine activities, thereby minimizing our footprint

while still maintaining an agile, competitive approach. We also augment our small molecule discovery activities through research collaborations and in-licensing arrangements with other companies engaged in small molecule discovery, including:

- STORM Therapeutics LTD (STORM), which is focused on the discovery and development of inhibitors of novel RNA modifying enzymes, including ADAR1;
- Aurigene, which is focused on the discovery and development of novel small molecules as therapies for cancer; and
- StemSynergy Therapeutics, Inc. (StemSynergy), which is focused on the discovery and development of novel oncology compounds aimed to inhibit tumor growth by targeting Casein Kinase 1 alpha (CK1α) and the Notch pathway.

For additional information on these research collaborations and in-licensing arrangements related to our small molecule programs, see "—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities."

Amongst our small molecule programs, furthest along are XL092, which was discovered at Exelixis, and XL102 and XL114, which were discovered at Aurigene. XL092 and XL102 entered the clinic in 2019 and 2021, respectively, and we plan to initiate a phase 1 clinical trial for XL114 in the first half of 2022. For additional information on these clinical trial programs, see "—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates." In addition, we continue to make progress on multiple, additional lead optimization programs for inhibitors of a variety of targets that we believe play significant roles in tumor growth, and we anticipate that some of these other programs could reach development candidate status in 2022.

Biotherapeutics Programs

We are also focusing our drug discovery activities on discovering and advancing various biotherapeutics that have the potential to become anti-cancer therapies, such as bispecific antibodies, ADCs and other innovative treatments. The great potential of these classes has been evidenced by the multiple regulatory approvals for the commercial sale of ADCs in the past several years. To facilitate the growth of these programs, we have established multiple research collaborations and in-licensing arrangements and entered into other strategic transactions that provide us with access to antibodies and binders, which are the starting point for use with additional technology platforms that we employ to generate next-generation ADCs or multispecific antibodies. Our current research collaborations and in-licensing arrangements for biotherapeutics programs include:

- WuXi Biologics Ireland Limited, a wholly owned subsidiary of WuXi Biologics (Cayman) Inc. (individually and collectively referred to as WuXi Bio), which is focused on leveraging WuXi Bio's panel of mAbs for the development of ADC, bispecific and certain other novel tumor-targeting biotherapeutics applications;
- Adagene Inc. (Adagene), which is focused on using Adagene's SAFEbodyTM technology to develop novel masked ADCs or other innovative biotherapeutics with potential for improved therapeutic index;
- Catalent, Inc.'s wholly owned subsidiaries Redwood Bioscience, Inc., R.P. Scherer Technologies, LLC and Catalent Pharma Solutions, Inc. (individually and collectively referred to as Catalent), which is focused on the discovery and development of multiple ADCs using Catalent's proprietary SMARTag® site-specific bioconjugation technology;
- NBE-Therapeutics AG (NBE), which is focused on the discovery and development of multiple ADCs by leveraging NBE's unique expertise and proprietary platforms in ADC discovery, including NBE's SMAC-Technology™ (a site-specific conjugation technology) and novel payloads;
- Iconic, which is focused on the advancement of a next-generation TF-targeting ADC program in solid tumors; and
- Invenra, Inc. (Invenra), which is focused on the discovery and development of novel binders and multispecific antibodies for the treatment of cancer.

We have already made significant progress under these arrangements and believe we will continue to do so in 2022 and future years. For example, based on promising preclinical data for XB002, we exercised our exclusive option to license XB002 in December 2020. Following the FDA's acceptance of our IND for XB002 in April 2021, we initiated a phase 1 clinical trial in June 2021. For additional information on XB002, see "—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates—XB002 Development Program." Also, as a direct result of these arrangements, we designated XB010, our first ADC advanced internally, as a development candidate in late 2021.

XB010, which targets the tumor antigen 5T4, incorporates antibodies sourced from Invenra and was constructed using Catalent's SMARTag site-specific bioconjugation platform.

In addition, in May 2021, we executed an asset purchase agreement with GamaMabs Pharma SA (GamaMabs), under which we will, upon the closing of the asset purchase and subject to certain conditions, acquire all rights, title and interest in GamaMabs' antibody program directed at anti-Müllerian hormone receptor 2 (AMHR2), a novel oncology target with relevance in multiple forms of cancer. And most recently, in January 2022, we announced an amendment to our May 2019 exclusive option and license agreement with Iconic to acquire broad rights to use the anti-TF antibody used in XB002 for any application, including conjugated to other payloads. For additional information on these specific research collaborations, in-licensing arrangements and other strategic transactions related to our biotherapeutics programs, see "—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities."

Collaborations and Business Development Activities

We have established multiple collaborations with leading biopharmaceutical companies for the commercialization and further development of the cabozantinib franchise. Additionally, we have made considerable progress under our existing research collaborations and in-licensing arrangements to further enhance our early-stage pipeline and expand our ability to discover, develop and commercialize novel therapies with the goal of providing new treatment options for cancer patients and their physicians. We expect to enter into additional, external collaborative relationships around assets and technologies that complement our drug discovery and clinical development efforts. Consistent with our business strategy prior to the commercialization of our first product, COMETRIQ, we also entered into other collaborations with leading pharmaceutical companies including Genentech and Daiichi Sankyo for other compounds and programs in our portfolio. Under each of our collaborations, we are entitled to receive milestones and royalties or, in the case of cobimetinib, royalties from sales outside the U.S. and a share of profits (or losses) from commercialization in the U.S.

Cabozantinib Commercial Collaborations

Ipsen Collaboration

In February 2016, we entered into a collaboration and license agreement with Ipsen for the commercialization and further development of cabozantinib. Under the collaboration agreement, Ipsen received exclusive commercialization rights for current and potential future cabozantinib indications outside of the U.S., Canada and Japan. The collaboration agreement was subsequently amended on three occasions, including in December 2016 to include commercialization rights in Canada. We have also agreed to collaborate with Ipsen on the development of cabozantinib for current and potential future indications. The parties' efforts are governed through a joint steering committee and appropriate subcommittees established to guide and oversee the collaboration's operation and strategic direction; provided, however, that we retain final decision-making authority with respect to cabozantinib's ongoing development.

In consideration for the exclusive license and other rights contained in the collaboration agreement, including commercialization rights in Canada, Ipsen paid us aggregate upfront payments of $210.0 million in 2016. As of December 31, 2021, we achieved aggregate milestone payments of $462.5 million related to regulatory and commercial progress by Ipsen since the inception of the collaboration agreement, including a milestone payment during 2021 of $12.5 million upon Ipsen's submission of a variation application to the EMA for CABOMETYX as a treatment for patients with previously treated, RAI-refractory DTC. In addition, we recorded in license revenues a $100.0 million milestone from Ipsen in connection with the achievement of $400.0 million of net sales of cabozantinib in the related Ipsen license territory over four consecutive quarters, and we expect to receive the milestone payment in the first quarter of 2022.

We are also eligible to receive future development and regulatory milestone payments from Ipsen, totaling an aggregate of $46.5 million upon additional approvals of cabozantinib in future indications and/or jurisdictions, as well as contingent payments of up to $350.0 million and CAD$26.5 million associated with future sales milestones. We will further receive royalties on net sales of cabozantinib by Ipsen outside of the U.S. and Japan. We were initially entitled to receive a tiered royalty of 2% to 12% on the initial $150.0 million of net sales; this amount was reached in the second quarter of 2018. During the year ended December 31, 2021 and going forward, we are entitled to receive a tiered royalty of 22% to 26% on annual net sales, with separate tiers for Canada; these 22% to 26% royalty tiers reset each calendar year. As of December 31, 2021, we have earned royalties of $272.1 million on net sales of cabozantinib by Ipsen since the inception of the collaboration agreement.

We received notification that, effective January 1, 2021, Royalty Pharma plc (Royalty Pharma) acquired from GlaxoSmithKline (GSK) all rights, title and interest in royalties on total net sales of any product containing cabozantinib for non-U.S. markets for the full term of the royalty and for the U.S. market through September 2026, after which time U.S. royalties will revert back to GSK. Accordingly, and consistent with our historical agreement with GSK, we are required to pay a 3% royalty to Royalty Pharma on total net sales of any product incorporating cabozantinib, including net sales by Ipsen.

We are responsible for funding cabozantinib-related development costs for those trials in existence at the time we entered into the collaboration agreement with Ipsen; global development costs for additional trials are shared between the parties, with Ipsen reimbursing us for 35% of such costs, provided Ipsen chooses to opt into such trials. In accordance with the collaboration agreement, Ipsen has opted into and is co-funding certain clinical trials, including: CheckMate -9ER, COSMIC-021, COSMIC-311, COSMIC-312, CONTACT-01 and CONTACT-02. With respect to Ipsen's decision in the second quarter of 2021 to opt into and co-fund COSMIC-311 development costs, Ipsen is now responsible for 35% of the global development costs of COSMIC-311 and is obligated to reimburse us for these costs, as well as an additional payment calculated as a percentage of COSMIC-311 development costs, triggered by the timing of the exercise of its option.

We remain responsible for manufacturing and supply of cabozantinib for all development and commercialization activities under the collaboration agreement. Relatedly, we entered into a supply agreement with Ipsen to supply finished and labeled drug product to Ipsen for distribution in the territories outside of the U.S. and Japan for the term of the collaboration agreement as well as a quality agreement that provides respective quality responsibilities for the aforementioned supply. Furthermore, at the time we entered into the collaboration agreement, the parties also entered into a pharmacovigilance agreement, which defines each partner's responsibilities for safety reporting. The pharmacovigilance agreement also requires us to maintain the global safety database for cabozantinib. To meet our obligations to regulatory authorities for the reporting of safety data from territories outside of the U.S. and Japan from sources other than our sponsored global clinical development trials, we rely on data collected and reported to us by Ipsen.

Unless earlier terminated, the collaboration agreement has a term that continues, on a product-by-product and country-by-country basis, until the latter of (1) the expiration of patent claims related to cabozantinib, (2) the expiration of regulatory exclusivity covering cabozantinib or (3) ten years after the first commercial sale of cabozantinib, other than COMETRIQ. The supply agreement will continue in effect until expiration or termination of the collaboration agreement. The collaboration agreement may be terminated for cause by either party based on uncured material breach of either the collaboration agreement or the supply agreement by the other party, bankruptcy of the other party or for safety reasons. We may terminate the collaboration agreement if Ipsen challenges or opposes any patent covered by the collaboration agreement. Ipsen may terminate the collaboration agreement if the FDA or EMA orders or requires substantially all cabozantinib clinical trials to be terminated. Ipsen also has the right to terminate the collaboration agreement on a region-by-region basis after the first commercial sale of cabozantinib in advanced RCC in the given region. Upon termination by either party, all licenses granted by us to Ipsen will automatically terminate, and, except in the event of a termination by Ipsen for our material breach, the licenses granted by Ipsen to us shall survive such termination and shall automatically become worldwide, or, if Ipsen were to terminate only for a particular region, then for the terminated region. Following termination by us for Ipsen's material breach, or termination by Ipsen without cause or because we undergo a change of control by a party engaged in a competing program, Ipsen is prohibited from competing with us for a period of time.

Takeda Collaboration

In January 2017, we entered into a collaboration and license agreement with Takeda, which was subsequently amended on three occasions to, among other things, modify the amount of reimbursements we receive for costs associated with our required pharmacovigilance activities and milestones we are eligible to receive, as well as modify certain cost sharing obligations related to the Japan-specific development costs associated with CONTACT-01 and CONTACT-02. Under the collaboration agreement, Takeda has exclusive commercialization rights for current and potential future cabozantinib indications in Japan, and the parties have agreed to collaborate on the clinical development of cabozantinib in Japan. The operation and strategic direction of the parties' collaboration is governed through a joint executive committee and appropriate subcommittees.

In consideration for the exclusive license and other rights contained in the collaboration agreement, we received an upfront payment of $50.0 million from Takeda in 2017. As of December 31, 2021, we have also achieved regulatory and development milestones in the aggregate of $127.0 million related to regulatory and commercial progress by Takeda since the inception of the collaboration agreement, including milestone payments during 2021 of (1) $20.0 million upon Takeda's first commercial sale in Japan of CABOMETYX in combination with OPDIVO for the treatment of patients with unresectable or metastatic RCC and (2) $15.0 million in connection with the initiations of CONTACT-01 and CONTACT-02. We are eligible

to receive additional regulatory and development milestone payments, without limit, for additional potential future indications.

We are further eligible to receive commercial milestones, including milestone payments earned for the first commercial sale of a product, of up to $119.0 million. We also receive royalties on the net sales of cabozantinib in Japan. We are entitled to receive a tiered royalty of 15% to 24% on the initial $300.0 million of net sales, and following this initial $300.0 million of net sales, we are then entitled to receive a tiered royalty of 20% to 30% on annual net sales thereafter; these 20% to 30% royalty tiers reset each calendar year. As of December 31, 2021, we have earned royalties of $10.2 million on net sales of cabozantinib by Takeda since the inception of the collaboration agreement.

Consistent with our historical agreement with GSK, we are required to pay a 3% royalty to Royalty Pharma on total net sales of any product incorporating cabozantinib, including net sales by Takeda.

Except for CONTACT-01 and CONTACT-02, Takeda is responsible for 20% of the costs associated with the cabozantinib development plan's current and future trials, provided Takeda opts into such trials, and 100% of costs associated with the cabozantinib development activities that are exclusively for the benefit of Japan. In accordance with the collaboration agreement, Takeda has opted into and is co-funding CheckMate -9ER, certain cohorts of COSMIC-021, CONTACT-01 and CONTACT-02.

Under the collaboration agreement, we are responsible for the manufacturing and supply of cabozantinib for all development and commercialization activities under the collaboration agreement. Relatedly, we entered into a clinical supply agreement covering the supply of cabozantinib to Takeda for the term of the collaboration agreement, as well as a quality agreement that provides respective quality responsibilities for the aforementioned supply. Furthermore, at the time we entered into the collaboration agreement, the parties also entered into a safety data exchange agreement, which defines each partner's responsibility for safety reporting. This agreement also requires us to maintain the global safety database for cabozantinib. To meet our obligations to regulatory authorities for the reporting of safety data from Japan from sources other than our sponsored global clinical development trials, we rely on data collected and reported to us by Takeda.

Unless earlier terminated, the collaboration agreement has a term that continues, on a product-by-product basis, until the earlier of (1) two years after first generic entry with respect to such product in Japan or (2) the later of (A) the expiration of patent claims related to cabozantinib and (B) the expiration of regulatory exclusivity covering cabozantinib in Japan. The collaboration agreement may be terminated for cause by either party based on uncured material breach by the other party, bankruptcy of the other party or for safety reasons. For clarity, Takeda's failure to achieve specified levels of commercial performance, based upon sales volume and/or promotional effort, during the first six years of the collaboration will constitute a material breach of the collaboration agreement. We may terminate the agreement if Takeda challenges or opposes any patent covered by the collaboration agreement. After the commercial launch of cabozantinib in Japan, Takeda may terminate the collaboration agreement upon twelve months' prior written notice following the third anniversary of the first commercial sale of cabozantinib in Japan. Upon termination by either party, all licenses granted by us to Takeda will automatically terminate, and the licenses granted by Takeda to us shall survive such termination and shall automatically become worldwide.

Cabozantinib Development Collaborations

BMS

In February 2017, we entered into a clinical trial collaboration agreement with BMS for the purpose of exploring the therapeutic potential of cabozantinib in combination with BMS's ICIs, nivolumab and/or ipilimumab, to treat a variety of types of cancer. As part of the collaboration, we are evaluating the triplet combination of cabozantinib, nivolumab and ipilimumab as a treatment option for RCC in the COSMIC-313 trial. For a description of the COSMIC-313 trial, see "—Exelixis Development Programs—Cabozantinib Development Program—Trials Conducted Under our Clinical Collaboration Agreements—Combination Studies with BMS."

Under the collaboration agreement with BMS, which was subsequently amended on three occasions, each party granted to the other a non-exclusive, worldwide (within the collaboration territory as defined in the collaboration agreement and its supplemental agreements), non-transferable, royalty-free license to use the other party's compounds in the conduct of each clinical trial. The parties' efforts are governed through a joint development committee established to guide and oversee the collaboration's operation. Each trial is conducted under a combination IND application, unless otherwise required by a regulatory authority. Each party is responsible for supplying finished drug product for the

applicable clinical trial, and responsibility for the payment of costs for each such trial will be determined on a trial-by-trial basis. Following the FDA's approval of CABOMETYX in combination with OPDIVO as a first-line treatment of patients with advanced RCC, we and BMS commenced the commercial launch of the combination and have agreed to pursue commercialization and marketing efforts independently.

Roche

In February 2017, we entered into a master clinical supply agreement with Roche for the purpose of evaluating cabozantinib and Roche's ICI, atezolizumab, in locally advanced or metastatic solid tumors. Under this agreement with Roche, in June 2017, we initiated COSMIC-021 and in December 2018, we initiated COSMIC-312. We are the sponsor of both trials, and Roche is providing atezolizumab free of charge. For descriptions of the COSMIC-021 and COSMIC-312 trials, see "—Exelixis Development Programs—Cabozantinib Development Program—Trials Conducted Under our Clinical Collaboration Agreements—Combination Studies with Roche."

Building upon encouraging clinical activity observed in COSMIC-021, in December 2019 we entered into a joint clinical research agreement with Roche for the purpose of further evaluating the combination of cabozantinib with atezolizumab in patients with locally advanced or metastatic solid tumors, including in the CONTACT-01, CONTACT-02 and CONTACT-03 studies. If a party to the joint clinical research agreement proposes any additional combined therapy trials beyond these three ongoing phase 3 pivotal trials, the joint clinical research agreement provides that such proposing party must notify the other party and that if agreed to, any such additional combined therapy trial will become part of the collaboration, or if not agreed to, the proposing party may conduct such additional combined therapy trial independently, subject to specified restrictions set forth in the joint clinical research agreement.

Under the joint clinical research agreement, each party granted to the other a non-exclusive, worldwide (excluding, in our case, territory already the subject of a license by us to Takeda), non-transferable, royalty-free license, with a right to sublicense (subject to limitations), to use the other party's intellectual property and compounds solely as necessary for the party to perform its obligations under the joint clinical research agreement. The parties' efforts will be governed through a joint steering committee established to guide and oversee the collaboration and the conduct of the combined therapy trials. Each party will be responsible for providing clinical supply for all combined therapy trials, and the cost of the supply will be borne by such party. The clinical trial expenses for each combined therapy trial agreed to be conducted jointly under the joint clinical research agreement will be shared equally between the parties, and the clinical trial expenses for each additional combined therapy trial not agreed to be conducted jointly under the joint clinical research agreement will be borne by the proposing party, except that the cost of clinical supply for all combined therapy trials will be borne by the party that owns the applicable product.

Unless earlier terminated, the joint clinical research agreement provides that it will remain in effect until the completion of all combined therapy trials under the collaboration, the delivery of all related trial data to both parties, and the completion of any then agreed-upon additional analyses. The joint clinical research agreement may be terminated for cause by either party based on any uncured material breach by the other party, bankruptcy of the other party or for safety reasons. Upon termination by either party, the licenses granted to each party will terminate upon completion of any ongoing activities under the joint clinical research agreement.

XL092 Clinical Collaborations

In an effort to diversify our exploration of the therapeutic potential of XL092, we have also entered into multiple supply agreements to evaluate XL092 in various combination trials, including with Roche's atezolizumab, Merck KGaA and Pfizer's avelumab, BMS' nivolumab and ipilimumab and Nektar's bempegaldesleukin. These supply agreements will facilitate the efficient exploration of the safety and efficacy of XL092 in combinations with a variety of established cancer therapies as we continue to build a broad development program for XL092. For descriptions of our ongoing clinical trials evaluating XL092 in combination with other therapies, see "—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates—XL092 Development Program."

Research Collaborations, In-licensing Arrangements and Other Business Development Activities

STORM

In October 2021, we entered into an exclusive collaboration and license agreement with STORM to discover and advance novel drug candidates intended for the treatment of cancer. Our collaboration focuses initially on the RNA modifying enzyme ADAR1, building on early work by STORM applying its proprietary RNA epigenetic platform, as well as exploring an additional undisclosed target. Under the agreement, we made an upfront payment in exchange for exclusive licenses to these two discovery programs. STORM is responsible for discovery and generation of lead candidates for both target programs, and we will assume responsibility for IND-enabling studies and all subsequent clinical development, manufacturing and commercialization activities. STORM is eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales. We have also committed to contribute research funding to STORM for discovery and preclinical development work for each program.

GamaMabs

In May 2021, we entered into an asset purchase agreement with GamaMabs to acquire all rights, title and interest in GamaMabs' AMHR2 antibody program. Under the agreement, we made an upfront payment in exchange for an initial technology transfer of certain materials and documents, additional payments for subsequent technology transfers and will make a final payment upon the closing of the transaction. As a result of the transaction, we will own or control 100% of GamaMabs' AMHR2 antibody program, including all assets pertaining to GamaMabs' mAb drug product murlentamab (GM-102). GamaMabs is eligible for potential development and regulatory milestone payments.

WuXi Bio

In March 2021, we entered into an exclusive license agreement with WuXi Bio to support the continued expansion of our oncology biotherapeutics pipeline by leveraging WuXi Bio's panel of mAbs for the development of ADC, bispecific and certain other novel tumor-targeting biotherapeutics applications. Under the agreement, we made an upfront payment in exchange for an exclusive license to a panel of mAbs directed to a preclinically validated target discovered using WuXi Bio's integrated technology platforms. We will assume responsibility for all subsequent clinical development, manufacturing and commercialization activities under the agreement. WuXi Bio is eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales.

Adagene

In February 2021, we entered into a collaboration and license agreement with Adagene to utilize Adagene's SAFEbody technology platform to generate masked versions of mAbs from our growing preclinical pipeline for the development of ADCs or other innovative biotherapeutics against Exelixis-nominated targets. Under the agreement, we made an upfront payment in exchange for an exclusive, worldwide license to develop and commercialize any potential ADC products generated by Adagene with respect to an initial target, as well as a second target we may nominate during the collaboration term. For each target that we nominate, we would then assume responsibility for all subsequent clinical development, manufacturing and commercialization for that program. Adagene is eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales .

Catalent

In September 2020, we entered into a collaboration and license agreement with Catalent to develop multiple ADCs using Catalent's proprietary SMARTag site-specific bioconjugation technology. Under the agreement, we made an upfront payment in exchange for an exclusive option to license up to four targets using Catalent's ADC platform over a three-year period. In addition, we have the right to extend the target selection term to five years and nominate up to two additional targets for an additional payment. For each option we decide to exercise, we will be required to pay an exercise fee, and we would then assume responsibility for all subsequent clinical development, manufacturing and commercialization for that program. Catalent would then become eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales. We have also committed to contribute research funding to Catalent for discovery and preclinical development work.

NBE

In September 2020, we entered into a collaboration and license agreement with NBE to discover and develop multiple ADCs for oncology applications by leveraging NBE's unique expertise and proprietary platforms in ADC discovery,

including NBE's SMAC-Technology and novel payloads. Under the Agreement, we made an upfront payment in exchange for exclusive options to nominate four targets using NBE's ADC platform over a two-year period. In addition, within the first 18 months of the agreement term, we also have the right to extend the target selection term to three years for an additional payment. For each option we decide to exercise, we will be required to pay an exercise fee, and we would then assume responsibility for all subsequent clinical development, manufacturing and commercialization connected with any resulting program. NBE would then become eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales. We have also committed to contribute research funding to NBE for discovery and preclinical development work.

Aurigene

In July 2019, we entered into an exclusive collaboration, option and license agreement with Aurigene to in-license as many as six oncology target programs to discover and develop small molecules as therapies for cancer, and in April 2021, we expanded the collaboration to include three additional early discovery programs for a total of nine programs. Under the agreement, we made upfront payments in exchange for exclusive options to license eight of the nine programs to date, and we will pay an additional upfront payment upon the nomination of the ninth program. Based on encouraging preclinical data for XL102, the lead Aurigene program targeting CDK7, we exercised our exclusive option to license XL102 in December 2020, resulting in our assuming responsibility for all subsequent clinical development, manufacturing and commercialization of XL102 and payment of an exercise fee to Aurigene. We also submitted an IND for XL102 in November 2020, and following the FDA's acceptance of the IND in December 2020, we initiated a phase 1 clinical trial of XL102 in January 2021 designed to evaluate its pharmacokinetics, safety, tolerability and preliminary efficacy, both as a single agent and in combination with other anticancer therapies. For additional information on XL102, see "—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates—XL102 Development Program." In addition, we exercised our exclusive option to in-license XL114, Aurigene's novel CBM inhibitor, in October 2021, resulting in our assuming responsibility for all subsequent clinical development, manufacturing and commercialization of XL114 and payment of an option exercise fee to Aurigene. Following the FDA's acceptance of our IND application for the small molecule in October 2021, we plan to initiate a phase 1 clinical trial evaluating XL114 as a monotherapy in patients with NHL in the first half of 2022. For additional information on XL114, see "—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates—XL114 Development Program." With respect to each of XL102 and XL114, Aurigene is eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales.

Beyond XL102 and XL114, we are continuing to work with Aurigene to advance the other small molecule programs through preclinical development. For each additional option we decide to exercise, we will be required to pay an exercise fee, and we would then assume responsibility for all subsequent clinical development, manufacturing and commercialization for that program. Aurigene would then become eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales. We are also responsible for research funding for the discovery and preclinical development work on these programs. Under the agreement, Aurigene retains limited development and commercial rights for India and Russia.

Iconic

In May 2019, we entered into an exclusive option and license agreement with Iconic to advance an innovative next-generation ADC program for cancer, leveraging Iconic's expertise in targeting TF in solid tumors. Under the original May 2019 agreement, we gained an exclusive option to license XB002, Iconic's lead TF ADC program, in exchange for an upfront payment to Iconic and a commitment for preclinical development funding. Based on encouraging preclinical data, we exercised our exclusive option to license XB002 in December 2020, resulting in our assuming responsibility for all subsequent clinical development, manufacturing and commercialization for XB002 and payment of an option exercise fee to Iconic. Following the FDA's acceptance of our IND for XB002 in April 2021, we initiated a phase 1 clinical trial of XB002 in June 2021 designed to evaluate its pharmacokinetics, safety, tolerability and preliminary efficacy as a monotherapy in patients with advanced solid tumors. For additional information on XLB002, see "—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates—XB002 Development Program."

In January 2022, we announced an amendment to our agreement with Iconic, which we entered into in December 2021, to acquire broad rights to use the anti-TF antibody used in XB002 for any application, including conjugated to other payloads, as well as rights within oncology to a number of other anti-TF antibodies developed by Iconic, including for use in ADCs and multispecific biotherapeutics. Under the amended agreement, we made a final payment to Iconic and will not

owe Iconic any further payments, but we will continue to be responsible for milestone payments and royalties owed to other companies pursuant to prior agreements between Iconic and those companies.

Invenra

In May 2018, we entered into a collaboration and license agreement with Invenra to discover and develop multispecific antibodies for the treatment of cancer. Invenra is responsible for antibody lead discovery and generation while we will lead IND-enabling studies, manufacturing, clinical development in single-agent and combination therapy regimens, and future regulatory and commercialization activities. The collaboration agreement provides that we will receive an exclusive, worldwide license to one preclinical, multispecific antibody asset, and that we will pursue multiple additional discovery projects across three different programs during the term of the collaboration. In October 2019, we expanded our collaboration to include the development of novel binders against six additional targets, which we can use to generate multispecific antibodies based on Invenra's B-Body™ technology platform, or with other platforms and formats at our option. We amended the agreement again in March 2020 and January 2021 to enable the use of target binders in non-Invenra platform-based modalities, such as ADC platforms, and to enable the development of biparatropic antibodies, respectively. Then in August 2021, we further expanded our collaboration to include an additional 20 targets for biotherapeutics discovery and development, for which we agreed to pay Invenra exclusivity payments and research program funding over a three-year period.

Under the collaboration, Invenra is eligible for project initiation fees and potential development, regulatory and commercial milestone payments, as well as tiered royalties on net sales of any approved products. We also have the right to exercise options with respect to certain of Invenra's other research programs in exchange for an option exercise payment, and Invenra is eligible for milestone payments and royalties for any products that arise from these optioned research programs.

StemSynergy

In January 2018, we entered into an exclusive collaboration and license agreement with StemSynergy for the discovery and development of novel oncology compounds targeting CK1α, a component of the Wnt signaling pathway implicated in key oncogenic processes, including in colorectal cancers. One such compound, EXEL-4329, reached development candidate status in 2021. In May 2021, we amended the agreement to provide for an additional research platform to explore inhibitors of the Notch pathway, a major developmental pathway that regulates cancer stem cells in Notch-driven cancers, such as certain types of T-cell lymphomas and esophageal adenocarcinomas. Under the agreement, we paid StemSynergy upfront payments in each of 2018 and 2021, and StemSynergy is eligible for additional research and development funding on an as needed basis. StemSynergy is also eligible for potential development, regulatory and commercial milestone payments, as well as royalties on potential sales. We will be solely responsible for the commercialization of products that arise from the collaboration.

Other Collaborations

Prior to the commercialization of our first product, COMETRIQ, our primary business strategy was focused on the development and out-license of compounds to pharmaceutical and biotechnology companies under collaboration agreements that allowed us to retain economic participation in compounds and support additional development of our proprietary products. Our collaboration agreements with Genentech and Daiichi Sankyo described below are representative of this historical strategy. We have since evolved and are now a fully-integrated biopharmaceutical company focused on driving the expansion and depth of our product offerings through the continued development of the cabozantinib franchise and drug discovery efforts, including research collaborations, in-licensing arrangements and other strategic transactions that align with our oncology drug development, regulatory and commercialization expertise, all to improve care and outcomes for people with cancer around the world. While the historical collaboration agreements described below have the potential to provide future revenue, and while we have already received some collaboration revenues from these arrangements, we do not expect to receive significant revenues from these historical collaboration agreements unless and until our partnered compounds generate substantial sales in the territories and indications where they are approved. If these events occur, then the milestone payments, royalties or other rights and benefits under our historical collaboration agreements could become substantial.

Genentech - Cobimetinib

In December 2006, we out-licensed the further development and commercialization of cobimetinib to Genentech pursuant to a worldwide collaboration agreement. Cobimetinib is a reversible inhibitor of MEK, a kinase that is a

component of the RAS/RAF/MEK/ERK pathway. Under the collaboration agreement, Genentech received an exclusive worldwide revenue-bearing license to cobimetinib and is responsible for all future clinical development of the compound. On November 10, 2015, the FDA approved cobimetinib, under the brand name COTELLIC, in combination with Genentech's ZELBORAF (vemurafenib) as a treatment for patients with BRAF V600E or V600K mutation-positive advanced melanoma. COTELLIC in combination with ZELBORAF has also been approved in Switzerland, the EU, Canada, Australia, Brazil and multiple additional countries for use in the same indication. On July 30, 2020, the FDA approved COTELLIC, in combination with Genentech's ZELBORAF and TECENTRIQ® (atezolizumab) for the treatment of BRAF V600 mutation-positive advanced melanoma in previously untreated patients.

Under the collaboration agreement, as amended in July 2017, we share in the profits and losses received or incurred in connection with COTELLIC's commercialization in the U.S. In addition to our profit share in the U.S., we are entitled to low double-digit royalties on net sales of COTELLIC outside the U.S. During 2021, we earned royalties of $4.1 million on net sales of COTELLIC outside the U.S. and a $8.1 million profit on the profit and loss sharing of U.S. actual sales which are recorded in collaboration services revenues. Since the inception of the collaboration agreement, we have also received aggregate upfront and milestone payments of $50.0 million and are not eligible for any additional milestone payments.

In addition to its established commercialization of COTELLIC, Genentech continues to progress the clinical development, regulatory status and commercial potential of cobimetinib. Cobimetinib is being evaluated in a broad development program consisting of multiple clinical trials by Genentech or through Genentech's IST program. Should these trials yield supporting data and Genentech obtain regulatory approvals based on such supporting data, we believe that cobimetinib may provide us with an additional source of revenue in the future.

Daiichi Sankyo - Esaxerenone

In March 2006, we entered into a collaboration agreement with Daiichi Sankyo for the discovery, development and commercialization of novel therapies targeted against the MR, a nuclear hormone receptor implicated in a variety of cardiovascular and metabolic diseases. Under the collaboration agreement, we granted to Daiichi Sankyo an exclusive, worldwide license to certain intellectual property primarily relating to compounds that modulate MR, including esaxerenone, an oral, non-steroidal, selective MR antagonist. Daiichi Sankyo is responsible for all further preclinical and clinical development, regulatory, manufacturing and commercialization activities for the compounds and we do not have rights to reacquire such compounds.

In January 2019, the Japanese MHLW first approved esaxerenone under the brand name MINNEBRO, as a treatment essential hypertension in Japan. As of December 31, 2021, we have received an aggregate of $65.5 million in development, regulatory and commercialization milestone payments related to MINNEBRO over the life of the collaboration agreement and are eligible to receive additional commercialization milestone payments of up to $90.0 million. We are also entitled to receive low double-digit royalties on sales of MINNEBRO. As of December 31, 2021, we have earned royalties of $5.3 million on net sales of MINNEBRO by Daiichi Sankyo since the approval of MINNEBRO in January 2019. Pursuant to a license agreement we entered into with Ligand Pharmaceuticals, Inc. (Ligand), we are required to pay a royalty of 0.5% to Ligand on net sales of MINNEBRO.

Daiichi Sankyo has further advanced the development program for esaxerenone, and in November 2019, Daiichi Sankyo announced positive results from a phase 3 pivotal trial evaluating esaxerenone as a treatment option for patients in Japan with diabetic nephropathy. Should Daiichi Sankyo obtain regulatory approval based on these results, and taking into account the approval of MINNEBRO by the MHLW for the treatment of hypertension and Daiichi Sankyo's subsequent commercial sales of MINNEBRO, we believe that esaxerenone may provide an additional source of revenue in the future.

Manufacturing and Product Supply

We do not own or operate manufacturing or distribution facilities for chemistry, manufacturing and control (CMC) development activities, preclinical, clinical or commercial production and distribution for our current products. Instead, we rely on various third-party contract manufacturing organizations to conduct these operations on our behalf. As our operations continue to grow in these areas, we continue to expand our supply chain through secondary third-party contract manufacturers, distributors and suppliers. Specifically, we entered into agreements with secondary contract manufacturing organizations to produce additional commercial supplies of CABOMETYX tablets and cabozantinib drug substance, which bolsters our commercial supply chain and serves to mitigate the risk of supply chain interruptions or other failures. For our portfolio of small molecules and biotherapeutics, we continue to expand our network through well-established and reputable global third-party contract manufacturers for our CMC development and manufacturing that have good

regulatory standing, suitable manufacturing capacities and capabilities. These third parties must comply with applicable regulatory requirements, including the FDA's Current Good Manufacturing Practice (GMP), the EC's Guidelines on Good Distribution Practice (GDP), as well as other stringent regulatory requirements enforced by the FDA or foreign regulatory agencies, as applicable, and are subject to routine inspections by such regulatory agencies. In addition, through our third-party contract manufacturers and data service providers, we continue to provide serialized commercial products as required to comply with the Drug Supply Chain Security Act (DSCSA).

We monitor and evaluate the performance of our third-party contract manufacturers on an ongoing basis for compliance with these requirements and to affirm their continuing capabilities to meet both our commercial and clinical needs. We also have contracted with a third-party logistics provider, with multiple distribution locations, to provide shipping and warehousing services for our commercial supply of both CABOMETYX and COMETRIQ in the U.S. We employ highly skilled personnel with both technical and manufacturing experience to diligently manage the activities at our third-party contract manufacturers and other supply chain partners, and our quality department audits them on a periodic basis.

We source raw materials that are used to manufacture our drug substance from multiple third-party suppliers in Asia, Europe and North America. We stock sufficient quantities of these materials and provide them to our third-party drug substance contract manufacturers so they can manufacture adequate drug substance quantities per our requirements, for both clinical and commercial purposes. We then store drug substance at third-party facilities and provide appropriate amounts to our third-party drug product contract manufacturers, who then manufacture, package and label our specified quantities of finished goods for COMETRIQ and CABOMETYX, respectively. In addition, we rely on our third-party contract manufacturers to source materials such as excipients, components and reagents, which are required to manufacture our drug substance and finished drug product.

In addition to having expanded our supply chain to include secondary contract manufacturing organizations, we have established and continue to maintain sufficient safety stock inventories for our drug substance and drug products, and we store these quantities in multiple locations. The quantities that we store are based on our business needs and take into account scenarios for market demand, production lead times, potential supply interruptions and shelf life for our drug substance and drug products. While our response to the COVID-19 pandemic has included more frequent engagement with our vendors to maintain the consistency and effectiveness of our third-party contract manufacturers and other supply chain partners, we have not experienced significant production delays or seen significant impairment to our supply chain as a result of the COVID-19 pandemic. For a more detailed discussion of the impact of the COVID-19 pandemic and our risk mitigation efforts, see "Management's Discussion and Analysis of Financial Condition and Results of Operations—COVID-19 Update" in Part II, Item 7 of this Annual Report on Form 10-K. We believe that our current manufacturing network has the appropriate capacity to produce sufficient commercial quantities of CABOMETYX to support the currently approved RCC, HCC and DTC indications, as well as potential additional indications if trials evaluating CABOMETYX in those indications prove to be successful and gain regulatory approval in the future. Our manufacturing footprint also enables us to fulfill our supply obligations for CABOMETYX and COMETRIQ to our collaboration partners for global development and commercial purposes.

Marketing and Sales

We have a fully integrated commercial team consisting of sales, marketing, market access, and commercial operations functions. Our sales team promotes CABOMETYX and COMETRIQ in the U.S. We market our products in the U.S. and concentrate our efforts on oncologists, oncology nurses, pharmacists and other healthcare professionals. In addition to using customary in-person pharmaceutical company practices, we also utilize digital marketing technologies to expand our engagement opportunities with customers.

Our commercial products, CABOMETYX and COMETRIQ, are sold initially through wholesale distribution and specialty pharmacy channels and then, if applicable, resold to hospitals and other organizations that provide CABOMETYX and COMETRIQ to end-user patients. To facilitate our commercial activities in the U.S., we also employ various third parties, such as advertising agencies, market research firms and vendors providing other sales-support related services as needed, including digital marketing and other non-personal promotion. We believe that our commercial team and distribution practices are sufficient to facilitate our marketing efforts in reaching our target audience and our delivery of our products to patients in a timely and compliant fashion.

In addition, we rely on Ipsen and Takeda for ongoing and further commercialization and distribution of CABOMETYX in territories outside of the U.S., as well as for access and distribution activities for the approved products under named patient use programs or similar programs with the effect of introducing earlier patient access to CABOMETYX,

and we also rely on Ipsen for these same activities with respect to the commercialization and distribution of COMETRIQ outside of the U.S. For COTELLIC, we rely on Genentech, as our collaboration partner, for all current and future commercialization and marketing activities, with the exception of the limited co-promotion activities highlighted above.

To help ensure that all eligible patients in the U.S. have appropriate access to CABOMETYX and COMETRIQ, we have established a comprehensive reimbursement and patient support program called Exelixis Access Services (EASE). Through EASE, we provide co-pay assistance to qualified, commercially insured patients to help minimize out-of-pocket costs and provide free drug to uninsured or under-insured patients who meet certain clinical and financial criteria. In addition, EASE provides comprehensive reimbursement support services, such as prior authorization support, benefits investigation and, if needed, appeals support. Beyond financial assistance, patients who participate in EASE also receive treatment coordination through a dedicated case manager, as well as clinical outreach and support from a network of oncology nurses or other healthcare professionals who help many of these patients better understand how to take their medication and mitigate side effects.

Environmental, Health and Safety

Our research and development processes involve the controlled use of certain hazardous materials and chemicals. In the U.S., at the federal, state and local levels, and in other foreign countries, we are subject to environmental, health and workplace safety laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous materials. While we have incurred, and may continue to incur, expenditures to maintain compliance with these laws and regulations, we do not expect the cost of complying with these laws and regulations to be material.

Laboratory Safety Program

Due to the focus of our business in discovering and developing drug products, many of our employees work in our on-site laboratory facilities. All new laboratory staff are trained on chemical hygiene, the use of personal protective equipment, and certain other relevant laboratory safety topics, such as working with blood-borne pathogens, and current staff are retrained regularly. We also extend these trainings to facilities staff and others who support our work in the labs. In an effort to maintain a safe environment for all staff, we regularly perform thorough safety inspections of our laboratories, and continuously update our procedures based on the observations made during these inspections. Additionally, we conduct periodic industrial hygiene monitoring to ensure lab staff working with certain known hazardous chemicals do not exceed regulated exposure limits, and we regularly test and certify fume hoods, biosafety cabinets and other individual pieces of equipment on which employees rely to maintain a safe work environment.

Workplace Safety Measures in Response to COVID-19

We will continue to monitor the latest guidance issued by health authorities and have instituted several policies and procedures to protect against the spread of COVID-19 among our workforce. Since the third quarter of 2021, we have implemented a vaccination mandate and maintain several enhanced safety and social distancing protocols at our headquarters. In addition, we also offer on-site, rapid PCR COVID-19 testing, and utilize a mobile device app and web interface, which enable our team members to perform daily symptom tracking and schedule on-site tests at the Exelixis headquarters, and which also provide contact tracing and educational resources for any team member who may have tested positive.

Other policies and procedures currently include frequent disinfection of common areas by our operations staff and investments in re-engineering workspace safety, such as providing ample supplies of hand sanitizer, sanitizing wipes and facemasks for use by our staff, and adjusting our ventilation systems in an effort to minimize risks of airborne transmission. Although the COVID-19 pandemic has presented several new challenges for us, to date, we have only experienced a modest impact on our productivity without significant interruptions in our general business operations. For a more detailed discussion of the impact of the COVID-19 pandemic and our risk mitigation efforts, see “Management’s Discussion and Analysis of Financial Condition and Results of Operations—COVID-19 Update” in Part II, Item 7 of this Annual Report on Form 10-K.

Government Regulation

Clinical Development

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, manufacture and marketing of pharmaceutical products. These agencies and other federal, state and local entities regulate, among other things, research and development activities and the testing, marketing approval, manufacture, quality control, safety, effectiveness, labeling, storage, distribution, post-marketing safety reporting, export, import, record keeping, advertising and promotion of our products.

The process required by the FDA before product candidates may be marketed in the U.S. generally involves the following:

- nonclinical laboratory and animal tests, some of which must be conducted in accordance with Good Laboratory Practices (GLP);
- submission of an IND, which contains results of nonclinical studies (*e.g.*, laboratory evaluations of the chemistry, formulation, stability and toxicity of the product candidate), together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, and must become effective before human clinical trials may begin;
- approval by an independent institutional review board or ethics committee at each clinical trial site before each trial may be initiated;
- adequate and well-controlled human clinical trials conducted in accordance with the protocol, IND and Good Clinical Practice (GCP) to establish the safety and efficacy of the investigational drug candidate for its proposed intended use;
- for drug products, submission of a New Drug Application (NDA) to the FDA for commercial marketing, or generally of an sNDA, for approval of a new indication if the product is already approved for another indication;
- for biotherapeutic products, submission of a Biologics License Application (BLA) to the FDA for commercial marketing, or generally a supplemental Biologics License Application (sBLA) for approval of a new indication if the product is already approved for another indication;
- pre-approval inspection of manufacturing facilities and selected clinical investigators, clinical trial sites and/or Exelixis as the clinical trial sponsor for their compliance with GMP and GCP, respectively;
- payment of user fees for FDA review of an NDA or BLA unless a fee waiver applies;
- agreement with the FDA on the final labeling for the product;
- if the FDA convenes an advisory committee, satisfactory completion of the advisory committee review; and
- FDA approval of the NDA or sNDA, or BLA or sBLA.

For purposes of NDA approval, human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1 studies*, which involve the initial introduction of a new drug product candidate into humans, are initially conducted in a limited number of subjects to test the product candidate for safety, tolerability, absorption, metabolism, distribution and excretion in healthy humans or patients. In rare cases, a Phase 1 study that is designed to assess effectiveness may serve as the basis for FDA marketing approval of a drug or for a label expansion. For instance, at FDA's discretion, a product may receive approval based on a Phase 1b study if effectiveness results from the study are extremely compelling, approval of the drug would address a significant unmet patient need, and the drug is being approved through the accelerated approval pathway. As discussed below, Accelerated Approval generally requires a post-approval study to confirm clinical benefit.
- *Phase 2 studies* are conducted with groups of patients afflicted with a specified disease in order to provide enough data to evaluate the preliminary efficacy, optimal dosage, and common short-term side effect and risks associated with the drug. Multiple phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive phase 3 clinical trials. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.
- *Phase 3 studies* are conducted to gather the additional information about effectiveness and safety across a higher number of patients and evaluate the overall benefit-risk relationship of the product candidate following earlier phase evaluations, which will have provided preliminary evidence suggesting an effective dosage range

and acceptable safety profile for the product candidate. Phase 3 trials are also intended to provide an adequate basis for physician labeling of the product if it is approved.

The FDA may require, or companies may pursue, additional clinical trials after a product is approved. These so-called post-marketing or "phase 4" studies may be deemed a condition to be satisfied after a drug receives approval. Failure to satisfy such post-marketing commitments can result in FDA enforcement action, up to and including withdrawal of NDA approval.

FDA Review and Approval

For approval of a new drug or changes to the labeling of an approved drug, including new indications, the results of product development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA, or as part of an sNDA. The submission of an NDA requires payment of a substantial user fee to the FDA. The FDA may convene an advisory committee to provide clinical insight on NDA review questions, although the FDA is not required to follow the recommendations of an advisory committee. The FDA may initially issue a Refuse to File letter for an incomplete NDA or sNDA, or it may deny approval of an NDA or sNDA by way of a Complete Response letter if the applicable regulatory criteria are not satisfied, or alternatively require additional clinical and/or nonclinical data and/or an additional phase 3 pivotal clinical trial. Once issued, the FDA may withdraw product approval if ongoing regulatory standards are not met or if safety problems occur after the product reaches the market. Satisfaction of FDA development and approval requirements or similar requirements of state, local and foreign regulatory agencies typically takes several years, and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Any products manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including obtaining prior FDA approval of certain changes to the approved NDA, record-keeping requirements, and reporting of adverse experiences with, and interruptions in the manufacture of, the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies. Thus, we and our third-party contract manufacturing organizations are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMP, which impose certain manufacturing requirements (including procedural and documentation requirements) upon us and our third-party contract manufacturing organizations.

In the U.S., the Orphan Drug Act of 1983, as amended, provides incentives for the development of drugs and biotherapeutic products for rare diseases or conditions that affect fewer than 200,000 people in the U.S. (or for which there is no reasonable expectation that the cost of developing and making available the drug in the U.S. for such disease or condition will be recovered from sales of the drug in the U.S.). Certain of the incentives turn on the drug first being designated as an orphan drug. To be eligible for designation as an orphan drug (Orphan Drug Designation), the drug must have the potential to treat such rare disease or condition as described above. In addition, the FDA must not have previously approved a drug considered the "same drug," as defined in the FDA's orphan drug regulations, for the same orphan-designated indication or the sponsor of the subsequent drug must provide a plausible hypothesis of clinical superiority over the previously approved same drug. Upon receipt of Orphan Drug Designation, the sponsor is eligible for tax credits of up to 25% for qualified clinical trial expenses and waiver of the Prescription Drug User Fee Act application fee. In addition, upon marketing approval, an orphan-designated drug could be eligible for seven years of market exclusivity if no drug considered the same drug was previously approved for the same orphan condition (or if the subsequent drug is demonstrated to be clinically superior to any such previously approved same drug). Such orphan drug exclusivity, if awarded, would only block the approval of any drug considered the same drug for the same orphan indication. Moreover, a subsequent same drug could break an approved drug's orphan exclusivity through a demonstration of clinical superiority over the previously approved drug.

Expedited FDA Approval Pathways

The FDA has various programs that are intended to expedite or simplify the process for developing and reviewing promising drugs, or to provide for the approval of a drug on the basis of a surrogate endpoint. Generally, drugs that are eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs and those that offer meaningful benefits over existing treatments. Examples of such programs included Fast Track designation, breakthrough therapy designation, priority review and accelerated approval, and the eligibility criteria of and benefits for each program vary:

- Fast Track is a process designed to facilitate the development and expedite the review of drugs intended to treat serious or life-threatening diseases or conditions that demonstrate the potential to fill unmet medical needs, by providing, among other things, eligibility for accelerated approval if relevant criteria are met, and rolling review,

which allows submission of individually completed sections of an NDA or for FDA review before the entire submission is completed.

- Breakthrough therapy designation is a process designed to expedite the development and review of drugs that are intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review, and rolling review.
- Priority review is designed to shorten the review period for drugs that treat serious conditions and that, if approved, would offer significant advances in safety or effectiveness or would provide a treatment where no adequate therapy exists. Under priority review, the FDA aims to take action on the application within six months as compared to a standard review time of 10 months. Sponsors may also obtain a priority review voucher upon approval of an NDA for certain qualifying diseases and conditions that can be applied to a subsequent NDA submission
- Accelerated approval provides for an earlier approval for a new drug that is intended to treat a serious or life-threatening disease or condition and that provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint, or an intermediate clinical endpoint, which is considered reasonably likely to predict clinical benefit. As a condition of approval, the FDA requires that a sponsor of a product candidate receiving accelerated approval perform post-marketing clinical trials or provide data on established clinical endpoints from the same trial to confirm the clinical benefit as predicted by the surrogate marker trial. The failure to conduct such trials, or confirm the clinically meaningful outcome in such trials, may result in withdrawal of the approval of the drug or the indication approved under accelerated approval.

Specifically, with respect to oncology products, the FDA may review applications under the Real-Time Oncology Review (RTOR) pilot program established by the FDA's Oncology Center of Excellence. The RTOR pilot program, which allows an applicant to pre-submit components of the application to allow the FDA to review clinical data before the complete filing is submitted, aims to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible, while maintaining and improving review quality. Drugs considered for review under the RTOR pilot program must be likely to demonstrate substantial improvements over available therapy, which may include drugs previously granted breakthrough therapy designation for the same or other indications, and must have straight-forward study designs and endpoints that can be easily interpreted.

Abbreviated FDA Approval Pathways and Generic Products

The Drug Price Competition and Patent Term Restoration Act of 1984 (The Hatch-Waxman Act) established two abbreviated approval pathways for drug products in which potential competitors may rely upon the FDA's prior approval of the same or similar drug product.

- *Abbreviated New Drug Application (ANDA).* An ANDA may be approved by the FDA if the applicant demonstrates that the proposed generic product is the same as the approved drug, which is referred to as the Reference Listed Drug (RLD). Generally, an ANDA must contain data and information showing that the proposed generic product and RLD (1) have the same active ingredient, in the same strength and dosage form, to be delivered via the same route of administration, (2) are intended for the same uses, and (3) are bioequivalent. This is instead of independently demonstrating the proposed product's safety and effectiveness through clinical development. Conducting bioequivalence testing is generally less time consuming and costly than conducting a full set of clinical trials in humans. In this regard, the FDA has published draft guidance containing product-specific bioequivalence recommendations for drug products containing cabozantinib, the active pharmaceutical ingredient in CABOMETYX and COMETRIQ, as it does for many FDA-approved drug products.

- *505(b)(2) NDAs.* A 505(b)(2) NDA is an application for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. Under Section 505(b)(2) NDA of the Federal Food, Drug, and Cosmetic Act (FDCA), an applicant may rely, in part, on the FDA's previous approval of a similar product, or published literature, in support of its application. If the 505(b)(2) applicant establishes that reliance on the FDA's prior findings of safety and efficacy for an approved product is

scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies. The FDA may require additional studies or measurements, including comparability studies.

Unlike a full NDA for which the sponsor has conducted or obtained a right of reference to all the data essential to approval, the filing of an ANDA or a 505(b)(2) NDA may be delayed due to patent or exclusivity protections covering an approved product. The Hatch-Waxman Act provides (a) up to five years of exclusivity for the first approval of a new chemical entity (NCE) exclusivity and (b) three years of exclusivity for approval of an NDA or sNDA for a product that is not an NCE but rather where the application contains new clinical studies conducted or sponsored by the sponsor and considered essential to the approval of the NDA or sNDA (three-year "changes" exclusivity). NCE exclusivity runs from the time of approval of the NDA and bars FDA from accepting for review of any ANDA or 505(b)(2) NDA for a drug containing the same active moiety for five years (or for four years if the application contains a Paragraph IV certification that a reference product patent is invalid or not infringed by the ANDA/505(b)(2) NDA product). The three-year "changes" exclusivity generally bars the FDA from approving any ANDA or 505(b)(2) NDA application that relies on the information supporting the approval of the drug or the change to the drug for which the information was submitted and the exclusivity granted.

Both Congress and the FDA are considering, and have enacted, various legislative and regulatory proposals focused on drug competition, including legislation focused on drug patenting and provision of drug to generic applicants for testing. For example, the Ensuring Innovation Act, enacted in April 2021, amended the FDA's statutory authority for granting NCE exclusivity to reflect the agency's existing regulations and longstanding interpretation that award NCE exclusivity based on a drug's active moiety, as opposed to its active ingredient, which is intended to limit the applicability of NCE exclusivity, thereby potentially facilitating generic competition. The FDA has also released, and continues to implement, a Drug Competition Action Plan, which proposes actions to broaden access to generic drugs and lower consumers' healthcare costs by, among other things, improving the efficiency of the generic drug approval process and supporting the development of complex generic drugs. In addition, the Further Consolidated Appropriations Act, 2020, which incorporated the framework from the Creating and Restoring Equal Access To Equivalent Samples (CREATES) legislation, purports to promote competition in the market for drugs and biotherapeutic products by facilitating the timely entry of lower-cost generic and biosimilar versions of those drugs and biotherapeutic products, including by allowing ANDA, 505(b)(2) NDA or biosimilar developers to obtain access to branded drug and biotherapeutic product samples.

Orange Book Listing. An NDA sponsor must identify to the FDA patents that claim the drug substance or drug product or approved method of using the drug. When the drug is approved, those patents are among the information about the product that is listed in the FDA publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the *Orange Book*. Any applicant who files an ANDA or a 505(b)(2) NDA must certify, for each patent listed in the Orange Book for the RLD that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA, (2) such patent has expired, (3) the listed patent will expire on a particular date and approval is sought after patent expiration, or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. An ANDA or 505(b)(2) NDA applicant may also submit a statement that it intends to carve-out from the labeling of its product an RLD's use that is protected by exclusivity or a method of use patent. The fourth certification described above is known as a Paragraph IV certification. A notice of the Paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the reference NDA holder. The reference NDA holder and patent owners may initiate a patent infringement lawsuit in response to the Paragraph IV notice. Filing such a lawsuit within 45 days of the receipt of the Paragraph IV certification notice prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit, or a decision in the infringement case that is favorable to the ANDA or 505(b)(2) NDA applicant. The ANDA or 505(b)(2) NDA also will not receive final approval until any applicable non-patent exclusivity listed in the Orange Book for the RLD has expired. We intend to defend vigorously any patents for our approved products.

Regulatory Approval Outside of the United States

In addition to regulations in the U.S., we are subject to regulations of other countries governing clinical trials and the manufacturing, commercial sales and distribution of our products outside of the U.S. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of countries outside of the U.S. before we can commence clinical trials in such countries and approval of the regulators of such countries or economic areas, such as the EU, before we may market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

The way clinical trials are conducted in the EU has undergone a major change with the application of Regulation (EU) 536/2014, repealing the existing Directive 2001/20/EC. This new regulation harmonizes the assessment and supervision processes for clinical trials throughout the EU, via an EU portal and database, which the EMA will maintain in collaboration with the Member States and the EC. Following the EC's confirmation of full functionality of the Clinical Trials Information System (CTIS) through an independent audit, which was published in the Official Journal of the European Union in August 2021, Regulation (EU) 536/2014 became applicable concurrent with the CTIS "go-live" date on January 31, 2022.

Under EU regulatory systems, a company may submit a marketing authorization application (MAA) either under centralized or decentralized procedure. Under the centralized procedure, MAAs are submitted to the EMA for scientific review by the Committee for Medicinal Products for Human Use (CHMP) so that an opinion is issued on product approvability. The opinion is considered by the EC which is responsible for granting the centralized marketing authorization in the form of a binding EC decision. If the application is approved, the EC grants a single marketing authorization that is valid for all EU Member States as well as Iceland, Liechtenstein and Norway, collectively the European Economic Area. The decentralized and mutual recognition procedures, as well as national authorization procedure are available for products for which the centralized procedure is not compulsory. The mutual recognition procedure provides for the EU Member States selected by the applicant to mutually recognize a national marketing authorization that has already been granted by the competent authority of another Member State, referred to as the Reference Member State (RMS). The decentralized procedure is used when the product in question has yet to be granted a marketing authorization in any Member State. Under this procedure the applicant can select the Member State that will act as the RMS. In both the mutual recognition and decentralized procedures, the RMS reviews the application and submits its assessment of the application to the Member States where marketing authorizations are being sought, referred to as Concerned Member States. Within 90 days of receiving the application and assessment report, each Concerned Member State must decide whether to recognize the RMS assessment or reject it on the basis of potential serious risk to public health. If the disputed points cannot be resolved, the matter is eventually referred to the Coordination Group on Mutual Recognition and Decentralised Procedures in the first instance to reach an agreement and failing to reach such an agreement, a referral to the EMA and the CHMP for arbitration that will result in an opinion to form the basis of a decision to be issued by the EC binding on all Member States. If the application is successful during the decentralized or mutual recognition procedure, national marketing authorizations will be granted by the competent authorities in each of the Member States chosen by the applicant.

Conditional marketing authorizations may be granted in the centralized procedure for a limited number of medicinal products for human use referenced in EU law applicable to conditional marketing authorizations where the clinical dataset is not comprehensive, if (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) unmet medical needs will be fulfilled and (4) the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required.

As in the U.S., we may apply for designation of a product as an orphan drug for the treatment of a specific indication in the EU before the application for marketing authorization is made. In the EU, orphan designation is available for products in development which are either: (a) intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the EU; or (b) intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition affecting a larger number of persons but when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. Additionally, the sponsor of an application for designation of a product as an orphan drug in the EU must establish that there exists no satisfactory authorized method of diagnosis, prevention, or treatment of the condition or even if such treatment exists, the product will be of significant benefit to those affected by that condition.

Orphan drugs in the EU enjoy economic and marketing benefits, including up to ten years of market exclusivity for the approved indication unless another applicant for a similar medicinal product can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product. The period of market exclusivity may be reduced to six years if at the end of the fifth year it is established that the criteria for orphan designation are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Healthcare and Privacy Regulation

Federal and state healthcare laws, including fraud and abuse and health information privacy and security laws, also govern our business. If we fail to comply with those laws, we could face substantial penalties and our business, results of operations, financial condition and prospects could be adversely affected. The laws that may affect our ability to operate

include, but are not limited to: the federal Anti-Kickback Statute (AKS), which prohibits, among other things, soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce or reward for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as Medicare and Medicaid; the FDCA and its implementing regulations, which prohibit, among other things, the introduction or delivery for introduction into interstate commerce of any drug that is adulterated or misbranded; and federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent. Additionally, we are subject to state law equivalents of each of the above federal laws, which may be broader in scope and apply regardless of whether the payer is a governmental healthcare program, and many of which differ from each other in significant ways and may not have the same effect, further complicate compliance efforts.

Numerous federal and state laws, including state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use and disclosure of personal information. For example, the California Consumer Privacy Act of 2018, as amended (CCPA), went into operation on January 1, 2020 and broadly defines personal information, affords California residents expanded privacy rights and protections and provides for civil penalties for violations and a private right of action related to certain data security breaches. These protections will be expanded by the California Privacy Rights Act (CPRA), which was approved by California voters in November 2020 and will be operational in most key respects on January 1, 2023. Similar legislative proposals have passed or are being advanced in other states, and Congress is considering additional federal privacy legislation. In addition, most healthcare professionals and facilities who may prescribe our products and from whom we may obtain patient health information, are subject to privacy and security requirements under the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology and Clinical Health Act (HIPAA). Although we are not considered to be a covered entity or business associate under HIPAA with respect to our clinical and commercial activities, we could be subject to penalties if we use or disclose individually identifiable health information in a manner not authorized or permitted by HIPAA. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business, including laws in all 50 states requiring security breach notification in some circumstances. The CCPA, CPRA, HIPAA and these other laws could create liability for us or increase our cost of doing business. International laws, such as the EU General Data Protection Regulation 2016/679 (GDPR), could also apply to our operations. Failure to provide adequate privacy protections and maintain compliance with applicable privacy laws could jeopardize business transactions across borders and result in significant penalties.

In addition, the Patient Protection and Affordable Care Act of 2010, as amended (PPACA) created a federal requirement under the federal Open Payments program, that requires certain manufacturers to track and report to the Centers for Medicare & Medicaid Services annually certain payments and other transfers of value provided to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistance and nurse practitioners) and teaching hospitals, as well as ownership interests held by such physicians and their immediate family during the previous calendar year.

Because our products are covered in the U.S. by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require us to pay substantial rebates or offer our drugs at substantial discounts to certain purchasers (including “covered entities” purchasing under the 340B Drug Discount Program (the 340B Program)). We are also required to discount our products to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas and regulatory guidance, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources. Failure to properly calculate prices, or to offer required discounts or rebates could subject us to substantial penalties.

Coverage and Reimbursement

Sales of our approved products and any future products of ours will depend, in part, on the extent to which their costs will be covered by third-party payers, such as government health programs, commercial insurance and managed healthcare organizations. Each third-party payer may have its own policy regarding what products it will cover, the conditions under which it will cover such products, and how much it will pay for such products. Third-party payers may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the FDA-approved drugs for a particular indication. Moreover, a third-party payer’s decision to provide coverage for a drug product

does not guarantee what reimbursement rate, if any, will be approved. Patients may be less likely to use our products if coverage is not provided and reimbursement may not cover a significant portion of the cost of our products.

In the U.S. and other potentially significant markets for our products, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which may result in lower average selling prices. In some cases, for example, third-party payers try to encourage the use of less expensive generic products through their prescription benefits coverage and reimbursement and co-pay policies. Further, the increased emphasis on managed healthcare in the U.S. and on country-specific and national pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing coverage and/or reimbursement controls and measures, could have a material adverse impact on our net product revenues and results of operations.

Healthcare Reform

The U.S. and some foreign countries are considering proposals or have enacted legislative and regulatory changes to the healthcare system that could affect our ability to sell our products profitably. Among policy makers and payers in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access.

There has been increasing legislative and enforcement interest in the U.S. with respect to drug pricing practices. In particular, there have been several recent U.S. Congressional inquiries, hearings and proposed and enacted federal legislation and rules, as well as executive orders, designed to, among other things: reduce or limit the prices of drugs and make them more affordable for patients (including, for example, by tying the prices that Medicare reimburses for physician-administered drugs to the prices of drugs in other countries); reform the structure and financing of Medicare Part D pharmaceutical benefits; implement additional data collection and transparency reporting regarding drug pricing, rebates, fees and other remuneration provided by drug manufacturers; enable the government to negotiate prices under Medicare; revise rules associated with the calculation of average manufacturer price and best price under Medicaid; eliminate the AKS discount safe harbor protection for manufacturer rebate arrangements with Medicare Part D plan sponsors; create new AKS safe harbors applicable to certain point-of-sale discounts to patients and fixed fee administrative fee payment arrangements with pharmacy benefit managers; and revise the rebate methodology under the Medicaid Drug Rebate Program. For instance, President Biden issued an executive order in July 2021 supporting legislation to enact some of these drug pricing reforms, and in response, the U.S. Department of Health and Human Services (HHS) released a Comprehensive Plan for Addressing High Drug Prices in September 2021 with specific legislative and administrative policies that Congress could enact to help improve affordability of and access to prescription drugs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biotherapeutic product pricing, including restrictions on pricing or reimbursement at the state government level, limitations on discounts to patients, marketing cost disclosure and transparency measures, and, in some cases, policies to encourage importation from other countries (subject to federal approval) and bulk purchasing, including the National Medicaid Pooling Initiative. These laws may affect our sales, marketing, and other promotional activities by imposing administrative and compliance burdens on us. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state and federal authorities.

The U.S. pharmaceutical industry has already been significantly impacted by major legislative initiatives and related political contests. For instance, efforts to repeal, substantially modify or invalidate some or all of the provisions of the PPACA, some of which have been successful, create considerable uncertainties for all businesses involved in healthcare, including our own. In addition, there are pending federal and state-level legislative proposals that would significantly expand government-provided health insurance coverage, ranging from establishing a single-payer, national health insurance system to more limited “buy-in” options to existing public health insurance programs, each of which could have a significant impact on the healthcare industry. It is also possible that additional governmental actions will be taken in response to the ongoing COVID-19 pandemic, and that such actions would have a significant impact on these public health insurance programs.

As a result of these developments and trends, third-party payers are increasingly attempting to contain healthcare costs by limiting coverage and the level of reimbursement of new drugs. These entities could refuse, limit or condition

coverage for our products, such as by using tiered reimbursement or pressing for new forms of contracting, including, for example, the movement by insurers towards "value-based" contracting, any of which could adversely affect product sales. Due to general uncertainty in the current regulatory and healthcare policy environment, and specifically regarding positions that the Biden Administration may take with respect to these issues, we are unable to predict the impact of any legislative, regulatory, third-party payer or policy actions, including potential cost containment and healthcare reform measures.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before its cost may be funded within the respective national healthcare system. The requirements governing drug pricing vary widely from country to country. For example, EU Member States may restrict the range of medicinal products for which their national healthcare systems provide reimbursement and may control the prices of medicinal products for human use. A Member State may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profits the medicinal product generates for the company placing it on the market. Pricing and reimbursement negotiations with governmental authorities or payers in EU Member States can take six to 12 months or longer after the initial marketing authorization is granted for a product, or after the marketing authorization for a new indication is granted. To obtain reimbursement and/or pricing approval in some countries, drug manufacturers and collaboration partners may also be required to conduct a study or otherwise provide data that seeks to establish the cost effectiveness of a new drug compared with other available established therapies. Other cost-control initiatives are similarly focused on affordability and accessibility, such as the Regulation on Health Technology Assessment (HTA) adopted in December 2021 and other upcoming legislative and policy changes aimed at increasing cooperation between EU Member States, and once enacted may further impact the price and reimbursement status of many medicinal products. There can be no assurance that any country that has price controls, reimbursement limitations or other requirements for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products on cost-effectiveness grounds. Historically, products launched in EU Member States and other non-U.S. jurisdictions do not follow the price structures of the U.S., and they generally tend to be priced significantly lower.

Competition

There are many companies focused on the development of small molecules, antibodies and other treatments for cancer. Our competitors and potential competitors include major pharmaceutical and biotechnology companies, as well as academic research institutions, clinical reference laboratories and government agencies that are pursuing research activities similar to ours. Many of the organizations competing with us have greater capital resources, larger research and development staff and facilities, deeper regulatory expertise and more extensive product manufacturing and commercial capabilities than we do, which may afford them a competitive advantage.

Competition for Cabozantinib

We believe that our ability to successfully compete will depend on, among other things:

- efficacy, safety and reliability of cabozantinib, both alone and in combination with other therapies;
- timing and scope of regulatory approval;
- the speed at which we develop cabozantinib for the treatment of additional tumor types beyond its approved indications;
- our ability to complete clinical development and obtain regulatory approvals for cabozantinib, both alone and in combination with other therapies;
- our ability to manufacture and sell commercial quantities of cabozantinib product to the market;
- our ability to successfully commercialize cabozantinib, both as a single agent and as part of any combination therapy regimen, and secure coverage and adequate reimbursement in approved indications;
- product acceptance by physicians and other health care providers;
- the level of our collaboration partners' investments in the resources necessary to successfully commercialize cabozantinib, or any combination therapy regimen that includes cabozantinib, in territories where they are approved;
- skills of our employees and our ability to recruit and retain skilled employees;
- protection of our intellectual property, including our ability to enforce our intellectual property rights against potential generic competition; and
- the availability of substantial capital resources to fund development and commercialization activities.

We believe that the quality and breadth of activity observed with cabozantinib, the skill of our employees and our ability to recruit and retain skilled employees, our patent portfolio and our capabilities for research and drug development are competitive strengths. However, many large pharmaceutical and biotechnology companies have significantly larger intellectual property estates than we do, more substantial capital resources than we have, and greater capabilities and experience than we do in preclinical and clinical development, sales, marketing, manufacturing and regulatory affairs.

Furthermore, the specific indications for which CABOMETYX is currently or may be approved, based on the results from clinical trials currently evaluating cabozantinib, are highly competitive. Several novel therapies and combinations of therapies have been approved, are in advanced stages of clinical development or are under expedited regulatory review in these indications, and these other therapies are currently competing or are expected to compete with CABOMETYX. While we have had success in adapting our development strategy for the cabozantinib franchise to address the competitive landscape, including through evaluation of therapies that combine ICIs with other targeted agents, it is uncertain whether current and future clinical trials, including those evaluating cabozantinib in combination with an ICI in HCC, NSCLC and mCRPC, will lead to regulatory approvals, or whether physicians will prescribe regimens containing cabozantinib instead of competing product combinations in approved indications.

Below is a summary of the principal competition for cabozantinib in the indications for which it is approved or for which it has been or is currently being evaluated in potentially label-enabling trials, both as a single agent and in combination with other therapies. The information below does not include all competitor products, but rather those approved products that have or we believe may capture significant market share within their respective indications, or with respect to therapies still in development, those that are likely to overlap with patient populations that are or may be treated with cabozantinib or a combination therapy regimen that includes cabozantinib.

Competition in Approved Cabozantinib Indications

CABOMETYX - RCC: We believe the principal competition for CABOMETYX in advanced RCC includes: the combination of Merck & Co.'s pembrolizumab and Pfizer's axitinib; the combination of BMS's ipilimumab and nivolumab; and the combination of Merck & Co.'s pembrolizumab and Eisai's lenvatinib. Additionally, there are a variety of therapies being developed for advanced RCC, including: the combination of Peloton Therapeutics' (a wholly owned subsidiary of Merck & Co.) belzutifan (also known as MK-6482) and Eisai's lenvatinib; the combination of Merck & Co.'s pembrolizumab, Eisai's lenvatinib and Peloton Therapeutics' belzutifan; the combination of Merck & Co.'s pembrolizumab and quavonlimab and Eisai's lenvatinib; and the combination of BMS' nivolumab and Nektar's bempegaldesleukin.

The competitive landscape for RCC is evolving rapidly, especially given the entrance and increased adoption of ICI and ICI-TKI combination therapies into the RCC treatment landscape, particularly in the first-line setting. This has led to changing trends in prescribing and sequencing of certain drugs and combinations across different lines of therapy. It is difficult to predict how these changes will affect sales of CABOMETYX during 2022 and going forward.

CABOMETYX - HCC: We believe the principal competition for CABOMETYX in previously treated HCC includes: Bayer's regorafenib; and Eisai's lenvatinib. Additionally, there are a variety of therapies being developed for previously treated HCC, including the combination of Roche's atezolizumab and either Eisai's Lenvatinib or Bayer's and Onyx's sorafenib.

The competitive landscape for HCC has significantly changed with the increased adoption of ICI combination therapies in the first-line setting, which may lead to an increase in prescribing and sequencing of TKIs in subsequent lines of therapy. It is difficult to predict how these changes will affect sales of CABOMETYX during 2022 and going forward.

CABOMETYX - DTC: We believe the principal competition for CABOMETYX in its previously treated DTC indication includes two treatments that are also approved for previously untreated DTC: Bayer's and Onyx's sorafenib; and Eisai's lenvatinib. In addition, we believe there is also competition for CABOMETYX from therapies approved to treat patients with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are RAI-refractory (if RAI is appropriate), including: Blueprint Medicine's and Roche's pralsetinib; and Loxo Oncology's (a wholly owned subsidiary of Eli Lilly) selpercatinib.

Other than the approvals of RET inhibitors to treat certain DTC patients, there has been little change in the competitive landscape for RAI-refractory DTC treatments during recent years. Due the limited number of ongoing late-stage clinical trials in this DTC indication, we do not except additional competitors to emerge during 2022.

COMETRIQ - MTC: We believe that the principal competing anti-cancer therapy to COMETRIQ in progressive, metastatic MTC is Genzyme's vandetanib, which has been approved by the FDA and the EC for the treatment of symptomatic or progressive MTC in patients with unresectable, locally advanced, or metastatic disease, as well as other therapies that have been recently approved to treat patients with advanced or metastatic RET-mutant MTC who require systemic therapy, including: Blueprint Medicine's and Roche's pralsetinib; and Loxo Oncology's selpercatinib.

Other than the recent approvals of RET inhibitors to treat certain MTC patients, there has been little change in the treatment landscape for progressive, metastatic MTC during recent years, and due to the limited number of ongoing late-stage clinical trials in this indication, we do not expect many additional competitors to emerge in 2022.

Competition in Potential Cabozantinib Indications

Cabozantinib in combination with ICI - HCC: COSMIC-312, the phase 3 pivotal trial evaluating the combination of cabozantinib and atezolizumab in patients with previously untreated HCC, is continuing as planned to final analysis of OS, and we intend to submit an sNDA to the FDA for the combination regimen if supported by the final OS analysis. Should the combination of cabozantinib and atezolizumab be approved for the treatment of patients with previously untreated advanced HCC, we believe its principal competition may include: the combination of Merck & Co.'s pembrolizumab and Eisai's lenvatinib; the combination of Roche's bevacizumab and atezolizumab; and the combination of AstraZeneca's durvalumab and tremelimumab.

Cabozantinib in combination with ICI – NSCLC: We are evaluating the combination of cabozantinib and atezolizumab in CONTACT-01, a phase 3 pivotal trial evaluating the combination of cabozantinib and atezolizumab in patients with metastatic NSCLC who have been previously treated with an ICI and platinum-containing chemotherapy. Should the combination of cabozantinib and atezolizumab be approved for the treatment of patients with NSCLC, we believe its principal competition may include: Sanofi's docetaxel; the combination of Sanofi's docetaxel and Eli Lilly's ramucirumab; the combination of BMS' nivolumab and Mirati's sitravatinib; the combination of Merck & Co.'s pembrolizumab and Eisai's lenvatinib; Daiichi Sankyo's DS-1062; and generic versions of docetaxel.

Cabozantinib in combination with ICI – mCRPC: We are evaluating the combination of cabozantinib and atezolizumab in CONTACT-02, a phase 3 pivotal trial evaluating the combination of cabozantinib and atezolizumab in patients with mCRPC who have been previously treated with one NHT. Should the combination of cabozantinib and atezolizumab be approved for the treatment of patients with mCRPC, we believe its principal competition may include: Janssen Biotech's (a wholly owned subsidiary of Johnson & Johnson) abiraterone; Astellas Pharma's and Pfizer's enzalutamide; Sanofi's docetaxel; the combination of Merck & Co.'s pembrolizumab and Sanofi's docetaxel; the combination of Merck & Co.'s pembrolizumab and Astellas Pharma's and Pfizer's enzalutamide; the combination of BMS' nivolumab and Sanofi's docetaxel; Veru Pharma's sabizabulin; and generic versions of abiraterone and docetaxel. In addition, we believe there may be competition for the combination of cabozantinib and atezolizumab in mCRPC from therapies in late-stage development focused on the subset of mCRPC patients who are prostate-specific membrane antigen positive, including: Novartis' ^{177}Lu-PSMA-617; POINT Biopharma's ^{177}Lu-PNT2002; Telix International's ^{177}Lu-DOTA-rosopatamab; and Curium US LLC's ^{177}Lu-PSMA-I&T.

Competition for Cobimetinib and Esaxerenone

There is competition for both cobimetinib and esaxerenone in the specific indications and territories where they are approved, and there are regular new entrants and developments in all aspects of these markets. However, given the relatively lesser degree of adoption of these therapies within the broader markets in which they compete and their minimal contribution to our total revenues as out-licensed products, we do not believe changes in the competitive landscape in these indications will have a material impact on our business.

Patents and Proprietary Rights

We actively seek patent protection in the U.S., EU and selected other foreign jurisdictions to cover our drug candidates and related technologies. Patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country. We have numerous patents and pending patent applications that relate to methods of screening drug targets, compounds that modulate drug targets, as well as methods of making and using such compounds.

While many patent applications have been filed relating to the drug candidates that we have developed, the majority of these are not yet issued or allowed. To our knowledge, we own all global patents associated with cabozantinib and cobimetinib, and we either own or have in-licensed all global patents for our other drug candidates, as further described below.

Cabozantinib

Cabozantinib is covered by more than 15 issued patents in the U.S., building from U.S. Pat. No. 7,579,473, for the composition of matter of cabozantinib (the '473 Patent) and pharmaceutical compositions thereof. This composition of matter patent would expire in September 2024, but we have been granted a patent term extension to extend the term to August 2026. The following table describes the US patents that cover our marketed cabozantinib products, and which are listed in the Orange Book. Except as otherwise noted, the stated expiration dates include any patent term extensions already granted. In addition to the composition of matter patent referenced above, the table includes patents directed to, among other things, particular salts, polymorphs, formulations, or use of the compound in the treatment of specified diseases or conditions. We continue to pursue additional patents and patent term extensions in the U.S. and other territories covering various aspects of our cabozantinib products that may, if issued, extend exclusivity beyond the expiration of the patents listed in the table.

Product	Patent No.	General Subject Matter	Patent Expiration
CABOMETYX	7,579,473	Composition of matter	2026
	8,497,284	Methods of treatment	2024
	8,877,776	Salt and polymorphic forms of cabozantinib	2030
	9,724,342	Formulations of cabozantinib	2033
	10,034,873	Methods of treatment	2031
	10,039,757	Methods of treatment	2031
	11,091,439	Salt and polymorphic forms of cabozantinib	2030
	11,091,440	Formulations of cabozantinib	2030
	11,098,015	Methods of treatment	2030
	11,141,413	Methods of treatment	2037
COMETRIQ	7,579,473	Composition of matter	2026
	8,877,776	Salt and polymorphic forms of cabozantinib	2030
	9,717,720	Formulations of cabozantinib	2032
	11,091,439	Salt and polymorphic forms of cabozantinib	2030
	11,091,440	Formulations of cabozantinib	2030
	11,098,015	Methods of treatment	2030

Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise with respect to patents and patent applications required for the commercialization of medicines containing cabozantinib. For example, in September 2019, we received a Paragraph IV notice letter regarding an ANDA submitted to the FDA by MSN Pharmaceuticals, Inc. (MSN), requesting approval to market a generic version of CABOMETYX tablets, which MSN then amended with additional Paragraph IV certifications in May 2020 to include the '473 Patent and U.S. Patent No. 8,497,284. In response, we filed patent infringement lawsuits against MSN in the United States District Court for the District of Delaware (the Delaware District Court) in October 2019 and May 2020, which were later consolidated and include infringement claims related to the '473 Patent and U.S. Patent No. 8,497,284. In addition, in May 2021, we received Paragraph IV certification notice letters regarding an ANDA submitted to the FDA by Teva Pharmaceuticals Development, Inc. and Teva Pharmaceuticals USA, Inc. (individually and collectively referred to as Teva), requesting approval to market a generic version of CABOMETYX tablets. In response, we filed a patent infringement lawsuit against Teva, along with Teva Pharmaceutical Industries Limited (Teva Parent), in the Delaware District Court in June 2021. We cannot predict the outcome of these lawsuits or provide assurance that these lawsuits will prevent the introduction of a generic version of CABOMETYX for any particular length of time, or at all. For a more detailed discussion of these litigation matters, see "Legal Proceedings" in Part I, Item 3 of this Annual Report on Form 10-K.

In the EU, cabozantinib is protected by issued patents covering the composition of matter and methods of use. The issued patent would expire in September 2024, but we have applied for and either have obtained, or expect to obtain Supplementary Protection Certificates in the EU to extend the term to 2029. In addition to the composition of matter patent, the table below includes certain later-expiring patents directed to the commercial product, including, particular salts, polymorphs, formulations, or use of the compound in the treatment of specified diseases or conditions.

Product	Patent No.	General Subject Matter	Patent Expiration
CABOMETYX	2213661	Composition of matter and methods of treatment	2029
	2387563	Salt and polymorphic forms of cabozantinib and methods of treatment	2030
COMETRIQ	2213661	Composition of matter and methods of treatment	2029
	2387563	Salt and polymorphic forms of cabozantinib and methods of treatment	2030

In September 2021, in a final decision before the Technical Board of Appeal, the Opposition Division of the European Patent Office upheld the validity of EP patent 2387563, directed to crystalline forms of cabozantinib malate, pharmaceutical compositions and certain uses thereof. This ruling favors continuing exclusivity of our cabozantinib patent portfolio in the EU through the expiration date of EP patent 2387563 in 2030.

Similarly, in Japan, cabozantinib is protected by issued patents covering the composition of matter, and salts thereof, as well as pharmaceutical compositions and related methods of use, and Takeda has applied for patent term extension in Japan to extend the term to 2029. Foreign counterparts of the issued U.S. and European composition of matter patents have been issued in Australia and Canada and are anticipated to expire in 2024. We have other filed patent applications and issued patents in the U.S. and other selected countries covering certain synthetic methods, salts, polymorphs, formulations, prodrugs, metabolites and combinations of cabozantinib that, if issued, are anticipated to expire as late as 2037. Outside the U.S. and Japan, cabozantinib is licensed to Ipsen, and in Japan, cabozantinib is licensed to Takeda, each in accordance with the respective collaboration agreements. A discussion of risks and uncertainties that may affect our patent position and other proprietary rights is set forth in “Risk Factors,” contained in Part I, Item 1A of this Annual Report on Form 10-K.

Other Drug Candidates

We also have issued patents and pending patent applications, and will continue to file new patent applications, in the U.S., the EU and other selected countries covering our other drug candidates in clinical and/or preclinical development, including XL092, XB002, XL102 and XL114.

We have obtained licenses from various parties that give us rights to technologies that we deem to be necessary or desirable for our research and development. These licenses (both exclusive and non-exclusive) may require us to pay royalties as well as upfront and milestone payments.

We require our scientific personnel to maintain laboratory notebooks and other research records in accordance with our policies, which are designed to strengthen and support our intellectual property protection. In addition to our patented intellectual property, we also rely on trade secrets and other proprietary information, especially when we do not believe that patent protection is appropriate or can be obtained. We also require all of our employees and consultants, outside scientific collaborators, sponsored researchers and other advisors who receive proprietary information from us to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all proprietary information developed or made known to the individual during the course of the individual’s relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. Furthermore, our agreements with employees and, in most circumstances, our agreements with consultants, outside scientific collaborators, sponsored researchers and other advisors expressly provide that all inventions, concepts, developments, copyrights, trademarks or other intellectual property developed by an employee during the employment period, or developed by a service provider during the service period or utilizing our proprietary drugs or information, shall be our exclusive property. There can be no assurance, however, that these agreements will provide meaningful protection or adequate remedies for our trade secrets in the event of unauthorized use or disclosure of such information.

Human Capital Management

Our Employees and Commitment to Diversity, Equity and Inclusion

As of December 31, 2021, we had 954 full-time equivalent employees, representing a 23% increase in our employee workforce as compared to December 31, 2020. Of these employees, 509 are members of our various research and development teams and 445 are members of our various commercial and general and administrative teams. Of these employees, 149 hold Ph.D. degrees, 19 hold M.D. (or foreign equivalent) degrees, 30 hold PharmD degrees and 88 hold other professional degrees such as a J.D. or M.B.A. None of our employees are represented by a labor union, and we consider our employee relations to be good.

During the past five years, our employee turnover has remained consistently below average for the U.S. life sciences industry generally. Given our expanding operations and need to further grow our headcount to support our business, we continually assess employee turnover, recruitment initiatives, compensation and benefits programs, safety in performing critical laboratory work, diversity and other matters relevant to human capital management, and we review results with our Board of Directors on a periodic basis.

We are an equal opportunity employer and maintain policies that prohibit unlawful discrimination based on race, color, religion, gender, sexual orientation, gender identity/expression, national origin/ancestry, age, disability, marital and veteran status. We are proud to employ a diverse workforce that, as of December 31, 2021, was 55% non-white and 53% women. In addition, as of December 31, 2021, 50% of our positions that manage other employees directly were held by non-whites and 47% were held by women, and after giving effect to the hiring of our new Chief Medical Officer in January 2022, women made up 33% of our senior leadership team. We strive to build and nurture a culture where all employees feel empowered to be their authentic selves. We respect and appreciate each employee's unique perspective and experiences, and value their contributions to our mission. It is important that we celebrate, encourage and support similarities and differences to drive innovation for the benefit of our employees, patients and community.

Culture, Compensation and Benefits

At Exelixis, we value being exceptional in what we do and how we lead, excelling for patients by going the extra mile to care for them and exceeding together as a business and contributor to the scientific community. We strive to live these values every day across the company, integrating them into everything from our interview, hiring and onboarding processes, to our performance evaluation, rewards and promotion programs.

We provide generous compensation packages designed to attract and retain high-quality employees, and all of our employees are eligible for cash bonuses and grants of equity awards. We regularly evaluate our compensation programs with an independent compensation consultant and utilize industry benchmarking in an effort to ensure they are competitive compared to similar biotechnology and biopharmaceutical companies with which we compete for talent, as well as fair and equitable across our workforce with respect to gender, race and other personal characteristics. In addition, we are proud to provide a variety of programs and services to help employees meet and balance their needs at work, at home and in life, including an attractive mix of healthcare, insurance and other benefit plans. We deliver a benefits program that is designed to keep our employees and their families healthy, which includes not only medical, dental and vision benefits, but also dependent care, mental health and other wellness benefits. For a discussion of workplace safety measures we have taken, including as a result of the COVID-19 pandemic, see "—Environmental, Health and Safety."

Beyond compensation and benefits, we also value career development for all employees, and we offer a tuition reimbursement program, as well as professional development courses ranging from technical training, competency-based workshops and leadership development programs facilitated by external partners who are experts in their respective fields. Direct managers also take an active role in identifying individualized development plans to assist their employees in realizing their full potential and creating opportunities for promotions and added responsibilities that enhance the engagement and retention of our workforce.

Corporate Information

We were incorporated in Delaware in November 1994 as Exelixis Pharmaceuticals, Inc. and changed our name to Exelixis, Inc. in February 2000. Our principal executive offices are located at 1851 Harbor Bay Parkway, Alameda, California 94502. Our telephone number is (650) 837-7000. We maintain a site on the worldwide web at www.exelixis.com; however, information found on our website is not incorporated by reference into this report.

We make available free of charge on or through our website our Securities and Exchange Commission (SEC) filings, including our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The SEC maintains a site on the worldwide web that contains reports, proxy and information statements and other information regarding our filings at www.sec.gov.

Item 1A. Risk Factors

In addition to the risks discussed elsewhere in this report, the following are important factors that make an investment in our securities speculative or risky, and that could cause actual results or events to differ materially from those contained in any forward-looking statements made by us or on our behalf. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not currently known to us or that we deem immaterial also may impair our business operations. If any of the following risks or such other risks actually occur, our business and the value of your investment in our company could be harmed.

Risks Related to the Commercialization of Our Products

Our ability to grow our company is dependent upon the commercial success of CABOMETYX in its approved indications and the continued clinical development, regulatory approval, clinical acceptance and commercial success of the cabozantinib franchise in additional indications.

We anticipate that for the foreseeable future, our ability to maintain or meaningfully increase cash flow to fund our business operations and growth will depend upon the continued commercial success of CABOMETYX, both alone and in combination with other therapies, as a treatment for the highly competitive indications for which it is approved, and possibly for other indications for which cabozantinib has been or is currently being evaluated in potentially label-enabling clinical trials, if warranted by the data generated from these trials. In this regard, part of our strategy is to pursue additional indications for CABOMETYX and increase the number of cancer patients who could potentially benefit from this medicine. However, we cannot be certain that the clinical trials we and our collaboration partners are conducting will demonstrate adequate safety and efficacy in these additional indications to receive regulatory approval in the major commercial markets where CABOMETYX is approved. Even if we and our collaboration partners receive the required regulatory approvals to market cabozantinib for additional indications, we and our collaboration partners may not be able to commercialize CABOMETYX effectively and successfully in these additional indications. If revenue from CABOMETYX decreases or remains flat, or if we are unable to expand the number of labeled indications for which CABOMETYX is approved, or if we or our collaboration partners fail to achieve anticipated product royalties and collaboration milestones, we may need to reduce our operating expenses, access other sources of cash or otherwise modify our business plans, which could have a material adverse impact on our business, financial condition and results of operations.

Our ability to grow revenues from sales of CABOMETYX depends upon the degree of market acceptance among physicians, patients, healthcare payers, and the medical community.

Our ability to increase or maintain revenues from sales of CABOMETYX for its approved indications is, and if approved for additional indications will be, highly dependent upon the extent of market acceptance of CABOMETYX among physicians, patients, foreign and U.S. government healthcare payers such as Medicare and Medicaid, commercial healthcare plans and the medical community. Market acceptance for CABOMETYX could be impacted by numerous factors, including the effectiveness and safety profile, or the perceived effectiveness and safety profile, of CABOMETYX compared to competing products, the strength of CABOMETYX sales and marketing efforts and changes in pricing and reimbursement for CABOMETYX. If CABOMETYX does not continue to be prescribed broadly for the treatment of patients in its approved indications, our product revenues could flatten or decrease, which could have a material adverse impact on our business, financial condition and results of operations.

Our competitors may develop products and technologies that impair the relative value of our marketed products and any future product candidates.

The biopharmaceutical industry is competitive and characterized by constant technological change and diverse offerings of products, particularly in the area of oncology therapies. Many of our competitors have greater capital resources, larger research and development staff and facilities, deeper regulatory expertise and more extensive product manufacturing and commercial capabilities than we do, which may afford them a competitive advantage. Further, our

competitors may be more effective at in-licensing and developing new commercial products that could render our products, and those of our collaboration partners, obsolete and noncompetitive. We face, and will continue to face, intense competition from biopharmaceutical companies, as well as academic research institutions, clinical reference laboratories and government agencies that are pursuing scientific and clinical research activities similar to ours.

Furthermore, the specific indications for which CABOMETYX is currently or may be approved, based on the results from clinical trials currently evaluating cabozantinib, are highly competitive. Several novel therapies and combinations of therapies have been approved, are in advanced stages of clinical development or are under expedited regulatory review in these indications, and these other therapies are currently competing or are expected to compete with CABOMETYX. While we have had success in adapting our development strategy for the cabozantinib franchise to address the competitive landscape, including through evaluation of therapies that combine ICIs with other targeted agents, it is uncertain whether current and future clinical trials, including those evaluating cabozantinib in combination with an ICI in HCC, NSCLC and mCRPC, will lead to regulatory approvals, or whether physicians will prescribe regimens containing cabozantinib instead of competing product combinations in approved indications.

If we are unable to maintain or increase our sales, marketing, market access and product distribution capabilities for our products, we may be unable to maximize product revenues, which could have a material adverse impact on our business, financial condition and results of operations.

Maintaining our sales, marketing, market access and product distribution capabilities requires significant resources, and there are numerous risks involved with maintaining and continuously improving our commercial organization, including our potential inability to successfully recruit, train, retain and incentivize adequate numbers of qualified and effective sales and marketing personnel. We are competing for talent with numerous commercial- and precommercial-stage, oncology-focused biopharmaceutical companies seeking to build out and maintain their commercial organizations, as well as larger biopharmaceutical organizations that have extensive, well-funded and more experienced sales and marketing operations, and we may be unable to maintain or adequately scale our commercial organization as a result of such competition. Also, to the extent that the commercial opportunities for CABOMETYX grow over time, we may not properly scale the size and experience of our commercialization teams to market and sell CABOMETYX successfully in an expanded number of indications. If we are unable to maintain or scale our commercial function appropriately, or should we have to revert back to primarily telephonic and virtual interactions in lieu of in-person meetings with healthcare professionals for an extended period of time as a result of the COVID-19 pandemic, we may not be able to maximize product revenues, which could have a material adverse impact on our business, financial condition and results of operations.

If we are unable to obtain or maintain coverage and reimbursement for our products from third-party payers, our business will suffer.

Our ability to commercialize our products successfully is highly dependent on the extent to which health insurance coverage and reimbursement is, and will be, available from third-party payers, including foreign and U.S. governmental payers, such as Medicare and Medicaid, and private health insurers. Third-party payers continue to scrutinize and manage access to pharmaceutical products and services and may limit reimbursement for newly approved products and indications. Patients are generally not capable of paying for CABOMETYX or COMETRIQ themselves and rely on third-party payers to pay for, or subsidize, the costs of their medications, among other medical costs. Accordingly, market acceptance of CABOMETYX and COMETRIQ is dependent on the extent to which coverage and reimbursement is available from third-party payers. These entities could refuse, limit or condition coverage for our products, such as by using tiered reimbursement or pressing for new forms of contracting. If third-party payers do not provide coverage or reimbursement for CABOMETYX or COMETRIQ, our revenues and results of operations will suffer. In addition, even if third-party payers provide some coverage or reimbursement for CABOMETYX or COMETRIQ, the availability of such coverage or reimbursement for prescription drugs under private health insurance and managed care plans, which often varies based on the type of contract or plan purchased, may not be sufficient for patients to afford CABOMETYX or COMETRIQ.

Current healthcare laws and regulations in the U.S. and future legislative or regulatory reforms to the U.S. healthcare system may affect our ability to commercialize our marketed products profitably.

Federal and state governments in the U.S. are considering legislative and regulatory proposals to change the U.S. healthcare system in ways that could affect our ability to continue to commercialize CABOMETYX and COMETRIQ profitably. Similarly, among policy makers and payers, there is significant interest in promoting such changes with the stated goals of containing healthcare costs, improving quality and expanding patient access. The life sciences industry and specifically the

market for the sale, insurance coverage and distribution of pharmaceuticals has been a particular focus of these efforts and would likely be significantly affected by any major legislative or regulatory initiatives.

For instance, efforts to repeal, substantially modify or invalidate some or all of the provisions of the PPACA, some of which have been successful, create considerable uncertainties for all businesses involved in healthcare, including our own. Although such efforts have not significantly impacted our business to date, it is possible that the PPACA will be subject to additional judicial or legislative challenges in the future, which may have a material adverse impact on our business, financial condition and results of operations, and we cannot predict how future healthcare reform measures of the Biden Administration and federal or state legislative or administrative changes relating to healthcare reform will affect our business.

In addition, there are pending federal and state-level legislative proposals that would significantly expand government-provided health insurance coverage, ranging from establishing a single-payer, national health insurance system to more limited "buy-in" options to existing public health insurance programs, each of which could have a significant impact on the healthcare industry. It is also possible that additional governmental actions will be taken in response to the ongoing COVID-19 pandemic, and that such actions would have a significant impact on these public health insurance programs. While we cannot predict how future legislation (or enacted legislation that has yet to be implemented) will affect our business, such proposals could have the potential to impact access to and sales of our products. Furthermore, the expansion of the 340B Program has increased the number of purchasers who are eligible for significant discounts on branded drugs, including our marketed products. Because we participate in the 340B Program to sell a portion of our marketed products, changes in the administration of the program could have a material adverse impact on our revenues, including the implementation of the program's Administrative Dispute Resolution Process, which is in part intended to resolve claims by covered entities that manufacturers have overcharged them for covered outpatient drugs, and for which the Office of Management and Budget initiated review of a new proposed rule titled "340B Drug Pricing Program; Administrative Dispute Resolution" in November 2021. Due to general uncertainty in the current regulatory and healthcare policy environment, and specifically regarding positions that the Biden Administration may take with respect to these issues, we are unable to predict the impact of any legislative, regulatory, third-party payer or policy actions, including potential cost containment and healthcare reform measures. If enacted, we and any third parties we may engage may be unable to adapt to any changes implemented as a result of such measures, and we may have difficulties in sustaining profitability or otherwise experience a material adverse impact on our business, financial condition and results of operations.

Pricing for pharmaceutical products in the U.S. has come under increasing attention and scrutiny by federal and state governments, legislative bodies and enforcement agencies. This may result in actions that have the effect of reducing our revenue or harming our business or reputation.

There continue to be U.S. Congressional inquiries, hearings and proposed and enacted federal legislation and rules, as well as executive orders, designed to, among other things: reduce or limit the prices of drugs and make them more affordable for patients (including, for example, by tying the prices that Medicare reimburses for physician-administered drugs to the prices of drugs in other countries); reform the structure and financing of Medicare Part D pharmaceutical benefits; implement additional data collection and transparency reporting regarding drug pricing, rebates, fees and other remuneration provided by drug manufacturers; enable the government to negotiate prices under Medicare; revise rules associated with the calculation of average manufacturer price and best price under Medicaid; eliminate the AKS discount safe harbor protection for manufacturer rebate arrangements with Medicare Part D plan sponsors; create new AKS safe harbors applicable to certain point-of-sale discounts to patients and fixed fee administrative fee payment arrangements with pharmacy benefit managers; and revise the rebate methodology under the Medicaid Drug Rebate Program. For instance, President Biden issued an executive order in July 2021 supporting legislation to enact some of these drug pricing reforms, and in response, HHS released a Comprehensive Plan for Addressing High Drug Prices in September 2021 with specific legislative and administrative policies that Congress could enact to help improve affordability of and access to prescription drugs. While we cannot know the final form or timing of any such legislative, regulatory and/or administrative measures, some of the pending and enacted legislative proposals or executive rulemaking if implemented without successful legal challenges, would likely have a significant and far-reaching impact on the biopharmaceutical industry and therefore also likely have a material adverse impact on our business, financial condition and results of operations.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biotherapeutic product pricing, including restrictions on pricing or reimbursement at the state government level, limitations on discounts to patients, marketing cost disclosure and transparency measures, and, in some cases, policies to encourage importation from other countries (subject to federal approval) and bulk purchasing, including

the National Medicaid Pooling Initiative. In particular, the obligation to provide notices of price increases to purchasers under laws such as California's SB-17 may influence customer ordering patterns for CABOMETYX and COMETRIQ, which in turn may increase the volatility of our revenues as a reflection of changes in inventory volumes. Furthermore, adoption of these drug pricing transparency regulations, and our associated compliance obligations, may increase our general and administrative costs and/or diminish our revenues. Implementation of these federal and/or state cost-containment measures or other healthcare reforms may limit our ability to generate product revenue or commercialize our products, and in the case of drug pricing transparency regulations, may result in fluctuations in our results of operations.

Lengthy regulatory pricing and reimbursement procedures and cost control initiatives imposed by governments outside the U.S. could delay the marketing of and/or result in downward pressure on the price of our approved products, resulting in a decrease in revenue.

Outside the U.S., including major markets in the EU and Japan, the pricing and reimbursement of prescription pharmaceuticals is generally subject to governmental control. In these countries, pricing and reimbursement negotiations with governmental authorities or payers can take six to 12 months or longer after the initial marketing authorization is granted for a product, or after the marketing authorization for a new indication is granted. This can substantially delay broad availability of the product. To obtain reimbursement and/or pricing approval in some countries, our collaboration partners Ipsen and Takeda may also be required to conduct a study or otherwise provide data that seeks to establish the cost effectiveness of CABOMETYX compared with other available established therapies. The conduct of such a study could also result in delays in the commercialization of CABOMETYX.

Additionally, cost-control initiatives, increasingly based on affordability and accessibility, as well as post-marketing assessments of the added value of CABOMETYX and COMETRIQ as compared to existing treatments, could influence the prices paid for and net revenues we realize from CABOMETYX and COMETRIQ, or the indications for which we are able to obtain reimbursement, which would result in lower license revenues to us. Upcoming legislative and policy changes in the EU are aimed at increasing cooperation between the EU Member States. Such initiatives, particularly the HTA adopted in December 2021, may further impact the price and reimbursement status of CABOMETYX and COMETRIQ in the future.

The entrance of generic competitors and legislative and regulatory action designed to reduce barriers to the development, approval and adoption of generic drugs in the U.S. could limit the revenue we derive from our products, most notably CABOMETYX, which could have a material adverse impact on our business, financial condition and results of operations.

Under the FDCA, the FDA can approve an ANDA for a generic version of a branded drug without the applicant undertaking the human clinical testing necessary to obtain approval to market a new drug. The FDA can also approve an NDA under section 505(b)(2) of the FDCA that relies in part on the agency's findings of safety and/or effectiveness for a previously approved drug, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Both the ANDA and 505(b)(2) NDA processes are discussed in more detail above in "Item 1. Business—Government Regulation—FDA Review and Approval—Abbreviated FDA Approval Pathways and Generic Products" in this Annual Report on Form 10-K. In either case, if an ANDA or 505(b)(2) NDA applicant submits an application referencing one of our marketed products prior to the expiry of one or more our Orange Book-listed patents for the applicable product, we may litigate with the potential generic competitor to protect our patent rights, which would result in substantial costs, divert the attention of management, and could have an adverse impact on our stock price. For example, MSN and Teva have separately submitted ANDAs to the FDA requesting approval to market their respective generic versions of CABOMETYX tablets, and we have subsequently filed patent lawsuits against both companies. For a more detailed discussion of these litigation matters, see "Legal Proceedings" in Part I, Item 3 of this Annual Report on Form 10-K. It is possible that MSN, Teva or other companies, following FDA approval of an ANDA or 505(b)(2) NDA, could introduce generic or otherwise competitor versions of our marketed products before our patents expire if they do not infringe our patents or if it is determined that our patents are invalid or unenforceable, and we expect that generic cabozantinib products would be offered at a significantly lower price compared to our marketed cabozantinib products. Therefore, regardless of the regulatory approach, the introduction of a generic version of cabozantinib would likely decrease our revenues derived from the U.S. sales of CABOMETYX and thereby materially harm our business, financial condition and results of operations. There are also equivalent procedures in the EU permitting authorization of generic versions and biosimilars of medicinal products authorized in the EU once related data and market exclusivity periods have expired.

The U.S. federal government has also taken numerous legislative and regulatory actions to expedite the development and approval of generic drugs and biosimilars. Both Congress and the FDA are considering, and have enacted,

various legislative and regulatory proposals focused on drug competition, including legislation focused on drug patenting and provision of drug to generic applicants for testing. For example, the Ensuring Innovation Act, enacted in April 2021, amended the FDA's statutory authority for granting NCE exclusivity to reflect the agency's existing regulations and longstanding interpretation that award NCE exclusivity based on a drug's active moiety, as opposed to its active ingredient, which is intended to limit the applicability of NCE exclusivity, thereby potentially facilitating generic competition. The FDA has also released a Drug Competition Action Plan, which proposes actions to broaden access to generic drugs and lower consumers' healthcare costs by, among other things, improving the efficiency of the generic drug approval process and supporting the development of complex generic drugs. In addition, the Further Consolidated Appropriations Act, 2020, which incorporated the framework from the CREATES legislation, purports to promote competition in the market for drugs and biotherapeutic products by facilitating the timely entry of lower-cost generic and biosimilar versions of those drugs and biotherapeutic products, including by allowing ANDA, 505(b)(2) NDA or biosimilar developers to obtain access to branded drug and biotherapeutic product samples. While the full impact of these provisions is unclear at this time, its provisions do have the potential to facilitate the development and future approval of generic versions of our products, introducing generic competition that could have a material adverse impact on our business, financial condition and results of operations.

Risks Related to Healthcare Regulatory and Other Legal Compliance Matters

We are subject to healthcare laws, regulations and enforcement; our failure to comply with those laws could have a material adverse impact on our business, financial condition and results of operations.

We are subject to federal and state healthcare laws and regulations, which laws and regulations are enforced by the federal government and the states in which we conduct our business. Should our compliance controls prove ineffective at preventing or mitigating the risk and impact of improper business conduct or inaccurate reporting, we could be subject to enforcement of the following, including, without limitation:

- the federal AKS;
- the FDCA and its implementing regulations;
- federal civil and criminal false claims laws, including the civil False Claims Act, and the Civil Monetary Penalties Law;
- federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA and its implementing regulations, as amended;
- state law equivalents of each of the above federal laws;
- the Open Payments program of the PPACA;
- state and local laws and regulations that require drug manufacturers to file reports relating to marketing activities, payments and other remuneration and items of value provided to healthcare professionals and entities; and
- state and federal pharmaceutical price and price reporting laws and regulations.

In addition, we may be subject to the Foreign Corrupt Practices Act, a U.S. law which regulates certain financial relationships with foreign government officials (which could include, for example, medical professionals employed by national healthcare programs) and its foreign equivalents, as well as federal and state consumer protection and unfair competition laws.

These federal and state healthcare laws and regulations govern drug marketing practices, including off-label promotion. If our operations are found, or even alleged, to be in violation of the laws described above or other governmental regulations that apply to us, we, or our officers or employees, may be subject to significant penalties, including administrative civil and criminal penalties, damages, fines, regulatory penalties, the curtailment or restructuring of our operations, exclusion from participation in Medicare, Medicaid and other federal and state healthcare programs, imprisonment, reputational harm, additional reporting requirements and oversight, any of which would adversely affect our ability to sell our products and operate our business and also adversely affect our financial results. Furthermore, responding to any such allegation and/or defending against any such enforcement actions can be time-consuming and would require significant financial and personnel resources. Therefore, if any state or the federal government initiates an enforcement action against us, our business may be impaired, and even if we are ultimately successful in our defense, litigating these actions could result in substantial costs and divert the attention of management.

Enhanced governmental and private scrutiny over, or investigations or litigation involving, pharmaceutical manufacturer patient assistance programs and donations to patient assistance foundations created by charitable organizations could negatively impact our business practices, harm our reputation, divert the attention of management and increase our expenses.

To help patients afford our products, we have a patient assistance program and also occasionally make donations to independent charitable foundations that help financially needy patients. These types of programs designed to assist patients with affording pharmaceuticals have become the subject of Congressional interest and enhanced government scrutiny. The HHS Office of Inspector General established guidelines permitting pharmaceutical manufacturers to make donations to charitable organizations that provide co-pay assistance to Medicare patients, provided that manufacturers meet certain specified compliance requirements. In the event we make such donations but are found not to have complied with these guidelines and other laws or regulations respecting the operation of these programs, we could be subject to significant damages, fines, penalties or other criminal, civil or administrative sanctions or enforcement actions. We also rely on a third-party hub provider and exercise oversight to monitor patient assistance program activities. Hub providers are generally hired by manufacturers to assist patients with insurance coverage, financial assistance and treatment support after the patients receive a prescription from their healthcare professional. For manufacturers of specialty pharmaceuticals (including our marketed products), the ability to have a single point of contact for their therapies helps ensure efficient medication distribution to patients. Accordingly, our hub activities are also subject to scrutiny and may create risk for us if not conducted appropriately. A variety of entities, including independent charitable foundations and pharmaceutical manufacturers, but not including our company, have received subpoenas from the U.S. Department of Justice and other enforcement authorities seeking information related to their patient assistance programs and support. Should we or our hub providers receive a subpoena or other process, regardless of whether we are ultimately found to have complied with the regulations governing patient assistance programs, this type of government investigation could negatively impact our business practices, harm our reputation, divert the attention of management and increase our expenses.

We are subject to laws and regulations relating to privacy, data protection and the collection and processing of personal data. Failure to maintain compliance with these regulations could create additional liabilities for us.

The legislative and regulatory landscape for privacy and data protection continues to evolve in the U.S. and other jurisdictions around the world. For example, the CCPA went into operation in 2020 and affords California residents expanded privacy rights and protections, including civil penalties for violations and statutory damages under a private right of action for data security breaches. These protections will be expanded by the CPRA, which will be operational in most key respects on January 1, 2023. Similar legislative proposals have passed or are being advanced in other states, and Congress is also considering additional federal privacy legislation. In addition, most healthcare professionals and facilities are subject to privacy and security requirements under HIPAA with respect to our clinical and commercial activities. Although we are not considered to be a covered entity or business associate under HIPAA, we could be subject to penalties if we use or disclose individually identifiable health information in a manner not authorized or permitted by HIPAA. Other countries also have, or are developing, laws governing the collection, use and transmission of personal information. For example, in the EU, the GDPR regulates the processing of personal data of individuals within the EU, even if, under certain circumstances, that processing occurs outside the EU, and also places restrictions on transfers of such data to countries outside of the EU, including the U.S. Should we fail to provide adequate privacy or data security protections or maintain compliance with these laws and regulations, including the CCPA, CPRA and GDPR, we could be subject to sanctions or other penalties, litigation, an increase in our cost of doing business and questions concerning the validity of our data processing activities, including clinical trials.

Risks Related to Growth of Our Product Portfolio and Research and Development

Clinical testing of cabozantinib for new indications, or of new product candidates, is a lengthy, costly, complex and uncertain process that may fail ultimately to demonstrate safety and efficacy data for those products sufficiently differentiated to compete in our highly competitive market environment.

Clinical trials are inherently risky and may reveal that cabozantinib, despite its approval for certain indications, or a new product candidate, is ineffective or has an unacceptable safety profile with respect to an intended use. Such results may significantly decrease the likelihood of regulatory approval of a product candidate or of an approved product for a new indication. Moreover, the results of preliminary studies do not necessarily predict clinical or commercial success, and late-stage or other potentially label-enabling clinical trials may fail to confirm the results observed in early-stage trials or preliminary studies. Although we have established timelines for manufacturing and clinical development of cabozantinib

and our other product candidates based on existing knowledge of our compounds in development and industry metrics, we may not be able to meet those timelines.

We may experience numerous unforeseen events, during or as a result of clinical investigations, that could delay or prevent commercialization of cabozantinib in new indications or of new product candidates, and in some cases, as described in the risk factor titled, "*If the COVID-19 pandemic is further prolonged or becomes more severe, our business operations and corresponding financial results could suffer, which could have a material adverse impact on our financial condition and prospects for growth,*" the COVID-19 pandemic has already increased and may further increase the potential for such events to occur. These events may include:

- lack of acceptable efficacy or a tolerable safety profile;
- negative or inconclusive clinical trial results that require us to conduct further testing or to abandon projects;
- discovery or commercialization by our competitors of other compounds or therapies that show significantly improved safety or efficacy compared to cabozantinib or our other product candidates;
- our inability to identify and maintain a sufficient number of trial sites;
- lower-than-anticipated patient registration or enrollment in our clinical testing;
- additional complexities posed by clinical trials evaluating cabozantinib or our other product candidates in combination with other therapies, including extended timelines to provide for collaboration on clinical development planning, the failure by our collaboration partners to provide us with an adequate and timely supply of product that complies with the applicable quality and regulatory requirements for a combination trial
- reduced staffing or shortages in laboratory supplies and other resources necessary to complete the trials;
- failure of our third-party contract research organizations or investigators to satisfy their contractual obligations, including deviating from any trial protocols; and
- withholding of authorization from regulators or institutional review boards to commence or conduct clinical trials or delays, variations, suspensions or terminations of clinical research for various reasons, including noncompliance with regulatory requirements or a determination by these regulators and institutional review boards that participating patients are being exposed to unacceptable health risks.

If there are further delays in or termination of the clinical testing of cabozantinib or our other product candidates due to any of the events described above or otherwise, our expenses could increase and our ability to generate revenues could be impaired, either of which could adversely impact our financial results. Furthermore, we rely on our collaboration partners to fund a significant portion of our clinical development programs. Should one or all of our collaboration partners decline to support future planned clinical trials, we will be entirely responsible for financing the further development of the cabozantinib franchise or our other product candidates and, as a result, we may be unable to execute our current business plans, which could have a material adverse impact on our business, financial condition and results of operations.

We may not be able to pursue the further development of the cabozantinib franchise or our other product candidates or meet current or future requirements of the FDA or regulatory authorities in other jurisdictions in accordance with our stated timelines or at all. Our planned clinical trials may not begin on time, or at all, may not be completed on schedule, or at all, may not be sufficient for registration of our product candidates or otherwise may not result in an approvable product. The duration and the cost of clinical trials vary significantly as a result of factors relating to the clinical trial, including, among others: the characteristics of the product candidate under investigation; the number of patients who ultimately participate in the clinical trial; the duration of patient follow-up; the number of clinical sites included in the trials; and the length of time required to enroll eligible patients.

Any delay could limit our ability to generate revenues, cause us to incur additional expense and cause the market price of our common stock to decline significantly. Our partners under our collaboration agreements may experience similar risks with respect to the compounds we have out-licensed to them. If any of the events described above were to occur with such programs or compounds, the likelihood of receipt of milestones and royalties under such collaboration agreements could decrease.

The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, uncertain and subject to change, and may not result in regulatory approvals for additional cabozantinib indications or for our other product candidates, which could have a material adverse impact on our business, financial condition and results of operations.

The activities associated with the research, development and commercialization of the cabozantinib franchise and our other product candidates are subject to extensive regulation by the FDA and other regulatory agencies in the U.S., as well as by comparable regulatory authorities in other territories. The processes of obtaining regulatory approvals in the U.S. and other foreign jurisdictions is expensive and often takes many years, if approval is obtained at all, and they can vary substantially based upon the type, complexity and novelty of the product candidates involved. For example, before an NDA or sNDA can be submitted to the FDA, or a marketing authorization application to the EMA or any application or submission to comparable regulatory authorities in other jurisdictions, the product candidate must undergo extensive clinical trials, which can take many years and require substantial expenditures.

Any clinical trial may fail to produce results satisfactory to the FDA or regulatory authorities in other jurisdictions. The FDA has substantial discretion in the approval process and may refuse to approve any NDA or sNDA or decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, we may encounter delays or rejections based upon changes in policy, which could cause delays in the approval or rejection of an application for cabozantinib or for our other product candidates. For example, the FDA launched Project Optimus in 2021 as an initiative to reform the dose optimization and dose selection paradigm in oncology drug development, which was driven by the FDA's concerns that the current paradigm for dose selection may result in doses and schedules of molecularly targeted therapies that are inadequately characterized before initiating pivotal trials. Through collaboration with the biopharmaceutical industry, academia and other stakeholders, the FDA's goal for this initiative is to advance an oncology dose-finding and dose optimization paradigm that emphasizes dose selections that maximize efficacy as well as safety and tolerability. In support of this initiative, FDA may request sponsors of oncology product candidates to conduct dose optimization studies pre- or post-approval. Recently, in part due to questions raised by the process underlying the approval of the Alzheimer's disease drug Aduhelm®, government authorities and other stakeholders have been scrutinizing the accelerated approval pathway, with some stakeholders advocating for reforms. Even prior to the Aduhelm approval, FDA has held Oncologic Drugs Advisory Committee meetings to discuss accelerated approvals for which confirmatory trials have not verified clinical benefit. Such scrutiny, among other factors, has resulted in voluntary withdrawals of certain products and indications approved on an accelerated basis. Moreover, spurred by the Aduhelm controversy, the HHS Office of Inspector General has initiated an assessment of how the FDA implements the accelerated approval pathway. At this time, it is not clear what impact, if any, these developments may have on the statutory accelerated approval pathway or our business, financial condition and results of operations.

Even if the FDA or a comparable authority in another jurisdiction approves cabozantinib for one or more new indications, such approval may be limited, imposing significant restrictions on the indicated uses, conditions for use, labeling, distribution, and/or production of the product and could impose requirements for post-marketing studies, including additional research and clinical trials, all of which may result in significant expense and limit our and our collaboration partners' ability to commercialize cabozantinib in one or more new indications. Failure to complete post-marketing requirements of the FDA in connection with a specific approval in accordance with the timelines and conditions set forth by the FDA could significantly increase costs or delay, limit or ultimately restrict the commercialization of cabozantinib in that indication. Regulatory agencies could also impose various administrative, civil or criminal sanctions for failure to comply with regulatory requirements, including withdrawal of product approval. Further, current or any future laws or executive orders governing FDA or foreign regulatory approval processes that may be enacted or executed could have a material adverse impact on our business, financial condition and results of operations.

We may be unable to expand our discovery and development pipeline, which could limit our growth and revenue potential.

Our business is focused on the discovery, development and commercialization of new medicines for difficult-to-treat cancers. In this regard, we have invested in substantial technical, financial and human resources toward drug discovery activities with the goal of identifying new product candidates to advance into clinical trials. Notwithstanding this investment, many programs that initially show promise will ultimately fail to yield product candidates for multiple reasons. For example, product candidates may, on further study, be shown to have inadequate efficacy, harmful side effects, suboptimal pharmaceutical profiles or other characteristics suggesting that they are unlikely to be commercially viable products.

Apart from our drug discovery efforts, our strategy to expand our development pipeline is also dependent on our ability to successfully identify and acquire or in-license relevant product candidates and technologies. However, the in-licensing and acquisition of product candidates and technologies is a highly competitive area, and many other companies are pursuing the same or similar product candidates and technologies to those that we may consider attractive. In particular, larger companies with more capital resources and more extensive clinical development and commercialization capabilities may have a competitive advantage over us. Furthermore, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We may also be unable to in-license or acquire additional product candidates and technologies on acceptable terms that would allow us to realize an appropriate return on our investment. Even if we succeed in our efforts to obtain rights to suitable product candidates and technologies, the competitive business environment may result in higher acquisition or licensing costs, and our investment in these potential products and technologies will remain subject to the inherent risks associated with the development and commercialization of new medicines. In certain circumstances, we may also be reliant on the licensor for the continued development of the in-licensed technology and their efforts to safeguard their underlying intellectual property.

With respect to acquisitions, we may not be able to integrate the target company successfully into our existing business, maintain the key business relationships of the target company, or retain key personnel of the acquired business. Furthermore, we could assume unknown or contingent liabilities or otherwise incur unanticipated expenses. Any acquisitions or investments made by us also could result in our spending significant amounts, issuing dilutive securities, assuming or incurring significant debt obligations and contingent liabilities, incurring large one-time expenses and acquiring intangible assets that could result in significant future amortization expense and significant write-offs, any of which could harm our financial condition and results of operations. If our drug discovery efforts, including research collaborations, in-licensing arrangements and other business development activities, do not result in suitable product candidates, our business and prospects for growth could suffer.

Risks Related to Financial Matters and Capital Requirements

Our profitability could be negatively impacted if expenses associated with our extensive clinical development, business development and commercialization activities, both for the cabozantinib franchise and our earlier-stage product candidates, grow more quickly than the revenues we generate.

Although we reported net income of $231.1 million and $111.8 million for the years ended December 31, 2021 and 2020, respectively, we may not be able to maintain or increase profitability on a quarterly or annual basis, and we are unable to predict the extent of future profits or losses. The amount of our net profits or losses will depend, in part, on: the level of sales of CABOMETYX and COMETRIQ in the U.S.; our achievement of development, regulatory and commercial milestones, if any, under our collaboration agreements; the amount of royalties from sales of CABOMETYX and COMETRIQ outside of the U.S. under our collaboration agreements; other collaboration revenues; and the level of our expenses, including those associated with our extensive drug discovery, clinical development and business development activities, both for the cabozantinib franchise and our earlier-stage product candidates, as well as our general business expansion plans. Our expected future expenses in particular may also be increased by inflationary pressures, whether resulting from the effects of the COVID-19 pandemic or otherwise, which could increase the costs of outside services, labor, raw materials and finished drug product. We expect to continue to spend substantial amounts to fund the continued development of the cabozantinib franchise for additional indications and the commercialization of our approved products. In addition, we intend to continue to expand our oncology product pipeline through our drug discovery efforts, including research collaborations, in-licensing arrangements and other strategic transactions that align with our oncology drug development, regulatory and commercial expertise, which efforts could involve substantial costs. To offset these costs in the future, we will need to generate substantial revenues. If these costs exceed our current expectations, or we fail to achieve anticipated revenue targets, the market value of our common stock may decline.

If additional capital is not available to us when we need it, we may be unable to expand our product offerings and maintain business growth.

Our commitment of cash resources to CABOMETYX and the reinvestment in our product pipeline through the continued development of the cabozantinib franchise and our earlier-stage product candidates, and increasing drug discovery activities, as well as through the execution of business development transactions, could require us to obtain additional capital. We may seek such additional capital through some or all of the following methods: corporate collaborations; licensing arrangements; and public or private debt or equity financings. Our ability to obtain additional capital may depend on prevailing economic conditions and financial, business and other factors beyond our control. We do not know whether additional capital will be available when needed, or that, if available, we will obtain additional capital on

terms favorable to us or our stockholders. If we are unable to raise additional funds when we need them, we may be unable to expand our product offerings and maintain business growth, which could have a material adverse impact on our business, financial condition and results of operations.

Risks Related to Our Relationships with Third Parties

We rely on Ipsen and Takeda for the commercial success of CABOMETYX in its approved indications outside of the U.S., and we are unable to control the amount or timing of resources expended by these collaboration partners in the commercialization of CABOMETYX in its approved indications outside of the U.S.

We rely upon the regulatory, commercial, medical affairs, market access and other expertise and resources of our collaboration partners, Ipsen and Takeda, for commercialization of CABOMETYX in their respective territories outside of the U.S. We cannot control the amount and timing of resources that our collaboration partners dedicate to the commercialization of CABOMETYX, or to its marketing and distribution, and our ability to generate revenues from the commercialization of CABOMETYX by our collaboration partners depends on their ability to obtain and maintain regulatory approvals for, achieve market acceptance of, and to otherwise effectively market, CABOMETYX in its approved indications in their respective territories. Further, the operations of our collaboration partners, and ultimately their sales of CABOMETYX in their respective territories outside of the U.S., could be adversely affected by the degree and effectiveness of their respective corporate responses to the COVID-19 pandemic, as well as by the imposition of governmental price or other controls, political and economic instability, trade restrictions or barriers and changes in tariffs, escalating global trade and political tensions, or other factors. If our collaboration partners are unable or unwilling to invest the resources necessary to commercialize CABOMETYX successfully in the EU, Japan and other international territories where it has been approved, this could reduce the amount of revenue we are due to receive under these collaboration agreements, thus resulting in harm to our business and operations.

Our clinical, regulatory and commercial collaborations with major companies make us reliant on those companies for their continued performance and investments, which subjects us to a number of risks.

We have established clinical and commercial collaborations with leading biopharmaceutical companies for the development and commercialization of our products, and our dependence on these collaboration partners subjects us to a number of risks, including, but not limited to:

- our collaboration partners' decision to terminate our collaboration, or their failure to comply with the terms of our collaboration agreements and related ancillary agreements, either intentionally or as a result of negligence or other insufficient performance;
- our inability to control the amount and timing of resources that our collaboration partners devote to the development or commercialization of our products;
- the possibility that our collaboration partners may stop or delay clinical trials, fail to supply us on a timely basis with product required for a combination trial, or deliver product that fails to meet appropriate quality and regulatory standards;
- disputes that may arise between us and our collaboration partners that result in the delay or termination of the development or commercialization of our drug candidates, or that diminish or delay receipt of the economic benefits we are entitled to receive under the collaboration, or that result in costly litigation or arbitration;
- the possibility that our collaboration partners may experience financial difficulties that prevent them from fulfilling their obligations under our agreements;
- our collaboration partners' inability to obtain regulatory approvals in a timely manner, or at all;
- our collaboration partners' failure to comply with legal and regulatory requirements relevant to the authorization, marketing, distribution and supply of our marketed products in the territories outside the U.S. where they are approved; and
- our collaboration partners' failure to properly maintain or defend our intellectual property rights or their use of our intellectual property rights or proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential litigation.

If any of these risks materialize, we may not receive collaboration revenues or otherwise realize anticipated benefits from such collaborations, and our product development efforts and prospects for growth could be delayed or disrupted, all of which could have a material adverse impact on our business, financial condition and results of operations.

Our growth potential is dependent in part upon companies with which we have entered into research collaborations, in-licensing arrangements and similar business development relationships.

To expand our early-stage product pipeline, we have augmented our drug discovery activities with multiple research collaborations and in-licensing arrangements with other companies. Our dependence on our relationships with these research and in-licensing partners subjects us to numerous risks, including, but not limited to:

- our research and in-licensing partners' decision to terminate our relationship, or their failure to comply with the terms of our agreements, either intentionally or as a result of negligent performance;
- disputes that may arise between us and our research and in-licensing partners that result in the delay or termination of research activities with respect to any in-licensed assets or supporting technology platforms;
- the possibility that our research and in-licensing partners may experience financial difficulties that prevent them from fulfilling their obligations under our agreements;
- our research and in-licensing partners' failure to properly maintain or defend their intellectual property rights or their use of third-party intellectual property rights or proprietary information in such a way as to invite litigation that could jeopardize or invalidate our license to develop these assets or utilize technology platforms;
- laws, regulations or practices imposed by countries outside the U.S. that could impact or inhibit scientific research or the development of healthcare products by foreign competitors or otherwise disadvantage healthcare products made by foreign competitors, as well as general political or economic instability in those countries, any of which could complicate, interfere with or impede our relationships with our ex-U.S. research, development and in-licensing partners; and
- our research and in-licensing partners' failure to comply with applicable healthcare laws, as well as established guidelines, laws and regulations related to GMP and GLP.

If any of these risks materialize, we may not be able to expand our product pipeline or otherwise realize a return on the resources we will have invested to develop these early-stage assets, which could have a material adverse impact on our financial condition and prospects for growth.

If third parties upon which we rely to perform clinical trials for cabozantinib in new indications or for new product candidates do not perform as contractually required or expected, we may not be able to obtain regulatory approval for or commercialize cabozantinib or other product candidates beyond currently approved indications.

We do not have the ability to conduct clinical trials for cabozantinib or for new potential product candidates independently, so we rely on independent third parties for the performance of these trials, such as the U.S. federal government, third-party contract research organizations, medical institutions, clinical investigators and contract laboratories to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or regulatory obligations or meet expected deadlines, or if the third parties must be replaced or if the quality or accuracy of the data they generate or provide is compromised due to their failure to adhere to our clinical trial or data security protocols or regulatory requirements or for other reasons, our preclinical development activities or clinical trials may be extended, delayed, suspended or terminated, and we may not be able to obtain regulatory approval for or commercialize cabozantinib beyond currently approved indications or obtain regulatory approval for our other product candidates. In addition, due to the complexity of our research initiatives, we may be unable to engage with third-party contract research organizations that have the necessary experience and sophistication to help advance our drug discovery efforts, which would impede our ability to identify, develop and commercialize our potential product candidates.

We lack our own manufacturing and distribution capabilities necessary for us to produce materials required for certain preclinical activities and to produce and distribute our products for clinical development or for commercial sale, and our reliance on third parties for these services subjects us to various risks.

We do not own or operate manufacturing or distribution facilities for CMC development activities, preclinical, clinical or commercial production and distribution for our current products and new product candidates. Instead, we rely on various third-party contract manufacturing organizations to conduct these operations on our behalf. As our operations continue to grow in these areas, we continue to expand our supply chain through secondary third-party contract manufacturers, distributors and suppliers. To establish and manage our supply chain requires a significant financial commitment, the creation of numerous third-party contractual relationships and continued oversight of these third parties to fulfill compliance with applicable regulatory requirements. Although we maintain significant resources to directly and effectively oversee the activities and relationships with the companies in our supply chain, we do not have direct control over their operations.

Our third-party contract manufacturers may not be able to produce material on a timely basis or manufacture material with the required quality standards, or in the quantity required to meet our preclinical, clinical development and commercial needs and applicable regulatory requirements, including as a result of the COVID-19 pandemic. Although we have not yet experienced significant production delays or seen significant impairment to our supply chain as a result of the COVID-19 pandemic, our third-party contract manufacturers, distributors and suppliers could experience operational delays due to facility closures and other hardships as a result of the COVID-19 pandemic or otherwise, which could impact our supply chain by potentially causing delays to or disruptions in the supply of our commercial or clinical products or product candidates. If our third-party contract manufacturers, distributors and suppliers do not continue to supply us with our products or product candidates in a timely fashion and in compliance with applicable quality and regulatory requirements, or if they otherwise fail or refuse to comply with their obligations to us under our manufacturing, distribution and supply arrangements, we may not have adequate remedies for any breach. Furthermore, their failure to supply us could impair or preclude meeting commercial or clinical product supply requirements for us or our partners, which could delay product development and future commercialization efforts and have a material adverse impact on our business, financial condition and results of operations. In addition, through our third-party contract manufacturers and data service providers, we continue to provide serialized commercial products as required to comply with the DSCSA. If our third-party contract manufacturers or data service providers fail to support our efforts to continue to comply with DSCSA and any future federal or state electronic pedigree requirements, we may face legal penalties or be restricted from selling our products.

If third-party scientific advisors and contractors we rely on to assist with our drug discovery efforts do not perform as expected, the expansion of our product pipeline may be delayed.

We work with scientific advisors at academic and other institutions, as well as third-party contractors in various locations throughout the world, that assist us in our research and development efforts, including in drug discovery and preclinical development strategy. These third parties are not our employees and may have other commitments or contractual obligations that limit their availability to us. Although these third-party scientific advisors and contractors generally agree not to do competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. There has also been increased scrutiny surrounding the disclosures of payments made to medical researchers from companies in the pharmaceutical industry, and it is possible that the academic and other institutions that employ these medical researchers may prevent us from engaging them as scientific advisors and contractors or otherwise limit our access to these experts, or that the scientific advisors themselves may now be more reluctant to work with industry partners. Even if these scientific advisors and contractors with whom we have engaged intend to meet their contractual obligations, their ability to perform services may be impacted by increased demand for such services from other companies or by other external factors, such as reduced capacity to perform services, as we experienced in the early stages of the COVID-19 pandemic. If we experience additional delays in the receipt of services, lose work performed by these scientific advisors and contractors or are unable to engage them in the first place, our discovery and development efforts with respect to the matters on which they were working or would work in the future may be significantly delayed or otherwise adversely affected.

Risks Related to Our Information Technology and Intellectual Property

Data breaches, cyber-attacks and other failures in our information technology operations and infrastructure could compromise our intellectual property or other sensitive information, damage our operations and cause significant harm to our business and reputation.

In the ordinary course of our business, we and our third-party service providers, such as contract research organizations, collect, maintain and transmit sensitive data on our networks and systems, including our intellectual property and proprietary or confidential business information (such as research data and personal information) and confidential information with respect to our customers, clinical trial patients and our collaboration partners. We have also outsourced significant elements of our information technology infrastructure to third parties and, as a result, such third parties may or could have access to our confidential information. The secure maintenance of this information is critical to our business and reputation, and while we have enhanced and are continuing to enhance our cybersecurity efforts commensurate with the growth and complexity of our business, our systems and those of third-party service providers may be vulnerable to a cyber-attack. In addition, we are heavily dependent on the functioning of our information technology infrastructure to carry out our business processes, such as external and internal communications or access to clinical data and other key business information. Accordingly, both inadvertent disruptions to this infrastructure and cyber-attacks could cause us to incur significant remediation or litigation costs, result in product development delays, disrupt critical business operations, expend key information technology resources and divert the attention of management.

Although the aggregate impact of cyber-attacks on our operations and financial condition has not been material to date, we and our third-party service providers have frequently been the target of threats of this nature and expect them to continue. Any future data breach and/or unauthorized access or disclosure of our information or intellectual property could compromise our intellectual property and expose our sensitive business information or sensitive business information of our collaboration partners, which may lead to significant liability for us. A data security breach could also lead to public exposure of personal information of our clinical trial patients, employees or others and result in harm to our reputation and business, compel us to comply with federal and/or state breach notification laws and foreign law equivalents including the GDPR, subject us to investigations and mandatory corrective action, or otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could disrupt our business, result in increased costs or loss of revenue, and/or result in significant financial exposure. Furthermore, the costs of maintaining or upgrading our cybersecurity systems (including the recruitment and retention of experienced information technology professionals, who are in high demand) at the level necessary to keep up with our expanding operations and prevent against potential attacks are increasing, and despite our best efforts, our network security and data recovery measures and those of our third-party service providers may still not be adequate to protect against such security breaches and disruptions, which could cause material harm to our business, financial condition and results of operations.

If we are unable to adequately protect our intellectual property, third parties may be able to use our technology, which could adversely affect our ability to compete in the market.

Our success will depend in part upon our ability to obtain patents and maintain adequate protection of the intellectual property related to our technologies and products. The patent positions of biopharmaceutical companies, including our patent position, are generally uncertain and involve complex legal and factual questions. We will be able to protect our intellectual property rights from unauthorized use by third parties only to the extent that our technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. We will continue to apply for patents covering our technologies and products as, where and when we deem lawful and appropriate. However, these applications may be challenged or may fail to result in issued patents. Our issued patents have been and may in the future be challenged by third parties as invalid or unenforceable under U.S. or foreign laws, or they may be infringed by third parties, and we are from time to time involved in the defense and enforcement of our patents or other intellectual property rights in a court of law, U.S. Patent and Trademark Office *inter partes* review or reexamination proceeding, foreign opposition proceeding or related legal and administrative proceeding in the U.S. and elsewhere. The costs of defending our patents or enforcing our proprietary rights in post-issuance administrative proceedings and litigation can be substantial and the outcome can be uncertain. An adverse outcome may allow third parties to use our intellectual property without a license and/or allow third parties to introduce generic and other competing products, any of which would negatively impact our business. Third parties may also attempt to invalidate or design around our patents, or assert that they are invalid or otherwise unenforceable, and seek to introduce generic versions of cabozantinib. For example, we received Paragraph IV certification notice letters from MSN and Teva concerning the respective ANDAs that each had filed with the FDA seeking approval to market their respective generic versions of CABOMETYX tablets. Should MSN, Teva or any other third parties receive FDA approval of an ANDA or a 505(b)(2) NDA with respect to cabozantinib, it is possible that such company or companies could introduce generic versions of our marketed products before our patents expire if they do not infringe our patents or if it is determined that our patents are invalid or unenforceable, and the resulting generic competition could have a material adverse impact on our business, financial condition and results of operations.

In addition, because patent applications can take many years to issue, third parties may have pending applications, unknown to us, which may later result in issued patents that cover the production, manufacture, commercialization or use of our product candidates. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing competing products. They may also be negatively impacted by the decisions of foreign courts, which could limit the protection contemplated by the original regulatory approval and our ability to thwart the development of competing products that might otherwise have been determined to infringe our intellectual property rights. Furthermore, others may independently develop similar or alternative technologies or design around our patents. In addition, our patents may be challenged or invalidated or may fail to provide us with any competitive advantages, if, for example, others were the first to invent or to file patent applications for closely related inventions.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the U.S., and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. Many countries, including certain countries in the EU, have compulsory licensing laws based on related EU rules, under which a patent owner may be compelled to grant licenses to third parties (for example, the patent owner has failed to “work” the invention in that country or the third party has patented improvements). In addition, many countries

limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the patent. Initiatives seeking compulsory licensing of life-saving drugs are also becoming increasingly prevalent in developing countries either through direct legislation or international initiatives. Governments in those developing countries could require that we grant compulsory licenses to allow competitors to manufacture and sell their own versions of our products or product candidates, thereby reducing our product sales. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the aggressive enforcement of patent and other intellectual property protection, which makes it difficult to stop infringement. We also rely on trade secret protection for some of our confidential and proprietary information, and we are taking security measures to protect our proprietary information and trade secrets, particularly in light of recent instances of data loss and misappropriation of intellectual property in the biopharmaceutical industry. However, these measures may not provide adequate protection, and while we seek to protect our proprietary information by entering into confidentiality agreements with employees, partners and consultants, as well as maintain cybersecurity protocols within our information technology infrastructure, we cannot provide assurance that our proprietary information will not be disclosed, or that we can meaningfully protect our trade secrets. In addition, our competitors may independently develop substantially equivalent proprietary information or may otherwise gain access to our trade secrets.

Litigation or third-party claims of intellectual property infringement could require us to spend substantial time and money and adversely affect our ability to develop and commercialize products.

Our commercial success depends in part upon our ability to avoid infringing patents and proprietary rights of third parties and not to breach any licenses that we have entered into with regard to our technologies and the technologies of third parties. Other parties have filed, and in the future are likely to file, patent applications covering products and technologies that we have developed or intend to develop. If patents covering technologies required by our operations are issued to others, we may have to obtain licenses from third parties, which may not be available on commercially reasonable terms, or at all, and may require us to pay substantial royalties, grant a cross-license to some of our patents to another patent holder or redesign the formulation of a product candidate so that we do not infringe third-party patents, which may be impossible to accomplish or could require substantial time and expense. In addition, we may be subject to claims that our employees or independent contractors have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers, or that they used or sought to use patent inventions belonging to their former employers. Furthermore, third parties may obtain patents that relate to our technologies and claim that use of such technologies infringes on their patents or otherwise employs their proprietary technology without authorization. Regardless of their merit, such claims could require us to incur substantial costs and divert the attention of management and key technical personnel in defending ourselves against any such claims or enforcing our own patents. In the event of any third party's successful claim of patent infringement or misappropriation of trade secrets, we may lose valuable intellectual property rights or personnel, which could impede or prevent the achievement of our product development goals, or we may be required to pay damages and obtain one or more licenses from these third parties, subjecting us to substantial royalty payment obligations. We may not be able to obtain these licenses on commercially reasonable terms, or at all. Defense of any lawsuit or failure to obtain any of these licenses could adversely affect our ability to develop and commercialize products.

Risks Related to Our Operations, Managing Our Growth and Employee Matters

If the COVID-19 pandemic is further prolonged or becomes more severe, our business operations and corresponding financial results could suffer, which could have a material adverse impact on our financial condition and prospects for growth.

To date, the COVID-19 pandemic has had a modest impact on our business operations, in particular with respect to our clinical trial, drug discovery and commercial activities. For example, to varying degrees and at different rates across our clinical trials, we experienced declines in screening and enrollment activity during the early days of the COVID-19 pandemic, as well as delays in new site activations and restrictions on the access to treatment sites that is necessary to monitor clinical study progress and administration. As the COVID-19 pandemic continues to have a significant presence in various parts of the world, particularly with the emergence of the Delta, Omicron and other SARS-CoV-2 variants, the impact on our clinical development operations could continue or grow more severe. We anticipate that a further prolonged, or more severe, global public health crisis could limit our ability to identify and work with clinical investigators at clinical trial sites globally to enroll, initiate and maintain treatment per protocol of patients for our ongoing clinical trials. Disruptions to medical and administrative operations at clinical trial sites, including staffing and materials shortages and the implementation of crisis management initiatives, have and may continue to reduce personnel and other resources necessary to conduct our clinical trials, which could further delay some of our clinical trial plans or may require certain trials to be temporarily suspended.

Moreover, quarantines and travel restrictions have impeded and may continue to impede patient movement or interrupt healthcare services, which we anticipate over time, could also delay, interfere with and potentially negatively impact clinical trial execution, and ultimately results, particularly with respect to clinical trials evaluating our or our collaboration partners' product candidates that must be administered via intravenous infusion. In addition, increased costs connected with our efforts to mitigate the adverse impacts resulting from the COVID-19 pandemic on our clinical trials could cause the expenses we incur in conducting those clinical trials to increase considerably. Depending upon the duration and severity of the COVID-19 pandemic, we could also experience delays in planning and conducting new clinical trials of the investigative product candidates entering and advancing through our development pipeline, which could increase the operating expenses associated with these trials and adversely affect their timelines for completion and ultimately our ability to obtain regulatory approvals.

Both drug discovery work in our laboratories and outsourced drug discovery activities have fully resumed following temporary suspensions during the early days of the COVID-19 pandemic; however, we may be unable to maximize the potential of these programs due to the imposition of increased safety protocols, and should the effects of the COVID-19 pandemic become more severe, we may have to again scale back or suspend activities in the future. We are also reliant on laboratory materials manufactured and distributed from areas impacted by both the COVID-19 pandemic and other natural disasters, for which supply has become limited. If we are unable to obtain the requisite materials to conduct our planned drug discovery activities, we may be required to redirect the focus of, or even suspend, such activities. Should the COVID-19 pandemic be further prolonged or grow in severity, we may ultimately be unable to achieve our drug discovery and preclinical development objectives within the previously disclosed timelines, which could have a material adverse impact on our prospects for growth.

While we believe that our commercial business has, to date, only experienced a modest impact related to the COVID-19 pandemic, it remains possible that over a longer period, changes to our standard sales and marketing practices, including any shifts from in-person back to primarily telephonic and virtual interactions with healthcare professionals, could negatively impact the flow of important information regarding our medicines, which along with obstacles to patient access to healthcare professionals, could diminish sales of our marketed products.

Although as of the date of this Annual Report on Form 10-K, we continue to maintain sufficient safety stock inventories for our drug substance and drug products and have not experienced significant production delays or seen significant impairment to our supply chain as a result of the COVID-19 pandemic, our third-party contract manufacturers and suppliers could experience operational delays due to facility closures and other hardships as a result of the COVID-19 pandemic, which could impact our supply chain by potentially causing delays to or disruptions in the supply of our commercial or clinical products or product candidates. These delays or disruptions could be further exacerbated if the COVID-19 pandemic begins to impact essential distribution systems, which could substantially increase delivery times and costs, or otherwise adversely affect our ability to provide our products to customers and clinical trial sites and generate product revenues.

In addition, as a result of broad economic shifts during and as a consequence of efforts to address unemployment and other negative economic effects of the COVID-19 pandemic, we may experience reductions in the net price of our products. For example, there may be a substantial shift from private health insurance coverage to government insurance coverage, or additional downward pressure on the prices government purchasers will pay for our products due to significant increases in government debt incurred in connection with relief efforts, as well as significant increases in demand for our patient assistance and/or free drug program or other impacts that may not be foreseeable, all or any of which would adversely affect our product revenues.

While we expect the COVID-19 pandemic to continue to have varying degrees of adverse impact on our business operations and, potentially in the future, our financial results, the extent of such adverse impact will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time. Such developments include, but are not limited to: continued spread of the Delta and Omicron variants in the U.S. and other countries and the potential emergence of other SARS-CoV-2 variants that may prove especially contagious or virulent, the ultimate duration of the pandemic and resulting disruptions to normal business and personal activities in the U.S. and in other countries, and the effectiveness of actions taken globally to contain and treat the disease, including the rate at which vaccinations are made available and are administered, the percentage of the population that becomes fully vaccinated and the effectiveness of the vaccines against Delta, Omicron or other SARS-CoV-2 variants. These continuing or future effects could materially and adversely affect our business, financial condition, results of operations and growth prospects, and exacerbate the other risks and uncertainties described elsewhere in this ''Risk Factors'' section.

If we are unable to manage our growth, there could be a material adverse impact on our business, financial condition and results of operations, and our prospects may be adversely affected.

We have experienced and expect to continue to experience growth in the number of our employees and in the scope of our operations, in particular as we continue to expand the cabozantinib franchise into new indications and grow our pipeline of product candidates. This growth places significant demands on our management and resources, and our current and planned personnel and operating practices may not be adequate to support our growth. To effectively manage our growth, we must continue to improve existing, and implement new, facilities, operational and financial systems, and procedures and controls, as well as expand, train and manage our growing employee base, and there can be no assurance that we will effectively manage our growth without experiencing operating inefficiencies or control deficiencies. We continue to increase our management personnel to oversee our expanding operations, and recruiting and retaining qualified individuals is difficult. If we are unable to manage our growth effectively, including as a result of the COVID-19 pandemic or otherwise, or we are unsuccessful in recruiting qualified management personnel, there could be a material adverse impact on our business, financial condition and results of operations.

The loss of key personnel or the inability to retain and, where necessary, attract additional personnel could impair our ability to operate and expand our operations.

We are highly dependent upon the principal members of our management, as well as clinical, commercial and scientific staff, the loss of whose services might adversely impact the achievement of our objectives. Also, we may not have sufficient personnel to execute our business plans. Retaining and, where necessary, recruiting qualified clinical, commercial, scientific and pharmaceutical operations personnel will be critical to support activities related to advancing the development program for the cabozantinib franchise and our other product candidates, successfully executing upon our commercialization plan for the cabozantinib franchise and our proprietary research and development efforts. Competition is intense for experienced clinical, commercial, scientific and pharmaceutical operations personnel, and we may be unable to retain or recruit such personnel with the expertise or experience necessary to allow us to successfully develop and commercialize our products. Further, all of our employees are employed “at will” and, therefore, may leave our employment at any time.

Risks Related to Environmental and Product Liability

We use hazardous chemicals and biological materials in our business. Any claims relating to improper handling, storage or disposal of these materials could be time consuming and costly.

Our research and development processes involve the controlled use of hazardous materials, including chemicals and biological materials, and our operations can produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge, or any resultant injury from these materials, and we may face liability under applicable laws for any injury or contamination that results from our use or the use by our collaboration partners or other third parties of these materials. Such liability may exceed our insurance coverage and our total assets, and in addition, we may be required to indemnify our collaboration partners against all damages and other liabilities arising out of our development activities or products produced in connection with our collaborations with them. Moreover, our continued compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development and production efforts.

We face potential product liability exposure far in excess of our limited insurance coverage.

We may be held liable if any product we or our collaboration partners develop or commercialize causes injury or is found otherwise unsuitable during product testing, manufacturing, marketing or sale. Regardless of merit or eventual outcome, product liability claims could result in decreased demand for our products and product candidates, injury to our reputation, withdrawal of patients from our clinical trials, product recall, substantial monetary awards to third parties and the inability to commercialize any products that we may develop in the future. We maintain limited product liability insurance coverage for our clinical trials and commercial activities for cabozantinib. However, our insurance may not be sufficient to reimburse us for expenses or losses we may suffer. Moreover, if insurance coverage becomes more expensive, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability.

Risks Related to Our Common Stock

Our stock price has been and may in the future be highly volatile.

The trading price of our common stock has been highly volatile, and it may remain highly volatile or fluctuate substantially due to factors such as the following, many of which we cannot control:

- the announcement of FDA or other regulatory approval or non-approval, or delays in the FDA or other regulatory review process with respect to cabozantinib, our collaboration partners' product candidates being developed in combination with cabozantinib, or our competitors' product candidates;
- the commercial performance of both CABOMETYX and COMETRIQ and the revenues we generate from those approved products, including royalties paid under our collaboration and license agreements;
- adverse or inconclusive results or announcements related to our or our collaboration partners' clinical trials or delays in those clinical trials;
- the timing of achievement of our clinical, regulatory, partnering, commercial and other milestones for the cabozantinib franchise or any of our other programs or product candidates;
- our ability to make future investments in the expansion of our pipeline through drug discovery, including future research collaborations, in-licensing arrangements and other strategic transactions;
- our ability to obtain the materials and services, including an adequate product supply for any approved drug product, from our third-party vendors or do so at acceptable prices;
- the timing and amount of expenses incurred for clinical development and manufacturing of cabozantinib;
- actions taken by regulatory agencies, both in the U.S. and abroad, with respect to cabozantinib or our clinical trials for cabozantinib;
- unanticipated regulatory actions taken by the FDA as a result of changing FDA standards and practices concerning the review of product candidates, including approvals at earlier stages of clinical development or with lesser developed data sets and expedited reviews;
- the announcement of new products or clinical trial data by our competitors;
- the announcement of regulatory applications, such as MSN's and Teva's respective ANDAs, seeking approval of generic versions of our marketed products;
- quarterly variations in our or our competitors' results of operations;
- changes in our relationships with our collaboration partners, including the termination or modification of our agreements, or other events or conflicts that may affect our collaboration partners' timing and willingness to develop, or if approved, commercialize our products and product candidates out-licensed to them;
- the announcement of an in-licensed product candidate or strategic acquisition;
- litigation, including intellectual property infringement and product liability lawsuits, involving us;
- changes in earnings estimates or recommendations by securities analysts, or financial guidance from our management team, and any failure to achieve the operating results projected by securities analysts or by our management team;
- the entry into new financing arrangements;
- developments in the biopharmaceutical industry;
- sales of large blocks of our common stock or sales of our common stock by our executive officers, directors and significant stockholders;
- additions and departures of key personnel or board members;
- the disposition of any of our technologies or compounds; and
- general market, economic and political conditions and other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

These and other factors could have material adverse impact on the market price of our common stock. In addition, the stock markets in general, and the markets for biotechnology and pharmaceutical stocks in particular, have historically experienced significant volatility that has often been unrelated or disproportionate to the operating performance of particular companies. Likewise, as a result of significant changes in U.S. or global political and economic conditions, policies governing foreign trade and healthcare spending and delivery, or future potential U.S. federal government shutdowns, the financial markets could continue to experience significant volatility that could also continue to negatively impact the

markets for biotechnology and pharmaceutical stocks. These broad market fluctuations have adversely affected and may in the future adversely affect the trading price of our common stock. Excessive volatility may continue for an extended period of time following the date of this report.

In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been initiated. A securities class action suit against us could result in substantial costs and divert the attention of management, which could have a material adverse impact on our business, financial condition and results of operations.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent or deter attempts by our stockholders to replace or remove our current management, which could cause the market price of our common stock to decline.

Provisions in our corporate charter and bylaws may discourage, delay or prevent an acquisition of us, a change in control, or attempts by our stockholders to replace or remove members of our current Board of Directors. Because our Board of Directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

- a prohibition on actions by our stockholders by written consent;
- the ability of our Board of Directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our Board of Directors; and
- advance notice requirements for director nominations and stockholder proposals.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters is located in Alameda, California, where we lease a total of 254,690 square feet of space. We took possession of an additional 25,749 square feet of space in 2021. The lease expires in October 2031. We have two five-year options to extend the lease. In October 2019, we entered into a build-to-suit lease agreement (the Build-to-Suit Lease) for approximately 220,000 square feet of additional office facilities adjacent to our current corporate headquarters. The term of the Build-to-Suit Lease is for a period of 242 months, which will begin on the substantial completion of the building and tenant improvements by the lessor. We currently anticipate that the term will begin in the first quarter of 2022. We believe these leased facilities are sufficient to accommodate our current and near-term needs.

Item 3. Legal Proceedings

In September 2019, we received a notice letter regarding an ANDA submitted to the FDA by MSN, requesting approval to market a generic version of CABOMETYX tablets. MSN's initial notice letter included a Paragraph IV certification with respect to our U.S. Patent Nos. 8,877,776 (salt and polymorphic forms), 9,724,342 (formulations), 10,034,873 (methods of treatment) and 10,039,757 (methods of treatment), which are listed in the Orange Book for CABOMETYX. MSN's initial notice letter did not provide a Paragraph IV certification against the '473 Patent (composition of matter) or U.S. Patent No. 8,497,284 (methods of treatment), each of which is listed in the Orange Book. On October 29, 2019, we filed a complaint in the Delaware District Court for patent infringement against MSN asserting infringement of U.S. Patent No. 8,877,776 arising from MSN's ANDA filing with the FDA. On November 20, 2019, MSN filed its response to the complaint, alleging that the asserted claims of U.S. Patent No. 8,877,776 are invalid and not infringed. On May 5, 2020, we received notice from MSN that it had amended its ANDA to include additional Paragraph IV certifications. In particular, the ANDA requested approval to market a generic version of CABOMETYX tablets prior to expiration of two previously unasserted CABOMETYX patents: the '473 Patent and U.S. Patent No. 8,497,284. On May 11, 2020, we filed a complaint in the Delaware

District Court for patent infringement against MSN asserting infringement of the ‘473 Patent and U.S. Patent No. 8,497,284 arising from MSN’s amended ANDA filing with the FDA. Neither of our complaints have alleged infringement of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757. On May 22, 2020, MSN filed its response to the complaint, alleging that the asserted claims of the ‘473 Patent and U.S. Patent No. 8,497,284 are invalid and not infringed. On March 23, 2021, MSN filed its First Amended Answer and Counterclaims (amending its prior filing from May 22, 2020), seeking, among other things, a declaratory judgment that U.S. Patent No. 9,809,549 is invalid and would not be infringed by MSN if its generic version of CABOMETYX tablets were approved by the FDA. U.S. Patent No. 9,809,549 is not listed in the Orange Book. On April 7, 2021, we filed our response to MSN’s First Amended Answer and Counterclaims, denying, among other things, that U.S. Patent No. 9,809,549 is invalid or would not be infringed.

On October 1, 2021, pursuant to a stipulation between us and MSN, the Delaware District Court entered an order that (i) MSN’s submission of its ANDA constitutes infringement of certain claims relating to the ‘473 Patent and U.S. Patent No. 8,497,284, if those claims are not found to be invalid, and (ii) upon approval, MSN’s commercial manufacture, use, sale or offer for sale within the U.S., and importation into the U.S., of MSN’s ANDA product prior to the expiration of the ‘473 Patent and U.S. Patent No. 8,497,284 would also infringe certain claims of each patent, if those claims are not found to be invalid. Then, on October 12, 2021, pursuant to a separate stipulation between us and MSN, the Delaware District Court entered an order dismissing MSN’s counterclaims with respect to U.S. Patent No. 9,809,549. In our complaints, we are seeking, among other relief, an order that the effective date of any FDA approval of MSN’s ANDA be a date no earlier than the expiration of all of the ‘473 Patent, U.S. Patent No. 8,497,284 and U.S. Patent No. 8,877,776, the latest of which expires on October 8, 2030, and equitable relief enjoining MSN from infringing these patents. A bench trial has been scheduled for May 2022.

On January 11, 2022, we received notice from MSN that it had further amended its ANDA to assert additional Paragraph IV certifications. The ANDA now requests approval to market a generic version of CABOMETYX tablets prior to expiration of four previously-unasserted CABOMETYX patents that are now listed in the Orange Book: U.S. Patent Nos. 11,091,439 (salt and polymorphic forms) 11,091,440 (formulations) and 11,098,015 (methods of treatment). We have 45 days from the receipt of the January 11, 2022 notice to file a patent infringement claim against MSN relating to the newly challenged patents.

In May 2021, we received notice letters from Teva regarding an ANDA Teva submitted to the FDA, requesting approval to market a generic version of CABOMETYX tablets. Teva’s notice letters included a Paragraph IV certification with respect to our U.S. Patent Nos. 9,724,342 (formulations), 10,034,873 (methods of treatment) and 10,039,757 (methods of treatment), which are listed in the Orange Book and expire in 2033, 2031 and 2031, respectively. Teva’s notice letters did not provide a Paragraph IV certification against any additional CABOMETYX patents. On June 17, 2021, we filed a complaint in the Delaware District Court for patent infringement against Teva, along with Teva Parent, asserting infringement of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757 arising from Teva’s ANDA filing with the FDA. On August 27, 2021, Teva filed its answer and counterclaims to the complaint, alleging that the asserted claims of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757 are invalid and not infringed, and on August 23, 2021, we and Teva entered into a stipulation wherein Teva Parent was dismissed without prejudice from this lawsuit and agreed to be bound by any stipulation, judgment, order or decision rendered as to Teva, including any appeals and any order granting preliminary or permanent injunctive relief against Teva. On September 17, 2021, we filed an answer to Teva’s counterclaims. We are seeking, among other relief, an order that the effective date of any FDA approval of Teva’s ANDA be a date no earlier than the expiration of all of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757, the latest of which expires on July 9, 2033, and equitable relief enjoining Teva from infringing these patents. On February 8, 2022, the parties filed a stipulation to stay all proceedings, which was granted by the Delaware District Court on February 9, 2022. The stipulation and order were filed under seal.

We may also from time to time become a party or subject to various other legal proceedings and claims, either asserted or unasserted, which arise in the ordinary course of business. Some of these proceedings have involved, and may involve in the future, claims that are subject to substantial uncertainties and unascertainable damages.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock has traded on the Nasdaq Global Select Market under the symbol "EXEL" since April 11, 2000.

Holders

On February 7, 2022, there were 347 holders of record of our common stock. The number of record holders is based upon the actual number of holders registered on our books at such date and does not include holders of shares in "street names" or persons, partnerships, associations, corporations or other entities identified in security position listings maintained by depository trust companies.

Dividends

Since inception, we have not paid dividends on our common stock. We currently intend to retain all future earnings, if any, for use in our business and currently do not plan to pay any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our Board of Directors.

Unregistered Sales of Equity Securities

There were no unregistered sales of equity securities by us during the year ended December 31, 2021.

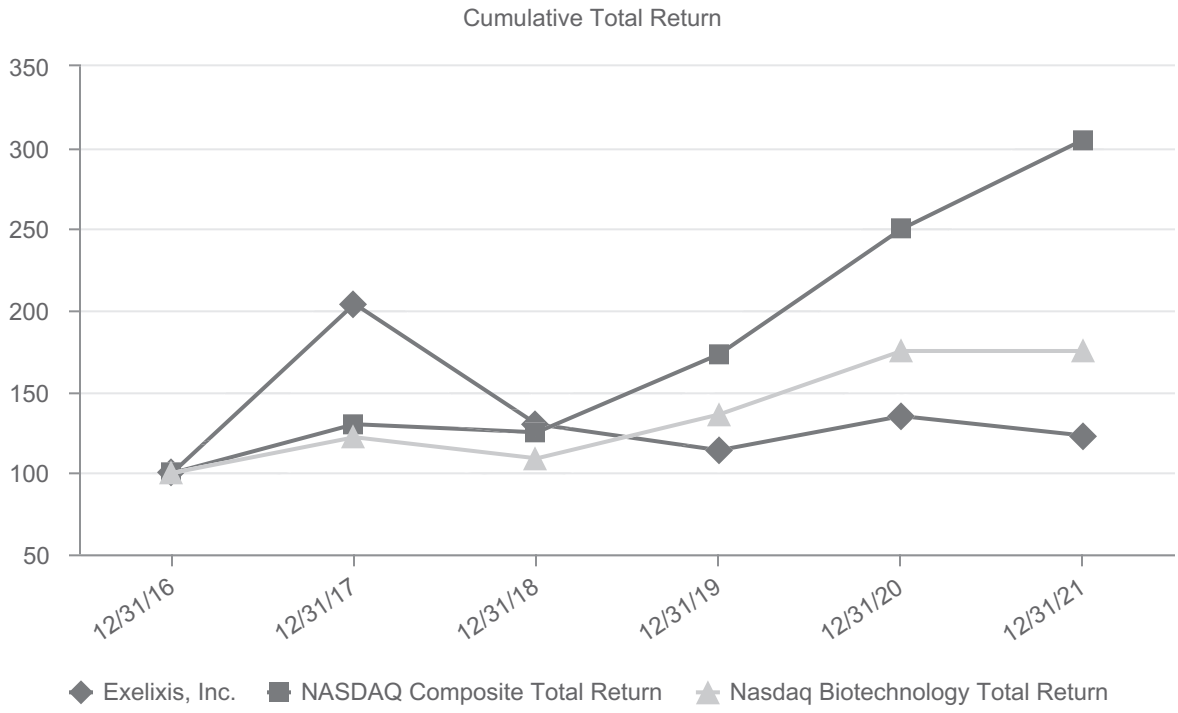
Repurchases of Equity Securities

There were no repurchases of our common stock during the year ended December 31, 2021.

Performance

This performance graph shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities under that Section and shall not be deemed to be incorporated by reference into any filing of ours under the Securities Act of 1933, as amended.

The following graph compares, for the five-year period ended December 31, 2021, the cumulative total return for our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes that $100 was invested on December 31, 2016 in each of our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index and assumes reinvestment of any dividends. The stock price performance on the following graph is not necessarily indicative of future stock price performance.



	Year Ended December 31,					
	2016	2017	2018	2019	2020	2021
Exelixis, Inc.	100	204	130	114	135	123
Nasdaq Composite Total Return	100	130	125	173	250	305
Nasdaq Biotechnology Total Return	100	122	109	136	175	175

Item 6. Reserved

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Some of the statements under "Management's Discussion and Analysis of Financial Condition and Results of Operations" are forward-looking statements. These statements are based on our current expectations, assumptions, estimates and projections about our business and our industry and involve known and unknown risks, uncertainties and other factors that may cause our company's or our industry's results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied in, or contemplated by, the forward-looking statements. Our actual results and the timing of events may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include those discussed in "Item 1A. Risk Factors" as well as those discussed elsewhere in this Annual Report on Form 10-K. These and many other factors could affect our future financial and operating results. We undertake no obligation to update any forward-looking statement to reflect events after the date of this report.

Overview

We are an oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Using our considerable drug discovery, development and commercialization resources and capabilities, we have invented and brought to market innovative therapies that appropriately balance patient benefits and risks; we will continue to build on this foundation as we strive to provide cancer patients with new treatment options that improve upon current standards of care.

Today, four products that originated in Exelixis laboratories are available to be prescribed to patients. Sales related to our flagship molecule, cabozantinib, account for the large majority of our revenues. Cabozantinib is an inhibitor of multiple tyrosine kinases including MET, AXL, VEGF receptors and RET and has been approved by the FDA and in 61 other countries as: CABOMETYX tablets approved for advanced RCC, both alone and in combination with OPDIVO, for previously treated HCC and, currently by the FDA, for previously treated, RAI-refractory DTC; and COMETRIQ capsules approved for progressive MTC. For these types of cancer, cabozantinib has become or is becoming an important drug in their selection of effective therapies.

The other two products resulting from our discovery efforts are: COTELLIC, an inhibitor of MEK, approved as part of multiple combination regimens to treat specific forms of advanced melanoma and marketed under a collaboration with Genentech; and MINNEBRO, an oral, non-steroidal, selective blocker of the mineralocorticoid receptor, approved for the treatment of hypertension in Japan and licensed to Daiichi Sankyo. For additional information about these products, see "Business—Collaborations and Business Development Activities—Other Collaborations" in Part I, Item 1 of this Annual Report on Form 10-K.

Our plan is to utilize our operating cash flows and cash and investments to expand the cabozantinib franchise by potentially adding new indications in areas of unmet medical need. We will also leverage our operating cash flows to continue advancing our diverse small molecule and biotherapeutics programs, exploring multiple modalities and mechanisms of action to discover new oncology drugs. So far, these drug discovery and preclinical activities have resulted in four clinical-stage compounds: XL092, a next-generation oral TKI; XB002, a TF-targeting ADC; XL102, a potent, selective and orally bioavailable covalent inhibitor of CDK7; and XL114, a novel anti-cancer compound that inhibits the CBM complex.

Cabozantinib Franchise

On January 22, 2021, the FDA approved CABOMETYX in combination with OPDIVO as a first-line treatment of patients with advanced RCC. This regulatory milestone expands upon the FDA's prior approvals of CABOMETYX as a monotherapy for previously treated patients with advanced RCC in April 2016 and for previously untreated patients with advanced RCC in December 2017. Additionally, in January 2019, the FDA approved CABOMETYX for the treatment of patients with HCC who have been previously treated with sorafenib, and most recently, on September 17, 2021, the FDA approved CABOMETYX for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGF receptor-targeted therapy and who are RAI-refractory or ineligible.

To develop and commercialize CABOMETYX and COMETRIQ outside the U.S., we have entered into license agreements with Ipsen and Takeda. We granted to Ipsen the rights to develop and commercialize cabozantinib outside of the U.S. and Japan, and to Takeda the rights to develop and commercialize cabozantinib in Japan. Both Ipsen and Takeda also contribute financially and operationally to the further global development and commercialization of the cabozantinib franchise in other potential indications, and we continue to work closely with them on these activities. Utilizing its regulatory expertise and established international oncology marketing network, Ipsen has continued to execute on its

commercialization plans for CABOMETYX, having received regulatory approvals and launched in multiple territories outside of the U.S., including in the EU, the U.K. and Canada, as a treatment for advanced RCC and for HCC in adults who have previously been treated with sorafenib. In addition, in March 2021, Ipsen and BMS received regulatory approval from the EC for CABOMETYX in combination with OPDIVO as a first-line treatment for patients with advanced RCC, and both Ipsen and BMS plan to submit applications to approve the combination in other territories beyond the EU. Ipsen also submitted a variation application to the EMA to approve CABOMETYX as a treatment for patients with previously treated, RAI-refractory DTC, with the EMA validating the variation and beginning its centralized review process in August 2021. With respect to the Japanese market, Takeda received Manufacturing and Marketing Approvals in 2020 from the Japanese MHLW of CABOMETYX as a treatment of patients with curatively unresectable or metastatic RCC and as a treatment of patients with unresectable HCC who progressed after cancer chemotherapy. Most recently, in August 2021, Takeda and Ono Pharmaceutical Co., Ltd. (Ono), BMS' development and commercialization partner in Japan, received Manufacturing and Marketing Approval from the Japanese MHLW of CABOMETYX in combination with OPDIVO as a treatment for unresectable or metastatic RCC.

In addition to our regulatory and commercialization efforts in the U.S. and the support provided to our collaboration partners for rest-of-world regulatory and commercialization activities, we are also pursuing other indications for cabozantinib that have the potential to increase the number of cancer patients who could potentially benefit from this medicine. We continue to evaluate cabozantinib, both as a single agent and in combination with ICIs, in a broad development program comprising over 100 ongoing or planned clinical trials across multiple tumor types. We, along with our collaboration partners, sponsor some of the trials, and independent investigators conduct the remaining trials through our CRADA with NCI-CTEP or our IST program. Informed by the available data from these clinical trials, we advanced the development program for the cabozantinib franchise with potentially label-enabling trials, including COSMIC-311, and positive results from COSMIC-311 served as the basis for the FDA's September 2021 DTC approval for CABOMETYX.

Building on preclinical and clinical observations that cabozantinib in combination with ICIs may promote a more immune-permissive tumor environment, we initiated numerous pivotal studies to further explore these combination regimens. The first of these studies to deliver results was CheckMate -9ER, and positive results from CheckMate -9ER served as the basis for the FDA's, EC's and MHLW's approvals of CABOMETYX in combination with OPDIVO as a first-line treatment of patients with advanced RCC in January 2021, March 2021 and August 2021, respectively. We are also collaborating with BMS on COSMIC-313, a phase 3 pivotal trial evaluating the triplet combination of cabozantinib, nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab in patients with previously untreated advanced intermediate- or poor-risk RCC. Enrollment for COSMIC-313 was completed in March 2021, and we expect to report top-line results of the event-driven analyses from the trial in the first half of 2022.

To expand our exploration of combinations with ICIs, we also initiated multiple trials evaluating cabozantinib in combination with Roche's ICI, atezolizumab. COSMIC-021 is a broad phase 1b study evaluating the safety and tolerability of cabozantinib in combination with atezolizumab in patients with a wide variety of locally advanced or metastatic solid tumors. Based on encouraging efficacy and safety data that has emerged from the trial, certain cohorts have been expanded, including Cohort 6 evaluating patients with mCRPC who have been previously treated with enzalutamide and/or abiraterone acetate and experienced radiographic disease progression in soft tissue and another cohort evaluating patients with NSCLC who have been previously treated with an ICI. We announced data from Cohort 6 in May 2021 and presented more detailed results from Cohort 6 at the ESMO 2021 Congress in September 2021.

Although, following our discussions with the FDA, we will not pursue a regulatory submission for the combination regimen in mCRPC based solely on the Cohort 6 results, data from COSMIC-021 have been instrumental in guiding our clinical development strategy for cabozantinib in combination with ICIs, including supporting the initiation of COSMIC-312, a phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus sorafenib in previously untreated advanced HCC, and three phase 3 pivotal trials in collaboration with Roche, CONTACT-01, CONTACT-02 and CONTACT-03, evaluating the combination of cabozantinib with atezolizumab in patients with metastatic NSCLC, mCRPC and advanced RCC, respectively. CONTACT-01 and CONTACT-03 are sponsored by Roche and co-funded by us; CONTACT-02 is sponsored by us and co-funded by Roche. In June 2021, we announced results from COSMIC-312. The trial met one of the primary endpoints, demonstrating significant improvement in BIRC assessed PFS at the planned primary analysis, reducing the risk of disease progression or death by 37% compared with sorafenib. The interim analysis for the second primary endpoint of OS, performed at the same time as the primary analysis for PFS, did not reach statistical significance. The trial is continuing as planned to the final analysis of OS, anticipated during the first quarter of 2022, and we intend to submit an sNDA to the FDA for the combination regimen if supported by the final OS analysis.

For additional information on our cabozantinib clinical trials, see "Business—Exelixis Development Programs—Cabozantinib Development Program" in Part I, Item 1 of this Annual Report on Form 10-K.

Pipeline Activities

Our small molecule discovery programs are supported by a robust and expanding infrastructure, including a library of 4.6 million compounds. We have extensive experience in the identification and optimization of drug candidates against multiple target classes for oncology, inflammation and metabolic diseases. The first compound to enter the clinic following our re-initiation of drug discovery activities in 2017 was XL092, a next-generation oral TKI that targets VEGF receptors, MET, AXL, MER and other kinases implicated in cancer's growth and spread. In designing XL092, we sought to build upon our experience with cabozantinib, retaining a similar target profile while improving key characteristics, including the pharmacokinetic half-life. To date, we have initiated two large phase 1b clinical trials studying XL092: STELLAR-001 and STELLAR-002. STELLAR-001 is a phase 1b clinical trial evaluating XL092, both as a monotherapy and in combination with either atezolizumab or Merck KGaA's and Pfizer's avelumab. We are continuing to enroll patients into the dose-escalation cohorts of the combination part of the trial, and we expect that once recommended doses are established for single-agent XL092, XL092 in combination with atezolizumab and XL092 in combination with avelumab, the trial will begin to enroll expansion cohorts for patients with clear cell and non-clear cell RCC, CRC, hormone-receptor positive breast cancer, mCRPC and UC. STELLAR-002 is a phase 1b clinical trial evaluating XL092 in combination with either nivolumab, nivolumab and ipilimumab, or nivolumab and Nektar's bempegaldesleukin. We are enrolling patients with advanced solid tumors in dose-escalation cohorts, and depending on the dose-escalation results, STELLAR-002 may enroll expansion cohorts for patients with clear cell and non-clear cell RCC, mCRPC and UC. To better understand the individual contribution of the therapies, treatment arms in the expansion cohorts may include XL092 as a single-agent in addition to the ICI combination regimens. In addition to clinical updates for XL092 expected in 2022, we plan to initiate the first global phase 3 pivotal trial for the compound in the first half of the year, and other pivotal trials may follow throughout the year. This first planned trial, STELLAR-303, will evaluate XL092 in combination with atezolizumab versus regorafenib in patients with metastatic microsatellite stable CRC who have progressed after or are intolerant to the current standard of care.

We also augment our small molecule discovery activities through research collaborations and in-licensing arrangements with other companies. The most advanced compounds to emerge from these arrangements are XL102 , the lead program targeting CDK7 under our collaboration with Aurigene, and XL114, Aurigene's novel anti-cancer compound that inhibits the CBM complex. Based on encouraging preclinical data, we have exercised our exclusive options to license each of XL102 and XL114 from Aurigene and initiated a phase 1 clinical trial evaluating XL102 in January 2021; we plan to initiate a phase 1 clinical trial for XL114 in the first half of 2022.

Beyond small molecules, we have also launched rigorous efforts to discover and advance various biotherapeutics that have the potential to become anti-cancer therapies, such as bispecific antibodies, ADCs and other innovative treatments. ADCs in particular present a unique opportunity for new cancer treatments, given their capabilities to deliver anti-cancer payload drugs to targets with increased precision while minimizing impact on healthy tissues, and have been validated by the multiple regulatory approvals for the commercial sale of ADCs in the past several years. To facilitate the growth of these programs, we have established multiple research collaborations and in-licensing arrangements and entered into other strategic transactions that provide us with access to antibodies or other binders, which are the starting point for use with additional technology platforms that we employ to generate next-generation ADCs or multispecific antibodies. We have already made significant progress under these arrangements and believe we will continue to do so in 2022 and future years. For example, based on promising preclinical data for XB002, Iconic's lead TF-targeting ADC program, we exercised our exclusive option to license XB002 in December 2020 and initiated a phase 1 clinical trial in June 2021. We have expanded our access to antibodies through arrangements with WuXi Bio, focused on leveraging WuXi Bio's panel of mAbs against an undisclosed target for the development of ADC, bispecific and certain other novel tumor-targeting biotherapeutics, and through the execution of an asset purchase agreement with GamaMabs, under which we will, upon the closing of the asset purchase and subject to certain conditions, acquire all rights, title and interest in GamaMabs' antibody program directed at AMHR2. These antibodies, as well as those originating from our collaboration with Invenra, which was expanded in August 2021 to include an additional 20 oncology targets, provide starting points for the construction of ADCs through our collaborations with NBE and Catalent, utilizing their site-specific conjugation technologies and payloads. In addition, our collaboration with Adagene, focused on using Adagene's SAFEbody technology to develop novel masked ADCs or other innovative biotherapeutics, provides potential for developing ADCs or other biotherapeutics with improved therapeutic index. As a direct result of these arrangements, we designated XB010, our first ADC advanced internally, as a development candidate in late 2021. XB010, which targets the tumor antigen 5T4, incorporates antibodies sourced from Invenra and was constructed using and Catalent's SMARTag site-specific bioconjugation platform.

For additional information on these early-stage trials of our small molecule and biotherapeutic product candidates, see "Business—Exelixis Development Programs—Other Development Programs - Advancing Exelixis' Future Cancer Therapy Candidates" in Part I, Item 1 of this Annual Report on Form 10-K. For additional information on our specific research collaborations, in-licensing arrangements and other strategic transactions related to our small molecule and biotherapeutics programs, see "Business—Collaborations and Business Development Activities—Research Collaborations, In-licensing Arrangements and Other Business Development Activities" in Part I, Item 1 of this Annual Report on Form 10-K.

As of the date of this Annual Report, we are currently advancing more than 10 discovery programs and expect to progress up to five new development candidates into preclinical development during 2022. In addition, we will continue to engage in business development initiatives with the goal of acquiring and in-licensing promising oncology platforms and assets and then further characterize and develop them utilizing our established preclinical and clinical development infrastructure.

COVID-19 Update

As of the date of this Annual Report on Form 10-K, the COVID-19 pandemic continues to have a modest impact on our business operations, in particular with respect to our clinical trial and commercial activities. We have and continue to undertake considerable efforts to mitigate the various problems presented by this crisis, including as described below:

Clinical Trials. To varying degrees and at different rates across our global clinical trials, we experienced declines in screening and enrollment activity during the early days of the COVID-19 pandemic, as well as delays in new site activations and restrictions on the access to treatment sites that is necessary to monitor clinical study progress and administration. However, we and our collaboration partners, including principal investigators and personnel at clinical trial sites, have been successful overall in preventing material delays to our ongoing and planned clinical trials due to the COVID-19 pandemic. We have done this through ongoing assessment of the COVID-19 pandemic's impact, which has included staffing and materials shortages and other operational disruptions at clinical trial sites, and wherever possible, we take proactive steps in compliance with guidance issued by the FDA, EMA and other regulatory agencies to support the safety of our patients and their access to treatment, as well as to maintain the high quality of our clinical trials. We recognize, however, that we may have to make further operational adjustments to our ongoing and planned clinical trials and that patient enrollment, and new clinical trial site initiations may again be slowed due to recurring COVID-19 outbreaks and potential reintroduction of certain restrictions intended to mitigate the spread of COVID-19.

Drug Discovery and Preclinical Development. We have fully resumed drug discovery in our laboratories following a temporary suspension of these activities while we observed the shelter in place orders issued by the State of California and Alameda County. While this temporary suspension combined with interruptions in the portion of drug discovery work outsourced to third-party contractors in regions first impacted by COVID-19 caused us to experience modest delays in the advancement of certain of our early-stage programs, we continued to substantially progress our product pipeline despite the COVID-19 pandemic, including the submission of INDs for XB002, XL102 and XL114.

Commercial Activities. Despite the challenges posed by the COVID-19 pandemic, including requiring us to temporarily shift to telephonic and virtual interactions with healthcare professionals, we believe our commercial business was only modestly impacted. Our field employees have now partially resumed their in-person promotional activities while supplementing these activities with telephonic and virtual interactions and we believe they are well-positioned to execute on our commercial objectives.

Supply Chain. We have not experienced significant production delays or seen any significant impairment to our supply chain as a result of the COVID-19 pandemic. In addition, we continue to maintain sufficient safety stock inventories for our commercial drug substance and drug products. We continue to work closely with our third-party contract manufacturers, distributors, suppliers, comparator drug sourcing vendors and collaboration partners to safeguard both the timely production and delivery of our products.

General Business Operations. We have taken numerous precautions, some temporary and others still in place, to help mitigate the risk of transmission of the virus in the workplace, including: initially reducing the number of our employees working on-site at our Alameda headquarters; implementing a vaccination mandate and maintaining enhanced safety and social distancing protocols for those employees who have returned to working on-site, as well as initiating an on-site COVID-19 testing program and limiting certain non-essential business travel for our employees. While most of our employees worked remotely during much of 2020 and early 2021, our Alameda-based workforce has largely returned to working on-site at our headquarters consistent with the policies in place

prior to the COVID-19 pandemic. As of the date of this Annual Report on Form 10-K, the COVID-19 pandemic has only had a modest impact on our productivity and has not caused significant interruptions in our general business operations. For a discussion of workplace safety measures we have taken as a result of the COVID-19 pandemic, see "Business—Environmental, Health and Safety—Workplace Safety Measures in Response to COVID-19" in Part I, Item 1 of this Annual Report on Form 10-K.

The circumstances and public health requirements surrounding the COVID-19 pandemic continue to be subject to rapid change, and we will continue to monitor new developments that could pose additional risks for us, including the spread of the Delta and Omicron variants in the U.S. and other countries and the potential emergence of other SARS-CoV-2 variants that may prove especially contagious or virulent. Despite our mitigation efforts, we may experience delays or an inability to execute on our clinical and preclinical development plans, reduced revenues or other adverse impacts to our business, which are described in more detail in "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K. We recognize that this pandemic will continue to present unique challenges for us throughout 2022, and potentially into 2023.

For additional information regarding our business, see "Business" in Part I, Item 1 of this Annual Report on Form 10-K.

2021 Business Updates and Financial Highlights

During 2021, we continued to execute on our business objectives, generating significant revenues from operations and enabling us to continue to seek to maximize the clinical and commercial potential of our products and expand our product pipeline. Significant business updates and financial highlights for 2021 and subsequent to year-end include:

Business Updates

- In January 2021, the FDA approved the combination of CABOMETYX and OPDIVO as a first-line treatment of patients with advanced RCC, and we commenced the commercial launch of the combination upon such approval.
- In January 2021, we announced the initiation of a phase 1 clinical trial evaluating XL102, both as a single agent and in combination with other anti-cancer therapies in patients with inoperable, locally advanced or metastatic solid tumors.
- In February 2021, we announced a collaboration and license agreement with Adagene to utilize Adagene's SAFEbody technology platform to generate masked versions of mAbs from our growing preclinical pipeline for the development of ADCs or other innovative biotherapeutics.
- In February 2021, cabozantinib was the subject of multiple data presentations in forms of RCC and other genitourinary cancers at the virtual 2021 ASCO Genitourinary Cancers Symposium.
- In March 2021, we announced an exclusive license agreement with WuXi Bio for a panel of mAbs, which were discovered based on WuXi Bio's integrated technology platforms for the development of ADC, bispecific and certain other novel tumor-targeting biotherapeutic applications.
- In March 2021, we announced a clinical trial collaboration and supply agreement with Merck KGaA and Pfizer to evaluate XL092 in combination with avelumab in patients with locally advanced or metastatic UC as part of the ongoing STELLAR-001 phase 1b dose escalation study.
- In March 2021, we announced the completion of enrollment for COSMIC-313, a phase 3 pivotal trial evaluating the triplet combination of cabozantinib, nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab in patients with previously untreated advanced intermediate- or poor-risk RCC. We expect to report top-line results of the event-driven analyses from the trial in the first half of 2022.
- In March 2021 and April 2021, Ipsen and BMS, respectively, received regulatory approval from the EC for CABOMETYX in combination with OPDIVO as a first-line treatment for patients with advanced RCC.
- In April 2021, we announced the FDA's acceptance of the IND for XB002 and initiated a phase 1 trial evaluating the ADC in patients with advanced solid tumors in June 2021.

- In May 2021, we announced an asset purchase agreement with GamaMabs to acquire GamaMabs' antibody program directed at AMHR2.
- In June 2021, cabozantinib was the subject of multiple data presentations in forms of RCC and DTC at the 2021 ASCO Annual Meeting.
- In June 2021, we filed a patent lawsuit against Teva, following receipt of two Paragraph IV certification notice letters from Teva informing us that it had filed an ANDA with the FDA requesting approval to market a generic version of CABOMETYX tablets. For a more detailed discussion of this litigation matter, see "Legal Proceedings" in Part I, Item 3 of this Annual Report on Form 10-K.
- In June 2021, we announced results from the phase 3 COSMIC-312 trial, in which the combination of cabozantinib and atezolizumab met one of the primary endpoints, demonstrating significant improvement in PFS versus sorafenib in patients with previously untreated advanced HCC at the planned primary analysis. The interim OS analysis performed at the same time as the primary analysis for PFS did not demonstrate a statistically significant benefit for the combination. Detailed results from COSMIC-312 were later presented at the ESMO Asia Virtual Oncology Week in November 2021. The trial is continuing as planned to the final analysis of OS, anticipated during the first quarter of 2022, and we intend to submit an sNDA to the FDA for the combination regimen if supported by the final OS analysis.
- In August 2021, we announced the expansion of our discovery and licensing collaboration with Invenra to include an additional 20 oncology targets for multispecific antibody, ADC and other biotherapeutics candidate discovery and development.
- In August 2021, Takeda and Ono received regulatory approval from the Japanese MHLW to manufacture and market CABOMETYX in combination with OPDIVO as a treatment for unresectable or metastatic RCC.
- In September 2021, the FDA approved CABOMETYX for the treatment of adult and pediatric patients 12 and older with locally advanced or metastatic DTC that has progressed following prior VEGF receptor-targeted therapy and who are RAI-refractory or ineligible, and we commenced the commercial launch of CABOMETYX in this indication upon such approval.
- In September 2021, cabozantinib was the subject of multiple data presentations in previously untreated advanced RCC, previously treated RAI-refractory DTC and mCRPC at the ESMO 2021 Congress.
- In October 2021, we announced an exclusive collaboration and license agreement with STORM to discover and develop inhibitors of novel RNA modifying enzymes, including ADAR1.
- In October 2021, we and Aurigene announced that we exercised our exclusive option for XL114, Aurigene's novel anti-cancer compound that inhibits the CBM complex, resulting in our assuming responsibility for all subsequent clinical development, manufacturing and commercialization of XL114. Following the FDA's acceptance of the IND for XL114 in October 2021, we plan to initiate a phase 1 clinical trial evaluating XL114 as a monotherapy in patients with NHL in the first half of 2022
- In November 2021, we announced the completion of enrollment for CONTACT-01, a phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus docetaxel in patients with metastatic NSCLC who have been previously treated with an ICI and platinum-containing chemotherapy. Based on current event rates, we anticipate announcing results of the interim OS analysis in the second half of 2022.
- In December 2021, we announced the initiation of STELLAR-002, a phase 1b clinical trial evaluating XL092 in combination with either nivolumab, nivolumab and ipilimumab, or nivolumab and bempegaldesleukin in patients with advanced solid tumors. Previously in June 2021, we announced a clinical trial collaboration and supply agreement with BMS pursuant to which BMS is providing nivolumab, ipilimumab and bempegaldesleukin for use in the trial.
- In December 2021, we appointed Jacqueline Wright to our Board of Directors. Ms. Wright currently serves as Corporate Vice President & Chief Digital Officer, U.S. Business at Microsoft Corporation.

- In January 2022, we appointed Vicki L. Goodman, M.D., as Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer. Dr. Goodman had previously served as Vice President, Clinical Research and Therapeutic Area Head, Late Stage Oncology at Merck & Co.
- In January 2022, we announced the completion of enrollment for CONTACT-03, a phase 3 pivotal trial evaluating the efficacy and safety of cabozantinib in combination with atezolizumab versus cabozantinib alone in patients with locally advanced or metastatic RCC who progressed during or following treatment with an ICI as the immediate preceding therapy. Based on current event rates, we anticipate announcing results of PFS and the first interim OS analysis in the second half of 2022.
- In January 2022, we announced an amendment to our exclusive option and license agreement with Iconic to acquire broad rights to use the anti-TF antibody incorporated into XB002 for any application, including conjugated to other payloads, as well as rights within oncology to a number of other anti-TF antibodies developed by Iconic, including for use in ADCs and multispecific biotherapeutics.
- In January 2022, we presented encouraging data from two early-stage studies evaluating cabozantinib in combination with ICIs in patients with previously treated CRC at the 2022 ASCO Gastrointestinal Cancers Symposium: cohort 16 from COSMIC-021, evaluating cabozantinib in combination with atezolizumab in patients with metastatic CRC who were previously treated with fluoropyrimidine-containing chemotherapy; and cohort 2 from CAMILLA, the phase 2 IST evaluating cabozantinib in combination with durvalumab in patients with advanced mismatch repair proficient/micro satellite stable CRC patients who were chemotherapy-refractory.
- In February 2022, cabozantinib will be the subject of multiple data presentations in forms of RCC and other genitourinary cancers at the 2022 ASCO Genitourinary Cancers Symposium.

2021 Financial Highlights

- Net product revenues for 2021 were $1,077.3 million, compared to $741.6 million for 2020.
- Total revenues for 2021 were $1,435.0 million, compared to $987.5 million for 2020.
- Research and development expenses for 2021 were $693.7 million, compared to $547.9 million for 2020.
- Selling, general and administrative expenses for 2021 were $401.7 million, compared to $293.4 million for 2020.
- Provision for income taxes for 2021 was $63.1 million, compared to $19.1 million for 2020.
- Net income for 2021 was $231.1 million, or $0.73 per share, basic and $0.72 per share, diluted, compared to $111.8 million, or $0.36 per share, basic and $0.35 per share diluted, for 2020.
- Cash and investments increased to $1.9 billion at December 31, 2021, compared to $1.5 billion at December 31, 2020.

See *"Results of Operations"* below for a discussion of the detailed components and analysis of the amounts above.

Outlook, Challenges and Risks

We will continue to face a number of challenges and risks that may impact our ability to execute on our 2022 business objectives, and some of these risks to our business have been or may be exacerbated by the COVID-19 pandemic. In particular, for the foreseeable future, we expect our ability to generate sufficient cash flow to fund our business operations and growth will depend upon the continued commercial success of CABOMETYX, both alone and in combination with other therapies, as a treatment for the highly competitive indications for which it is approved, and possibly for other indications for which cabozantinib has been or is currently being evaluated in potentially label-enabling clinical trials, if warranted by the data generated from these trials. However, we cannot be certain that the clinical trials we and our collaboration partners are conducting will demonstrate adequate safety and efficacy in these additional indications to receive regulatory approval in the major commercial markets where CABOMETYX is approved. Even if we and our collaboration partners receive the required regulatory approvals to market cabozantinib for additional indications, we and our collaboration partners may not be able to commercialize CABOMETYX effectively and successfully in these additional indications. In addition, CABOMETYX will only continue to be commercially successful if private third-party and government payers continue to provide coverage and reimbursement. However, as is the case for all innovative pharmaceutical therapies, obtaining and maintaining coverage and reimbursement for CABOMETYX is becoming increasingly difficult, both within the U.S. and in foreign markets, because of growing concerns over healthcare cost containment and corresponding policy initiatives and activities aimed at expanding access to, and restricting the prices of, pharmaceuticals.

Achievement of our 2022 business objectives will also depend on our ability to maintain a competitive position with respect to the shifting landscape of therapeutic strategy for the treatment of cancer, which we may not be able to do. While we have had success in adapting our development strategy for the cabozantinib franchise and other product candidates to address the competitive landscape, including through evaluation of therapies that combine ICIs with other targeted agents, it is uncertain whether current and future clinical trials will lead to regulatory approvals, or whether physicians will prescribe regimens containing our products instead of competing product combinations in approved indications. Moreover, the complexities of this development strategy have required and are likely to continue to require collaboration with some of our competitors. In the longer term, we may eventually face competition from potential manufacturers of generic versions of our marketed products, including the proposed generic versions of CABOMETYX tablets that are the subject of ANDAs submitted to the FDA by MSN and Teva, and the approval of either MSN's or Teva's ANDA could significantly decrease our revenues derived from the U.S. sales of CABOMETYX and thereby materially harm our business, financial condition and results of operations. Separately, our research and development objectives may be impeded by the challenges of scaling our organization to meet the demands of expanded drug development, unanticipated delays in clinical testing and the inherent risks and uncertainties associated with drug discovery operations, all of which may be increased as a result of the COVID-19 pandemic. In connection with efforts to expand our product pipeline, we may be unsuccessful in discovering new drug candidates or identifying appropriate candidates for in-licensing or acquisition.

Some of these challenges and risks are specific to our business, and others are common to companies in the biopharmaceutical industry with development and commercial operations. As described under "—COVID-19 Update" above, these risks have been or may be exacerbated by the COVID-19 pandemic. For a more detailed discussion of challenges and risks we face, including those relating to the COVID-19 pandemic, see "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K.

Results of Operations

We have adopted a 52- or 53-week fiscal year policy that ends on the Friday closest to December 31st. Fiscal 2021, which was a 52-week fiscal year, ended December 31, 2021 and fiscal year 2020, which was a 52-week fiscal year, ended January 1, 2021. For convenience, references in this report as of and for the fiscal year ended January 1, 2021 are indicated as being as of and for the year ended December 31, 2020.

This discussion and analysis generally addresses 2021 and 2020 items and year-over-year comparisons between 2021 and 2020. Discussions of 2019 items and year-over-year comparisons between 2020 and 2019 that are not included in this Annual Report on Form 10-K can be found in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2020, submitted to the U.S. Securities and Exchange Commission (SEC) on February 10, 2021.

Revenues

Revenues by category were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Net product revenues	$ 1,077,256	$ 741,550	45%
License revenues	249,956	167,295	49%
Collaboration services revenues	107,758	78,693	37%
Total revenues	$ 1,434,970	$ 987,538	45%

Net Product Revenues

Gross product revenues, discounts and allowances, and net product revenues were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Gross product revenues	$ 1,452,913	$ 962,591	51%
Discounts and allowances	(375,657)	(221,041)	70%
Net product revenues	$ 1,077,256	$ 741,550	45%

Net product revenues by product were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
CABOMETYX	$ 1,054,050	$ 718,687	47%
COMETRIQ	23,206	22,863	2%
Net product revenues	$ 1,077,256	$ 741,550	45%

The increase in net product revenues for the year ended December 31, 2021, as compared to 2020, was related to a 42% increase in the number of CABOMETYX units sold that was primarily driven by the strong uptake for the combination therapy of CABOMETYX and OPDIVO following approval by the FDA in January 2021, and to a lesser extent a 3% increase in the average net selling price of CABOMETYX.

We project our fiscal 2022 net product revenues will increase over fiscal 2021, primarily as a result of the growth in the number of units sold following the FDA's approval of CABOMETYX in combination with OPDIVO as a first line treatment of patients with advanced RCC, in part due to the longer duration of therapy for this combination, as well as an increase in selling price reflecting the continued evolution of the metastatic RCC, HCC and DTC treatment landscapes.

We recognize product revenues net of discounts and allowances that are described in "Note 1. Organization and Summary of Significant Accounting Policies" to our "Notes to Consolidated Financial Statements" included in Part II, Item 8

of this Annual Report on Form 10-K. Discounts and allowances as a percentage of gross revenue have increased over time as the number of patients participating in government programs has increased and as the discounts given and rebates paid to government payers have also increased. The increase in discounts and allowances for the year ended December 31, 2021, as compared to 2020, was primarily the result of an increase in Public Health Service hospital utilization and the dollar amount of the related chargebacks, and to a lesser extent, an increase in Medicaid utilization and the dollar amount of the related Medicaid rebates.

We project our discounts and allowances as a percentage of gross revenues may increase during fiscal 2022, for similar reasons noted above.

License Revenues

License revenues include: (a) the recognition of the portion of milestone payments allocated to the transfer of intellectual property licenses for which it had become probable in the related period that the milestone would be achieved and a significant reversal of revenues would not occur in future periods; (b) royalty revenues and (c) the profit on the U.S. commercialization of COTELLIC from Genentech.

See "Note 3. Collaborations and Business Development Activities—Cabozantinib Commercial Collaborations—Performance Obligations and Transaction Prices for our Ipsen and Takeda Collaborations" in the "Notes to Consolidated Financial Statements—*Performance Obligations and Transaction Prices for our Ipsen and Takeda Collaborations*" contained in Part II, Item 8 of this Annual Report on Form 10-K for a discussion on the allocation of transaction price which impacts the proportion of milestone revenues allocated to license revenues and collaboration services revenues.

Milestone revenues, which are allocated between license revenues and collaboration services revenues, were $133.8 million for the year ended December 31, 2021, as compared to $86.5 million for 2020.

- Milestone revenues for the year ended December 31, 2021 included: (1) $100.0 million related to a commercial sales milestone from Ipsen upon their achievement of $400.0 million of net sales of cabozantinib in the related Ipsen license territory over four consecutive quarters, (2) $11.9 million related to a $12.5 million regulatory milestone Ipsen achieved upon submission of a variation application to the EMA for CABOMETYX as a treatment for patients with previously treated, RAI-refractory DTC and (3) $18.9 million in connection with a $20.0 million milestone achieved following Takeda's first commercial sale in Japan of CABOMETYX in combination with OPDIVO for the treatment of patients with curatively unresectable or metastatic RCC;
- Milestone revenues for the year ended December 31, 2020 included: (1) $25.7 million in connection with a $31.0 million milestone achieved upon Takeda's first commercial sale of CABOMETYX for the treatment of patients with curatively unresectable or metastatic RCC in Japan; (2) $19.0 million in connection with a $20.0 million development milestone from Ipsen for the initiation of a phase 3 pivotal trial; (3) $9.3 million in connection with a $10.0 million milestone for Takeda's and Ono's submission of a supplemental application to the Japanese MHLW for Manufacturing and Marketing Approval of CABOMETYX in combination with OPDIVO for the treatment of patients with unresectable, advanced or metastatic RCC; (4) $14.0 million in connection with a $15.0 million milestone achieved upon Takeda's first commercial sale of CABOMETYX for the treatment of patients with advanced HCC; and (5) $14.0 million in connection with $15.0 million in milestones from Takeda for the initiation of two phase 3 pivotal clinical trials that were deemed probable of being achieved in 2021.

Due to uncertainties surrounding the timing and achievement of development, regulatory and commercial milestones, it is difficult to predict the timing of future milestones revenues; consequently, milestones may vary significantly from period to period.

Royalty revenues increased primarily as a result of an increase in Ipsen's net sales of cabozantinib outside of the U.S. and Japan. Ipsen royalty revenues were $97.2 million for the year ended December 31, 2021, as compared to $76.2 million for 2020. Ipsen's net sales of cabozantinib have continued to grow since their first commercial sale of the product in the fourth quarter of 2016, as a result of increased demand of CABOMETYX, due to regulatory approval in new territories, including the more recent regulatory approval in the EU for the combination therapy of CABOMETYX and OPDIVO received in March 2021. Royalty revenues for the year ended December 31, 2021 also included $7.9 million, as compared to $2.3 million for 2020, related to Takeda's net sales of CABOMETYX, which have continued to grow since their first commercial sale of product in Japan in 2020. Additionally, Takeda royalty revenues have increased due to the August 2021 regulatory approval in Japan for the combination therapy of CABOMETYX and OPDIVO. As of December 31, 2021, CABOMETYX is approved and commercially available in 61 countries outside of the U.S.

Our share of profits on the U.S. commercialization of COTELLIC under our collaboration agreement with Genentech was $8.1 million for the year ended December 31, 2021, as compared to $6.3 million for 2020. We also earned royalty revenues on ex-U.S. net sales of COTELLIC by Genentech of $4.1 million for the year ended December 31, 2021, as compared to $5.1 million for 2020.

We project our license revenues may decrease in fiscal 2022, as compared to fiscal 2021, as a result of the anticipated achievement of fewer milestones in 2022, partially offset by an increase in royalty revenues related to an increase in product sales by Ipsen and Takeda.

Collaboration Services Revenues

Collaboration services revenues include the recognition of deferred revenues for the portion of upfront and milestone payments that have been allocated to research and development services performance obligations, development cost reimbursements earned under our collaboration agreements, and product supply revenues, which are net of product supply costs and the royalties we pay to Royalty Pharma on sales by Ipsen and Takeda of products containing cabozantinib.

Development cost reimbursements were $116.8 million for the year ended December 31, 2021, as compared to $76.3 million for 2020. The increase in development cost reimbursement was primarily attributable to Ipsen's decision to opt in and co-fund COSMIC-311 development costs in the second quarter of 2021. Ipsen is now responsible for 35% of the global development costs of COSMIC-311 and is obligated to reimburse us for these costs, as well as an additional payment calculated as a percentage of COSMIC-311 development costs, triggered by the timing of the exercise of its option.

Accordingly, collaboration services revenues for the year ended December 31, 2021, includes a cumulative catch-up of $43.2 million recognized in the second quarter of 2021 for Ipsen's share of global development costs incurred since the beginning of the study. The increase in development cost reimbursements for the year ended December 31, 2021 was partially offset by a decrease in total spending for the COSMIC-312 and COSMIC-021 studies.

Collaboration services revenues were reduced by $14.3 million with respect to the 3% royalty we are required to pay on the net sales by Ipsen and Takeda of any product incorporating cabozantinib for the year ended December 31, 2021, as compared to $10.6 million for 2020. As royalty generating sales of cabozantinib by Ipsen and Takeda have increased as described above, our royalty payments have also increased.

We project our collaboration services revenues may decrease in fiscal 2022, as compared to fiscal 2021, primarily as a result of decreased development cost reimbursements related to Ipsen's opt in and co-funding of COSMIC-311 and the related cumulative catch-up in development cost reimbursements recognized in fiscal 2021 for which no similar event is projected to occur in 2022.

Cost of Goods Sold

The cost of goods sold and our gross margins were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Cost of goods sold	$ 52,873	$ 36,272	46%
Gross margin %	95 %	95 %	

Cost of goods sold is related to our product revenues and consists of a 3% royalty payable on U.S. net sales of any product incorporating cabozantinib, as well as the cost of inventory sold, indirect labor costs, write-downs related to expiring, excess and obsolete inventory, and other third-party logistics costs. The increase in cost of goods sold for the year ended December 31, 2021, as compared to 2020, was the result of increases in royalty payments as a result of increased U.S. CABOMETYX sales and certain other period costs. We project our fiscal 2022 gross margin to remain consistent with fiscal 2021.

Research and Development Expenses

We do not track fully burdened research and development expenses on a project-by-project basis. We group our research and development expenses into three categories: (1) development; (2) drug discovery; and (3) other. Our development group leads the development and implementation of our clinical and regulatory strategies and prioritizes disease indications in which our compounds are being or may be studied in clinical trials. Our drug discovery group utilizes a variety of technologies, including in-licensed technologies, to enable the rapid discovery, optimization and extensive characterization of lead compounds and biotherapeutics such that we are able to select development candidates with the best potential for further evaluation and advancement into clinical development.

Research and development expenses by category were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Research and development expenses:			
Development:			
Clinical trial costs	$ 225,018	$ 248,684	-10%
Personnel expenses	112,083	85,900	30%
Licenses and other collaboration costs[(1)]	38,500	—	N/A
Consulting and outside services	25,463	16,975	50%
Other development costs [(2)]	26,429	22,421	18%
Total development	427,493	373,980	14%
Drug discovery:			
License and other collaboration costs[(1)]	137,568	96,437	43%
Other drug discovery [(2)]	49,760	30,253	64%
Total drug discovery	187,328	126,690	48%
Stock-based compensation	46,654	37,198	25%
Other research and development[(3)]	32,241	9,983	223%
Total research and development expenses	$ 693,716	$ 547,851	27%

(1) License and other collaboration costs presented in total development includes upfront license fees and development milestone payments associated with programs currently in clinical development stage while license and other collaboration costs presented in total drug discovery includes upfront license fees, development milestone payments, program initiation fees, and research funding commitments associated with programs in preclinical development stage.

(2) Primarily includes personnel expenses, consulting and outside services and laboratory supplies, if not separately presented.

(3) Includes the allocation of general corporate costs to research and development services, and development cost reimbursements in connection with our collaboration arrangement with Roche executed in December 2019.

The increase in research and development expenses for the year ended December 31, 2021, as compared to 2020, was primarily related to increases in license and other collaboration costs, personnel expenses, stock-based compensation and other research and development costs, partially offset by a decrease in clinical trial costs. Drug discovery related license and other collaboration costs increased primarily due to increases in upfront license fees, including, in connection with our recent amended agreement with Iconic in the fourth quarter of 2021 for rights to additional compounds, and other increases in program initiation fees, development milestones, and research funding commitments related to business development activities. Development related license and other collaboration costs increased primarily due to our recent amended agreement with Iconic to buyout future contingent milestone payments and a development milestone we deemed probable of achievement under certain of our in-licensing collaboration arrangements. Personnel expenses increased primarily due to an increase in headcount to support our expanding discovery and development organization. Stock-based compensation expense increased primarily due to an increase related to service-based RSUs associated with higher headcount. Other research and development costs increased primarily related to technology services and related investments in support of digital transformation initiatives and an increase in allocated corporate costs, which were

partially offset by development cost reimbursements in connection with our collaboration arrangement with Roche. Clinical trial costs decreased primarily due to lower costs associated with the COSMIC-312 and COSMIC-021 studies.

In addition to reviewing the three categories of research and development expenses described above, we principally consider qualitative factors in making decisions regarding our research and development programs. These factors include enrollment in clinical trials for our drug candidates, preliminary data and final results from clinical trials, the potential indications for our drug candidates, the clinical and commercial potential for our drug candidates, and competitive dynamics. We also make our research and development decisions in the context of our overall business strategy.
We are focusing a significant amount of our development efforts on cabozantinib to maximize the therapeutic and commercial potential of this compound and, as a result, we project that a substantial portion of our research and development expenses will relate to the continuing clinical development program of cabozantinib, which includes over 100 ongoing or planned clinical trials across multiple indications. Notable ongoing company-sponsored studies resulting from this program include: COSMIC-313, for which BMS is providing nivolumab and ipilimumab free of charge and CONTACT-02 for which Roche is sharing the development costs and providing atezolizumab free of charge.

We are working to expand our oncology product pipeline through drug discovery efforts, which encompass our diverse small molecule and biotherapeutics programs exploring multiple modalities and mechanisms of action. In this regard, we conduct drug discovery activities with the goal of identifying new product candidates to advance into clinical trials. In addition, we will continue to engage in business development initiatives with the goal of acquiring and in-licensing promising oncology platforms and assets and then further characterize and develop them utilizing our established preclinical and clinical development infrastructure.

We project our research and development expenses may increase in fiscal 2022 as compared to fiscal 2021, driven by our ongoing clinical evaluation of cabozantinib, the initiation of new clinical trials and expansion of ongoing clinical trials evaluating other product candidates in our pipeline, including ongoing and planned early-stage trials evaluating XL092, XB002, XL102 and XL114, and anticipated business development activities.

The length of time required for clinical development of a particular product candidate and our development costs for that product candidate may be impacted by the scope and timing of enrollment in clinical trials for the product candidate, our decisions to develop a product candidate for additional indications and whether we pursue development of the product candidate or a particular indication with a collaborator or independently. For example, cabozantinib is being developed in multiple indications, and we do not yet know for how many of those indications we will ultimately pursue regulatory approval. In this regard, our decisions to pursue regulatory approval of cabozantinib for additional indications depend on several variables outside of our control, including the strength of the data generated in our prior, ongoing and potential future clinical trials. Furthermore, the scope and number of clinical trials required to obtain regulatory approval for each pursued indication is subject to the input of the applicable regulatory authorities, and we have not yet sought such input for all potential indications that we may elect to pursue. Even after having given such input, applicable regulatory authorities may subsequently require additional clinical studies prior to granting regulatory approval based on new data generated by us or other companies, or for other reasons outside of our control. As a condition to any regulatory approval, we may also be subject to post-marketing development commitments, including additional clinical trial requirements. As a result of the uncertainties discussed above, we are unable to determine the duration of, or total costs associated with the development of cabozantinib or any of our other research and development projects.

Our potential therapeutic products are subject to a lengthy and uncertain regulatory process that may not result in our receipt of the necessary regulatory approvals. Failure to receive the necessary regulatory approvals would prevent us from commercializing the product candidates affected, including cabozantinib in any additional indications. In addition, clinical trials of our potential product candidates may fail to demonstrate safety and efficacy, which could prevent or significantly delay regulatory approval. A discussion of the risks and uncertainties with respect to our research and development activities, including completing the development of our product candidates, and the consequences to our business, financial position and growth prospects can be found in “Risk Factors” in Part I, Item 1A of this Annual Report on Form 10-K.

Selling, General and Administrative Expenses

Selling, general and administrative expenses were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Selling, general and administrative expenses [(1)]	$ 328,549	$ 225,483	46%
Stock-based compensation	73,166	67,872	8%
Total Selling, general and administrative expenses	$ 401,715	$ 293,355	37%

(1) Excludes stock-based compensation allocated to selling, general and administrative expenses.

Selling, general and administrative expenses consist primarily of personnel expenses, stock-based compensation, marketing costs and certain other administrative costs.

The increase in selling, general and administrative expenses for the year ended December 31, 2021, as compared to 2020, was primarily related to increases in personnel expenses, marketing costs, legal costs, corporate giving and technology services. Personnel expenses increased primarily due to an increase in administrative headcount to support our commercial and research and development organizations. Marketing costs increased primarily to support the launch of the combination therapy of CABOMETYX and OPDIVO for the treatment of advanced RCC following approval by the FDA in January 2021. The increase in technology services relates to our digital transformation initiatives.

We project our selling, general and administrative expenses may increase in fiscal 2022, as compared to fiscal 2021 in support of our continued commercial investment in CABOMETYX and the growth in the broader organization.

Non-Operating Income

Non-operating income was as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Interest income	$ 7,672	$ 19,865	-61%
Other income (expense), net	(184)	912	N/A
Non-operating income	$ 7,488	$ 20,777	-64%

The decrease in non-operating income for the year ended December 31, 2021, as compared to 2020, was primarily the result of lower interest income due to lower interest rates.

Provision for Income Taxes

The provision for income taxes and the effective tax rates were as follows (dollars in thousands):

	Year Ended December 31,		Percent Change
	2021	2020	
Provision for income taxes	$ 63,091	$ 19,056	231%
Effective tax rate	21.4 %	14.6 %	47%

The increase in provision for income taxes for the year ended December 31, 2021, as compared to 2020, was primarily due to the increase in pre-tax income. The effective tax rate for the year ended December 31, 2021 differed from the U.S. federal statutory rate of 21% primarily due to non-deductible executive compensation, partially offset by excess tax benefits related to the exercise of certain stock options during the period and the generation of federal tax credits. The effective tax rate for the year ended December 31, 2020 differed from the U.S. federal statutory rate of 21% primarily due to excess tax benefits related to the exercise of certain stock options and federal tax credits, offset by non-deductible executive compensation during the period. We project that our effective tax rate will be between 20% and 22% in 2022.

Liquidity and Capital Resources

As of December 31, 2021, we had $1.9 billion in cash and investments, compared to $1.5 billion as of December 31, 2020. We anticipate that the aggregate of our current cash and cash equivalents, short-term and long-term investments available for operations, net product revenues and collaboration revenues will enable us to maintain our short-term operations and execute our long-term plans.

Our primary cash requirements for operating activities, which we project will increase in 2022 as compared to 2021, are for employee related expenditures; costs related to our development programs including payments to third party contract research organizations that conduct and manage global clinical trials; drug discovery programs, including payments made to collaboration partners for in-licensing arrangements for upfront and option exercise fees, research and development funding, and development, regulatory and commercial milestones; royalties paid on our net product sales; and cost of inventory and our leased facilities. Our primary source of operating cash is cash collections from customers related to net product sales which we project will increase in 2022 compared to 2021 and cash collections from our commercial collaboration arrangements with Ipsen, Takeda and others related to royalties earned, the achievement of certain development, regulatory and commercial milestones as well as cash payments to us for cost reimbursements under certain of our development programs. The timing of cash generated from commercial collaborations and required for in-licensing collaborations related to upfront payments, initiation fees, milestone payments and cost reimbursements may vary from period to period.

We also have cash requirements related to capital expenditures to support the planned growth of our business including investments in laboratory facilities and equipment. We project that we may continue to spend significant amounts of cash to fund the continued development and commercialization of cabozantinib. In addition, we intend to continue to expand our oncology product pipeline through our drug discovery efforts, including additional research collaborations, in-licensing arrangements and other strategic transactions that align with our oncology drug development, and regulatory and commercial expertise. Financing these activities could materially impact our liquidity and capital resources and may require us to incur debt or raise additional funds through the issuance of equity. Furthermore, even though we believe we have sufficient funds for our current and future operating plans, we may choose to incur debt or raise additional funds through the issuance of equity based on market conditions or strategic considerations.

Letters of Credit

We have obtained standby letters of credit related to our lease obligations and certain other obligations with combined credit limits of $16.7 million and $1.6 million as of December 31, 2021 and 2020, respectively.

In January 2021, we entered into a standby letter of credit as guarantee of our obligation to fund our portion of the tenant improvements related to our build-to-suit lease at our corporate campus. The letter of credit is secured by our short-term investments, which are recorded as restricted cash equivalents and presented in other long-term assets in our Consolidated Balance Sheets and will be reduced as we fund our portion of the tenant improvements. As of December 31, 2021, restricted cash equivalents included $15.2 million of short-term investments as collateral under our standby letter of credit for our portion of the tenant improvements.

Sources and Uses of Cash (dollars in thousands):

	December 31,		Percent Change
	2021	2020	
Working capital	$ 1,497,157	$ 1,240,737	21%
Cash, cash equivalents, restricted cash equivalents and investments	$ 1,854,908	$ 1,538,842	21%

Working capital**:** The increase in working capital as of December 31, 2021, as compared to December 31, 2020, was primarily due to an increase in net product revenues and collaboration revenues, including a $100.0 million milestone from Ipsen, and proceeds received from issuing common stock under our employee equity incentive plans. These increases were partially offset by the reclassification of certain investments from short-term to other long-term assets related to the standby letter of credit noted above, cash used for capital expenditures incurred in connection with expanding our laboratory facilities and acquiring related equipment, cash paid for tax withholding on equity awards, and a net increase in

operating liabilities, including a $55.0 million collaboration liability related to the Iconic amended agreement. In the future, our working capital may be impacted by some or all of these factors, the amounts and timing of which are variable.

***Cash, cash equivalents, restricted cash equivalent and investments*:** Cash and cash equivalents primarily consist of cash deposits held at major banks, commercial paper and other securities with original maturities 90 days or less. Restricted cash equivalents and investments relate to our letter of credit agreements and are invested in short-term marketable securities. For additional information regarding our cash, cash equivalents, restricted cash equivalents and investments, see "Note 4. Cash and Investments," in our "Notes to Consolidated Financial Statements" contained in Part II, Item 8 of this Annual Report on Form 10-K. The increase in cash, cash equivalents, restricted cash equivalent and investments at December 31, 2021, as compared to December 31, 2020, was primarily due to cash inflows generated by our operations, including collections of amounts due from customers, partially offset by operating cash payments for employee related expenditures, our development and discovery programs, and capital expenditures.

Cash flow activities were as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Net cash provided by operating activities	$ 400,804	$ 208,982
Net cash used in investing activities	$ (42,884)	$ (131,215)
Net cash used in financing activities	$ (14,801)	$ (25,132)

Operating Activities

Our primary source of operating cash flows is cash collections from customers related to our net product sales and cash collections from our commercial collaboration arrangements. Our primary uses of cash from operating activities are for employee related costs, costs related to our development and discovery programs, cash payments for inventory, royalties paid on our net product sales, and our leased facilities.

Cash provided by operating activities is derived by adjusting our net income for non-cash operating items such as deferred taxes, stock-based compensation, depreciation, non-cash lease expense, and changes in operating assets and liabilities, which reflect timing differences between the receipt and payment of cash associated with transactions and when they are recognized in our Consolidated Statements of Income.

Net cash provided by operating activities increased for the year ended December 31, 2021, as compared to 2020, primarily due to an increase in cash received on sales of our products, an increase in cash received from our commercial collaboration arrangements and net favorable changes in operating assets and liabilities, partially offset by an increase in cash paid for operating expenses.

Investing Activities

The changes in cash flows from investing activities primarily relates to the timing of marketable securities investment activity and capital expenditures. Our capital expenditures primarily consist of investments to expand our operations and acquire assets that further our research and development.

Net cash used in investing activities decreased for the year ended December 31, 2021 as compared to 2020 primarily due to a net increase in cash proceeds from maturities and sales of investments, net of investment purchases partially offset by an increase in capital expenditures. In 2021, capital expenditures primarily consisted of investments in leasehold improvements and equipment related to an expansion of laboratory facilities at our corporate campus and technology infrastructure investments to support our digital transformation initiatives.

Financing Activities

The changes in cash flows from financing activities primarily relate to proceeds from employee stock programs and taxes paid related to net share settlement of equity awards.

Net cash used in financing activities decreased for the year ended December 31, 2021, as compared to 2020 primarily as a result of lower withholding taxes remitted to the government related to net share settlements of equity awards and to a lesser extent a decrease in proceeds received from the issuance of common stock under our equity incentive and stock purchase plans.

Contractual Obligations

As of December 31, 2021, we anticipate the aggregate of our cash, cash equivalents and short-term investments and cash generated from operations to be sufficient to fund our contractual obligations, as well as cash requirements to support our ongoing operations and capital expenditures. Our contractual obligations as of December 31, 2021 primarily consist of:

Operating leases: We have certain lease agreements related to our corporate campus facilities, under which we are obligated to make minimum lease payments. As of December 31, 2021, we had $11.4 million of minimum lease payments due in one year and $289.1 million due over the remaining lease term. We entered into the build-to-suit lease agreement in October 2019, the term of the lease is for a period of 242 months, which is expected to begin in the first quarter of 2022. The amounts presented herein include the estimated lease commitment payments at the estimated commencement of the lease, subject to adjustment dependent upon the actual total development costs of the premises.

Purchase obligations: Purchase obligations include firm purchase commitments related to manufacturing of inventory, software services and other facilities and equipment. As of December 31, 2021, we had $40.0 million total purchase obligations due within one year and $10.6 million due after one year.

Contingent payments: We have committed to make certain contingent payments for potential future milestones, research funding commitments and royalties to certain collaboration partners as part of our agreements with those parties. We do not expect these contingent payments to have a significant impact on our liquidity in the near term.

Notes 3 and 11 of “Notes to Consolidated Financial Statements” contained in Part II, Item 8 of this Annual Report on Form 10-K include additional information regarding our contractual obligations and contingencies.

As of December 31, 2021, we did not have any material off-balance-sheet arrangements, as defined by applicable SEC regulations.

Critical Accounting Policies and Estimates

The preparation of our Consolidated Financial Statements conforms to accounting principles generally accepted in the U.S. which requires management to make judgments, estimates and assumptions that affect the reported amounts of assets, liabilities, equity, revenues and expenses, and related disclosures. An accounting policy is considered to be critical if it requires an accounting estimate to be made based on assumptions about matters that are highly uncertain at the time the estimate is made, and if different estimates that reasonably could have been used, or changes in the accounting estimates that are reasonably likely to occur periodically, could materially impact our Consolidated Financial Statements. On an ongoing basis, management evaluates its estimates including, but not limited to: those related to revenue recognition, including determining the nature and timing of satisfaction of performance obligations, and determining the standalone selling price of performance obligations, and variable consideration such as rebates, chargebacks, sales returns and sales allowances as well as milestones included in collaboration arrangements; the amounts of revenues and expenses under our profit and loss sharing agreement; recoverability of inventory; the accrual for certain liabilities including accrued clinical trial liabilities; and valuations of equity awards used to determine stock-based compensation, including certain awards with vesting subject to market or performance conditions; and the amounts of deferred tax assets and liabilities including the related valuation allowance. We base our estimates on historical experience and on various other market-specific and other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Our senior management has discussed the development, selection and disclosure of these estimates with the Audit Committee of our Board of Directors. Actual results could differ materially from those estimates.

We believe our critical accounting policies relating to revenue recognition, inventory, clinical trial accruals, stock-based compensation and income taxes reflect the more significant estimates and assumptions used in the preparation of our Consolidated Financial Statements.

For a complete description of our significant accounting policies, see “Note 1. Organization and Summary of Significant Accounting Policies” in the “Notes to Consolidated Financial Statements” contained in Part II, Item 8 of this Annual Report on Form 10-K.

Revenue Recognition

Net Product Revenues and Discounts and Allowances

We recognize revenues when our customers obtain control of promised goods or services, in an amount that reflects the consideration to which we are entitled to in exchange for those goods or services. We calculate gross product revenues based on the price that we charge to the specialty pharmacies and distributors in the U.S. We estimate our domestic net product revenues by deducting from our gross product revenues: (a) trade allowances, such as discounts for prompt payment; (b) estimated government rebates and chargebacks; (c) certain other fees paid to specialty pharmacies, distributors and commercial payors; and (d) returns.

We initially record estimates for these deductions at the time we recognize the related gross product revenue. We base our estimates for the expected utilization on customer and payer data received from the specialty pharmacies and distributors and historical utilization rates as well as third-party market research data. We update our estimates every quarter to reflect actual claims and other current information. Actual rebates and chargebacks claimed for prior periods have varied from our estimates by less than 1% of the amount deducted from gross product revenues for the years ended December 31, 2021 and 2020. Our current estimates may differ significantly from actual results.

Collaboration Revenues

We enter into collaboration arrangements with third parties, under which we license certain rights to our intellectual property, and account for the arrangements as either license revenue or collaboration services revenue when the counterparty is a customer. The terms of these arrangements typically include payment to us for one or more of the following: non-refundable, up-front license fees; development, regulatory and commercial milestone payments; product supply services; development cost reimbursements; profit sharing arrangements; and royalties on net sales of licensed products.

As part of the accounting for these arrangements, we must develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the contract. We use key assumptions to determine the standalone selling price, which may include forecast revenues and costs, clinical development timelines and costs, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success. At the inception of each arrangement that includes development milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. At the end of each subsequent reporting period, we re-evaluate the probability of earning of such development milestones and any related constraint, and if necessary, adjust our estimate of the overall transaction price. For arrangements that may include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sale occurs or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). Development milestone adjustments are recorded on a cumulative catch-up basis, which would affect collaboration services revenues in the period of adjustment. In addition, in recording revenues for our research and development services performance obligations, we use projected development cost estimates to determine the amount of revenue to record as we satisfy this performance obligation.

Inventory

We value inventory at the lower of cost or net realizable value. We determine the cost of inventory using the standard-cost method, which approximates actual cost based on a first-in, first-out method. We analyze our inventory levels quarterly and write down inventory subject to expiry in excess of expected requirements, or that has a cost basis in excess of its expected net realizable value. On a quarterly basis, we analyze our estimated production levels for the following twelve-month period, which is our normal operating cycle, and reclassify inventory we expect to use or sell in periods beyond the next twelve months into other long-term assets in the Consolidated Balance Sheets.

Clinical Trial and Collaboration Accruals

We execute all of our clinical trials with support from contract research organizations and other vendors and we accrue costs for clinical trial activities performed by these third parties based upon the estimated amount of work completed on each trial. For clinical trial expenses, the significant factors used in estimating accruals include the number of patients enrolled, the activities to be performed for each patient, the number of active clinical sites and the duration for which the patients will be enrolled in the trial. Certain of our in-licensing collaboration arrangements includes contingent

considerations in the form of development, regulatory and commercial milestones payments. We recognize the contingent considerations when they are deemed probable of achievement which requires judgment as to the probability and timing of the achievement of the underlying milestones. We monitor patient enrollment levels and assess the related research and development activities progress, including the probability of achieving milestones payments associated to the respective terms and conditions of our in-licensing and collaboration arrangements to the extent possible through internal reviews and estimates of the operational progress of our discovery and early-stage clinical development programs, correspondence with contract research organizations and review of contractual terms. We base our estimates on the best information available at the time. However, additional information may become available to us, which may allow us to make a more accurate estimate in future periods. If we do not identify costs that we have begun to incur or if we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates.

Stock-based Compensation

Stock-based compensation expense requires us to estimate the fair value of stock options, performance-based restricted stock units (PSUs) and PSUs subject to market conditions, and the estimated the number of shares subject to PSUs that will ultimately vest. To determine the fair value, we use models that require a number of complex and subjective assumptions including our stock price volatility, employee exercise patterns and risk-free interest rates. The value of a stock option is derived from its potential for appreciation. The more volatile the stock, the more valuable the option becomes because of the greater possibility of significant changes in stock price. Because there is a market for options on our common stock, we consider implied volatility as well as our historical volatility when developing an estimate of expected volatility. The expected option term also has a significant effect on the value of the option. The longer the term, the more time the option holder has to allow the stock price to increase without a cash investment and thus, the more valuable the option. Further, lengthier option terms provide more opportunity to take advantage of market highs. However, empirical data show that employees typically do not wait until the end of the contractual term of a nontransferable option to exercise. Accordingly, we are required to estimate the expected term of the option for input to an option-pricing model. Monte Carlo simulation models are used to determine grant date fair value of awards with market conditions. The assumptions used in calculating the fair value of stock options and PSUs represent management's best estimates, but these estimates involve inherent uncertainties and the application of management judgment. As a result, if factors change and we use different assumptions, our stock-based compensation expense could be materially different in the future.

We recognize stock-based compensation for PSUs over the requisite service period only for awards which we estimate will ultimately vest, which requires judgment as to the probability and timing of the achievement of the underlying performance goals. Significant factors we consider in making those judgments include forecasts of our product revenues and those of our collaboration partners, estimates regarding the operational progress of late-stage clinical development programs and discovery pipeline expansion performance targets. To the extent actual results, or updated estimates, differ from current estimates, such amounts are recorded as a cumulative adjustment in the period estimates are revised and as such, can materially affect our stock-based compensation expense in the current period and in the future.

Income Taxes

We compute our income tax provision or benefit under the asset and liability method. Significant estimates are required in determining our income tax provision or benefit. We base some of these estimates on interpretations of existing tax laws or regulations. We recognize deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Under this method, deferred tax assets and liabilities are determined on the basis of the difference between the tax basis of assets and liabilities and their respective financial reporting amounts (temporary differences) at enacted tax rates in effect for the years in which the differences are expected to reverse. A valuation allowance is established for deferred tax assets for which it is more likely than not that some portion or all of the deferred tax assets, including net operating losses and tax credits, will not be realized. We periodically re-assess the need for a valuation allowance against our deferred tax assets based on various factors including our historical earnings experience by taxing jurisdiction, and forecasts of future operating results and utilization of net operating losses and tax credits prior to their expiration. Significant judgment is required in making this assessment and, to the extent that we deem a reversal of any portion of our valuation allowance against our deferred tax assets to be appropriate, we recognize a tax benefit against our income tax provision in the period of such reversal.

Recent Accounting Pronouncements

For a description of the expected impact of recent accounting pronouncements, see "Note 1. Organization and Summary of Significant Accounting Policies" in the "Notes to Consolidated Financial Statements" contained in Part II, Item 8

of this Annual Report on Form 10-K.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to cash flow and earnings fluctuations as a result of certain market risks. These market risks primarily relate to credit risk, changes in interest rates and foreign exchange rates. Our investment portfolio is used to preserve our capital until it is required to fund operations, including our research and development activities. None of these market risk-sensitive instruments are held for trading purposes. We do not have derivative financial instruments in our investment portfolio.

Credit Risk

We manage credit risk associated with our investment portfolio through our investment policy, which limits purchases to high-quality issuers and limits the amount of our portfolio that can be invested in a single issuer.

Interest Rate Risk

We invest our cash in a variety of financial instruments, principally securities issued by the U.S. government and its agencies, investment-grade corporate bonds and commercial paper, and money market funds. These investments are denominated in U.S. Dollars. All of our interest-bearing securities are subject to interest rate risk and could decline in value if interest rates fluctuate. Substantially all of our investment portfolio consists of marketable securities with active secondary or resale markets to help ensure portfolio liquidity, and we have implemented guidelines limiting the term-to-maturity of our investment instruments. Due to the conservative and short-term nature of these instruments, we do not believe that we have a material exposure to interest rate risk. If market interest rates were to increase or decrease by one percentage point, the fair value of our investment portfolio would increase or decrease by an immaterial amount.

Foreign Exchange Rate Risk

Fluctuations in the exchange rates of the U.S. dollar and foreign currencies may have the effect of increasing or decreasing our revenues and expenses. Royalty revenues and sales-based milestones we receive from our collaboration agreements with Ipsen, Takeda and Genentech are a percentage of the net sales made by those collaboration partners from sales made in countries outside the U.S. and are denominated in currencies in which the product is sold, which is predominantly the Euro or Japanese Yen. Research and development expenses include clinical trial services performed by third-party contract research organizations and other vendors located outside the U.S. that may bill us in currencies where their services are provided, which is predominantly the Euro. If the U.S. dollar strengthens against a foreign currency, then our royalty revenues will decrease for the same number of units sold in that foreign currency and the date we achieve certain sales-based milestones may also be delayed. Similarly, if the U.S. dollar weakens against a foreign currency, then our research and development expenses would increase. However, we believe that we are not subject to material risks arising from changes in foreign exchange rates and that a hypothetical 10% increase or decrease in foreign exchange rates would not have a material adverse impact on our financial condition, results of operations or cash flows.

Item 8. Financial Statements and Supplementary Data

EXELIXIS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Exelixis, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Exelixis, Inc. (the Company) as of December 31, 2021 and January 1, 2021, the related consolidated statements of income, comprehensive income, stockholders' equity and cash flows for each of the three fiscal years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and January 1, 2021, and the results of its operations and its cash flows for each of the three fiscal years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 18, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

	Revenue recognition - product sales and accounts receivable
Description of the Matter	During the year ended December 31, 2021, the Company's gross product revenues were $1,452.9 million. As discussed in Note 1 of the financial statements, the Company sells its products principally to specialty distributors and specialty pharmacy providers, or collectively, Customers. These Customers subsequently resell the products to health care providers and patients. Revenues from product sales are recognized when control is transferred to the Customer.

Auditing the Company's product sales was challenging, specifically related to the effort required to audit Customer sales activity to assess whether incentives resulted in orders in excess of demand and whether any such transactions meet the criteria for revenue recognition. This involved judgmentally assessing factors including market demand, Customer ordering patterns, Customer inventory levels, contractual terms and incentives offered.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls designed to monitor and review inventory levels in the channel and sales under Customer incentive programs. This includes testing relevant controls over the information systems that are important to the initiation, recording and billing of revenue transactions as well as controls over the completeness and accuracy of the data used.

Our audit procedures over the Company's product sales included, among others, examination of inventory channel reports for unusual trends or transactions as well as performing analytical procedures to detect and investigate anomalies within the data. Procedures included those to detect sales of short dated product near year end as well as testing the completeness and accuracy of the underlying data. We also examined the terms and conditions of any new or amended contracts with Customers and its impact on the Company's returns reserve. We also confirmed the terms and conditions of contracts directly with a selection of Customers, including whether there are side agreements and terms not formally included in the contract that may impact the Company's returns reserve. In addition, we obtained written representations from members of the commercial function and the market access group regarding changes to Customer incentives and the completeness of the terms and conditions reported to the legal and accounting departments.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2002.

Redwood City, California
February 18, 2022

EXELIXIS, INC.
CONSOLIDATED BALANCE SHEETS
(in thousands, except per share data)

	December 31,	
	2021	**2020**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 647,169	$ 319,217
Short-term investments	819,905	887,319
Trade receivables, net	282,650	160,875
Inventory	27,493	20,973
Prepaid expenses and other current assets	57,530	57,011
Total current assets	1,834,747	1,445,395
Long-term investments	371,112	330,751
Property and equipment, net	104,031	67,384
Deferred tax assets, net	111,663	156,711
Goodwill	63,684	63,684
Other long-term assets	131,002	73,408
Total assets	$ 2,616,239	$ 2,137,333
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 24,258	$ 23,632
Accrued compensation and benefits	61,969	51,189
Accrued clinical trial liabilities	77,544	52,251
Rebates and fees due to customers	33,700	20,683
Accrued collaboration liabilities	86,753	12,456
Other current liabilities	53,366	44,447
Total current liabilities	337,590	204,658
Long-term portion of deferred revenue	8,739	3,755
Long-term portion of operating lease liabilities	51,272	49,086
Other long-term liabilities	8,023	721
Total liabilities	405,624	258,220
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.001 par value, 10,000 shares authorized and no shares issued	—	—
Common stock, $0.001 par value; 400,000 shares authorized; issued and outstanding: 318,842 and 311,627 at December 31, 2021 and 2020, respectively	319	312
Additional paid-in capital	2,427,561	2,321,895
Accumulated other comprehensive income	(758)	4,476
Accumulated deficit	(216,507)	(447,570)
Total stockholders' equity	2,210,615	1,879,113
Total liabilities and stockholders' equity	$ 2,616,239	$ 2,137,333

The accompanying notes are an integral part of these Consolidated Financial Statements.

EXELIXIS, INC.
CONSOLIDATED STATEMENTS OF INCOME
(in thousands, except per share data)

	Year Ended December 31,		
	2021	**2020**	**2019**
Revenues:			
Net product revenues	$ 1,077,256	$ 741,550	$ 759,950
License revenues	249,956	167,295	165,914
Collaboration services revenues	107,758	78,693	41,911
Total revenues	1,434,970	987,538	967,775
Operating expenses:			
Cost of goods sold	52,873	36,272	33,097
Research and development	693,716	547,851	336,964
Selling, general and administrative	401,715	293,355	228,244
Total operating expenses	1,148,304	877,478	598,305
Income from operations	286,666	110,060	369,470
Interest income	7,672	19,865	27,959
Other income (expense), net	(184)	912	680
Income before income taxes	294,154	130,837	398,109
Provision for income taxes	63,091	19,056	77,097
Net income	$ 231,063	$ 111,781	$ 321,012
Net income per share:			
Basic	$ 0.73	$ 0.36	$ 1.06
Diluted	$ 0.72	$ 0.35	$ 1.02
Weighted-average common shares outstanding:			
Basic	314,884	308,271	302,584
Diluted	322,359	318,001	315,009

The accompanying notes are an integral part of these Consolidated Financial Statements.

EXELIXIS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME
(in thousands)

	Year Ended December 31,		
	2021	**2020**	**2019**
Net income	$ 231,063	$ 111,781	$ 321,012
Other comprehensive income (loss):			
Net unrealized gains (losses) on available-for-sale debt securities, net of tax impact of $1,481, $(394), and $(1,049), respectively	(5,234)	1,407	3,770
Comprehensive income	$ 225,829	$ 113,188	$ 324,782

The accompanying notes are an integral part of these Consolidated Financial Statements.

EXELIXIS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2018	299,876	$ 300	$ 2,168,217	$ (701)	$ (880,363)	$ 1,287,453
Net income	—	—	—	—	321,012	321,012
Other comprehensive income	—	—	—	3,770	—	3,770
Issuance of common stock under equity incentive and stock purchase plans	4,955	5	27,032	—	—	27,037
Stock transactions associated with taxes withheld on equity awards	—	—	(9,904)	—	—	(9,904)
Stock-based compensation	—	—	56,602	—	—	56,602
Balance at December 31, 2019	304,831	305	2,241,947	3,069	(559,351)	1,685,970
Net income	—	—	—	—	111,781	111,781
Other comprehensive income	—	—	—	1,407	—	1,407
Issuance of common stock under equity incentive and stock purchase plans	6,796	7	24,896	—	—	24,903
Stock transactions associated with taxes withheld on equity awards	—	—	(50,018)	—	—	(50,018)
Stock-based compensation	—	—	105,070	—	—	105,070
Balance at December 31, 2020	311,627	312	2,321,895	4,476	(447,570)	1,879,113
Net income	—	—	—	—	231,063	231,063
Other comprehensive income	—	—	—	(5,234)	—	(5,234)
Issuance of common stock under equity incentive and stock purchase plans	7,215	7	24,360	—	—	24,367
Stock transactions associated with taxes withheld on equity awards	—	—	(39,142)	—	—	(39,142)
Stock-based compensation	—	—	120,448	—	—	120,448
Balance at December 31, 2021	318,842	$ 319	$ 2,427,561	$ (758)	$ (216,507)	$ 2,210,615

The accompanying notes are an integral part of these Consolidated Financial Statements.

EXELIXIS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,		
	2021	2020	2019
Net income	$ 231,063	$ 111,781	$ 321,012
Adjustments to reconcile net income to net cash provided by operating activities:			
Depreciation	13,630	9,141	8,348
Stock-based compensation	119,820	105,070	56,602
Non-cash lease expense	5,332	4,830	2,819
Deferred taxes	46,529	15,265	71,002
Other, net	23,443	3,035	88
Changes in operating assets and liabilities:			
Trade receivables, net	(122,324)	(42,470)	43,716
Inventory	(13,209)	(21,897)	(5,731)
Prepaid expenses and other assets	(39,875)	(25,831)	(5,723)
Deferred revenue	11,008	(1,051)	(9,301)
Accrued collaboration liabilities	70,297	600	4,437
Accounts payable and other liabilities	55,090	50,509	39,687
Net cash provided by operating activities	400,804	208,982	526,956
Cash flows from investing activities:			
Purchases of property, equipment and other	(64,225)	(30,345)	(12,834)
Purchases of investments	(1,357,168)	(1,070,269)	(1,182,682)
Proceeds from maturities and sales of investments	1,378,509	969,399	608,269
Net cash used in investing activities	(42,884)	(131,215)	(587,247)
Cash flows from financing activities:			
Proceeds from issuance of common stock under equity incentive and stock purchase plans	24,307	24,886	22,499
Taxes paid related to net share settlement of equity awards	(39,108)	(50,018)	(9,904)
Other, net	—	—	(42)
Net cash (used in) provided by financing activities	(14,801)	(25,132)	12,553
Net increase (decrease) in cash, cash equivalents and restricted cash equivalents	343,119	52,635	(47,738)
Cash, cash equivalents and restricted cash equivalents at beginning of period	320,772	268,137	315,875
Cash, cash equivalents and restricted cash equivalents at end of period	$ 663,891	$ 320,772	$ 268,137
Supplemental cash flow disclosures:			
Cash paid for taxes	$ 12,960	$ 4,115	$ 7,873
Non-cash operating activities:			
Right-of-use assets obtained in exchange for lease obligations	$ 4,893	$ 4,017	$ 29,562
Non-cash investing activities:			
Unpaid liabilities incurred in asset acquisition	$ 4,000	$ —	$ —
Unpaid liabilities incurred for purchases of property and equipment	$ 2,739	$ 842	$ 26
Unpaid liabilities incurred for unsettled investment purchases	$ —	$ 1,615	$ —
Accounts receivable for unsettled investment sales	$ —	$ 6,180	$ —

The accompanying notes are an integral part of these Consolidated Financial Statements.

EXELIXIS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 1. ORGANIZATION AND SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Organization

Exelixis, Inc. (Exelixis, we, our or us) is an oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Using our considerable drug discovery, development and commercialization resources and capabilities, we have invented and brought to market innovative therapies that appropriately balance patient benefits and risks; we will continue to build on this foundation as we strive to provide cancer patients with new treatment options that improve upon current standards of care.

Today, four products that originated in Exelixis laboratories are available to be prescribed to patients. Sales related to our flagship molecule, cabozantinib, account for the large majority of our revenues. Cabozantinib is an inhibitor of multiple tyrosine kinases including MET, AXL, VEGF receptors and RET and has been approved by the U.S. Food and Drug Administration (FDA) and in 61 other countries as: CABOMETYX® (cabozantinib) tablets approved for advanced renal cell carcinoma (RCC), both alone and in combination with Bristol-Myers Squibb Company's (BMS) OPDIVO® (nivolumab), for previously treated hepatocellular carcinoma (HCC) and, currently by the FDA, for previously treated, radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC); and COMETRIQ® (cabozantinib) capsules approved for progressive, metastatic medullary thyroid cancer (MTC). For physicians treating these types of cancer, cabozantinib has become or is becoming an important drug in their selection of effective therapies.

The other two products resulting from our discovery efforts are: COTELLIC® (cobimetinib), an inhibitor of MEK approved as part of multiple combination regimens to treat specific forms of advanced melanoma and marketed under a collaboration with Genentech, Inc. (a member of the Roche Group) (Genentech); and MINNEBRO® (esaxerenone), an oral, non-steroidal, selective blocker of the mineralocorticoid receptor (MR) approved for the treatment of hypertension in Japan and licensed to Daiichi Sankyo Company, Limited (Daiichi Sankyo).

Our plan is to utilize our operating cash flows and cash and investments to expand the cabozantinib franchise by potentially adding new indications in areas of unmet medical need. We will also leverage our operating cash flows to continue advancing our diverse small molecule and biotherapeutics programs, exploring multiple modalities and mechanisms of action to discover new oncology drugs.

Basis of Presentation

The accompanying Consolidated Financial Statements include the accounts of Exelixis and those of our wholly-owned subsidiaries. These entities' functional currency is the U.S. dollar. All intercompany balances and transactions have been eliminated.

We have adopted a 52- or 53-week fiscal year policy that ends on the Friday closest to December 31st. Fiscal year 2021, which was a 52-week fiscal year, ended on December 31, 2021, fiscal year 2020, which was a 52-week fiscal year, ended on January 1, 2021 and fiscal year 2019, which was a 53-week fiscal year, ended on January 3, 2020. For convenience, references in this report as of and for the fiscal years ended January 1, 2021 and January 3, 2020 are indicated as being as of and for the years ended December 31, 2020 and 2019, respectively.

We have made reclassifications to our prior years' Consolidated Financial Statements to conform to the current year's presentation. These reclassifications did not impact previously reported total revenues, income from operations, net income, total assets, total liabilities, total operating, investing or financing cash flows or total stockholders' equity.

Segment Information

We operate in one business segment that focuses on the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Our Chief Executive Officer, as the chief operating decision-maker, manages and allocates resources to our operations on a total consolidated basis. Consistent with this decision-making process, our Chief Executive Officer uses consolidated, single-segment financial information for purposes of evaluating performance, forecasting future period financial results, allocating resources and setting incentive targets.

All of our long-lived assets are located in the U.S. See “Note 2. Revenues” for enterprise-wide disclosures about product sales, revenues from major customers and revenues by geographic region.

Use of Estimates

The preparation of the accompanying Consolidated Financial Statements conforms to accounting principles generally accepted in the U.S., which requires management to make judgments, estimates and assumptions that affect the reported amounts of assets, liabilities, equity, revenues and expenses, and related disclosures. On an ongoing basis, we evaluate our significant estimates. We base our estimates on historical experience and on various other market-specific and other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results could differ materially from those estimates.

Recently Adopted Accounting Pronouncements

On January 1, 2021, we adopted the Accounting Standards Board’s (FASB) Accounting Standards Update (ASU) 2019-12*, Income Taxes* (Topic 740)-Simplifying the Accounting for Income Taxes (ASU 2019-12). ASU 2019-12 simplifies the accounting for income taxes by removing certain exceptions to the general principles in Accounting Standards Codification (ASC) Topic 740, Income Taxes and clarifying and amending existing guidance. Our adoption of ASU 2019-12 did not have a significant impact on the accompanying Consolidated Financial Statements.

Cash, Cash Equivalents, Restricted Cash Equivalents and Investments

We consider all highly liquid investments purchased with an original maturity of three months or less to be cash equivalents. Cash equivalents include high-grade, short-term investments in money market funds, certificates of deposit and marketable debt securities which are subject to minimal credit and market risk.

We designate all investments in marketable debt securities as available-for-sale and therefore, report such investments at fair value, with unrealized gains and losses recorded in accumulated other comprehensive income. For securities sold prior to maturity, the cost of securities sold is based on the specific identification method. We include realized gains and losses on the sale of investments in other income, net in the accompanying Consolidated Statements of Income.

We classify those investments that we do not require for use in current operations and that mature in more than 12 months as long-term investments in the accompanying Consolidated Balance Sheets. The classification of restricted cash equivalents as short-term or long-term is dependent upon the longer of the remaining term to maturity of the investment or the remaining term of the related restriction.

Investment Impairment

Quarterly, we assess each of our investments in available-for-sale debt securities whose fair value is below its cost basis to determine if the investment’s impairment is due to credit-related factors or noncredit-related factors. Factors considered in determining whether an impairment is credit-related include the extent to which the investment’s fair value is less than its cost basis, declines in published credit ratings, issuer default on interest or principal payments, and declines in the financial condition and near-term prospects of the issuer. If we determine a credit-related impairment exists, we will measure the credit loss based on a discounted cash flows model. Credit-related impairments on available-for-sale debt securities are recognized as an allowance for credit losses with a corresponding adjustment to other income, net in the accompanying Consolidated Statements of Income. The portion of the impairment that is not credit-related is recorded as a reduction of other comprehensive income (loss), net of applicable taxes.

We have elected to exclude accrued interest from both the fair value and the amortized cost basis of the available-for-sale debt securities for the purposes of identifying and measuring an impairment. We write-off accrued interest as a reduction of interest income when an issuer has defaulted on interest payments due on a security.

Fair Value Measurements

We define fair value as the amounts that would be received upon sale of an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date (exit price). When determining the fair value measurements for assets and liabilities which are required to be recorded at fair value, we consider the principal or most advantageous market in which we would transact and the market-based risk measurements or assumptions that

market participants would use in pricing the asset or liability, such as risks inherent in valuation techniques, transfer restrictions and credit risks.

Forward Foreign Currency Contracts

In January 2021, we initiated an operational hedging program and entered into forward contracts to hedge certain operational exposures for the changes in foreign currency exchange rates associated with assets or liabilities denominated in foreign currencies, primarily the Euro.

As of December 31, 2021, we had one forward contract outstanding to sell €9.8 million. The forward contract with a maturity of three months is recorded at fair value and is included in prepaid expenses and other current assets in the Consolidated Balance Sheets. The unrealized loss on the forward contract is not material as of December 31, 2021. The forward contract is considered a Level 2 in the fair value hierarchy of our fair value measurements. For the year ended December 31, 2021, we recognized $0.8 million of net gains on the maturity of our forward contracts, which is included in other income (expense), net on our Consolidated Statements of Income.

Foreign Currency Remeasurement

Monetary assets and liabilities denominated in currencies other than the functional currency are remeasured using exchange rates in effect at the end of the period and related gains or losses are recorded in other income, net in the accompanying Consolidated Statements of Income. Net foreign currency gains or losses were immaterial for the years ended December 31, 2021, 2020 and 2019, respectively.

Accounts Receivable

Trade receivables, net, contain amounts billed to our customers for product sales, and amounts billed to our collaboration partners for development, regulatory and sales-based milestone payments, royalties on the sale of licensed products, profit-sharing arrangements, development cost reimbursements, and payments for product supply services. Our customers are primarily pharmaceutical and biotechnology companies that are located in the U.S., and collaboration partners that are located in Europe and Japan. We record trade receivables net of allowances for credit losses and chargebacks, and cash discounts for prompt payment. We apply an aging method to estimate credit losses and consider our historical loss information, adjusted to account for current economic conditions, and reasonable and supportable forecasts of future economic conditions affecting our customers. We write off trade receivables and related allowances for credit losses when it becomes probable we will not collect the amount receivable. Write-offs for the years ended December 31, 2021 and 2020 have been insignificant.

Inventory

We value inventory at the lower of cost or net realizable value. We determine the cost of inventory using the standard-cost method, which approximates actual cost based on a first-in, first-out method. We analyze our inventory levels quarterly and write down inventory subject to expiry in excess of expected requirements, or that has a cost basis in excess of its expected net realizable value. These write downs are charged to either cost of goods sold or the cost of supplied product included in collaboration services revenues in the accompanying Consolidated Statements of Income. On a quarterly basis, we analyze our estimated production levels for the following twelve-month period, which is our normal operating cycle, and reclassify inventory we expect to use or sell in periods beyond the next twelve months into other long-term assets in the accompanying Consolidated Balance Sheets.

Property and Equipment

We record property and equipment at cost, net of depreciation. We compute depreciation using the straight-line method based on estimated useful lives of the assets, which ranges up to 15 years and depreciate leasehold improvements over the lesser of their estimated useful lives or the remainder of the lease term. We charge repairs and maintenance costs to expense as incurred. We periodically review property and equipment for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. We did not recognize impairment charges in any of the periods presented.

Goodwill

We recorded goodwill amounts as the excess of purchase price over identifiable net assets acquired based on their estimated fair value. We review the carrying amount of goodwill for impairment annually and whenever events or changes

in circumstance indicate that the carrying value may not be recoverable. We perform our annual assessment of the recoverability of our goodwill as of the first day of our fourth quarter. The assessment of recoverability may first consider qualitative factors to determine whether the existence of events or circumstances leads to a determination that it is more-likely-than-not that the fair value of a reporting unit is less than its carrying amount. We perform a quantitative assessment if the qualitative assessment results in a more-likely-than-not determination or if a qualitative assessment is not performed. The quantitative assessment considers whether the carrying amount of a reporting unit exceeds its fair value, in which case an impairment charge is recorded for the amount by which the carrying amount of a reporting unit exceeds its fair value, limited to the goodwill balance. We operate in one business segment, which is also considered to be our sole reporting unit and therefore, goodwill is tested for impairment at the enterprise level. We did not recognize any impairment charges in any of the periods presented.

Long-Lived Assets

The carrying value of our long-lived assets, which includes property and equipment, right-of-use assets and leasehold improvements, is reviewed for impairment whenever events or changes in circumstances indicate that the carrying value of the asset may not be recoverable. Should there be an indication of impairment, we test for recoverability by comparing the estimated undiscounted future cash flows expected to result from the use of the asset to the carrying amount of the asset or asset group. If the asset or asset group is determined to be impaired, any excess of the carrying value of the asset or asset group over its estimated fair value is recognized as an impairment loss.

Revenue

We account for revenues under the guidance of ASU Topic 606, *Revenues from Contracts with Customers* (Topic 606). Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration to which the entity is entitled to in exchange for those goods or services. To determine revenue recognition for arrangements that are within the scope of Topic 606, we perform the following five steps: (1) identify the contract(s) with a customer; (2) identify the performance obligations in the contract; (3) determine the transaction price; (4) allocate the transaction price to the performance obligations in the contract; and (5) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

Net Product Revenues

We sell our products principally to specialty distributors and specialty pharmacy providers, or collectively, our Customers. These Customers subsequently resell our products to health care providers and patients. In addition to distribution agreements with Customers, we enter into arrangements with health care providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of our products. Revenues from product sales are recognized when the Customer obtains control of our product, which occurs at a point in time, typically upon delivery to the Customer.

Product Sales Discounts and Allowances

We record revenues from product sales at the net sales price (transaction price), which includes estimates of variable consideration for which reserves are established primarily from discounts, chargebacks, rebates, co-pay assistance, returns and other allowances that are offered within contracts between us and our Customers, health care providers, payors and other indirect customers relating to the sales of our products. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (if the amount is payable to the Customer) or a current liability (if the amount is payable to a party other than a Customer). Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted Customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of our contracts. The amount of variable consideration that is included in the transaction price may be constrained, and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenues and earnings in the period such variances become known.

Chargebacks: Chargebacks are discounts that occur when contracted Customers purchase directly from a specialty distributor. Contracted Customers, which currently consist primarily of Public Health Service institutions, Federal government entities purchasing via the Federal Supply Schedule, Group Purchasing Organizations, and health maintenance organizations, generally purchase the product at a discounted price. The specialty distributor, in turn, charges back to us the difference between the price initially paid by the specialty distributor and the discounted price paid to the specialty distributor by the Customer. The allowance for chargebacks is based on actual chargebacks received and an estimate of sales to contracted Customers.

Discounts for Prompt Payment: Our Customers in the U.S. receive a discount of 2% for prompt payment. We expect our Customers will earn 100% of their prompt payment discounts and, therefore, we deduct the full amount of these discounts from total product sales when revenues are recognized.

Rebates: Allowances for rebates include mandated discounts under the Medicaid Drug Rebate Program, other government programs and commercial contracts. Rebate amounts owed after the final dispensing of the product to a benefit plan participant are based upon contractual agreements or legal requirements with public sector benefit providers, such as Medicaid. The allowance for rebates is based on statutory or contractual discount rates and expected utilization. Our estimates for the expected utilization of rebates are based on Customer and payer data received from the specialty pharmacies and distributors and historical utilization rates. Rebates are generally invoiced by the payer and paid in arrears, such that the accrual balance consists of an estimate of the amount expected to be incurred for the current quarter's shipments to our Customers, plus an accrual balance for known prior quarters' unpaid rebates. If actual future rebates vary from estimates, we may need to adjust our accruals, which would affect net product revenues in the period of adjustment.

Allowances for rebates also include amounts related to the Medicare Part D Coverage Gap Discount Program. In the U.S. during 2020, the Medicare Part D prescription drug benefit mandated participating manufacturers to fund 70% of the Medicare Part D insurance coverage gap for prescription drugs sold to eligible patients. Our estimates for expected Medicare Part D coverage gap amounts are based on Customer and payer data received from specialty pharmacies and distributors and historical utilization rates. Funding of the coverage gap is invoiced and paid in arrears so that the accrual balance consists of an estimate of the amount expected to be incurred for the current quarter's shipments to Customer, plus an accrual balance for known prior quarters' unpaid claims. If actual future funding varies from estimates, we may need to adjust our accruals, which would affect net product revenues in the period of adjustment.

Co-payment Assistance: Patients who have commercial insurance and meet certain eligibility requirements may receive co-payment assistance. We accrue a liability for co-payment assistance based on actual program participation and estimates of program redemption using Customer data provided by the specialty distributor that administers the copay program.

Other Customer Credits: We pay fees to our Customers for account management, data management and other administrative services. To the extent the services received are distinct from the sale of products to the Customer, we classify these payments in selling, general and administrative expenses in our Consolidated Statements of Income.

Collaboration Revenues

We assess whether our collaboration agreements are subject to ASC Topic 808, *Collaborative Arrangements* (Topic 808) based on whether they involve joint operating activities and whether both parties have active participation in the arrangement and are exposed to significant risks and rewards. To the extent that the arrangement falls within the scope of Topic 808, we apply by analogy the unit of account guidance under Topic 606 to identify distinct performance obligations, and then determine whether a customer relationship exists for each distinct performance obligation. If we determine a performance obligation within the arrangement is with a customer, we apply the guidance in Topic 606. If a portion of a distinct bundle of goods or services within an arrangement is not with a customer, then the unit of account is not within the scope of Topic 606, and the recognition and measurement of that unit of account shall be based on analogy to authoritative accounting literature or, if there is no appropriate analogy, a reasonable, rational, and consistently applied accounting policy election.

We enter into collaboration arrangements, under which we license certain rights to our intellectual property to third parties. The terms of these arrangements typically include payments to us for one or more of the following: nonrefundable up-front license fees; development, regulatory and sales-based milestone payments; product supply services; development cost reimbursements; profit-sharing arrangements; and royalties on net sales of licensed products. As part of the accounting for these arrangements, we develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the contract. These key assumptions may include

forecasted revenues, clinical development timelines and costs, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

Up-front License Fees: If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from nonrefundable up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license, which generally occurs at or near the inception of the contract. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenues from nonrefundable up-front fees. We evaluate the measure of progress at the end of each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Regulatory and Development Milestone Payments: At the inception of each arrangement that includes development milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until uncertainty associated with the approvals has been resolved. The transaction price is then allocated to each performance obligation, on a relative standalone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achieving such development and regulatory milestones and any related variable consideration constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis.

Product Supply Services: Arrangements that include a promise for the future supply of drug product for either clinical development or commercial supply at the licensee's discretion are generally considered as options. We assess if these options provide a material right to the licensee and if so, they are accounted for as separate performance obligations.

Development Cost Reimbursements: Our collaboration arrangements may include promises of future clinical development and drug safety services, as well as participation on certain joint committees. When such services are provided to a customer, and they are distinct from the licenses provided to our collaboration partners, these promises are accounted for as a separate performance obligation, which we estimate using internal development costs incurred and projections through the term of the arrangements. We record revenues for these services as the performance obligations are satisfied over time based on measure of progress. However, if we conclude that our collaboration partner is not a customer for those collaborative research and development activities, we present such payments as a reduction of research and development expenses.

Profit-sharing Arrangements: Under the terms of our collaboration agreement with Genentech for cobimetinib, we are entitled to a share of U.S. profits and losses received in connection with the commercialization of cobimetinib. We account for this arrangement in accordance with Topic 606. We have determined that we are an agent under the agreement and therefore revenues are recorded net of costs incurred. We record revenues for the variable consideration associated with the profits and losses under the collaboration agreement when it is probable that a significant reversal in the amount of cumulative revenues recognized will not occur.

Royalty and Sales-based Milestone Payments: For arrangements that include royalties and sales-based milestone payments, including milestone payments earned for the first commercial sale of a product, the license is deemed to be the predominant item to which such payments relate and we recognize revenues at the later of when the related sales occur or when the performance obligation to which the royalty has been allocated has been satisfied.

Cost of Goods Sold

Cost of goods sold is related to our product revenues and consists primarily of a 3% royalty we are required to pay on all net sales of any product incorporating cabozantinib, the cost of manufacturing, indirect labor costs, write-downs related to expiring and excess inventory, shipping and other third-party logistics and distribution costs for our product.

We consider regulatory approval of product candidates to be uncertain and product manufactured prior to regulatory approval may not be sold unless regulatory approval is obtained. As such, the manufacturing costs for product candidates incurred prior to regulatory approval were not capitalized as inventory but are expensed as research and development costs.

Research and Development Expenses

Research and development expenses consist of (1) direct and indirect internal costs for drug discovery; (2) upfront license and project initiation fees, license option fees and option exercise fees, funded research and milestone payments incurred or probable to be incurred for our in-licensing arrangements with our collaboration partners for research programs in development and prior to regulatory approval; and (3) development costs associated with our clinical trial projects, which include fees paid to Contract Research Organizations (CRO) performing work on our behalf.

Our clinical trial projects have been executed with support from third-party CROs, who specialize in conducting and managing global clinical trials. We accrue expenses for clinical trial activities performed by the CROs based upon the estimated amount of work completed on each trial. For clinical trial expenses, the significant factors used in estimating accruals include direct CRO costs, the number of patients enrolled, the number of active clinical sites involved, the duration for which the patients will be enrolled in the trial and patient out of pocket costs. We monitor patient enrollment levels and related activities to the extent possible through CRO meetings and correspondence, internal reviews and review of contractual terms. We base our estimates on the best information available at the time. However, additional information may become available to us which may allow us to make a more accurate estimate in future periods. In this event, we may be required to record adjustments to research and development expenses in future periods when the actual level of activity becomes more certain. As described further above, certain payments made to us from our collaboration partners may be presented as a reduction of research and development expense.

Leases

We determine if an arrangement includes a lease at the inception of the agreement. For each of our lease arrangements, we record a right-of-use asset representing our right to use an underlying asset for the lease term and a lease liability representing our obligation to make lease payments. Operating lease right-of-use assets and liabilities are recognized at the lease commencement date based on the net present value of lease payments over the lease term. In determining the discount rate used to calculate the net present value of lease payments, we use our incremental borrowing rate based on the information available at the lease commencement date. Our leases may include options to extend or terminate the lease which are included in the lease term when it is reasonably certain that we will exercise any such options. Lease expense for our operating leases is recognized on a straight-line basis over the lease term. We have elected not to apply the recognition requirements of *ASU 2016-02*, *Leases* (Topic 842) for short-term leases.

Advertising

Advertising expenses were $31.8 million, $25.1 million and $17.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. We expense the costs of advertising, including promotional expenses, as incurred. Advertising expenses are recorded in selling, general and administrative expenses.

Stock-Based Compensation

We account for stock-based payments to employees, including grants of service-based restricted stock units (RSUs), performance-based restricted stock units (PSUs), service-based stock options and purchases under our 2000 Employee Stock Purchase Plan (ESPP) in accordance with ASC 718, *Compensation-Stock Compensation*, which requires that stock-based payments (to the extent they are compensatory) be recognized in our Consolidated Statements of Income based on their fair values. We account for forfeitures of stock-based awards as they occur. The expense for stock-based compensation is based on the grant date fair value of the award. The grant date fair value of RSUs and PSUs are estimated as the value of the underlying shares of our common stock. The grant date fair values are estimated using a Monte Carlo simulation pricing model for certain PSUs with market vesting conditions and a Black-Scholes Merton option pricing model for other stock options. Both option pricing models require the input of subjective assumptions. These variables include, but are not limited to, the expected volatility of our stock price and the expected term of the awards. We consider both implied and historical volatility when developing an estimate of expected volatility. We estimate the term using historical data. We recognize compensation expense over the requisite service period on an accelerated basis for awards with a market or performance condition and on a straight-line basis for service-based stock options and awards. Compensation expense related to PSUs is recognized when we determine that it is probable that the performance goals will be achieved, which we assess on a quarterly basis.

Provision for Income Taxes

Our provision for income taxes is computed under the asset and liability method. Significant estimates are required in determining our provision for income taxes. Some of these estimates are based on interpretations of existing tax laws or regulations. We recognize deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Under this method, deferred tax assets and liabilities are determined on the basis of the difference between the tax basis of assets and liabilities and their respective financial reporting amounts (temporary differences) at enacted tax rates in effect for the years in which the differences are expected to reverse. A valuation allowance is established for deferred tax assets for which it is more likely than not that some portion or all of the deferred tax assets, including net operating losses and tax credits, will not be realized. We periodically re-assess the need for a valuation allowance against our deferred tax assets based on various factors including our historical earnings experience by taxing jurisdiction, and forecasts of future operating results and utilization of net operating losses and tax credits prior to their expiration. Significant judgment is required in making this assessment and, to the extent that a reversal of any portion of our valuation allowance against our deferred tax assets is deemed appropriate, a tax benefit will be recognized against our provision for income taxes in the period of such reversal.

We recognize tax benefits from uncertain tax positions only if it is more likely than not that the tax position will be sustained upon examination by the tax authorities based on the technical merits of the position. An adverse resolution of one or more of these uncertain tax positions in any period could have a material impact on the results of operations for that period.

Recent Accounting Pronouncements Not Yet Adopted

There were no new accounting pronouncements issued since our filing of the Annual Report on Form 10-K for the year ended December 31, 2020, which could have a significant effect on our Consolidated Financial Statements.

NOTE 2. REVENUES

Revenues consisted of the following (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Product revenues:			
Gross product revenues	$ 1,452,913	$ 962,591	$ 957,621
Discounts and allowances	(375,657)	(221,041)	(197,671)
Net product revenues	1,077,256	741,550	759,950
Collaboration revenues:			
License revenues	249,956	167,295	165,914
Collaboration services revenues	107,758	78,693	41,911
Total collaboration revenues	357,714	245,988	207,825
Total revenues	$ 1,434,970	$ 987,538	$ 967,775

Net product revenues and license revenues are recorded in accordance with ASC Topic 606, *Revenue from Contracts with Customers* (Topic 606). License revenues include the recognition of the portion of milestone payments allocated to the transfer of intellectual property licenses for which it had become probable in the current period that the milestone would be achieved and a significant reversal of revenues would not occur, as well as royalty revenues and our share of profits under our collaboration agreement with Genentech. Collaboration services revenues were recorded in accordance with ASU 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606* and by analogy to Topic 606. Collaboration services revenues include the recognition of deferred revenues for the portion of upfront and milestone payments allocated to our research and development services performance obligations, development cost reimbursements earned under our collaboration agreements, product supply revenues, net of product supply costs, and the royalties we paid on sales of products containing cabozantinib by our collaboration partners. We received notification that, effective January 1, 2021, Royalty Pharma plc (Royalty Pharma) acquired from GlaxoSmithKline (GSK) all rights, title and interest in royalties on total net sales of any product containing cabozantinib for non-U.S. markets

for the full term of the royalty and for the U.S. market through September 2026, after which time U.S. royalties will revert back to GSK.

Net product revenues by product were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
CABOMETYX	$ 1,054,050	$ 718,687	$ 733,421
COMETRIQ	23,206	22,863	26,529
Net product revenues	$ 1,077,256	$ 741,550	$ 759,950

The percentage of total revenues by customer who individually accounted for 10% or more of our total revenues were as follows:

	Year Ended December 31,		
	2021	2020	2019
Ipsen Pharma SAS	21%	15%	16%
Affiliates of CVS Health Corporation	14%	14%	15%
Affiliates of McKesson Corporation	14%	12%	12%
Affiliates of AmerisourceBergen Corporation	14%	11%	11%
Affiliates of Optum Specialty Pharmacy	8%	11 %	13 %

As of December 31, 2021 and 2020, the percentage of trade receivables by customer who individually accounted for 10% or more of our trade receivables were as follows:

	December 31,	
	2021	2020
Ipsen Pharma SAS	50 %	23 %
Affiliates of AmerisourceBergen Corporation	11 %	11 %
Affiliates of McKesson Corporation	10 %	12 %
Affiliates of CVS Health Corporation	9 %	11 %
Takeda Pharmaceutical Company Limited	2 %	10 %

Total revenues by geographic region were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
U.S.	$ 1,089,396	$ 752,890	$ 770,244
Europe	302,073	151,631	152,771
Japan	43,501	83,017	44,760
Total revenues	$ 1,434,970	$ 987,538	$ 967,775

Total revenues include net product revenues attributed to geographic regions based on ship-to location and license and collaboration services revenues attributed to geographic regions based on the location of our collaboration partners' headquarters.

Product Sales Discounts and Allowances

The activities and ending reserve balances for each significant category of discounts and allowances (which constitute variable consideration) were as follows (in thousands):

	Chargebacks, Discounts for Prompt Payment and Other	Other Customer Credits/Fees and Co-pay Assistance	Rebates	Total
Balance at December 31, 2019	$ 7,514	$ 3,497	$ 15,222	$ 26,233
Provision related to sales made in:				
Current period	146,537	16,162	58,049	220,748
Prior periods	33	(352)	612	293
Payments and customer credits issued	(144,231)	(16,028)	(56,479)	(216,738)
Balance at December 31, 2020	9,853	3,279	17,404	30,536
Provision related to sales made in:				
Current period	243,119	30,728	100,361	374,208
Prior periods	(64)	(111)	1,624	1,449
Payments and customer credits issued	(238,283)	(25,021)	(94,564)	(357,868)
Balance at December 31, 2021	$ 14,625	$ 8,875	$ 24,825	$ 48,325

The allowance for chargebacks, discounts for prompt payment and other are recorded as a reduction of trade receivables, net, and the remaining reserves are recorded as rebates and fees due to customers in the accompanying Consolidated Balance Sheets.

Contract Assets and Liabilities

We receive payments from our collaboration partners based on billing schedules established in each contract. Amounts are recorded as accounts receivable when our right to consideration is unconditional. We may also recognize revenue in advance of the contractual billing schedule and such amounts are recorded as a contract asset when recognized. We may be required to defer recognition of revenue for upfront and milestone payments until we perform our obligations under these arrangements, and such amounts are recorded as deferred revenue upon receipt or when due. For those contracts that have multiple performance obligations, contract assets and liabilities are reported on a net basis at the contract level. Contract assets as of December 31, 2021 are primarily related to contract assets from Ipsen Pharma SAS (Ipsen) and contract liabilities as of December 31, 2021 are primarily related to deferred revenues from Takeda Pharmaceutical Company Limited (Takeda).

Contract assets and liabilities were as follows (in thousands):

	December 31,	
	2021	2020
Contract assets[1]	$ 1,665	$ —
Contract liabilities:		
Current portion[2]	$ 7,814	$ 1,790
Long-term portion[3]	8,739	3,755
Total contract liabilities	$ 16,553	$ 5,545

(1) Presented in other long-term assets in the accompanying Consolidated Balance Sheets.
(2) Presented in other current liabilities in the accompanying Consolidated Balance Sheets.
(3) Presented in the long-term portion of deferred revenues in the accompanying Consolidated Balance Sheets.

During the years ended December 31, 2021, 2020 and 2019, we recognized $8.5 million, $9.2 million and $6.5 million, respectively, in revenues that were included in the beginning deferred revenues balance for those years.

During the years ended December 31, 2021, 2020 and 2019, we recognized $148.7 million, $169.7 million and $161.2 million, respectively, in revenues for performance obligations satisfied in previous periods. Such revenues were primarily related to milestone and royalty payments allocated to our license performance obligations for our collaborations with Ipsen Pharma SAS (Ipsen), Takeda, Daiichi Sankyo and Genentech.

As of December 31, 2021, $87.5 million of the combined transaction prices for our Ipsen and Takeda collaborations were allocated to performance obligations that had not yet been satisfied. See "Note 3. Collaboration Agreements—Cabozantinib Collaborations —Performance Obligations and Transaction Prices for our Ipsen and Takeda Collaborations" for additional information about the expected timing to satisfy these performance obligations.

NOTE 3. COLLABORATION AGREEMENTS AND BUSINESS DEVELOPMENT ACTIVITIES

We have established multiple collaborations with leading biopharmaceutical companies for the commercialization and further development of our cabozantinib franchise. Additionally, we have made considerable progress under our existing research collaboration and in-licensing arrangements to further enhance our early-stage pipeline and expand our ability to discover, develop and commercialize novel therapies with the goal of providing new treatment options for cancer patients and their physicians. Historically, we also entered into other collaborations with leading biopharmaceutical companies pursuant to which we out-licensed other compounds and programs in our portfolio.

Under these collaborations, we are generally entitled to receive milestone and royalty payments, and for certain collaborations, to receive payments for product supply services, development cost reimbursements, and/or profit-sharing payments. See "Note 2. Revenues" for additional information on revenues recognized under our collaboration agreements during the years ended December 31, 2021, 2020 and 2019.

Cabozantinib Commercial Collaborations

Ipsen Collaboration

Description of the Collaboration

In February 2016, we entered into a collaboration agreement with Ipsen for the commercialization and further development of cabozantinib. Under the collaboration agreement, as amended, Ipsen received exclusive commercialization rights for current and potential future cabozantinib indications outside of the U.S. and Japan. We have also agreed to collaborate with Ipsen on the development of cabozantinib for current and potential future indications. The parties' efforts are governed through a joint steering committee and appropriate subcommittees established to guide and oversee the collaboration's operation and strategic direction; provided, however, that we retain final decision-making authority with respect to cabozantinib's ongoing development.

During the second quarter of 2021, Ipsen opted into and is now co-funding the development costs for COSMIC-311, our phase 3 pivotal trial evaluating cabozantinib versus placebo in patients with RAI-refractory DTC who have progressed after up to two VEGF receptor-targeted therapies. Under the collaboration agreement, Ipsen is now obligated to reimburse us for their share of COSMIC-311 global development costs, as well as an additional payment calculated as a percentage of such costs, triggered by the timing of the exercise of its option. We determined that the decision to opt in and co-fund the development costs for COSMIC-311 represented a contract modification for additional distinct services at their standalone selling price and therefore was treated as a separate contract under Topic 606. Accordingly, collaboration services revenues for the year ended December 31, 2021, includes a cumulative catch-up of $43.2 million for Ipsen's share of global development costs incurred since the beginning of the study and through the opt-in date.

Unless earlier terminated, the collaboration agreement has a term that continues, on a product-by-product and country-by-country basis, until the latter of (1) the expiration of patent claims related to cabozantinib, (2) the expiration of regulatory exclusivity covering cabozantinib or (3) ten years after the first commercial sale of cabozantinib, other than COMETRIQ. A related supply agreement will continue in effect until expiration or termination of the collaboration agreement. The collaboration agreement may be terminated for cause by either party based on uncured material breach of either the collaboration agreement or the supply agreement by the other party, bankruptcy of the other party or for safety

reasons. We may terminate the collaboration agreement if Ipsen challenges or opposes any patent covered by the collaboration agreement. Ipsen may terminate the collaboration agreement if the FDA or European Medicines Agency (EMA) orders or requires substantially all cabozantinib clinical trials to be terminated. Ipsen also has the right to terminate the collaboration agreement on a region-by-region basis after the first commercial sale of cabozantinib in advanced RCC in the given region. Upon termination by either party, all licenses granted by us to Ipsen will automatically terminate, and, except in the event of a termination by Ipsen for our material breach, the licenses granted by Ipsen to us shall survive such termination and shall automatically become worldwide, or, if Ipsen were to terminate only for a particular region, then for the terminated region. Following termination by us for Ipsen's material breach, or termination by Ipsen without cause or because we undergo a change of control by a party engaged in a competing program, Ipsen is prohibited from competing with us for a period of time.

Consideration under the Collaboration

In consideration for the exclusive license and other rights contained in the collaboration agreement, including commercialization rights in Canada, we received aggregate upfront payments of $210.0 million from Ipsen in 2016. As of December 31, 2021, we have achieved aggregate milestones of $462.5 million related to regulatory, development and sales-based threshold by Ipsen since the inception of the collaboration agreement, including $112.5 million, $20.0 million and $55.0 million in milestones achieved during the years ended December 31, 2021, 2020 and 2019, respectively.

As of December 31, 2021, we are eligible to receive additional regulatory and development milestone payments from Ipsen totaling an aggregate of $46.5 million, as well as sales-based milestones, including milestone payments earned for the first commercial sale of a product, of up to $350.0 million and CAD$26.5 million. We excluded these milestones from the transaction price as of December 31, 2021 because we determined such payments to be fully constrained under Topic 606 due to the fact that it was not probable that a significant reversal of cumulative revenue would not occur, given the inherent uncertainty of success with these milestones. We will adjust the constraint applied to the variable consideration at each reporting period as uncertain events are resolved or other changes in circumstances occur. As of December 31, 2021, $44.2 million of the transaction price allocated to our research and development services performance obligation had not been satisfied. See "—Performance Obligations and Transaction Prices for our Ipsen and Takeda Collaborations", below, for additional information related to the revenue recognition for this collaboration.

We also receive royalty revenues on the net sales of cabozantinib by Ipsen outside of the U.S. and Japan. During the year ended December 31, 2021 and going forward, we are entitled to receive a tiered royalty of 22% to 26% on annual net sales, with separate tiers for Canada; these royalty tiers reset each calendar year.

Any variable consideration related to royalties and sales-based milestones will be recognized when the related sales occur as these amounts have been determined to relate to the relevant transferred license and therefore are recognized as the related sales occur.

We are required to pay a 3% royalty on all net sales of any product incorporating cabozantinib, including net sales by Ipsen.

We are responsible for funding cabozantinib-related development costs for those trials in existence at the time we entered into the collaboration agreement with Ipsen; global development costs for additional trials are shared between the parties, with Ipsen reimbursing us for 35% of such costs, provided Ipsen chooses to opt into such trials. Ipsen has opted into and is co-funding certain clinical trials, including: CheckMate -9ER, COSMIC-021, COSMIC-311, COSMIC-312, CONTACT-01 and CONTACT-02.

We remain responsible for manufacturing and supply of cabozantinib for all development and commercialization activities under the collaboration agreement. Relatedly, we entered into a supply agreement with Ipsen to supply finished, labeled drug product to Ipsen for distribution in the territories outside of the U.S. and Japan for the term of the collaboration agreement. The product is supplied at our cost, as defined in the agreement.

Revenues from the Collaboration

Revenues under the collaboration agreement with Ipsen were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
License revenues	$ 207,982	$ 93,495	$ 117,360
Collaboration services revenues	94,091	58,136	35,411
Total	$ 302,073	$ 151,631	$ 152,771

Milestone revenues for the year ended December 31, 2021 included $100.0 million related to a commercial sales milestone from Ipsen upon their achievement of $400.0 million of net sales of cabozantinib in the related Ipsen license territory over four consecutive quarters and a $12.5 million regulatory milestone achieved upon submission of a variation application to the EMA for CABOMETYX as a treatment for patients with previously treated RAI-refractory DTC.

Takeda Collaboration

Description of the Collaboration

In January 2017, we entered into a collaboration and license agreement with Takeda, which was subsequently amended effective March 2018, May 2019 and September 2020, to, among other things, modify the amount of reimbursements we receive, for costs associated with our required pharmacovigilance activities and milestones we are eligible to receive, as well as modify certain cost-sharing obligations related to the Japan-specific development costs associated with CONTACT-01 and CONTACT-02. We determined the amendment in September 2020 represented a contract modification that was treated as a termination of an existing contract and the creation of a new contract under Topic 606. As a result, we allocated the remaining transaction price to the performance obligations identified in the contract. The two remaining performance obligations are the research and development services associated with committed studies and the research and development services associated with CONTACT-01, CONTACT-02, and certain cohorts of COSMIC-021 studies. In allocating the transaction price for the modified contract we estimated the standalone selling price for the performance obligations. We utilized development costs incurred for these obligations in process and the projections of costs through the term of the arrangement. Revenue is recognized when, or as, we satisfy our performance obligations by transferring the promised services to Takeda. Revenue is being recognized using the cost proportional performance method, based on costs incurred to perform the research and development services, since the level of costs incurred over time is thought to best reflect the transfer of services to Takeda.

Takeda is responsible for a portion of the costs associated with the cabozantinib development plan's current and future trials, provided Takeda opts into such trials, and 100% of costs associated with the cabozantinib development activities that are exclusively for the benefit of Japan. Takeda has opted into and is co-funding CheckMate -9ER, certain cohorts of COSMIC-021, CONTACT-01 and CONTACT-02. Under the collaboration agreement, as amended, Takeda has exclusive commercialization rights for current and potential future cabozantinib indications in Japan, and the parties have agreed to collaborate on the clinical development of cabozantinib in Japan. The operation and strategic direction of the parties' collaboration is governed through a joint executive committee and appropriate subcommittees.

Unless earlier terminated, the collaboration agreement has a term that continues, on a product-by-product basis, until the earlier of (1) two years after first generic entry with respect to such product in Japan or (2) the later of (A) the expiration of patent claims related to cabozantinib and (B) the expiration of regulatory exclusivity covering cabozantinib in Japan. The collaboration agreement may be terminated for cause by either party based on uncured material breach by the other party, bankruptcy of the other party or for safety reasons. For clarity, Takeda's failure to achieve specified levels of commercial performance, based upon sales volume and/or promotional effort, during the first six years of the collaboration will constitute a material breach of the collaboration agreement. We may terminate the agreement if Takeda challenges or opposes any patent covered by the collaboration agreement. After the commercial launch of cabozantinib in Japan, Takeda may terminate the collaboration agreement upon twelve months' prior written notice following the third anniversary of the first commercial sale of cabozantinib in Japan. Upon termination by either party, all licenses granted by us to Takeda will automatically terminate, and the licenses granted by Takeda to us shall survive such termination and shall automatically become worldwide.

Consideration under the Collaboration

In consideration for the exclusive license and other rights contained in the collaboration agreement, we received an upfront payment of $50.0 million from Takeda in 2017. As of December 31, 2021, we have also achieved regulatory and development milestones in the aggregate of $127.0 million since the inception of the collaboration agreement, including $35.0 million, $66.0 million and $16.0 million in milestones achieved during the years ended December 31, 2021, 2020 and 2019, respectively.

Under the collaboration agreement, as amended in 2020, we are eligible to receive additional regulatory and development milestone payments, without contractual limit, for additional potential future indications. We are further eligible to receive commercial milestones, including milestone payments earned for the first commercial sale of a product, of up to $119.0 million. We excluded these milestones from the transaction price as of December 31, 2021 because we determined such payments to be fully constrained under Topic 606 due to the fact that it was not probable that a significant reversal of cumulative revenue would not occur, given the inherent uncertainty of success with these milestones. We will adjust the constraint applied to the variable consideration at each reporting period as uncertain events are resolved or other changes in circumstances occur.

We also receive royalty revenues on the net sales of cabozantinib in Japan. We are entitled to receive a tiered royalty of 15% to 24% on the initial $300.0 million of net sales, and following this initial $300.0 million of net sales, we are then entitled to receive a tiered royalty of 20% to 30% on annual net sales thereafter; these 20% to 30% royalty tiers reset each calendar year. Any variable consideration related to royalties and sales-based milestones will be recognized when the related sales occur as these amounts have been determined to relate to the relevant transferred license and therefore are recognized as the related sales occur.

We are required to pay a 3% royalty on all net sales of any product incorporating cabozantinib, including net sales by Takeda.

Under the collaboration agreement, we are responsible for the manufacturing and supply of cabozantinib for all development and commercialization activities under the collaboration agreement. Additionally, we entered into a clinical supply agreement covering the supply of cabozantinib to Takeda for the term of the collaboration agreement, as well as a quality agreement that provides respective quality responsibilities for the aforementioned supply. Furthermore, at the time we entered into the collaboration agreement, the parties also entered into a safety data exchange agreement, which defines each partner's responsibility for safety reporting. This agreement also requires us to maintain the global safety database for cabozantinib. To meet our obligations to regulatory authorities for the reporting of safety data from Japan from sources other than our sponsored global clinical development trials, we rely on data collected and reported to us by Takeda.

Revenues from the Collaboration

Collaboration services revenues under the collaboration agreement with Takeda were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
License revenues	$ 26,058	$ 61,115	$ 18,112
Collaboration services revenues	13,667	20,557	6,510
Total collaboration revenues	$ 39,725	$ 81,672	$ 24,622

Milestone revenues for the year ended December 31, 2021 included $18.9 million recognized in connection with a $20.0 million milestone we achieved upon Takeda's first commercial sale in Japan of CABOMETYX in combination with OPDIVO for the treatment of patients with unresectable, advanced or metastatic RCC.

As of December 31, 2021, $43.3 million of the transaction price was allocated to our research and development services performance obligations that have not yet been satisfied.

Performance Obligations and Transaction Prices for our Ipsen and Takeda Collaborations

We identified two performance obligations for the Ipsen collaboration agreement: (1) the transfer of an exclusive license for the commercialization and further development of cabozantinib; and (2) research and development services,

which includes certain committed studies for the development of cabozantinib, pharmacovigilance services and participation on various joint committees (as defined in the specific collaboration agreements).

We identified two remaining performance obligations for the Takeda collaboration agreement due to the amendment in September 2020: (1) research and development services, which includes certain committed studies for the development of cabozantinib, pharmacovigilance services and participation on various joint committees (as defined in the specific collaboration agreements) and (2) the research and development services associated with CONTACT-01, CONTACT-02, and certain cohorts of COSMIC-021 studies. As part of the original contract, we had a performance obligation associated with the exclusive license for the commercialization and further development of cabozantinib, which was transferred in 2017.

We have allocated the transaction price for each of these collaborations to the identified performance obligations based on our best estimate of their relative standalone selling price. For the licenses, the estimate of the relative standalone selling price was determined using a discounted cash flow valuation utilizing forecasted revenues and costs. For research and development services the estimate of the relative standalone selling price was determined using an adjusted market assessment approach that relies on internal and external costs and market factors.

The portion of the transaction price allocated to our license performance obligation is recorded immediately as our license represents functional intellectual property that was transferred at a point in time. The portion of the transaction price allocated to our research and development services performance obligation is being recognized as revenue using the inputs method based on our internal development projected cost estimates through the current estimated patent expiration of cabozantinib in the European Union for the Ipsen Collaboration and Japan for the Takeda Collaboration, both of which are early 2030.

We adjust the constraint applied to the variable consideration for the collaboration agreements in each reporting period as uncertain events are resolved or other changes in circumstances occur and we allocate those changes in the transaction price between our performance obligations. During the years ended December 31, 2021, 2020 and 2019, the transaction price of the Ipsen and Takeda collaboration agreements increased as a result of the achievement of various milestones, and the reimbursements of research and development services related to committed and opt-in studies. We further updated the transaction price based upon the actual research and development services performed during the period and changes in our estimated reimbursements for our future research and development services. The portion of the increase in transaction price that was allocated to the previously satisfied performance obligations for the transfer of an intellectual property license was recognized during the period and the portion allocated to research and development services will be recognized in future periods as those services are delivered through early 2030. As of December 31, 2021, variable consideration related to the remaining unearned regulatory and development milestones for both agreements remained constrained due to the fact that it was not probable that a significant reversal of cumulative revenue would not occur.

Cabozantinib Development Collaborations

BMS

In February 2017, we entered into a clinical trial collaboration agreement with BMS for the purpose of exploring the therapeutic potential of cabozantinib in combination with BMS's immune checkpoint inhibitors (ICIs), nivolumab and/or ipilimumab, to treat a variety of types of cancer. As part of the collaboration, we are evaluating the triplet combination of cabozantinib, nivolumab and ipilimumab as a treatment option for RCC in the COSMIC-313 trial. Under the collaboration agreement with BMS, we may also evaluate these combinations in other phase 3 pivotal trials in various other tumor types.

Under the collaboration agreement with BMS, as subsequently amended effective March 2019, May 2019 and November 2019, each party granted to the other a non-exclusive, worldwide (within the collaboration territory as defined in the collaboration agreement and its supplemental agreements), non-transferable, royalty-free license to use the other party's compounds in the conduct of each clinical trial. The parties' efforts are governed through a joint development committee established to guide and oversee the collaboration's operation. Each trial is conducted under a combination Investigational New Drug application, unless otherwise required by a regulatory authority. Each party is responsible for supplying finished drug product for the applicable clinical trial, and responsibility for the payment of costs for each such trial will be determined on a trial-by-trial basis. Unless earlier terminated, the collaboration agreement will remain in effect until the completion of all clinical trials under the collaboration, all related trial data has been delivered to both parties and the completion of any then agreed upon analysis. The collaboration agreement may be terminated for cause by either party

based on uncured material breach by the other party, bankruptcy of the other party or for safety reasons. Upon termination by either party, the licenses granted to each party to conduct a combined therapy trial will terminate.

F. Hoffmann-La Roche Ltd. (Roche) Collaboration

In February 2017, we entered into a master clinical supply agreement with Roche for the purpose of evaluating cabozantinib and Roche's ICI, atezolizumab, in locally advanced or metastatic solid tumors. Under this agreement with Roche, in June 2017, we initiated COSMIC-021, a phase 1b dose escalation study that is evaluating the safety and tolerability of cabozantinib in combination with Roche's atezolizumab in patients with locally advanced or metastatic solid tumors, and in December 2018, we initiated COSMIC-312, a multicenter, randomized, controlled phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus sorafenib in previously untreated advanced HCC. We are the sponsor of both trials, and Roche is providing atezolizumab free of charge.

In December 2019, we entered into a joint clinical research agreement with Roche for the purpose of further evaluating the combination of cabozantinib with atezolizumab in patients with locally advanced or metastatic solid tumors, including in the phase 3 pivotal clinical trials in advanced non-small cell lung cancer (CONTACT-01), metastatic castration-resistant prostate cancer (CONTACT-02) and RCC (CONTACT-03). If a party to the joint clinical research agreement proposes any additional combined therapy trials beyond these phase 3 pivotal trials, the joint clinical research agreement provides that such proposing party must notify the other party and that if agreed to, any such additional combined therapy trial will become part of the collaboration, or if not agreed to, the proposing party may conduct such additional combined therapy trial independently, subject to specified restrictions set forth in the joint clinical research agreement.

In July 2020, a supplement to the joint clinical research agreement was signed amongst us, Roche and Takeda due to Takeda opting into fund the combined therapy trial of CONTACT-01 sponsored by Roche. Chugai was added as an affiliate of Roche. All parties including Chugai conduct combined therapy trials in Japan upon the terms of the joint clinical research agreement.

Under the joint clinical research agreement, each party granted to the other a non-exclusive, worldwide (excluding, in our case, territory already the subject of a license by us to Takeda), non-transferable, royalty-free license, with a right to sublicense (subject to limitations), to use the other party's intellectual property and compounds solely as necessary for the party to perform its obligations under the joint clinical research agreement. The parties' efforts will be governed through a joint steering committee established to guide and oversee the collaboration and the conduct of the combined therapy trials. Each party will be responsible for providing clinical supply of their drug for all combined therapy trials, and the cost of the supply will be borne by such party. The clinical trial expenses for each combined therapy trial agreed to be conducted jointly under the joint clinical research agreement will be shared equally between the parties, and the clinical trial expenses for each additional combined therapy trial not agreed to be conducted jointly under the joint clinical research agreement will be borne by the proposing party, except that the cost of clinical supply for all combined therapy trials will be borne by the party that owns the applicable product.

We determined the contract is within the scope of Topic 808 as it involves joint operating activities where both parties have active participation in the arrangement and are exposed to significant risks and rewards. Payments between us and Roche under this arrangement are not subject to other accounting literature. Payments due to Roche for our share of clinical trial costs incurred by Roche will be recorded as research and development expense and payments due from Roche for their share of clinical trial costs incurred by us will be recorded as a reduction of research and development expense.

Unless earlier terminated, the joint clinical research agreement provides that it will remain in effect until the completion of all combined therapy trials under the collaboration, the delivery of all related trial data to both parties, and the completion of any then agreed-upon additional analyses. The joint clinical research agreement may be terminated for cause by either party based on any uncured material breach by the other party, bankruptcy of the other party or for safety reasons. Upon termination by either party, the licenses granted to each party will terminate upon completion of any ongoing activities under the joint clinical research agreement.

GSK and Royalty Pharma

In October 2002, we established a product development and commercialization collaboration agreement with GSK, that required us to pay a 3% royalty to GSK on the total worldwide net sales of any product incorporating cabozantinib by us and our collaboration partners. As disclosed in Note 2, we received notification that, effective January 1, 2021, Royalty Pharma acquired from GSK all rights, title and interest in royalties on total net sales of any product containing cabozantinib for non-U.S. markets for the full term of the royalty and for U.S. market through September 2026, after which time U.S. royalties will revert back to GSK. Royalty revenues earned by GSK and Royalty Pharma in connection with our sales of cabozantinib are included in cost of goods sold and as a reduction of collaboration services revenues for sales by our collaboration partners. Such royalty revenues were $46.6 million, $32.7 million and $31.3 million during the years ended December 31, 2021, 2020 and 2019, respectively.

Other Collaborations

Genentech Collaboration

We have out-licensed to Genentech under a worldwide collaboration agreement, the development and commercialization of cobimetinib, under the brand name COTELLIC. The terms of the collaboration agreement require that we share in the profits and losses received or incurred in connection with the commercialization of COTELLIC in the U.S. In addition to our profit share in the U.S., we are entitled to low double-digit royalties on net sales of COTELLIC outside the U.S.

During the years ended December 31, 2021, 2020, and 2019, we recognized $12.1 million, $11.3 million, and $10.3 million, in revenues from profits and losses on U.S commercialization and royalties on ex-U.S. sales under the collaboration agreement with Genentech and are included within license revenues on our Consolidated Statements of Income.

Daiichi Sankyo

We have granted to Daiichi Sankyo an exclusive, worldwide license to certain intellectual property primarily relating to compounds that modulate MR, including esaxerenone, an oral, non-steroidal, selective MR antagonist. In January 2019, the Japanese Ministry of Health, Labour and Welfare approved esaxerenone, under the brand name MINNEBRO, as a treatment for patients with hypertension.

We have achieved milestones of $20.0 million for the year ended December 31, 2019 for the first commercial sale of MINNEBRO and are eligible to receive additional sales-based milestone payments of up to $90.0 million under this collaboration agreement. In addition, we are entitled to receive low double-digit royalties on sales of MINNEBRO.

License revenue under the collaboration agreement with Daiichi Sankyo was $3.8 million, $1.3 million and $20.1 million for the years ended December 31, 2021, 2020 and 2019, respectively.

Research Collaborations, In-Licensing Arrangements and Other Business Development Activities

We entered into collaborative arrangements with other pharmaceutical or biotechnology companies to develop and commercialize drug candidates or intellectual property. Our research collaborations and in-licensing arrangements are intended to enhance our early-stage pipeline and expand our ability to discover, develop and commercialize novel therapies with the goal of providing new treatment options for cancer patients and their physicians. Our research collaborations, in-licensing arrangements and other strategic transactions include upfront payments, development, regulatory, commercial milestone payments and royalty payments, contingent upon the occurrence of certain future events linked to the success of the asset in development. Certain of our research collaborations provide us exclusive options that give us the right to license programs developed under the research collaborations for further discovery and development. When we decide to exercise the options, we are required to pay an exercise fee and then assume the responsibilities for all subsequent clinical development, manufacturing and commercialization. In conjunction with each of these collaborative in-licensing arrangements, we were subject to upfront payments and will make payments for potential future development milestones of up to $254.3 million, regulatory milestones of up to $426.5 million and commercial milestones of up to $1,911.5 million, each in the aggregate per product or target, as well as royalties on future net product sales. In conjunction with an asset purchase agreement, we made payments of $10.0 million for the initial technology transfer, and subject to certain conditions, will make a $4.0 million payment upon the completion of the technology transfer of certain materials and documents specified in the asset purchase agreement. We will also make payments for potential future development milestones of up to $42.0 million and regulatory milestones of up to $22.5 million, per product.

In December 2021, we amended our collaboration agreement with Iconic to acquire broad rights to use the anti-TF antibody used in XB002 for any application, including conjugated to other payloads, as well as rights within oncology to a number of other anti-TF antibodies developed by Iconic, including for use in ADCs and multispecific biotherapeutics. Under the amended agreement, we agreed to pay a final one-time payment to Iconic of $55.0 million and will not owe any further payments, but we will continue to be responsible for milestone payments and royalties owed to other companies pursuant to prior agreements between Iconic and those companies. Upon signing the amendment, we recognized $55.0 million in research and development expense, which amount was payable as of December 31, 2021 and presented in accrued collaboration liabilities in our Consolidated Balance Sheets.

During the years ended December 31, 2021, 2020, and 2019, we recognized $176.1 million, $96.4 million and $47.7 million, respectively, relating to upfront license payments, research and development funding, development milestones, option fees and other fees within research and development expenses on the Consolidated Statements of Income.

NOTE 4. CASH AND INVESTMENTS

Cash, Cash Equivalents and Restricted Cash Equivalents

A reconciliation of cash, cash equivalents, and restricted cash equivalents reported in the accompanying Consolidated Balance Sheets to the amount reported within the accompanying Consolidated Statements of Cash Flows was as follows (in thousands):

	December 31,	
	2021	2020
Cash and cash equivalents	$ 647,169	$ 319,217
Restricted cash equivalents included in other long-term assets	16,722	1,555
Cash, cash equivalents, and restricted cash equivalents as reported within the accompanying Consolidated Statements of Cash Flows	$ 663,891	$ 320,772

Restricted cash equivalents are used to collateralize letters of credit and consist of money-market funds and certificates of deposit with original maturities of 90 days or less. The restricted cash equivalents are classified as other long-term assets based upon the remaining term of the underlying restriction. As of December 31, 2021, restricted cash equivalents included $15.2 million of short-term investments, which is collateral under our January 2021 standby letter of credit to guarantee our obligation to fund a portion of the total tenant improvements related to our build-to-suit lease at our corporate campus. As we fund these tenant improvements, our restricted cash becomes available for operations.

Cash, cash equivalents, restricted cash equivalents and investment

Cash, cash equivalents, restricted cash equivalents and investments consisted of the following (in thousands):

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Debt securities available-for-sale:				
Commercial paper	$ 945,801	$ 42	$ (2)	$ 945,841
Corporate bonds	541,774	876	(1,672)	540,978
U.S. Treasury and government-sponsored enterprises	33,965	1	(21)	33,945
Municipal bonds	12,924	15	(35)	12,904
Total debt securities available-for-sale	1,534,464	934	(1,730)	1,533,668
Cash	135,653	—	—	135,653
Money market funds	66,531	—	—	66,531
Certificates of deposit	119,056	—	—	119,056
Total cash, cash equivalents, restricted cash equivalents and investments	$ 1,855,704	$ 934	$ (1,730)	$ 1,854,908

	December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Debt securities available-for-sale:				
Commercial paper	$ 569,456	$ 372	$ —	$ 569,828
Corporate bonds	543,520	5,244	(7)	548,757
U.S. Treasury and government-sponsored enterprises	208,326	232	(4)	208,554
Municipal Bonds	28,680	83	(1)	28,762
Total debt securities available-for-sale	1,349,982	5,931	(12)	1,355,901
Cash	82,176	—	—	82,176
Money market funds	40,761	—	—	40,761
Certificates of deposit	60,004	—	—	60,004
Total cash, cash equivalents, restricted cash equivalents and investments	$ 1,532,923	$ 5,931	$ (12)	$ 1,538,842

Interest receivable was $2.9 million and $4.5 million as of December 31, 2021 and 2020, respectively, and is included in prepaid and other current assets in the accompanying Consolidated Balance Sheets.

Realized gains and losses on the sales of investments were insignificant during the years ended December 31, 2021, 2020 and 2019.

We manage credit risk associated with our investment portfolio through our investment policy, which limits purchases to high-quality issuers and limits the amount of our portfolio that can be invested in a single issuer. The fair value and gross unrealized losses on debt securities available-for-sale in an unrealized loss position were as follows (in thousands):

	December 31, 2021	
	Fair Value	Gross Unrealized Losses
Corporate bonds	$ 385,053	$ (1,672)
Commercial paper	43,290	(2)
U.S. Treasury and government-sponsored enterprises	18,962	(21)
Municipal bonds	7,475	(35)
Total	$ 454,780	$ (1,730)

	December 31, 2020	
	Fair Value	Gross Unrealized Losses
Corporate bonds	$ 28,445	$ (7)
U.S. Treasury and government-sponsored enterprises	21,989	(4)
Municipal bonds	5,865	(1)
Total	$ 56,299	$ (12)

All securities presented have been in an unrealized loss position for less than 12 months. There were 133 and 14 debt securities in an unrealized loss position as of December 31, 2021 and 2020, respectively. During the years ended December 31, 2021 and 2020, we did not record an allowance for credit losses or other impairment charges on our investment securities. Based upon our quarterly impairment review, we determined that the unrealized losses were not attributed to credit risk, but were primarily associated with changes in interest rates and market liquidity. Based on the scheduled maturities of our investments, we determined that it was more likely than not that we will hold these investments for a period of time sufficient for a recovery of our cost basis.

The fair value of debt securities available-for-sale by contractual maturity was as follows (in thousands):

	December 31,	
	2021	2020
Maturing in one year or less	$ 1,168,256	$ 1,034,150
Maturing after one year through five years	365,412	321,751
Total debt securities available-for-sale	$ 1,533,668	$ 1,355,901

NOTE 5. FAIR VALUE MEASUREMENTS

Fair value reflects the amounts that would be received upon sale of an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. The fair value hierarchy has the following three levels:

- Level 1 - quoted prices (unadjusted) in active markets for identical assets and liabilities;
- Level 2 - inputs other than level 1 that are observable either directly or indirectly, such as quoted prices in active markets for similar instruments or on industry models using data inputs, such as interest rates and prices that can be directly observed or corroborated in active markets; and
- Level 3 - unobservable inputs that are supported by little or no market activity that are significant to the fair value measurement.

The classifications within the fair value hierarchy of our financial assets that were measured and recorded at fair value on a recurring basis were as follows (in thousands):

	December 31, 2021		
	Level 1	Level 2	Total
Commercial paper	$ —	$ 945,841	$ 945,841
Corporate bonds	—	540,978	540,978
U.S. Treasury and government-sponsored enterprises	—	33,945	33,945
Municipal bonds	—	12,904	12,904
Total debt securities available-for-sale	—	1,533,668	1,533,668
Money market funds	66,531	—	66,531
Certificates of deposit	—	119,056	119,056
Total financial assets carried at fair value	$ 66,531	$ 1,652,724	$ 1,719,255

	December 31, 2020		
	Level 1	Level 2	Total
Commercial paper	$ —	$ 569,828	$ 569,828
Corporate bonds	—	548,757	548,757
U.S. Treasury and government-sponsored enterprises	—	208,554	208,554
Municipal bonds	—	28,762	28,762
Total debt securities available-for-sale	—	1,355,901	1,355,901
Money market funds	40,761	—	40,761
Certificates of deposit	—	60,004	60,004
Total financial assets carried at fair value	$ 40,761	$ 1,415,905	$ 1,456,666

When available, we value investments based on quoted prices for those financial instruments, which is a Level 1 input. Our remaining investments are valued using third-party pricing sources, which use observable market prices, interest rates and yield curves observable at commonly quoted intervals for similar assets as observable inputs for pricing, which is a Level 2 input.

The carrying amount of our remaining financial assets and liabilities, which include cash, receivables and payables, approximate their fair values due to their short-term nature.

NOTE 6. INVENTORY

Inventory consisted of the following (in thousands):

	December 31,	
	2021	2020
Raw materials	$ 8,867	$ 7,773
Work in process	27,717	20,610
Finished goods	12,927	7,291
Total	$ 49,511	$ 35,674
Balance Sheet classification:		
Current portion included in inventory	$ 27,493	$ 20,973
Long-term portion included in other long-term assets	22,018	14,701
Total	$ 49,511	$ 35,674

NOTE 7. PROPERTY AND EQUIPMENT

Property and equipment consisted of the following (in thousands):

		December 31,	
	Estimated Useful Lives	2021	2020
Leasehold improvements	up to 15 years	$ 73,589	$ 40,694
Computer equipment and software	3 years	14,877	18,376
Furniture and fixtures	7 years	15,780	14,931
Laboratory equipment	5 years	23,744	11,707
Construction in progress		16,872	16,360
Total property and equipment		144,862	102,068
Less: accumulated depreciation		(40,831)	(34,684)
Total property and equipment, net		$ 104,031	$ 67,384

Depreciation expense was $13.6 million, $9.1 million and $8.3 million during the years ended December 31, 2021, 2020 and 2019, respectively.

NOTE 8. EMPLOYEE BENEFIT PLANS

Equity Incentive Plans and ESPP

We allocated the stock-based compensation expense for our equity incentive plans and our ESPP as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Research and development	$ 46,654	$ 37,198	$ 19,374
Selling, general and administrative	73,166	67,872	37,228
Total stock-based compensation expense	$ 119,820	$ 105,070	$ 56,602

	Year Ended December 31,		
	2021	2020	2019
Stock options	$ 19,048	$ 19,863	$ 23,422
Restricted stock units	53,629	35,675	26,056
Performance stock units	43,428	47,106	4,878
ESPP	3,715	2,426	2,246
Total stock-based compensation expense	$ 119,820	$ 105,070	$ 56,602

We have several equity incentive plans under which we granted stock options and RSUs, including PSUs, to employees and directors. At December 31, 2021, 11,004,584 shares were available for grant under the Exelixis, Inc. 2017 Equity Incentive Plan (as amended and restated, the 2017 Plan). The share reserve is reduced by 1 share for each share issued pursuant to a stock option award and 1.5 shares for full value awards granted in the form of RSUs or PSUs. On May 20, 2020, at our 2020 Annual Meeting of Stockholders, our stockholders approved the amendment and restatement of the 2017 Plan. The amendment and restatement increased the share reserve under the 2017 Plan by 21,000,000 shares, subject to adjustment for certain changes in our capitalization, which became effective immediately upon stockholder approval.

The Board of Directors delegated responsibility for administration of our equity incentive plans to the Compensation Committee of our Board of Directors, including the authority to determine the term, exercise price and vesting requirements of each grant. Stock options granted to our employees and directors generally have a four-year vesting term and a one-year vesting term, respectively, an exercise price equal to the fair market value on the date of grant, and a seven-year life from the date of grant. RSUs granted to our employees and directors generally have a four-year vesting term and a one-year vesting term, respectively. PSUs granted pursuant to our equity incentive plans vest upon specified service conditions and the achievement of a performance target or market condition.

We have adopted a Change in Control and Severance Benefit Plan for certain executive officers. Eligible Change in Control and Severance Benefit Plan participants include employees with the title of vice president and above. If a participant's employment is terminated without cause during a period commencing one month before and ending thirteen months following a change in control, as defined in the plan document, then the Change in Control and Severance Benefit Plan participant is entitled to have the vesting of all their outstanding equity awards accelerated and the exercise period for their stock options extended to no more than one year.

We have an ESPP that allows for qualified employees (as defined in the ESPP) to purchase shares of our common stock at a price equal to the lower of 85% of the closing price at the beginning of the offering period or 85% of the closing price at the end of each six-month purchase period. As of December 31, 2021, we had 3,168,354 shares available for issuance under our ESPP. Pursuant to the ESPP, we issued 536,226, 534,419 and 483,009 shares of common stock at an average price per share of $17.76, $14.55 and $12.60 during the years ended December 31, 2021, 2020 and 2019, respectively. Cash received from purchases under the ESPP for the years ended December 31, 2021, 2020 and 2019 was $9.5 million, $7.8 million and $6.1 million, respectively.

We used a Black-Scholes Merton option pricing model to value stock options and ESPP purchases. The weighted average grant-date fair value per share of stock options and ESPP purchases were as follows:

	Year Ended December 31,		
	2021	2020	2019
Stock options	$ 9.04	$ 9.44	$ 8.19
ESPP	$ 6.12	$ 6.12	$ 4.85

The grant-date fair value of stock option grants and ESPP purchases was estimated using the following assumptions:

	Year Ended December 31,		
	2021	2020	2019
Stock options:			
Risk-free interest rate	0.74%	0.30%	1.77%
Dividend yield	—%	—%	—%
Volatility	51%	54%	48%
Expected life	4.6 years	4.4 years	4.3 years
ESPP:			
Risk-free interest rate	0.08 %	0.79 %	2.16 %
Dividend yield	— %	— %	— %
Volatility	47 %	52 %	50 %
Expected life	6 months	6 months	6 months

We considered both implied and historical volatility in developing our estimate of expected volatility. The assumption for the expected life of stock options is based on historical exercise patterns and post-vesting termination behavior. The risk-free interest rate is based on U.S. Treasury rates with the same or similar term as the underlying award. Our dividend rate is based on historical experience and our investors' current expectations.

The fair value of RSUs, including PSUs, was based on the closing price of the underlying common stock on the date of grant.

Activity for stock options during the year ended December 31, 2021 was as follows (in thousands**,** except per share amounts):

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
Stock options outstanding at December 31, 2020	16,129	$ 12.72		
Granted	2,573	$ 21.33		
Exercised	(4,486)	$ 4.23		
Cancelled	(545)	$ 21.15		
Stock options outstanding at December 31, 2021	13,671	$ 16.79	3.3 years	$ 48,860
Stock options exercisable at December 31, 2021	9,962	$ 15.23	2.4 years	$ 48,171

As of December 31, 2021, there was $27.8 million of unrecognized compensation expense related to our unvested stock options. The compensation expense for the unvested stock options will be recognized over a weighted-average period of 2.7 years.

The aggregate intrinsic value in the table above represents the total intrinsic value (the difference between our closing stock price on the last trading day of fiscal 2021 and the exercise prices, multiplied by the number of in-the-money stock options) that would have been received by the stock option holders had all stock option holders exercised their stock options on December 31, 2021. The total intrinsic value of stock options exercised during the years ended December 31, 2021, 2020 and 2019 was $76.0 million, $106.5 million and $54.1 million, respectively. Cash received from stock option exercises during the years ended December 31, 2021, 2020 and 2019 was $14.8 million, $26.9 million and $16.4 million, respectively.

Activity for RSUs during the year ended December 31, 2021 was as follows (in thousands, except per share amounts):

	Shares	Weighted Average Grant Date Fair Value	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
RSUs outstanding at December 31, 2020	5,378	$ 21.96		
Awarded	4,220	$ 21.34		
Vested and released	(2,020)	$ 22.03		
Forfeited	(750)	$ 21.69		
RSUs outstanding at December 31, 2021	6,828	$ 21.58	1.7 years	$ 124,824

As of December 31, 2021, there was $123.6 million of unrecognized compensation expense related to our unvested RSUs which will be recognized over a weighted-average period of 2.9 years.

Activity for PSUs, during the year ended December 31, 2021 was as follows (in thousands**,** except per share amounts):

	Shares	Weighted Average Grant Date Fair Value	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
PSUs outstanding at December 31, 2020	7,378	$ 21.70		
Awarded	2,056	$ 24.54		
Vested and released	(2,388)	$ 19.76		
Forfeited	(736)	$ 22.57		
PSUs outstanding at December 31, 2021	6,310	$ 23.00	3.0 years	$ 98,121

In March 2021, in connection with our long-term incentive compensation program, we awarded certain employees 1,027,650 (the 2021 target amount) PSUs, subject to a performance and a market condition (the 2021 PSUs). Pursuant to the terms of 2021 PSUs, the holders of the awards may earn up to 200% of the 2021 target amount, or up to 2,055,300 total shares, depending on the level of achievement of the performance condition related to certain net product revenues and a total shareholder return (TSR) market condition. The TSR market condition is based on our relative TSR percentile rank compared to companies in the Nasdaq Biotechnology Index during the performance period, which is January 2, 2021 through December 29, 2023. Fifty percent of the shares earned subject to the performance and market conditions will vest at the end of the performance period and the remainder will vest approximately one year later subject to an employee's continuous service. The 2021 PSUs will be forfeited if the performance condition at or above a threshold level is not achieved by December 29, 2023. The performance condition for a threshold of net product revenues relative to the 2021 PSUs was deemed probable of achievement in the fourth quarter of 2021.

A Monte Carlo simulation model was used to determine the grant date fair value of $24.54 for the 2021 PSUs based on the following assumptions:

Fair value of the Company's common stock on grant date	$ 21.31
Expected volatility	49 %
Risk-free interest rate	0.29 %
Dividend yield	— %

During the year ended December 31, 2020, in connection with our long-term incentive compensation program, we awarded 2,327,840 PSUs (the 2020 target amount) that will vest upon the achievement of performance targets related to clinical trial positive top-line results and product approvals by the FDA (the 2020 PSUs). Pursuant to the terms of the 2020 PSUs, employees may earn up to 200% of the 2020 target amount, or 4,655,680 total shares, depending on the volume and timing of achievement of the performance targets. The 2020 PSUs will be forfeited if the performance targets are not met by December 31, 2024. The performance condition for threshold achievement of a product approval by the FDA relative to the 2020 PSUs occurred in the third quarter of 2021 representing 25% of the 2020 target amount.

During the year ended December 31, 2019, in connection with our long-term incentive compensation program, we awarded 1,926,605 PSUs (the 2019 target amount) that vest upon the achievement of performance targets related to product approvals by the FDA (the 2019 PSUs). Pursuant to the terms of the 2019 PSUs, employees may earn up to 200% of the 2019 target amount, or 3,853,210 total shares, depending on the volume and timing of achievement of the performance targets. The performance condition for early achievement of the 2019 PSUs occurred during 2020 representing 150% of the 2019 target amount. The performance condition for earning the remaining 50% of the 2019 target amount occurred in early 2021.

During the year ended December 31, 2018, we awarded 693,131 PSUs that vest upon the achievement of certain product revenue, late-stage clinical development programs and discovery pipeline expansion performance targets (the 2018 PSUs). The performance targets for 167,726 remaining 2018 PSUs were achieved in 2021.

Expense recognition for PSUs commences when it is determined that attainment of the performance target is probable. Of the aggregate outstanding PSUs, 4,853,112 relate to awards for which we achieved the performance target. As of December 31, 2021, the remaining unrecognized compensation expense for the PSUs achieved or deemed probable of achievement related to the PSUs was $12.1 million, which will be recognized over a weighted-average period of 3.0 years. The total unrecognized compensation expense for the PSUs for which we have not yet determined that attainment of the performance target is probable was $121.6 million as of December 31, 2021.

Exelixis, Inc. 401(k) Plan (the 401(k) Plan)

We sponsor the 401(k) Plan under which we have historically made matching contributions to our employees' 401(k) accounts in the form of our common stock. Beginning in 2020, our matching contributions are in the form of cash. We recorded compensation expense of $9.5 million, $6.7 million and $4.6 million for the years ended December 31, 2021, 2020 and 2019, respectively, for matching contributions to our employees 401(k) accounts.

NOTE 9. PROVISION FOR INCOME TAXES

Our income before income taxes is derived solely from within the U.S. Our provision for income taxes was as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Current:			
Federal	$ 11,338	$ —	$ —
State	5,224	3,791	6,095
Total current tax expense	$ 16,562	$ 3,791	$ 6,095
Deferred:			
Federal	$ 46,416	$ 14,886	$ 71,580
State	113	379	(578)
Total deferred tax expense	46,529	15,265	71,002
Provision for income taxes	$ 63,091	$ 19,056	$ 77,097

The provision for income taxes for the years ended December 31, 2021, 2020, and 2019 primarily relates to the utilization of federal tax attributes and state taxes in jurisdictions outside of California, for which we do not have net operating loss carryforwards due to a limited operating history. Our historical net operating losses were sufficient to fully offset any federal taxable income for the years ended December 31, 2020 and 2019 but were not sufficient to fully offset federal taxable income for the year ended December 31, 2021.

The reconciliation of the U.S. federal income tax provision at the statutory federal income tax rate of 21% for each of the years ended December 31, 2021, 2020 and 2019, respectively, to our provision for income taxes was as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
U.S. federal income tax provision at statutory rate	$ 61,772	$ 27,476	$ 83,603
State tax (benefit) expense	1,336	(2,232)	1,148
Change in valuation allowance	2,883	5,525	3,208
Research credits	(6,263)	(11,356)	(8,299)
Stock-based compensation	(11,831)	(20,399)	(9,177)
Non-deductible executive compensation	11,182	18,067	4,228
Branded prescription drug fee	2,897	2,537	1,099
Other	1,115	(562)	1,287
Provision for income taxes	$ 63,091	$ 19,056	$ 77,097

Deferred tax assets and liabilities reflect the net tax effects of net operating loss and tax credit carryforwards and temporary differences between the carrying amounts of assets and liabilities for financial reporting and the amounts used for income tax purposes.

Our deferred tax assets and liabilities were as follows (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 17,993	$ 37,454
Tax credit carryforwards	101,460	126,625
Depreciation and amortization	7,764	18,414
Stock-based compensation	23,162	19,818
Lease liabilities	12,385	11,908
Accruals and reserves not currently deductible	19,531	12,207
Deferred revenue	8,040	7,637
Other assets	1,303	—
Total deferred tax assets	191,638	234,063
Valuation allowance	(70,068)	(67,185)
Net deferred tax assets	121,570	166,878
Deferred tax liabilities:		
Lease right-of-use assets	(9,907)	(9,510)
Other liabilities	—	(657)
Total deferred tax liabilities	(9,907)	(10,167)
Net deferred taxes	$ 111,663	$ 156,711

ASC Topic 740: Income Taxes (Topic 740) requires that the tax benefit of net operating losses, temporary differences and credit carry forwards be recorded as an asset to the extent that management assesses that realization is "more likely than not." Realization of the future tax benefits is dependent on our ability to generate sufficient taxable income within the carry forward period. As of each reporting date, management considers new evidence, both positive and negative, that could affect its view of the future realization of deferred tax assets. As of December 31, 2021, based on the evaluation and weighting of both positive and negative evidence, including our achievement of a cumulative three-year income position as of December 31, 2021 and forecasts of future operating results, as well as considering the utilization of net operating losses and tax credits prior to their expiration, management determined that there is sufficient positive evidence to conclude that it is more likely than not the deferred tax assets are realizable. As of December 31, 2021 and 2020, we continue to carry a valuation allowance of $70.1 million and $67.2 million, respectively, against our California state deferred tax assets. The valuation allowance increased by $2.9 million and $5.5 million during the years ended December 31, 2021 and 2020, respectively.

At December 31, 2021, we had federal business tax credits of approximately $101.0 million which expire in the years 2025 through 2041. We also had state net operating loss carryforwards of approximately $426.0 million, which expire in the years 2022 through 2036, California research and development tax credits of approximately $45.0 million, which do not expire, and California Competes Tax Credits of approximately $2.0 million, which expire in 2026.

Under the Internal Revenue Code and similar state provisions, certain substantial changes in our ownership could result in an annual limitation on the amount of net operating loss and credit carryforwards that can be utilized in future years to offset future taxable income. The annual limitation may result in the expiration of net operating losses and credit carryforwards before utilization. We completed a Section 382 analysis through December 31, 2021, and concluded that an ownership change, as defined under Section 382, had not occurred.

The following table summarizes the activity related to our unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Beginning balance	$ 80,941	$ 79,078	$ 76,060
Change relating to prior year provision	728	591	589
Change relating to current year provision	2,215	3,305	2,429
Reductions based on the lapse of the applicable statutes of limitations	(301)	(2,033)	—
Ending balance	$ 83,583	$ 80,941	$ 79,078

We do not anticipate that the amount of unrecognized tax benefits existing as of December 31, 2021 will significantly change over the next 12 months. As of December 31, 2021, we had $83.6 million in unrecognized tax benefits, of which $52.6 million would reduce our provision for income taxes and the effective tax rate, if recognized. Interest and penalties were nominal or zero for all periods presented. We have elected to record interest and penalties in the accompanying Consolidated Statements of Income as a component of income taxes.

We file U.S. and state income tax returns in jurisdictions with varying statues of limitations during which such tax returns may be audited and adjusted by the relevant tax authorities. The 2001 through 2021 tax years generally remain subject to examination by federal and most state tax authorities to the extent net operating losses and credits generated during these periods are being utilized in the open tax periods.

NOTE 10. NET INCOME PER SHARE

Net income per share - basic and diluted, were computed as follows (in thousands, except per share amounts):

	Year Ended December 31,		
	2021	2020	2019
Numerator:			
Net income	$ 231,063	$ 111,781	$ 321,012
Denominator:			
Weighted-average common shares outstanding - basic	314,884	308,271	302,584
Dilutive securities	7,475	9,730	12,425
Weighted-average common shares outstanding - diluted	322,359	318,001	315,009
Net income per share - basic	$ 0.73	$ 0.36	$ 1.06
Net income per share - diluted	$ 0.72	$ 0.35	$ 1.02

Dilutive securities included outstanding stock options, unvested RSUs and PSUs and ESPP contributions. Certain potential common shares were excluded from our calculation of weighted-average common shares outstanding - diluted because either they would have had an anti-dilutive effect on net income per share or they were related to shares from PSUs that were contingently issuable and the contingency had not been satisfied at the end of the reporting period. See “Note 8. Employee Benefit Plans” for a further description of our equity awards. The weighted-average potential common shares excluded from our calculation were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Anti-dilutive securities and contingently issuable shares excluded	14,305	10,959	9,111

NOTE 11. COMMITMENTS AND CONTINGENCIES

Leases

Headquarters Lease

In May 2017, we entered into a Lease Agreement (the Lease) for our corporate headquarters located in Alameda, California (the Initial Premises). The Lease was subsequently amended in October 2017, June 2018, April 2019, August 2019, January 2020 and December 2020, resulting in, among other things, an increase to the amount of space leased and changes to the lease term. Our right-of-use asset, lease liability and the related lease costs reflect the 254,690 square feet of space we have taken possession of as of December 31, 2021 (the Current Premises) under the amended Lease, including 25,749 square feet of space we took possession of in 2021.

The term of the Lease continues through October 31, 2031 (the Lease Term). We have two five-year options to extend the Lease; these optional periods have not been considered in the determination of the right-of-use asset or the lease liability for the Lease as we did not consider it reasonably certain that we would exercise any such options.

We have made certain tenant improvements on the Initial Premises, for which we received $8.2 million in reimbursements in January 2019. During 2020, we also made certain tenant improvements for which we have received $1.7 million in reimbursements in 2021 related to the additional space we obtained under the April 2019 amendment. We were also provided an allowance of up to $1.4 million in 2021 for certain planned tenant improvements to the additional space obtained under the December 2020 amendment.

The balance sheet classification of our operating lease assets and liabilities were as follows (in thousands):

	December 31,	
	2021	2020
Assets:		
Right-of-use assets included in other long-term assets	$ 45,122	$ 43,010
Liabilities:		
Current portion included in other current liabilities	$ 5,137	$ 3,025
Long-term portion of operating lease liabilities	51,272	49,086
Total operating lease liabilities	$ 56,409	$ 52,111

The components of operating lease costs, which are included in selling, general and administrative expenses in our Consolidated Statements of Income, were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Operating lease cost	$ 5,332	$ 4,825	$ 2,844
Variable lease cost	2,685	2,830	1,024
Total operating lease costs	$ 8,017	$ 7,655	$ 3,868

Cash paid for amounts included in the measurement of lease liabilities for the years ended December 31, 2021, 2020 and 2019 was $5.0 million, $4.6 million and $2.9 million, respectively, and was included in net cash provided by operating activities in our Consolidated Statements of Cash Flows.

As of December 31, 2021, the maturities of our operating lease liabilities were as follows (in thousands):

Year Ended December 31,	Amount
2022	$ 5,638
2023	5,995
2024	6,283
2025	6,478
2026	6,675
Thereafter	35,170
Total lease payments	66,239
Less:	
Imputed interest	(9,404)
Future tenant improvement reimbursements	(426)
Operating lease liabilities	$ 56,409

As of December 31, 2021, the weighted average discount rate used to determine the operating lease liability was 3.1% and the weighted average remaining lease term was 9.8 years.

Build-to-Suit Lease

In October 2019, we entered into a build-to-suit Lease Agreement (the Build-to-Suit Lease) for approximately 220,000 square feet of office space located in Alameda, California (the New Premises), adjacent to the Current Premises.

The term of the Build-to-Suit Lease is for a period of 242 months (the Term), which will begin upon the substantial completion of the building and tenant improvements by the lessor. We currently anticipate that the Term will begin in the first quarter of 2022 (which date will be the Lease Commencement Date). The monthly base rent under the Build-to-Suit Lease will equal a percentage of the total development costs incurred in connection with the development of the New Premises (excluding the cost of the tenant improvements in excess of the allowance provided by the lessor and any development costs we pay) and is currently estimated to be about $0.7 million, subject to an annual increase of 3% during the Term. We will also be responsible for paying operating expenses related to the New Premises. The rent payments will begin sixty days following commencement of the Term. We have been provided a tenant improvement allowance for the New Premises of approximately $16.5 million. To the extent that the total development costs of the New Premises exceeds $525 per square foot, we will also pay 50% of such excess costs prior to the commencement of the Term, and we are required to secure such amount by providing a letter of credit or depositing such amounts in an account with the lessor's lender.

The Build-to-Suit Lease includes two five-year options to extend the term of the Build-to-Suit Lease, exercisable under certain conditions and at a market rate determined in accordance with the Build-to-Suit Lease. We have a one-time option to terminate the Build-to-Suit Lease without cause after the 180th month of the Term, exercisable under certain conditions as described in the Build-to-Suit Lease and subject to a termination payment calculated in accordance with the Build-to-Suit Lease. In addition, we have a right of first offer to purchase the New Premises, subject to certain procedures and exclusions set forth in the Build-to-Suit Lease.

We have determined that, under the guidance provided in Topic 842, we do not have control of the New Premises during the construction period. Therefore, we will not record a right-of-use asset or lease liability for the Build-to-Suit Lease until the Lease Commencement Date. We will evaluate the classification of the Build-to-Suit Lease as an operating lease or financing lease at the Lease Commencement Date. We determined the cost of tenant improvements during the construction period are lessor assets and considered a prepayment of lease under Topic 842. The costs incurred as of December 31, 2021 of $36.8 million are recorded as other long-term assets in the Consolidated Balance Sheets.

Letters of Credit

We have obtained standby letters of credit related to our lease obligations and certain other obligations with combined credit limits of $16.7 million and $1.6 million as of December 31, 2021 and 2020, respectively.

In January 2021, we entered into a standby letter of credit as guarantee of our obligation to fund our portion of the tenant improvements related to our build-to-suit lease at our corporate campus. The letter of credit is secured by our short-term investments, which are recorded as restricted cash equivalents and presented in Other long-term assets in our Consolidated Balance Sheets and is reduced as we fund our portion of the tenant improvements. As of December 31, 2021, restricted cash equivalents included $15.2 million of short-term investments as collateral under our standby letter of credit for our portion of the tenant improvements.

Legal Proceedings

In September 2019, we received a notice letter regarding an Abbreviated New Drug Application (ANDA) submitted to the FDA by MSN Pharmaceuticals, Inc. (MSN), requesting approval to market a generic version of CABOMETYX tablets. MSN's initial notice letter included a Paragraph IV certification with respect to our U.S. Patent Nos. 8,877,776 (salt and polymorphic forms), 9,724,342 (formulations), 10,034,873 (methods of treatment) and 10,039,757 (methods of treatment), which are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations, also referred to as the *Orange Book*, for CABOMETYX. MSN's initial notice letter did not provide a Paragraph IV certification against U.S. Patent No. 7,579,473 (composition of matter) or U.S. Patent No. 8,497,284 (methods of treatment), each of which is listed in the Orange Book. On October 29, 2019, we filed a complaint in the United States District Court for the District of Delaware (the Delaware District Court) for patent infringement against MSN asserting infringement of U.S. Patent No. 8,877,776 arising from MSN's ANDA filing with the FDA. On November 20, 2019, MSN filed its response to the complaint, alleging that the asserted claims of U.S. Patent No. 8,877,776 are invalid and not infringed. On May 5, 2020, we received notice from MSN that it had amended its ANDA to include additional Paragraph IV certifications. In particular, the ANDA requested approval to market a generic version of CABOMETYX tablets prior to expiration of two previously unasserted CABOMETYX patents: U.S. Patent Nos. 7,579,473 and 8,497,284. On May 11, 2020, we filed a complaint in the Delaware District Court for patent infringement against MSN asserting infringement of U.S. Patent Nos. 7,579,473 and 8,497,284 arising from MSN's amended ANDA filing with the FDA. Neither of our complaints have alleged infringement of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757. On May 22, 2020, MSN filed its response to the complaint, alleging that the asserted claims of U.S. Patent Nos. 7,579,473 and 8,497,284 are invalid and not infringed. On March 23, 2021, MSN filed its First Amended Answer and Counterclaims (amending its prior filing from May 22, 2020), seeking, among other things, a declaratory judgment that U.S. Patent No. 9,809,549 is invalid and would not be infringed by MSN if its generic version of CABOMETYX tablets were approved by the FDA. U.S. Patent No. 9,809,549 is not listed in the Orange Book. On April 7, 2021, we filed our response to MSN's First Amended Answer and Counterclaims, denying, among other things, that U.S. Patent No. 9,809,549 is invalid or would not be infringed.

On October 1, 2021, pursuant to a stipulation between us and MSN, the Delaware District Court entered an order that (i) MSN's submission of its ANDA constitutes infringement of certain claims relating to U.S. Patent Nos. 7,579,473 and 8,497,284, if those claims are not found to be invalid, and (ii) upon approval, MSN's commercial manufacture, use, sale or offer for sale within the U.S., and importation into the U.S., of MSN's ANDA product prior to the expiration of U.S. Patent Nos. 7,579,473 and 8,497,284 would also infringe certain claims of each patent, if those claims are not found to be invalid. Then, on October 12, 2021, pursuant to a separate stipulation between us and MSN, the Delaware District Court entered an order dismissing MSN's counterclaims with respect to U.S. Patent No. 9,809,549. In our complaints, we are seeking, among other relief, an order that the effective date of any FDA approval of MSN's ANDA be a date no earlier than the expiration of all of U.S. Patent Nos. 7,579,473, 8,497,284 and 8,877,776, the latest of which expires on October 8, 2030, and equitable relief enjoining MSN from infringing these patents. A bench trial has been scheduled for May 2022.

On January 11, 2022, we received notice from MSN that it had further amended its ANDA to assert additional Paragraph IV certifications. The ANDA now requests approval to market a generic version of CABOMETYX tablets prior to expiration of four previously-unasserted CABOMETYX patents that are now listed in the Orange Book: U.S. Patent Nos. 11,091,439 (salt and polymorphic forms) 11,091,440 (formulations) and 11,098,015 (methods of treatment). We have 45 days from receipt of the January 11, 2022 notice to file a patent infringement claim against MSN relating to the newly challenged patents.

In May 2021, we received notice letters from Teva Pharmaceuticals Development, Inc. and Teva Pharmaceuticals USA, Inc. (individually and collectively referred to as Teva) regarding an ANDA Teva submitted to the FDA, requesting

approval to market a generic version of CABOMETYX tablets. Teva's notice letters included a Paragraph IV certification with respect to our U.S. Patent Nos. 9,724,342 (formulations), 10,034,873 (methods of treatment) and 10,039,757 (methods of treatment), which are listed in the Orange Book and expire in 2033, 2031 and 2031, respectively. Teva's notice letters did not provide a Paragraph IV certification against any additional CABOMETYX patents. On June 17, 2021, we filed a complaint in the Delaware District Court for patent infringement against Teva, along with Teva Pharmaceutical Industries Limited (Teva Parent), asserting infringement of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757 arising from Teva's ANDA filing with the FDA. On August 27, 2021, Teva filed its answer and counterclaims to the complaint, alleging that the asserted claims of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757 are invalid and not infringed, and on August 23, 2021, we and Teva entered into a stipulation wherein Teva Parent was dismissed without prejudice from this lawsuit and agreed to be bound by any stipulation, judgment, order or decision rendered as to Teva, including any appeals and any order granting preliminary or permanent injunctive relief against Teva. On September 17, 2021, we filed an answer to Teva's counterclaims. We are seeking, among other relief, an order that the effective date of any FDA approval of Teva's ANDA be a date no earlier than the expiration of all of U.S. Patent Nos. 9,724,342, 10,034,873 and 10,039,757, the latest of which expires on July 9, 2033, and equitable relief enjoining Teva from infringing these patents. On February 8, 2022, the parties filed a stipulation to stay all proceedings, which was granted by the Delaware District Court on February 9, 2022. The stipulation and order were filed under seal.

The sale of any generic version of CABOMETYX earlier than its patent expiration could significantly decrease our revenues derived from the U.S. sales of CABOMETYX and thereby materially harm our business, financial condition and results of operations. It is not possible at this time to determine the likelihood of an unfavorable outcome or estimate of the amount or range of any potential loss.

We may also from time to time become a party or subject to various other legal proceedings and claims, either asserted or unasserted, which arise in the ordinary course of business. Some of these proceedings have involved, and may involve in the future, claims that are subject to substantial uncertainties and unascertainable damages.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

Not applicable.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures. Based on the evaluation of our disclosure controls and procedures (as defined under Rules 13a-15(e) or 15d-15(e) under the Securities Exchange Act of 1934, as amended) required by Rules 13a-15(b) or 15d-15(b) under the Securities Exchange Act of 1934, as amended, our Chief Executive Officer and our Chief Financial Officer have concluded that as of the end of the period covered by this report, our disclosure controls and procedures were effective.

Limitations on the Effectiveness of Controls. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues, if any, within an organization have been detected. Accordingly, our disclosure controls and procedures are designed to provide reasonable, not absolute, assurance that the objectives of our disclosure control system are met. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Management's Report on Internal Control Over Financial Reporting. Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rules 13a-15(f) and 15(d)-15(f). Our internal control over financial reporting is a process designed under the supervision of our principal executive and principal financial officers to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

As of the end of our 2021 fiscal year, management conducted an assessment of the effectiveness of our internal control over financial reporting based on the framework established in the original *Internal Control – Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (COSO). Based on this assessment, management has determined that our internal control over financial reporting as of December 31, 2021 was effective. There were no material weaknesses in internal control over financial reporting identified by management.

The independent registered public accounting firm Ernst & Young LLP has issued an audit report on our internal control over financial reporting, which is included on the following page.

Changes in Internal Control Over Financial Reporting. There were no changes in our internal control over financial reporting that occurred during our most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Exelixis, Inc.

Opinion on Internal Control Over Financial Reporting

We have audited Exelixis, Inc.'s internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Exelixis, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and January 1, 2021 and, the related consolidated statements of income, comprehensive income, stockholders' equity and cash flows for each of the three fiscal years in the period ended December 31, 2021, and the related notes and our report dated February 18, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Redwood City, California
February 18, 2022

Item 9B. Other Information

Between February 15, 2022 and February 16, 2022, we entered into new indemnification agreements with each of our directors and executive officers, the form of which is attached as Exhibit 10.1 to this Form 10-K. Pursuant to the indemnification agreement, we are required to indemnify the director or executive officer for all direct and indirect costs, including attorney's fees, witness fees, and other out of pocket costs of whatever nature, incurred by the director or executive officer in any action or proceeding, whether actual, pending or threatened, subject to certain limitations, to which any of these people may be made a party by reason of the fact that he or she is or was a director or an executive officer of Exelixis or is or was serving or at any time serves at our request as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item relating to our directors and nominees, including information with respect to our audit committee, audit committee financial experts and procedures by which stockholders may recommend nominees to our Board of Directors, is incorporated by reference to the section entitled "Proposal 1 – Election of Directors" appearing in our Proxy Statement for our 2022 Annual Meeting of Stockholders to be filed with the SEC within 120 days after December 31, 2021, which we refer to as our 2022 Proxy Statement. The information required by this item regarding our executive officers is incorporated by reference to the section entitled "Information about our Executive Officers" appearing in our 2022 Proxy Statement. The information, if any, required by this item regarding compliance with Section 16(a) of the Securities Exchange Act of 1934, as amended, is incorporated by reference to the section entitled "Delinquent Section 16(a) Reports" appearing in our 2022 Proxy Statement.

Code of Ethics

We have adopted a Corporate Code of Conduct that applies to all of our directors, officers and employees, including our principal executive officer, principal financial officer and principal accounting officer. The Corporate Code of Conduct is posted on our website at www.exelixis.com under the caption "Investors & Media—Corporate Governance—Corporate Governance Documents and information."

We intend to satisfy the disclosure requirement under Item 5.05 of Form 8-K regarding an amendment to, or waiver from, a provision of this Corporate Code of Conduct by posting such information on our website, at the address and location specified above and, to the extent required by the listing standards of the Nasdaq Stock Market, by filing a Current Report on Form 8-K with the SEC, disclosing such information.

Item 11. Executive Compensation

The information required by this item is incorporated by reference to the sections entitled "Compensation of Executive Officers," "Compensation of Directors," "Compensation Committee Interlocks and Insider Participation" and "Compensation Committee Report" appearing in our 2022 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item relating to security ownership of certain beneficial owners and management is incorporated by reference to the section entitled “Security Ownership of Certain Beneficial Owners and Management” appearing in our 2022 Proxy Statement.

Equity Compensation Plan Information

The following table provides certain information about our common stock that may be issued upon the exercise of stock options and other rights under all of our existing equity compensation plans as of December 31, 2021, which consists of our 2000 Employee Stock Purchase Plan (the ESPP), our 2014 Equity Incentive Plan (the 2014 Plan), our 2016 Inducement Award Plan (the 2016 Plan) and our 2017 Equity Incentive Plan (the 2017 Plan):

Plan Category	Number of securities to be issued upon exercise of outstanding options, warrants and rights	Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a))
	(a)	(b)	(c)
Equity compensation plans approved by stockholders [1]	26,658,364	$ 8.50 [2]	14,172,938
Equity compensation plans not approved by stockholders [3]	150,700	$ 19.72	—
Total	26,809,064	$ 8.56	14,172,938

(1) Equity plans approved by our shareholders include the 2014 Plan, the 2017 Plan and the ESPP. As of December 31, 2021, a total of 3,168,354 shares of our common stock remained available for issuance under the ESPP, and up to a maximum of 534,037 shares of our common stock may be purchased in the current purchase period. The shares issuable pursuant to our ESPP are not included in the number of shares to be issued pursuant to rights outstanding or and the weighted-average exercise price of such rights as of December 31, 2021, as those numbers are not known.

(2) The weighted-average exercise price takes into account the shares subject to outstanding restricted stock units (RSUs), including such awards with performance conditions, which have no exercise price. The weighted-average exercise price, excluding such outstanding RSUs, is $16.76.

(3) Represents shares of our common stock issuable pursuant to the 2016 Plan. As of December 31, 2021, no shares of our common stock remained available for additional grants under the 2016 Plan. In November 2016, the Board adopted the 2016 Plan pursuant to which we reserved 1,500,000 shares of our common stock for issuance under the 2016 Plan. The only persons eligible to receive grants of Awards under the 2016 Plan are individuals who satisfy the standards for inducement grants under Nasdaq Marketplace Rule 5635(c)(4) and the related guidance under Nasdaq IM 5635-1 - that is, generally, a person not previously an employee or director of Exelixis, or following a bona fide period of non-employment, as an inducement material to the individual's entering into employment with Exelixis. An “Award” is any right to receive Exelixis common stock pursuant to the 2016 Plan, consisting of non-statutory stock options, stock appreciation rights, RSUs, or any other stock award.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is incorporated by reference to the sections entitled “Certain Relationships and Related Party Transactions” and “Proposal 1 – Election of Directors” appearing in our 2022 Proxy Statement.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated by reference to the section entitled “Proposal 2 – Ratification of Selection of Independent Registered Public Accounting Firm” appearing in our 2022 Proxy Statement.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) The following documents are being filed as part of this report:

(1) The following financial statements and the Report of Independent Registered Public Accounting Firm are included in Part II, Item 8:

(2) All financial statement schedules are omitted because the information is inapplicable or presented in the Notes to Consolidated Financial Statements.

(3) The following Exhibits are filed as part of this report.

		Incorporation by Reference				
Exhibit Number	Exhibit Description	Form	File Number	Exhibit/ Appendix Reference	Filing Date	Filed Herewith
3.1	Restated Certificate of Incorporation of Exelixis, Inc.	10-Q	000-30235	3.1	8/5/2021	
3.2	Amended and Restated Bylaws of Exelixis, Inc.	8-K	000-30235	3.1	3/3/2021	
4.1	Specimen Common Stock Certificate.	10-Q	333-96335	4.1	8/5/2021	
4.2	Description of the Common Stock of Exelixis, Inc. Registered Pursuant to Section 12 of the Securities Exchange Act of 1934, as amended					X
10.1†	Form of Indemnification Agreement					X
10.2†	Exelixis, Inc. 2000 Employee Stock Purchase Plan	Schedule 14A	000-30235	A	4/13/2016	
10.3†	Exelixis, Inc. 2014 Equity Incentive Plan	10-Q	000-30235	10.1	8/6/2020	
10.4†	Form of Stock Option Agreement under the Exelixis, Inc. 2014 Equity Incentive Plan	10-Q	000-30235	10.2	7/31/2014	
10.5†	Form of Stock Option Agreement (Non-Employee Director) under the Exelixis, Inc. 2014 Equity Incentive Plan	10-Q	000-30235	10.4	7/31/2014	
10.6†	Form of Restricted Stock Unit Agreement under the Exelixis, Inc. 2014 Equity Incentive Plan	10-Q	000-30235	10.5	7/31/2014	
10.7†	Exelixis, Inc. 2016 Inducement Award Plan	10-Q	000-30235	10.2	8/6/2020	
10.8†	Form of Stock Option Agreement under the 2016 Inducement Award Plan	8-K	000-30235	10.2	11/22/2016	
10.9†	Form of Restricted Stock Unit Agreement under the 2016 Inducement Award Plan	8-K	000-30235	10.2	11/22/2016	

Exhibit Number	Exhibit Description	Incorporation by Reference				Filed Herewith
		Form	File Number	Exhibit/ Appendix Reference	Filing Date	
10.10†	Exelixis, Inc. 2017 Equity Incentive Plan	10-Q	000-30235	10.3	8/6/2020	
10.11†	Form of Stock Option Agreement under the Exelixis, Inc. 2017 Equity Incentive Plan	10-K	00-30235	10.11	2/11/2021	
10.12†	Form of Stock Option Agreement (Non-Employee Director) under the Exelixis, Inc. 2017 Equity Incentive Plan	10-K	000-30235	10.22	2/26/2018	
10.13†	Form of Restricted Stock Unit Agreement under the Exelixis, Inc. 2017 Equity Incentive Plan	10-Q	000-30235	10.5	8/6/2020	
10.14†	Form of Restricted Stock Unit Agreement (Non-Employee Director) under the Exelixis, Inc. 2017 Equity Incentive Plan	10-Q	000-30235	10.6	8/6/2020	
10.15†	Non-Employee Director Equity Compensation Policy	10-Q	000-30235	10.4	5/5/2020	
10.16†	Offer Letter Agreement, dated February 3, 2000, between Exelixis, Inc. and Michael Morrissey, Ph.D.	10-Q	000-30235	10.43	8/5/2004	
10.17†	Offer Letter Agreement, dated June 30, 2015, between Exelixis, Inc. and Christopher Senner	10-Q	000-30235	10.5	11/10/2015	
10.18†	Offer Letter Agreement, dated December 2, 2021, between Exelixis, Inc. and Vicki L. Goodman, M.D.					X
10.19†	Offer Letter Agreement, dated February 10, 2014, between Exelixis, Inc. and Jeffrey J. Hessekiel.	10-Q	000-30235	10.4	5/1/2014	
10.20†	Offer Letter Agreement, dated August 11, 2000, between Exelixis, Inc. and Peter Lamb.	10-K	000-30235	10.24	2/29/2016	
10.21†	Offer Letter Agreement, dated August 19, 2010, between Exelixis, Inc. and Patrick J. Haley	10-K	000-30235	10.26	2/27/2017	
10.22†	Annual Cash Bonus Compensation Plan for Executives	8-K	000-30235	10.1	2/16/2018	
10.23†	Cash Compensation Information for Non-Employee Directors.	10-K	000-30235	10.29	2/25/2020	
10.24†	Exelixis, Inc. Change in Control and Severance Benefit Plan, as amended and restated.	10-Q	000-30235	10.5	5/2/2018	
10.25†	Policy for Recoupment of Variable Compensation	10-Q	000-30235	10.4	5/1/2019	
10.26	Lease Agreement dated May 2, 2017, between Ascentris 105, LLC and Exelixis, Inc.	10-Q	000-30235	10.1	8/2/2017	
10.27	First Amendment dated October 16, 2017, to Lease Agreement dated May 2, 2017, between Ascentris 105, LLC and Exelixis, Inc.	10-K	000-30235	10.39	2/26/2018	
10.28	Second Amendment dated June 13, 2018, to Lease Agreement dated May 2, 2017, between Ascentris 105, LLC and Exelixis, Inc.	10-Q	000-30235	10.2	8/1/2018	

Exhibit Number	Exhibit Description	Incorporation by Reference				Filed Herewith
		Form	File Number	Exhibit/ Appendix Reference	Filing Date	
10.29	Third Amendment dated April 1, 2019, to Lease Agreement dated May 2, 2017, between Ascentris 105, LLC and Exelixis, Inc.	8-K	000-30235	10.1	4/5/2019	
10.30	Fourth Amendment dated August 30, 2019, to Lease Agreement dated May 2, 2017, between Hillwood Enterprises, L.P. (as successor in interest to Ascentris 105, LLC) and Exelixis, Inc.	10-Q	000-30235	10.3	10/30/2019	
10.31	Fifth Amendment dated January 16, 2020, to Lease Agreement dated May 2, 2017, between Waterfront EDP, LLC (as successor in interest to Hillwood Enterprises, L.P.) and Exelixis, Inc.	10-K	000-30235	10.37	2/25/2020	
10.32	Sixth Amendment dated December 11, 2020, to Lease Agreement dated May 2, 2017, between SCG Harbor Bay Parkway Phase I, LLC (as successor in interest to Waterfront EDP, LLC) and Exelixis, Inc.	10-K	000-30235	10.32	2/10/2021	
10.33	Lease Agreement dated October 25, 2019, between Ernst Development Partners, Inc. and Exelixis, Inc.	10-Q	000-30235	10.2	10/30/2019	
10.34	First Amendment dated January 16, 2020, to Lease Agreement dated May 2, 2017, between Alameda BTS EDP, LLC (as successor in interest to Ernst Development Partners, Inc.) and Exelixis, Inc.	10-K	000-30235	10.39	2/25/2020	
10.35**	Collaboration and License Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.1	5/6/2021	
10.36**	First Amendment dated December 20, 2016, to the Collaboration and License Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.2	5/6/2021	
10.37**	Second Amendment dated September 14, 2017, to the Collaboration and License Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.3	5/6/2021	
10.38**	Third Amendment dated October 26, 2017, to the Collaboration and License Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.4	5/6/2021	
10.39**	Supply Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.5	5/6/2021	
10.40**	First Amendment dated October 26, 2017, to the Supply Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.6	5/6/2021	

Exhibit Number	Exhibit Description	Incorporation by Reference				Filed Herewith
		Form	File Number	Exhibit/ Appendix Reference	Filing Date	
10.41**	Second Amendment dated May 17, 2019, to the Supply Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS	10-Q	000-30235	10.2	7/31/2019	
10.42**	Third Amendment dated December 10, 2021, to the Supply Agreement dated February 29, 2016, by and between Exelixis, Inc. and Ipsen Pharma SAS					X
10.43*	Collaboration and License Agreement dated January 30, 2017, by and between Exelixis, Inc. and Takeda Pharmaceutical Company Limited	10-Q/A	000-30235	10.1	7/14/2017	
10.44*	First Amendment dated March 22, 2018, to the Collaboration and License Agreement dated January 30, 2017, by and between Exelixis, Inc. and Takeda Pharmaceutical Company Limited	10-Q	000-30235	10.1	8/1/2018	
10.45**	Second Amendment dated May 7, 2019, to the Collaboration and License Agreement dated January 30, 2017, by and between Exelixis, Inc. and Takeda Pharmaceutical Company Limited	10-Q	000-30235	10.3	7/31/2019	
10.46**	Third Amendment dated September 3, 2020, to the Collaboration and License Agreement dated January 30, 2017, by and between Exelixis, Inc. and Takeda Pharmaceutical Company Limited	10-Q	000-30235	10.1	11/5/2020	
10.47**	Joint Clinical Research Agreement dated December 18, 2019, by and between Exelixis, Inc. and F. Hoffmann-La Roche Ltd	10-K	000-30235	10.62	2/25/2020	
21.1	Subsidiaries of Exelixis, Inc.					X
23.1	Consent of Independent Registered Public Accounting Firm					X
24.1	Power of Attorney (contained on signature page)					X
31.1	Certification of Principal Executive Officer Pursuant to Exchange Act Rules 13a-14(a) and Rule 15d-14(a)					X
31.2	Certification of Principal Financial Officer Pursuant to Exchange Act Rules 13a-14(a) and Rule 15d-14(a)					X
32.1‡	Certifications of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350					X
101.INS	XBRL Instance Document	The XBRL instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.				
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X

Exhibit Number	Exhibit Description	Incorporation by Reference				Filed Herewith
		Form	File Number	Exhibit/ Appendix Reference	Filing Date	
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X
104	Cover Page Interactive Data File	Formatted as Inline XBRL and contained in Exhibit 101.				

† Management contract or compensatory plan.

* Confidential treatment granted for certain portions of this exhibit.

** Portions of this exhibit have been omitted as being immaterial and would be competitively harmful if publicly disclosed.

‡ This certification accompanies this Annual Report on Form 10-K, is not deemed filed with the SEC and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of this Annual Report on Form 10-K), irrespective of any general incorporation language contained in such filing.

ITEM 16. FORM 10-K SUMMARY

None provided.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized

EXELIXIS, INC.

February 18, 2022
Date

By: /s/ MICHAEL M. MORRISSEY
Michael M. Morrissey, Ph.D.
President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints **MICHAEL M. MORRISSEY**, **CHRISTOPHER J. SENNER** and **JEFFREY J. HESSEKIEL** and each or any one of them, his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ MICHAEL M. MORRISSEY **Michael M. Morrissey, Ph.D.**	Director, President and Chief Executive Officer (Principal Executive Officer)	February 18, 2022
/s/ CHRISTOPHER J. SENNER **Christopher J. Senner**	Executive Vice President and Chief Financial Officer (Principal Financial and Accounting Officer)	February 18, 2022
/s/ STELIOS PAPADOPOULOS **Stelios Papadopoulos, Ph.D.**	Chairman of the Board	February 18, 2022
/s/ CHARLES COHEN **Charles Cohen, Ph.D.**	Director	February 18, 2022
/s/ CARL B. FELDBAUM **Carl B. Feldbaum, Esq.**	Director	February 18, 2022
/s/ MARIA C. FREIRE **Maria C. Freire, Ph.D.**	Director	February 18, 2022

Signatures	Title	Date
/s/ ALAN M. GARBER **Alan M. Garber, M.D., Ph.D.**	Director	February 18, 2022
/s/ VINCENT T. MARCHESI **Vincent T. Marchesi, M.D., Ph.D.**	Director	February 18, 2022
/s/ GEORGE POSTE **George Poste, DVM, Ph.D., FRS**	Director	February 18, 2022
/s/ JULIE A. SMITH **Julie A. Smith**	Director	February 18, 2022
/s/ LANCE WILLSEY **Lance Willsey, M.D.**	Director	February 18, 2022
/s/ JACQUELINE WRIGHT **Jacqueline Wright**	Director	February 18, 2022
/s/ JACK L. WYSZOMIERSKI **Jack L. Wyszomierski**	Director	February 18, 2022

Corporate Information

Corporate Headquarters

Exelixis, Inc.
1851 Harbor Bay Parkway
Alameda, CA 94502
Phone: 650.837.7000
Fax: 650.837.8300

Website
www.exelixis.com

Twitter
@ExelixisInc

Facebook
www.facebook.com/ExelixisInc

LinkedIn
www.linkedin.com/company/Exelixis

Transfer Agent

For any inquiries regarding transfer requirements, lost stock certificates and address changes, please contact our transfer agent.

Computershare
P.O. Box 505000
Louisville, KY 40233-5000
Phone: 800.522.6645

Private Couriers/Registered Mail:
Computershare Investor Services
462 South 4th Street, Suite 1600
Louisville, KY 40202

Telephone Numbers:
Shareholder Services – Toll Free: 800.522.6645
TDD for Hearing Impaired: 800.952.9245
Foreign Shareowners: 201.680.6578

Website Address:
www.computershare.com/investor

Shareholder Online Inquiries:
https://www-us.computershare.com/investor/contact

Annual Meeting

To be held virtually on Wednesday, May 25, 2022, at 9:00 a.m. PT. View the meeting, submit questions and vote online at www.virtualshareholdermeeting.com/EXEL2022.

Corporate Counsel

Cooley LLP
Palo Alto, CA

Independent Auditors

Ernst & Young LLP
Redwood City, CA

Investor Relations / Form 10-K

Inquiries and requests for information, including copies of the Exelixis Annual Report on Form 10-K provided free of charge, may be directed to the company's Investor Relations Department by phone (650.837.7000), email (IR@exelixis.com) or via our website (www.exelixis.com).

Stock Information

The common stock of the company has traded on the Nasdaq Global Select Market under the symbol "EXEL" since April 11, 2000.

Board of Directors

Stelios Papadopoulos, Ph.D.
Co-Founder and Chair of the Board, Exelixis, Inc.

Charles Cohen, Ph.D.*
Chair of the Compensation Committee, Exelixis, Inc.; Former Chief Executive Officer of multiple privately held biotechnology companies, including Perform Biologics, Inc. and On Target Therapeutics, LLC

Carl B. Feldbaum, Esq.
Chair of the Risk Committee, Exelixis, Inc.; President Emeritus, Biotechnology Innovation Organization (BIO)

Maria C. Freire, Ph.D.
President, Executive Director and Director, Foundation for the National Institutes of Health

Alan M. Garber, M.D., Ph.D.
Chair of the Nominating and Corporate Governance Committee, Exelixis, Inc.; Provost, Harvard University; Mallinckrodt Professor of Health Care Policy, Harvard Medical School; Professor, Harvard Kennedy School of Government; Professor, Department of Economics, Harvard University

Vincent T. Marchesi, M.D., Ph.D.
Director, Boyer Center for Molecular Medicine and Professor of Pathology and Cell Biology, Yale University

Michael M. Morrissey, Ph.D.
President and Chief Executive Officer, Exelixis, Inc.

George Poste, DVM, Ph.D., FRS
Chair of the Research & Development Committee, Exelixis, Inc.; Chief Scientist, Complex Adaptive Systems Initiative and Regents' Professor and Del E. Webb Professor of Health Innovation, Arizona State University

Julie Anne Smith
President and Chief Executive Officer, ESCAPE Bio, Inc.

Lance Willsey, M.D.
Member of the Visiting Committee of the Department of Genitourinary Oncology at the Dana-Farber Cancer Institute, Harvard Medical School; Oncology Consultant; Founding Partner, DCF Capital

Jacqueline (Jacky) Wright
Corporate Vice President & Chief Digital Officer, U.S. Business, Microsoft Corporation

Jack L. Wyszomierski
Chair of the Audit Committee, Exelixis, Inc.; Former Executive Vice President and Chief Financial Officer, VWR International, LLC

Management Team

Michael M. Morrissey, Ph.D.
President and Chief Executive Officer

Christopher J. Senner
Executive Vice President and Chief Financial Officer

Vicki L. Goodman, M.D.
Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer

Peter Lamb, Ph.D.
Executive Vice President, Scientific Strategy and Chief Scientific Officer

P.J. Haley, MBA
Executive Vice President, Commercial

Dana T. Aftab, Ph.D.
Executive Vice President, Business Operations

Laura Dillard
Executive Vice President, Human Resources

Jeffrey J. Hessekiel, J.D.
Executive Vice President, General Counsel and Secretary

Susan T. Hubbard
Executive Vice President, Public Affairs and Investor Relations

*Dr. Cohen is not standing for re-election at the Annual Meeting and will resign from the Board effective as of the Annual Meeting.

This Annual Report contains forward-looking statements, including, without limitation, statements related to: Exelixis' business plans and commitments, including key clinical development and pipeline-building milestones expected for 2022 and beyond as Exelixis executes toward its vision of becoming a multi-product oncology company; the continued commercial success of CABOMETYX as a driver of Exelixis' growth and potential to expand the cabozantinib franchise into new indications; Exelixis' clinical development plans for cabozantinib, XL092, XB002, XL102, XL114 and other product candidates, including plans to initiate STELLAR-303 and other phase 3 pivotal trials for XL092; future data results expected in 2022; the therapeutic potential of Exelixis' early-stage small molecule and biotherapeutics product candidates for patients across a wide variety of cancer indications; Exelixis' belief it has created a powerful biologics discovery and development engine to drive long-term growth; Exelixis' planned preclinical and drug discovery activities, including advancing up to five new development candidates into preclinical testing in 2022; Exelixis' plans for expansion on the East Coast and potential future growth outside the U.S.; and other statements that are not historical facts. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and are based upon Exelixis' current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: the degree of market acceptance of CABOMETYX and other Exelixis products in the indications for which they are approved and in the territories where they are approved, and Exelixis and its partners' ability to obtain or maintain coverage and reimbursement for these products; the effectiveness of CABOMETYX and other Exelixis products in comparison to competing products; the level of costs associated with Exelixis' commercialization, research and development, in-licensing or acquisition of product candidates, and other activities; Exelixis' ability to maintain and scale adequate sales, marketing, market access and product distribution capabilities for its products or to enter into and maintain agreements with third parties to do so; the availability of data at the referenced times; the potential failure of cabozantinib and other Exelixis product candidates, both alone and in combination with other therapies, to demonstrate safety and/or efficacy in clinical testing; uncertainties inherent in the drug discovery and product development process; Exelixis' dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for partnered compounds in new indications, their adherence to their obligations under relevant collaboration agreements and the level of their investment in the resources necessary to complete clinical trials or successfully commercialize partnered compounds in the territories where they are approved; complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' continuing compliance with applicable legal and regulatory requirements; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib and other Exelixis products; Exelixis' dependence on third-party vendors for the development, manufacture and supply of its products and product candidates; Exelixis' ability to protect its intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of Exelixis' marketed products; changes in economic and business conditions, including as a result of the COVID-19 pandemic and other global events; and other factors discussed under the caption "Risk Factors" in Exelixis' Form 10-K, which is part of this Annual Report. All forward-looking statements in this Annual Report are based on information available to Exelixis as of the date of this Annual Report, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein, except as required by law.

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