EXELIXIS INC
Form 10-K
February 25, 2008
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)

OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended: December 28, 2007

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: 0-30235

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)

170 Harbor Way

P.O. Box 511

South San Francisco, CA 94083

(Address of principal executive offices, including zip code)

(650) 837-7000

(Registrant s telephone number, including area code)

Securities Registered Pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock $.001 Par Value per Share	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 x 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 x

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 x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of accelerated filer and large accelerated filer in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer x Accelerated filer ¨ Non-accelerated filer (Do not check if a smaller reporting company) ¨ Smaller reporting company ¨

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

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: $975,445,421 (Based on the closing sales price of the registrant s common stock on that date. Excludes an aggregate of 16,658,250 shares of the registrant s common stock held by officers, directors and affiliated stockholders. For purposes of determining whether a stockholder was an affiliate of the registrant at June 29, 2007, the registrant assumed that a stockholder was an affiliate of the registrant at June 29, 2007 if such stockholder (i) beneficially owned 10% or more of the registrant s common stock, as determined based on public filings, and/or (ii) was an executive officer or director or was affiliated with an executive officer or director of the registrant at June 29, 2007. 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.)

As of February 20, 2008, there were 105,073,846 shares of the registrant s common stock outstanding.

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 27, 2008, in connection with the registrant s 2008 Annual Meeting of Stockholders are incorporated herein by reference into Part III of this Annual Report on Form 10-K.

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EXELIXIS, INC.

FORM 10-K

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PART I

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. Words such as believe, anticipate, expect, intend, plan, will, may should, would, could, estimate, predict, potential, continue, encouraging or the negative of such terms or other similar expressions identify 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.

In 2006, Exelixis adopted a 52- or 53-week fiscal year that ends on the Friday closest to December 31st. Fiscal year 2006, a 52-week year, ended on December 29, 2006, fiscal year 2007, a 52-week year, ended on December 28, 2007 and fiscal year 2008, a 53-week year, will end on January 2, 2009. For convenience, references in this report as of and for the fiscal years ended December 29, 2006 and December 28, 2007 are indicated on a calendar year basis, ending December 31, 2006 and 2007, respectively.

ITEM 1. BUSINESS

Overview

We are committed to developing innovative therapies for cancer and other serious diseases. Through our integrated drug discovery and development activities, we are building a portfolio of novel compounds that we believe have the potential to be high-quality, differentiated pharmaceutical products. Our most advanced pharmaceutical programs focus on discovery and development of small molecule drugs for cancer.

Utilizing our library of more than 4.5 million compounds, we have integrated high-throughput processes, medicinal chemistry, bioinformatics, structural biology and early *in vivo* testing into a process that allows us to efficiently and rapidly identify highly qualified drug candidates that meet our extensive development criteria.

To date, we have filed 14 investigational new drug applications, or INDs. We believe that our deep pool of drug candidates will enable us to continue to file multiple new INDs each year for the foreseeable future. As our compounds advance into clinical development, we expect to generate a critical mass of data that will help us to understand the full clinical and commercial potential of our product candidates. In addition to guiding the potential commercialization of our innovative therapies, these data may contribute to the understanding of disease and help improve treatment outcomes.

Based on the strength of our expertise in biology, drug discovery, and development, we have established collaborations with major pharmaceutical and biotechnology companies that allow us to retain economic participation in compounds and support additional development of our proprietary products. Through these collaborations, we obtain license fees, research funding, a share of the profits and the opportunity to receive milestone payments and royalties (as applicable) from research results and subsequent product development activities. We also have collaborations in which we retain the right to co-promote products in the United States. We have ongoing commercial collaborations with several leading pharmaceutical and biotechnology companies, including SmithKline Beecham Corporation (which does business as GlaxoSmithKline), Bristol-Myers Squibb

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Company and Genentech, Inc. We expect to continue to use corporate partnering as a strategic tool to cultivate our assets, fund our operations and expand the therapeutic and commercial potential of our pipeline.

Our current development portfolio includes the following compounds, for which we are leading development:

Compound	Principal Targets	Indication	Stage of Development
XL647*	EGFR, HER2, VEGFR2	Cancer	Phase 2
XL880	MET, VEGFR2	Cancer	Phase 2
XL820	KIT, VEGFR2, PDGFR	Cancer	Phase 2
XL184	MET, VEGFR2, RET	Cancer	Phase 1/2
XL518**	MEK	Cancer	Phase 1
XL281	RAF	Cancer	Phase 1
XL019	JAK2	Cancer	Phase 1
XL844	CHK1, CHK2	Cancer	Phase 1
XL228	IGF1R , ABL, SRC	Cancer	Phase 1
XL147	PI3K	Cancer	Phase 1
XL765	PI3K, mTOR	Cancer	Phase 1

* Out-licensed to Symphony Evolution, Inc. and subject to a repurchase option as described elsewhere in this report.

** In co-development collaboration with Genentech, Inc.

In December 2007, GlaxoSmithKline exercised its option pursuant to our product development and commercialization agreement to further develop and commercialize XL880. We expect to transfer the XL880 development program to GlaxoSmithKline in the first quarter of 2008. Pursuant to the product development and commercialization agreement, GlaxoSmithKline has the option to elect to develop up to two additional compounds in our product pipeline, which may include XL820, XL184, XL281, XL844 and XL228.

In addition to the compounds identified in the table above, we have compounds in various stages of development that are being developed by our partners, such as Bristol-Myers Squibb, Daiichi Sankyo Company Limited and Wyeth Pharmaceuticals, a division of Wyeth. We also have compounds in preclinical development that we are developing internally.

Areas of Expertise

Integrated Drug Research, Discovery and Development Capabilities

We have built a multidisciplinary, integrated research and development platform that supports the complex, iterative nature of drug research, discovery and clinical development. Our platform has been designed to include all of the critical functions and expertise required to advance from gene to drug in a consistent and streamlined fashion. Our integrated approach supports advancement of candidate compounds from development candidate status to IND in less than 12 months.

Our organizational structure is designed to create a seamless and flexible research and development process. It is structured to provide one consistent set of goals and objectives to all departments within the research and development organization and to give us the flexibility to allocate and focus our diverse resources to address our most pressing needs. This organizational structure ensures that our earliest discovery activities generate data and information that inform our clinical development strategies, and enables us to apply what we learn about our drug candidates in the clinic to how we discover, assess and select new compounds for future development. We believe that this approach will allow us to align the target inhibition spectrum of a specific compound with the molecular profiles of specific cancer types and patient populations. We also believe that this strengthens our ability to select appropriate patients for clinical trials, which may allow significant efficacy to be demonstrated

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using smaller, shorter trials. Similarly, we use biological approaches to identify disease indications that give us a clear and potentially shorter path to the market, which may allow us to decrease our development times and bring drugs to market sooner.

Additionally, we are leveraging what we learn through preclinical pharmacodynamic studies to identify clinical biomarkers that can be utilized to determine early in the development process if the compound is having the expected effect on the target(s) and pathway(s) of interest and if patients are responding to it. This approach may result in an increased probability that patients receive effective therapies.

Drug Discovery

In addition to establishing an integrated research and development organizational structure, we have built an optimized drug discovery platform. We utilize a variety of high-throughput technologies to enable the rapid discovery, optimization and extensive characterization of lead compounds such that we are able to select development candidates with the best potential for further evaluation and advancement into the clinic. We have combined our ability to identify and validate novel targets with state-of-the-art drug discovery to effectively exploit both the chemical and biological sciences. In addition, we have built critical mass in all key operational areas. We believe that these human and technological resources enable us to: (1) effectively and rapidly qualify novel targets for high-throughput screening; (2) identify and optimize proprietary lead compounds; (3) develop extensive preclinical data to guide selection of patient populations, thereby maximizing the opportunity for obtaining significant clinical benefit; and (4) perform the broad range of preclinical testing required to fuel our pipeline and advance promising compounds through all stages of development. Key capabilities within drug discovery include: high-throughput screening, medicinal and combinatorial chemistry, cell biology, protein biochemistry, structural biology, pharmacology, biotherapeutics and informatics.

Translational Research

Our translational research group is focused on using the knowledge we generate in the discovery process about biological targets and the impact of our compounds on those targets to identify patient populations in which to test our compounds and methods for assessing compound activity. This includes understanding the role of specific targets in disease therapy, identifying gene mutations or gene variants that impact response to therapy and identifying biomarkers that can be used to assess drug responses early on in treatment. Key capabilities within translational research include: nonclinical development (encompassing toxicology, drug metabolism, pharmacokinetics and bioanalytics) and translational medicine.

Development

With the growth of our pipeline, we continue to invest in building our development expertise and resources. Our development group leads the development and implementation of our clinical and regulatory strategies. Working closely with the discovery and translational research groups, the development group prioritizes disease indications in which our compounds may be studied in clinical trials. The development group designs, directs, implements and oversees all areas of clinical operations, including identifying and selecting clinical investigators, recruiting study subjects to participate in our clinical trials, biostatistics, data management, drug safety evaluation, and adverse event reporting. The development group also is responsible for assuring that our development programs are conducted in compliance with all regulatory requirements. The group works closely with the cross functional project and clinical teams to facilitate the appropriate and efficient development of our diverse product pipeline. Key capabilities within development include clinical development, clinical operations, safety monitoring, biostatistics, programming and data management, regulatory strategy and program management.

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Our Strategy

Our business strategy is to leverage our biological expertise and integrated drug discovery capabilities to generate a pipeline of diverse development compounds with first-in-class or best-in-class potential that fulfill unmet medical needs in the treatment of cancer and potentially other serious diseases.

Because our continued success and growth as a company depend in part on our ability to advance current and future compounds successfully in clinical development, we have committed substantial resources to build a premier clinical development organization to accommodate our expanding pipeline of compounds. We continue to build critical mass of key internal expertise and capabilities to facilitate conducting multiple clinical trial programs with speed and rigor. Specifically, our business strategy includes the following key elements:

Selectively Develop Therapeutic Products with First-In-Class or Best-In-Class Potential

We have invested and plan to continue to make significant investments in discovering and developing proprietary product candidates, particularly in the area of cancer. We have committed substantial resources to building a first-rate drug discovery effort that is integrated with our unique understanding of the biological basis of a disease. Part of our strategy is to generate a large pipeline of diverse product candidates that provides us with the flexibility to select only those compounds that have both clinical and commercial potential. In developing compounds, our strategy is to pursue a variety of clinically validated, novel and proprietary targets. These decisions are data-driven, based on stringent criteria that incorporate intrinsic potency, selectivity, preclinical efficacy and tolerability and commercial viability. Our strategy is to commit resources only to those compounds that are commercially attractive and have the potential to be first-in-class or best-in-class therapeutics.

Target Multiple Pathways

We have extensive expertise and experience in modifying gene function *in vitro* and *in vivo* as a result of our work on model organisms for the discovery of novel targets and pathways relevant to the development, progression and treatment of cancer and other diseases. We believe that the most effective therapies for cancer will target multiple pathways, simultaneously turn off growth signals, increase rates of programmed cell death and reduce the growth of blood vessels necessary to support tumor growth. Many of our first-generation anticancer product candidates in our clinical pipeline are Spectrum Selective Kinase Inhibitors, or SSKIs, that have been optimized for balanced potency, specificity, tolerability and pharmacologic parameters. These SSKIs are designed to target multiple members of a family of proteins known as receptor tyrosine kinases, or RTKs, in a concerted manner. RTKs are validated targets for drug development, as evidenced by several recent approved cancer therapies. Because interactions among multiple RTKs contribute to the development and progression of disease, SSKIs may provide more effective disease control than compounds that target only one RTK or target multiple non-related RTKs. Additionally, because SSKIs are optimized for key *in vitro* and *in vivo* parameters, these compounds may also provide improved efficacy and enhanced safety profiles compared with combinations of single-target drugs that have not been optimized for use together.

Our second-generation compounds are designed to inhibit kinases that are points of convergence in critical signaling pathways employed by growth factor receptors to transmit their aberrant signals in tumor cells. The targets of several approved therapies transmit their signals through a number of common downstream pathways, such as the RAS/RAF/MEK/ERK, PI3 kinase/AKT/mTOR, and JAK/STAT pathways. These pathways also are often mutationally activated in a wide range of tumors. Thus, inhibition of key kinase targets in these pathways may provide superior efficacy, safety and tolerability compared to conventional chemotherapy and may enable entirely new approaches to cancer therapy.

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The majority of our compounds target one or more molecular pathways that control critical aspects of cancer cell growth, migration or survival. These include:

Cell Growth. In most normal adult tissues, cell growth is tightly controlled. However, cancer cells escape normal growth control and are driven to divide very rapidly. In many cases, this growth is driven by excessive activity of cellular growth factors and/or their receptors. This change in activity may result from mutations that allow the receptor to be active even when no growth factor is present or from expression of abnormally high levels of a growth factor or its receptor. This abnormal activity may also allow cancer cells to survive under conditions that would usually lead to cell death, which contributes to resistance to chemotherapy or radiation. Inhibition of growth factors or growth factor receptors is a validated approach to treating cancer, and several approved cancer therapies are designed to inhibit the activity of these proteins. Growth factor receptors that play a role in tumor cell growth include the stem cell factor receptor, or KIT, the platelet-derived growth factor receptor, or PDGFR, the epidermal growth factor receptor, or EGFR, the human epidermal growth factor receptor 2, or HER2, the hepatocyte growth factor receptor, or MET, the neuropathic growth factor rearranged during the transvection, or RET, and the insulin-like growth factor type 1 receptor, or IGF1R. Key kinases in signal transduction pathways downstream of growth factor receptors that promote cell growth include RAF, the MAP-ERK kinase, or MEK, the cytoplasmic tyrosine janus kinase 2, or JAK2, the phosphoinosotide-3 kinase, or PI3K, and the mammalian target of rapamycin, or mTOR.

Cell Survival. Normal cells often activate a self-destruct program known as programmed cell death or apoptosis under abnormal conditions that include the stresses that arise as a result of nutrient, oxygen or energy deprivation, for example. One of the hallmarks of tumor cells is the ability to survive under such conditions, an attribute that results from the inappropriate activation of survival signaling pathways. These pathways often become activated in tumor cells as a result of genetic alterations that result in either loss of the suppressor genes that negatively regulate such pathways or the activation of positive effectors of the pathway. Many growth factor receptors, including EGFR, HER2, MET, KIT, and IGF1R activate survival signaling pathways. Other key kinases in survival pathways include PI3K and mTOR.

Angiogenesis. Angiogenesis, the process by which new blood vessels form, is essential for the growth of tumors beyond a minimum size. In small tumors, cancer cells use existing blood vessels to get oxygen and nutrients needed for growth and to remove waste products. As tumors grow, the existing blood vessels are no longer sufficient to support the rapid pace of cancer cell growth, and continued growth and cancer cell survival requires the formation of new blood vessels. Tumor cells send out chemical signals that stimulate nearby blood vessels to grow into the tumor. In addition to providing essential oxygen and nutrients to the tumor, these new blood vessels also facilitate the migration of tumor cells into the blood system where they can travel to other parts of the body and give rise to metastatic disease. Inhibition of angiogenesis is a validated approach to treating cancer, and angiogenesis inhibitors have been approved by the U.S. Food and Drug Administration, or FDA, for the treatment of several types of cancer. RTKs that play a role in angiogenesis include the vascular endothelial growth factor receptor 2, or VEGFR2 (also known as KDR), PDGFR and MET.

Migration. Cell migration allows tumor cells to invade healthy tissue and spread to disparate parts of the body. A key target that has been shown to play a role in cell migration is MET.

Cell Cycle Regulation. In normal cells, the processes of DNA replication and cell division are tightly controlled. These processes work together to enforce cell cycle checkpoints that prevent cells with damaged DNA from progressing through the cell cycle, allowing time for the damage to be repaired. This system reduces the efficacy of a variety of cancer therapies that exert their effects through DNA damage. Inhibition of cell cycle check point proteins may increase the activity of a variety of DNA damaging agents, including radiation and some chemotherapies, and may increase the activity of these agents without increasing systemic toxicity. Cell cycle check point targets include the serine/threonine protein kinases CHK1 and CHK2.

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Leverage Strategic Collaborations

We are committed to retaining a significant interest in the value of our pipeline and product candidates. Our strategy is to leverage the strength of our extensive data and the broad potential of our development compounds to establish strategic alliances that create near-term revenue, while reducing our risk of product failure and retaining long-term rights to those compounds that succeed. We have established and intend to continue pursuing commercial relationships and key partnerships with major pharmaceutical and biotechnology companies based on the strength of our biological expertise and drug discovery and development capabilities. Our collaborations to date have provided us with substantial committed funding for our research and development efforts, the potential to earn significant milestones as well as opportunities to receive significant future payments, if our collaborators successfully develop and market products that result from our collaborative work. In addition, many of our strategic relationships provide us with or permit us to obtain co-development, co-promotion or other rights to products identified or developed in such collaborative relationships as a result of our efforts.

Management of Our Financial Resources

Fiscal discipline and pragmatic allocation of our resources are key components of our corporate strategy. We believe that making significant investments in preclinical development enhances our ability to generate multiple new, high-quality INDs and to rapidly advance these new drug candidates through clinical development. We believe the return on this investment will come in the form of higher clinical success rates, funding and partnership terms that allow us to retain increasing equity in the long-term value of our pipeline. We believe that this approach will enhance the quality and growth of our pipeline while maintaining our ability to fulfill obligations to corporate partners. We seek to finance our activities through a blend of funding opportunities, including: executing under our existing partnerships, which potentially triggers substantial milestones; exploring opportunities for new partnerships for our unpartnered assets, which have the potential to bring in near-term cash and defray late-stage development costs; evaluating the suitability of third-party financing vehicles with the aim to off-load a significant portion of our near-term clinical development expense and clinical risks; and opportunistically accessing the capital markets.

Our Pipeline

We have an extensive pipeline of compounds in various stages of development that will potentially treat cancer and various metabolic and cardiovascular disorders. All of our development compounds were generated through our internal drug discovery efforts.

Cancer Program

Our cancer program currently includes the following 11 compounds in clinical development.

XL647 is a potent and balanced inhibitor of EGFR, HER2 and VEGFR2, RTKs that are implicated in driving tumor growth and vascularization (blood vessel formation). The compound has been optimized for high potency and oral bioavailability, demonstrates excellent activity in target-specific cellular functional assays and has shown sustained inhibition of target RTKs *in vivo* following a single oral dose in preclinical studies. We have completed an initial phase 1 clinical trial of XL647, and the phase 2 clinical program in patients with non-small cell lung cancer is ongoing. Preliminary data from a phase 1 trial evaluating intermittent dosing of XL647 were presented in November 2005 at the 17th EORTC-NCI-AACR International Conference on Molecular Targets and Cancer Therapeutics, or the EORTC Symposium, and at the American Society of Clinical Oncology, or ASCO, annual meeting in June 2006. Updated data were presented in November 2006 at the 18th EORTC Symposium. Data from a second phase 1 trial evaluating daily dosing of XL647 were presented in October 2007 at the 19th EORTC Symposium. A phase 2 trial of XL647 in patients with advanced non-small cell lung cancer

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who have not previously been treated with chemotherapy was initiated in August 2006. Preliminary data from this trial were reported at the conference of the International Association for the Study of Lung Cancer in September 2007 and at the 19th EORTC Symposium in October 2007. A second phase 2 trial of XL647 in patients with advanced non-small cell lung cancer who have previously benefited from and then progressed on prior treatment with an EGFR inhibitor (erlotinib or gefitinib) was initiated in July 2007.

XL880 is a potent inhibitor of MET and VEGFR2, which play synergistic roles in promoting tumor growth and angiogenesis. Activation or overexpression of MET has been documented as a negative prognostic indicator in patients with various carcinomas and in patients with multiple myeloma, glioma and other solid tumors. Interim data from an ongoing phase 1 trial of XL880 were presented at the 2005 EORTC Symposium and at the 2006 ASCO Annual Meeting. Updated data were reported at the 2006 EORTC Symposium. Data from two phase 1 trials were reported at the 2007 ASCO Annual Meeting. A phase 2 clinical trial of XL880 was initiated in patients with hereditary or sporadic papillary renal cell carcinoma in June 2006, and data from this trial were reported at the 2007 EORTC Symposium. Another phase 2 trial was initiated in patients with metastatic, poorly differentiated diffuse gastric cancer in December 2006. Additionally, a phase 2 trial was initiated in head and neck cancer patients in August 2007. As described under Corporate Collaborations GlaxoSmithKline, in December 2007, GlaxoSmithKline exercised its option to further develop and commercialize XL880. We expect to transfer the XL880 development program to GlaxoSmithKline in the first quarter of 2008.

XL820 inhibits KIT as well as VEGFR2 and PDGFR, clinically validated targets implicated in a variety of human cancers. In preclinical tumor models of breast carcinoma, glioma and leukemia, the compound exhibited dose-dependent growth inhibition and has been shown to cause tumor regression. XL820 demonstrated potent activity in target-specific cellular functional assays. In biochemical and cellular assays, XL820 inhibits mutant forms of KIT that confer resistance to approved KIT inhibitors. XL820 has good oral bioavailability and has shown sustained inhibition of target RTKs *in vivo* following a single oral dose in preclinical studies. A phase 1 clinical trial of XL820 was initiated in July 2005 in patients with solid tumors for whom there are no other available therapies known to prolong survival. Preliminary data from this trial were reported by investigators at the 2006 and 2007 EORTC Symposia. A phase 2 trial was initiated in December 2007 in patients with gastrointestinal stromal tumors.

XL184 inhibits MET, RET and VEGFR2, key drivers of tumor growth and vascularization. The compelling preclinical efficacy of XL880, our first MET/VEGFR2 inhibitor, increased our interest in inhibitors of these RTKs and resulted in the discovery and development of XL184 as a distinct compound with potent activity. This SSKI has demonstrated dose-dependent tumor growth inhibition and tumor regression in a variety of tumor models, including thyroid, breast, colon, non-small cell lung cancer and glioblastoma. A phase 1 clinical trial in patients with solid tumors for whom there are no other available therapies was initiated in September 2005. Preliminary data from this study were reported by investigators at the 2006 and 2007 EORTC Symposia. A phase 1/2 trial was initiated in January 2008 in patients with non-small cell lung cancer who have failed prior therapy with erlotinib, and a phase 2 trial is planned in patients with advanced glioblastoma.

XL518 is a novel small molecule drug designed to inhibit the activity of MEK, a key component of the RAS/RAF/MEK/ERK signaling pathway. This pathway is frequently activated in human tumors and is required for transmission of growth-promoting signals from numerous receptor tyrosine kinases. Preclinical studies have demonstrated that XL518 is a potent and specific inhibitor of MEK with highly optimized pharmacokinetic and pharmacodynamic properties. XL518 exhibits oral bioavailability in multiple species and causes substantial and durable inhibition of ERK phosphorylation in xenograft tumor models. Administration of XL518 causes tumor regression in multiple xenograft models with mutationally-activated B-RAF or RAS. We filed an IND for XL518 in December 2006 and initiated a phase 1 clinical trial in May 2007. In December 2006, we entered into a worldwide co-development agreement with Genentech for the development and commercialization of XL518, as described under Corporate Collaborations Genentech.

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XL281 specifically targets RAF, which is a cytoplasmic serine/threonine kinase that lies immediately downstream of RAS, and is a key component of the RAS/RAF/MEK/ERK pathway that is frequently activated in human tumors. Activating mutations in B-RAF occur in approximately 60% of melanoma patients, indicating a potentially pivotal role for deregulation of this kinase in the progression of melanoma. XL281 is a potent and highly selective inhibitor of RAF kinases, is orally bioavailable and exhibits substantial efficacy in tumor xenograft models. A phase 1 trial was initiated in April 2007.

XL019 is a selective inhibitor of the cytoplasmic tyrosine kinase JAK2. JAK2 is activated by cytokine and growth factor receptors and phosphorylates members of the STAT family of inducible transcription factors. Activation of the JAK/STAT pathway promotes cell growth and survival, and is a common feature of human tumors. JAK2 is activated by mutation in the majority of patients with polycythemia vera and essential thrombocythemia and appears to drive the inappropriate growth of blood cells in these conditions. XL019 is a potent and selective inhibitor of JAK2, with excellent pharmacodynamic properties and an encouraging safety profile in preclinical models. A phase 1 trial was initiated in patients with myelofibrosis in August 2007, and data from this study were reported at the annual meeting of the American Society of Hematology in December 2007.

XL844 potently inhibits the checkpoint kinases CHK1 and CHK2, which induce cell cycle arrest in response to a variety of DNA damaging agents. Activation of these checkpoints following DNA damage allows for DNA repair and protects tumor cells from the cytotoxic effects of chemo- and radio-therapy. XL844 abrogates these cell cycle blocks and enhances tumor cell killing by a wide variety of chemotherapeutic agents and radiation *in vitro*. XL844 displays good pharmacokinetic properties and oral bioavailability, and increases the efficacy of chemotherapeutic agents without increasing systemic toxicity in preclinical tumor models. A phase 1 trial of XL844 in patients with chronic lymphocytic leukemia was initiated in September 2005, and was closed in 2007. A phase 1 trial evaluating XL844 in combination with gemcitabine was initiated in May 2007.

XL228 potently inhibits the T315I mutant form of ABL, which is resistant to inhibition by other targeted therapies approved for chronic myelogenous leukemia. In addition, XL228 targets IGF1R, an RTK that is highly expressed and activated in a broad range of human tumors and is thought to promote tumor growth, survival and resistance to chemotherapeutic agents. XL228 exhibited efficacy in a variety of solid tumor xenograft models. We filed an IND for XL228 in August 2006. We subsequently observed formulation stability data resulting in the need for minor changes in formulation. We then initiated a phase 1 clinical trial in May of 2007 in patients with chronic myelogenous leukemia who have failed or have been intolerant to irmatinib and dasatinib therapy, and a phase 1 trial in patients with solid tumors in October 2007. Preliminary data from the trial in patients with chronic myelogenous leukemia were reported at the annual meeting of the American Society of Hematology in 2007.

XL147 selectively targets PI3K. Upregulation of PI3K activity is one of the most common characteristics of human tumor cells and can result from activation of growth factor receptors, amplification of the PI3K gene, activating mutations in the PI3K gene, downregulation of the phosphatase and tensin homolog, or PTEN, lipid phosphatase or activating mutations in RAS. Activation of PI3K results in stimulation of AKT and mTOR kinases resulting in promotion of tumor cell growth and survival. This survival signal plays a significant role in conferring resistance to chemo- and radio-therapy by inhibiting apoptotic cell death. XL147 is a potent and selective inhibitor of PI3K with excellent pharmacokinetic and pharmacodynamic properties and compelling efficacy in several preclinical xenograft models both as a single agent and in combination with chemotherapy. We filed an IND for XL147 in March 2007 and initiated a phase 1 trial in June 2007. Preliminary data from this trial were reported at the 19th EORTC Symposium in October 2007.

XL765 targets both PI3K and mTOR, key kinases in the PI3K signaling pathway. mTOR is a serine/threonine kinase that controls the protein translation machinery and hence cell growth. mTOR is activated by growth factors via PI3K and AKT, but is also activated in a PI3K independent fashion in

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response to nutrient and energy levels. Thus, in some tumors targeting both PI3K and mTOR may provide additional benefit compared to selectively targeting PI3K. XL765 is a potent inhibitor of PI3K and mTOR with excellent pharmacokinetic and pharmacodynamic properties, and compelling efficacy in several preclinical xenograft models both as a single agent and in combination with chemotherapy. We filed an IND for XL765 in April 2007 and initiated a phase 1 trial in June 2007. Preliminary data from this trial were reported at the 19th EORTC Symposium in October 2007.

We currently have various compounds in preclinical development, including the following two compounds in late-stage preclinical development:

XL139 inhibits activation of Hedgehog, or HH, signaling by binding to smoothened, a key component of the signaling pathway. Genetic lesions that activate the HH pathway are key drivers of basal cell carcinoma and medulloblastoma formation in humans. In addition, activation of the HH signaling pathway via the action of the ligands SHh, IHh or DHh promotes cellular growth, and elevated ligand production and HH pathway activation is observed in a variety of human tumors including pancreatic carcinomas, small-cell lung cancer and glioblastomas. Signaling via the HH pathway is also thought to promote survival of cancer stem cells, which constitute a particularly chemo- and radio-resistant component of tumors. In preclinical models, XL139 potently inhibits HH signaling in tumors and significantly slows tumor growth. XL139 was advanced to development compound status in July 2007. As described under Corporate Collaborations Bristol-Myers Squibb 2007 Cancer Collaboration, in January 2008, Bristol-Myers Squibb exercised its option to develop and commercialize XL139, and we exercised our option to co-develop and co-commercialize XL139.

XL888 is a novel, synthetic inhibitor of HSP90, a chaperone protein that promotes the activity and stability of a range of key regulatory proteins including kinases. The activity of HSP90 is particularly prominent in tumor cells, where it promotes the activity of proteins controlling growth and survival. Natural product based inhibitors of HSP90 are currently in clinical trials and have shown encouraging signs of efficacy, but their utility is limited by poor pharmacokinetic properties and by their side effect profile. XL888 inhibits HSP90 with comparable potency to natural product-based inhibitors, but has good oral bioavailability and an improved tolerability profile in preclinical models. In multiple preclinical xenograft tumor models, XL888 exhibits substantial anti-tumor activity at well tolerated doses. XL888 was advanced to development compound status in October 2007, and we anticipate filing an IND in the second half of 2008.

We are committed to having preclinical and clinical data from our compounds presented at periodic peer review meetings.

Metabolic Program

We currently have various compounds in development that target metabolic and cardiovascular diseases. Our programs in metabolic and cardiovascular diseases originated from our acquisition of X-Ceptor Therapeutics, Inc. in October 2004. Our clinical stage compounds include:

XL652 targets the liver X receptors, or LXR, which modulate genes involved in regulation of lipid and cholesterol homeostasis. Activation of LXRα or LXRß in foam cells in atherosclerotic plaques promotes reverse cholesterol transport and results in marked anti-atherogenic activity in multiple preclinical models of atherosclerosis. However, prototype LXR agonists also activate LXRα in the liver resulting in increased fatty acid synthesis and consequent elevations in hepatic and circulating triglyceride levels, an unacceptable side effect. XL652 is a novel LXR agonist that effectively reduces atherosclerotic plaques in preclinical models at doses that do not result in triglyceride elevations. XL652 was developed under a collaboration with Bristol-Myers Squibb, which filed the foreign equivalent of an IND for XL652 in November 2007. For more information on our LXR collaboration, see Corporate Collaborations Bristol-Myers Squibb LXR Collaboration.

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XL335 targets the Farnesoid X Receptor, or FXR, which has been shown to function as a bile acid receptor regulating genes involved in lipid, cholesterol and bile acid homeostasis. We have identified proprietary, potent and selective FXR ligands (compounds that bind to a receptor) that have good oral bioavailability and drug metabolism and pharmacokinetic properties. In rodent models of dyslipidemia, these compounds lowered triglycerides by decreasing triglyceride synthesis and secretion. In addition, they improved the high-density lipoprotein (HDL)/low-density lipoprotein (LDL) ratio and are anti-atherogenic (prevent the formation of lipid deposits in the arteries) in animal models of atherosclerosis. XL335 is also effective in models of cholestasis (a condition in which bile excretion from the liver is blocked), cholesterol gallstones and liver fibrosis. These data suggest that small molecule ligands targeting FXR should function as novel therapeutic agents for treating symptoms and disease states associated with metabolic syndrome as well as certain liver disorders. In December 2005, we licensed the FXR program to Wyeth Pharmaceuticals. Wyeth Pharmaceuticals is responsible for all further preclinical and clinical development, regulatory, manufacturing and commercialization activities for the compounds. For information regarding on our collaboration with Wyeth Pharmaceuticals, see Corporate Collaborations Other Collaborations Wyeth Pharmaceuticals.

XL550 is a potent, selective, non-steroidal mineralocorticoid receptor, or MR, antagonist that is effective in animal models of hypertension and congestive heart failure. XL550 has shown excellent oral bioavailability and drug metabolism and pharmacokinetic properties in multiple preclinical models and has exhibited a significantly better pharmacokinetic and pharmacodynamic profile than existing steroid drugs. In multiple studies in various non-clinical species, XL550 shows potent anti-hypertensive action and anti-hypertrophic action on the heart, lung and kidney. In addition, XL550 shows 50-100 times greater potency vs. eplerenone in various in vivo studies related to hypertension and congestive heart failure in preclinical models. As a novel proprietary non-steroidal MR antagonist, XL550 has the potential to offer highly effective and safe therapeutic approaches for the treatment of hypertension and congestive heart failure. XL550 was licensed to Daiichi-Sankyo for development and commercialization in March 2006. See Corporate Collaborations Other Collaborations Daiichi-Sankyo.

Corporate Collaborations

We have established collaborations with major pharmaceutical and biotechnology companies based on the strength of our technologies and biological expertise to support additional development of our proprietary products. Through these collaborations, we obtain license fees, research funding, and the opportunity to receive milestone payments and royalties from research results and subsequent product development activities. Many of our collaborations have been structured strategically to provide us with access to technology that may help to advance our internal programs while at the same time enabling us to retain rights to use these technologies in different industries.

GlaxoSmithKline

In October 2002, we established a collaboration with GlaxoSmithKline to discover and develop novel therapeutics in the areas of vascular biology, inflammatory disease and oncology. The collaboration involved three agreements: (1) a Product Development and Commercialization Agreement, or PDA; (2) a Stock Purchase and Stock Issuance Agreement, or SPA; and (3) a Loan and Security Agreement, or LSA. Under the original PDA, GlaxoSmithKline paid us $30.0 million in an upfront fee and agreed to pay up to an additional $90.0 million in research and development funding over the first six years of the collaboration.

In January 2005, we amended the terms of the PDA, SPA and LSA. Under the amended PDA, GlaxoSmithKline selected a modified program election through which the focus of the collaboration was shifted to 12 internal programs at various stages of development (XL784, XL647, XL999, XL880, XL184, XL820, XL844, XL281, XL418, XL228 and two earlier stage oncology programs). Each program centers on compounds

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that are directed against one or more targets identified in the collaboration. GlaxoSmithKline has the option to elect to develop up to three of our compounds from the programs specified in the product development and commercialization agreement. In December 2007, GlaxoSmithKline exercised its development option for XL880. GlaxoSmithKline declined to exercise its development option for XL647 in July 2007 and its development option for XL784 in January 2008. In addition, in December 2007, we discontinued the development programs for XL999 and XL418. As a result of GlaxoSmithKline s exercise of its development option for XL880, GlaxoSmithKline has the right to select from the programs up to one additional compound, or two additional compounds if it extends the specified development term. The amount of acceptance milestones that we receive from GlaxoSmithKline will depend on the number of compounds selected, the timing of the selection of the compounds and, for those acceptances made after the end of the original development term, whether GlaxoSmithKline extended the development term. Delays in obtaining clinical proof-of-concept for compounds subject to GlaxoSmithKline s election rights may decrease the size of any GlaxoSmithKline milestones and negatively impact our financial position. GlaxoSmithKline retains exclusivity rights to the 32 specified targets that are encompassed by the 12 programs through the end of the specified development term, or any extension thereof by GlaxoSmithKline. After the end of the development term or any extension, GlaxoSmithKline retains exclusivity rights to a subset of these targets based on the compounds that they have selected for development. We have retained rights to all compounds not encompassed by the 12 programs that are part of the collaboration with GlaxoSmithKline and may work on any targets with the exception of the 32 targets or, if applicable, a subset, subject to GlaxoSmithKline s exclusivity rights.

In May 2005, we filed the third of three INDs required by the amended PDA to achieve a $30.0 million milestone, which we received from GlaxoSmithKline in May 2005. In May 2005, we also submitted two new development candidates to GlaxoSmithKline, thereby triggering an additional $5.0 million milestone, which we received in May 2005. We may also receive additional development related milestones and royalties on product sales and may have certain co-promotion rights to products in North America. In addition, under the amended PDA, GlaxoSmithKline agreed to provide research funding of $47.5 million over the remaining three-year term of the collaboration, all of which we received by the end of 2007. In connection with GlaxoSmithKline s exercise of its development option for XL880, we earned a selection milestone of $35.0 million, all of which was retained by GlaxoSmithKline to offset the $30.0 million milestone that GlaxoSmithKline paid to us in 2005 under the amended PDA. To date, we have received $65.0 million in upfront and milestone payments, $85.0 million in research and development funding and loans in the principal amount of $85.0 million.

The terms of the amended PDA and LSA allow us to use third-party financing vehicles to fund the further clinical development of our compounds XL647, XL784 and XL999, but any such compounds developed through clinical financing vehicles continued to be subject to GlaxoSmithKline s compound selection rights. In June 2005, we entered into a transaction to fund the clinical development of XL647, XL784 and XL999 through Symphony Evolution, Inc., which is described under Corporate Collaborations Symphony Evolution. GlaxoSmithKline has declined to exercise its compound selection right with respect to XL647 and XL784, and we have discontinued development of XL999.

Pursuant to the terms of the original SPA, the amended SPA and as a result of its modified program election, GlaxoSmithKline purchased a total of three million shares of our common stock. We have no further option to sell, and GlaxoSmithKline has no further obligation to purchase, additional shares of our common stock.

Bristol-Myers Squibb

2001 Cancer Collaboration. In July 2001, we entered into a cancer collaboration agreement with Bristol-Myers Squibb. Under the terms of the collaboration, Bristol-Myers Squibb paid us a $5.0 million upfront license fee and agreed to provide us with $3.0 million per year in research funding for a minimum of three years. In December 2003, the cancer collaboration was extended until January 2007, at which time Bristol-Myers Squibb elected to continue the collaboration until July 2009. The goal of the extension was to increase the total number

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and degree of validation of cancer targets that we will deliver to Bristol-Myers Squibb. Each company will maintain the option to obtain exclusive worldwide rights to equal numbers of validated targets arising from the collaboration. Under the terms of the extended collaboration, Bristol-Myers Squibb provided us with an upfront payment and agreed to provide increased annual research funding and milestones on certain cancer targets arising from the collaboration that progress through specified stages of validation. We will also be entitled to receive milestones on compounds in the event of successful clinical and regulatory events and royalties on commercialized products.

LXR Collaboration. In December 2005, we entered into a collaboration agreement with Bristol-Myers Squibb for the discovery, development and commercialization of novel therapies targeted against LXR, a nuclear hormone receptor implicated in a variety of cardiovascular and metabolic disorders. This agreement became effective in January 2006, at which time we granted Bristol-Myers Squibb an exclusive, worldwide license with respect to certain intellectual property primarily relating to compounds that modulate LXR. During the research term, we expect to jointly identify drug candidates with Bristol-Myers Squibb that are ready for IND-enabling studies. After the selection of a drug candidate for further clinical development by Bristol-Myers Squibb, Bristol-Myers Squibb has agreed to be solely responsible for further preclinical development as well as clinical development, regulatory, manufacturing and sales/marketing activities for the selected drug candidate. After Bristol-Myers Squibb s selection, except in certain termination scenarios described below, we would not have rights to reacquire the selected drug candidate.

Under the collaboration agreement, Bristol-Myers Squibb paid us a nonrefundable upfront payment in the amount of $17.5 million and was obligated to provide research and development funding of $10.0 million per year for an initial research period of two years. On September 20, 2007, the collaboration was extended at Bristol-Myers Squibb s request through January 12, 2009. Bristol-Myers Squibb also has retained the option to further extend the collaboration by an additional year.

Under the collaboration agreement, Bristol-Myers Squibb is required to pay us development and regulatory milestones of up to $140.0 million per product for up to two products from the collaboration. In addition, we are also entitled to receive sales milestones and royalties on sales of any products commercialized under the collaboration. In connection with the extension of the collaboration through January 2009, Bristol-Myers Squibb is obligated to pay to us additional research funding of $7.5 million. Bristol-Myers Squibb has the option to terminate the collaboration agreement at any time after January 2008, in which case Bristol-Myers Squibb s payment obligations would cease, its license relating to compounds that modulate LXR would terminate and revert to us, and we would receive, subject to certain terms and conditions, licenses from Bristol-Myers Squibb to research, develop and commercialize certain collaboration compounds that were discovered under the collaboration agreement. In December 2007, we received $5.0 million for achieving a development milestone.

2007 Cancer Collaboration. In December 2006, we entered into a worldwide collaboration with Bristol-Myers Squibb, which became effective in January 2007, to discover, develop and commercialize novel targeted therapies for the treatment of cancer. We are responsible for discovery and preclinical development of small molecule drug candidates directed against mutually selected targets. In January 2007, Bristol-Myers Squibb made an upfront payment of $60.0 million to us for which we granted Bristol-Myers Squibb the right to select up to three IND candidates from six future Exelixis compounds.

For each IND candidate selected, we are entitled to receive a $20.0 million selection milestone from Bristol-Myers Squibb. Once selected, Bristol-Myers Squibb will lead the further development and commercialization of the selected IND candidates. In addition, we have the right to opt in to co-promote the selected IND candidates, in which case we will equally share all development costs and profits in the United States. If we opt-in, we will be responsible for 35% of all development costs related to clinical trials intended to support regulatory approval in both the United States and the rest of the world, with the remaining 65% to be paid by Bristol-Meyers Squibb. This percentage ratio was intended to approximate a 50/50 split of development and commercialization costs in the United States. If we do not opt in to co-promote the selected IND candidates, we would be entitled to receive

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milestones and royalties in lieu of profits from sales in the United States. Outside of the United States, Bristol-Myers Squibb will have primary responsibility for development activities and we will be entitled to receive royalties on product sales. After exercising its co-development option, Bristol-Myers Squibb may, upon notice to us, terminate the agreement as to any product containing or comprising the selected candidate. In the event of such termination election, Bristol-Myers Squibb s license relating to such product would terminate and revert to us, and we would receive, subject to certain terms and conditions, licenses from Bristol-Myers Squibb to research, develop and commercialize certain collaboration compounds that were discovered.

In January 2008, Bristol-Myers Squibb exercised its option under the collaboration to develop and commercialize XL139. Under the terms of the collaboration agreement, the selection of XL139 by Bristol-Myers Squibb entitles us to a milestone payment of $20.0 million, which we received in February 2008. In addition, we exercised our option under the collaboration agreement to co-develop and co-commercialize XL139 in the United States. Following the transfer of the XL139 development program, which is expected to occur in the first quarter of 2008, Bristol-Myers Squibb will lead all global activities. The parties will co-develop and co-commercialize XL139 and equally share all development costs and profits in the United States. We will be entitled to receive double-digit royalties on product sales outside of the United States.

Genentech

Cancer Collaboration. In May 2005, we established a collaboration agreement with Genentech to discover and develop therapeutics for the treatment of cancer, inflammatory diseases, and tissue growth and repair. Under the terms of the collaboration agreement, we granted to Genentech a license to certain intellectual property. Genentech paid us a nonrefundable upfront license payment and is obligated to provide research and development funding over the three-year research term, totaling $16.0 million.

Under the collaboration agreement, Genentech has primary responsibility in the field of cancer for research and development activities as well as rights for commercialization of any products. In the fields of inflammatory disease and in the fields of tissue growth and repair, we initially have primary responsibility for research activities. After the expiration of the research term, we will have the option to elect to share a portion of the costs and profits associated with the development, manufacturing and commercialization of products in one of the fields. The research term under the collaboration agreement is three years and may be extended for one-year terms upon mutual consent. For all products under the collaboration agreement that are not elected as cost or profit sharing products, we may receive milestone and royalty payments.

MEK Collaboration. In December 2006, we entered into a worldwide co-development agreement with Genentech for the development and commercialization of XL518, a small-molecule inhibitor of MEK. Genentech paid upfront and milestone payments of $25.0 million in December 2006 and $15.0 million in January 2007 upon signing of the co-development agreement and with the submission of an IND for XL518. We initiated a phase 1 clinical trial of XL518 in the first quarter of 2007, and enrollment in this trial is ongoing.

Under the terms of the co-development agreement, we are responsible for developing XL518 through the end of a phase 1 clinical trial, and Genentech has the option to co-develop XL518, which Genentech may exercise after receipt of certain phase 1 data from us. If Genentech exercises its option to co-develop XL518, we will be entitled to receive an opt-in payment and we will be required to grant to Genentech an exclusive worldwide revenue-bearing license to XL518. Genentech will be responsible for all further development costs of XL518 and we will share equally in the U.S. commercialization costs. On an annual basis, we are entitled to an initial equal share of U.S. profits and losses, which will decrease as sales increase, and we are also entitled to royalties on non-U.S. sales. Genentech has the right to terminate the agreement without cause at any time. If Genentech terminates the co-development agreement without cause, all licenses that were granted to Genentech under the agreement terminate and revert to us. Additionally, we would receive, subject to certain conditions, licenses from Genentech to research, develop and commercialize reverted product candidates.

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Symphony Evolution

On June 9, 2005, we entered into a series of related agreements, including a purchase option agreement, providing for the financing of the clinical development of XL647 and two of our other product candidates, XL784 and XL999. In December 2006, we amended the purchase option agreement. Pursuant to the agreements, Symphony Evolution, Inc., or SEI, and its investors have invested $80.0 million to fund the clinical development of XL647, XL784 and XL999, and we have licensed to SEI our intellectual property rights related to these product candidates. SEI is a wholly owned subsidiary of Symphony Evolution Holdings LLC, or Holdings, which provided $40.0 million in funding to SEI on June 9, 2005 and an additional $40.0 million on June 9, 2006. We continue to be primarily responsible for the development of XL647, XL784 and XL999 in accordance with specified development plans and related development budgets.

Pursuant to the agreements, we received an exclusive purchase option that gives us the right to acquire all of the equity of SEI, thereby allowing us to reacquire XL647, XL784 and XL999. Under our amended purchase option agreement with SEI, we cannot repurchase a single product candidate without also repurchasing the other two product candidates. The Phase 2 clinical development program for XL647 is ongoing, and GlaxoSmithKline has declined to exercise its development option for XL647. In order to retain rights to XL647 after the expiration of the purchase option period, we would be required to reacquire XL647, XL784 and XL999 from SEI s investors through the exercise of our purchase option. In December 2007, we discontinued the development of XL999, and, in January 2008, GlaxoSmithKline declined to exercise its option to further develop and commercialize XL784. We do not intend to invest further in the development of XL784, but will seek a partner with which to take the compound forward, which would also require us to repurchase all three compounds from SEI s investors.

The amended purchase option allows us, at our sole election, to pay up to 100% of the purchase option exercise price in shares of our common stock. The purchase option is exercisable at any time until the earlier of June 9, 2009 or the 90th day after the date on which SEI provides us with financial statements showing cash and cash equivalents of less than $5.0 million at an exercise price equal to the sum of: (1) the total amount of capital invested in SEI by Holdings; and (2) an amount equal to 25% per year on such funded capital (with respect to the initial funded capital, compounded from June 9, 2005 and, with respect to the second draw amount, compounded from June 9, 2006).

Pursuant to the agreements, we issued to Holdings two five-year warrants to purchase 1.5 million shares of our common stock at $8.90 per share. In addition, should the purchase option expire unexercised until the earlier of June 9, 2009, or the 90th day after SEI provides us with financial statements showing cash and cash equivalents of less than $5.0 million, we are obligated to issue to Holdings an additional five-year warrant to purchase 500,000 shares of our common stock at a price per share equal to 125% of the market price of our common stock at the time of expiration of the purchase option.

Other Collaborations

Wyeth Pharmaceuticals. In December 2005, we entered into a license agreement with Wyeth Pharmaceuticals related to compounds targeting FXR, a nuclear hormone receptor implicated in a variety of metabolic and liver disorders. Under the terms of the agreement, we granted to Wyeth Pharmaceuticals an exclusive, worldwide license with respect to certain intellectual property primarily relating to compounds that modulate FXR. Wyeth Pharmaceuticals paid us a nonrefundable upfront payment in the amount of $10.0 million and we received $4.5 million in November 2006 for achieving a development milestone. In November 2007, Wyeth Pharmaceuticals paid us $2.5 million for achieving a second development milestone. Wyeth Pharmaceuticals is obligated to pay additional development and commercialization milestones of up to $140.5 million as well as royalties on sales of any products commercialized by Wyeth Pharmaceuticals under the agreement. Wyeth Pharmaceuticals will be responsible for all further preclinical and clinical development,

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regulatory, manufacturing and commercialization activities for the compounds. Subject to certain terms and conditions, Wyeth Pharmaceuticals has the option to terminate the license agreement.

Daiichi-Sankyo. In March 2006, we entered into a collaboration agreement with Daiichi Sankyo Company Limited for the discovery, development and commercialization of novel therapies targeted against MR, a nuclear hormone receptor implicated in a variety of cardiovascular and metabolic diseases. Under the terms of the agreement, we granted to Daiichi-Sankyo an exclusive, worldwide license to certain intellectual property primarily relating to compounds that modulate MR. After completion of the research term, Daiichi-Sankyo will be 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, except as described below.

Daiichi-Sankyo paid us a nonrefundable upfront payment in the amount of $20.0 million and is obligated to provide research and development funding of $3.8 million over a 15-month research term. In June 2007, the parties agreed to extend the research term for an additional six months. In November 2007, the parties decided not to further extend the research term. For each product from the collaboration, we are also entitled to receive payments upon attainment of pre-specified development, regulatory and commercialization milestones. In addition, we are also entitled to receive royalties on any sales of certain products commercialized under the collaboration. Daiichi-Sankyo may terminate the agreement upon 90 days written notice in which case Daiichi-Sankyo s payment obligations would cease, its license relating to compounds that modulate MR would terminate and revert to us, and we would receive, subject to certain terms and conditions, licenses from Daiichi-Sankyo to research, develop and commercialize compounds that were discovered under the collaboration.

Manufacturing and Raw Materials

We currently do not have manufacturing capabilities necessary to enable us to produce materials for our clinical trials. Raw materials and supplies required for the production of our product candidates are generally available from multiple suppliers. However, in some instances materials are available only from one supplier. In those cases where raw materials are only available through one supplier, we manage supplies, to the extent feasible, by ordering raw materials well in advance of scheduled needs. However, clinical trial schedules may be delayed due to interruptions of raw material supplies.

Government Regulation

The following section contains some general background information regarding the regulatory environment and processes affecting our industry and is designed to illustrate in general terms the nature of our business and the potential impact of government regulations on our business. It is not intended to be comprehensive or complete. Depending on specific circumstances, the information below may or may not apply to us or any of our product candidates. In addition, the information is not necessarily a description of activities that we have undertaken in the past or will undertake in the future. The regulatory context in which we operate is complex and constantly changing.

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 research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of our products.

The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- preclinical laboratory and animal tests;

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submission of an IND, which must become effective before clinical trials may begin;

adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug candidate for its intended use;

pre-approval inspection of manufacturing facilities and selected clinical investigators; and

FDA approval of a new drug application (NDA), or NDA supplement, for an approval of a new indication if the product is already approved for another indication.

The testing and approval process requires substantial time, effort and financial resources.

Prior to commencing the first clinical trial with a product candidate, we must submit an IND to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, arding the potential application of Section 871(m) to the Buffered PLUS.

Both U.S. and non-U.S. investors considering an investment in the Buffered PLUS should read the discussion under "Risk Factors" in this document and the discussion under "United States Federal Taxation" in the accompanying product supplement for PLUS and consult their tax advisers regarding all aspects of the U.S. federal income tax consequences of an investment in the Buffered PLUS, including possible alternative treatments, the issues presented by the aforementioned notice and any tax consequences arising under the laws of any state, local or non-U.S. taxing jurisdiction.

The discussion in the preceding paragraphs under "Tax considerations" and the discussion contained in the section entitled "United States Federal Taxation" in the accompanying product supplement for PLUS, insofar as they purport to describe provisions of U.S. federal income tax laws or legal conclusions with respect thereto, constitute the full opinion of Davis Polk & Wardwell LLP regarding the material U.S. federal tax consequences of an investment in the Buffered PLUS.

Use of proceeds and hedging:

The proceeds from the sale of the Buffered PLUS will be used by us for general corporate purposes. We will receive, in aggregate, $1,000 per Buffered PLUS issued, because, when we enter into hedging transactions in order to meet our obligations under the Buffered PLUS, our hedging counterparty will reimburse the cost of the agent's commissions. The costs of the Buffered PLUS borne by you and described beginning on page 2 above comprise the agent's commissions and the cost of issuing, structuring and hedging the Buffered PLUS.

On or prior to the pricing date, we hedged our anticipated exposure in connection with the Buffered PLUS by

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entering into hedging transactions with our affiliates and/or third party dealers. We expect our hedging counterparties to have taken positions in stocks of the underlying index and in futures and options contracts on the underlying index and any component stocks of the underlying index listed on major securities markets. Such purchase activity could have increased the value of the underlying index on the pricing date, and, therefore, could have increased the value at or above which the underlying index must close on the valuation date so that investors do not suffer a loss on their initial investment in the Buffered PLUS. In addition, through our affiliates, we are likely to modify our hedge position throughout the term of the Buffered PLUS, including on the valuation date, by purchasing and selling the stocks constituting the underlying index, futures or options contracts on the underlying index or its component stocks listed on major securities markets or positions in any other available securities or instruments that we may wish to use in connection with such hedging activities. As a result, these entities may be unwinding or adjusting hedge positions during the term of the Buffered PLUS, and the hedging strategy may involve greater and more frequent dynamic adjustments to the hedge as the valuation date approaches. We cannot give any assurance that our hedging activities will not affect the value of the underlying index, and, therefore, adversely affect the value of the Buffered PLUS or the payment you will receive at maturity. For further information on our use of proceeds and hedging, see "Use of Proceeds and Hedging" in the accompanying product supplement for PLUS.

Benefit plan investor considerations: Each fiduciary of a pension, profit-sharing or other employee benefit plan subject to Title I of the Employee Retirement Income Security Act of 1974, as amended ("ERISA") (a "Plan"), should consider the fiduciary standards of ERISA in the context of the Plan's particular circumstances before authorizing an investment in the Buffered PLUS. Accordingly, among other factors, the fiduciary should consider whether the investment would satisfy the prudence and diversification requirements of ERISA and would be consistent with the documents and instruments governing the Plan.

In addition, we and certain of our affiliates, including MS & Co., may each be considered a "party in interest" within the meaning of ERISA, or a "disqualified person" within the meaning of the Internal Revenue Code of 1986, as amended (the "Code"), with respect to many Plans, as well as many individual retirement accounts and Keogh plans (such accounts and plans, together with other plans, accounts and arrangements subject to Section 4975 of the Code, also "Plans"). ERISA Section 406 and Code Section 4975 generally prohibit transactions between Plans and parties in interest or disqualified persons. Prohibited transactions within the meaning of ERISA or the Code would likely arise, for example, if the Buffered PLUS are acquired by or with the assets of a Plan with respect to which MS & Co. or any of its affiliates is a service provider or other party in interest, unless the Buffered PLUS are acquired pursuant to an exemption from the "prohibited transaction" rules. A violation of these "prohibited transaction" rules could result in an excise tax or other liabilities under ERISA and/or Section 4975 of the Code for those persons, unless exemptive relief is available

under an applicable statutory or administrative exemption.

The U.S. Department of Labor has issued five prohibited transaction class exemptions ("PTCEs") that may provide exemptive relief for direct or indirect prohibited transactions resulting from the purchase or holding of the Buffered PLUS. Those class exemptions are PTCE 96-23 (for certain transactions determined by in-house asset managers), PTCE 95-60 (for certain transactions involving insurance company general accounts), PTCE 91-38 (for certain transactions involving bank collective investment funds), PTCE 90-1 (for certain transactions involving insurance company separate accounts) and PTCE 84-14 (for certain transactions determined by independent qualified professional asset managers). In addition, ERISA Section 408(b)(17) and Section 4975(d)(20) of the Code provide an exemption for the purchase and sale of securities and the related lending transactions, provided that neither the issuer of the securities nor any of its affiliates has or exercises any discretionary authority or control or renders any investment advice with respect to the assets of the Plan involved in the transaction and provided further that the Plan pays no more, and receives no less, than "adequate consideration" in connection with the transaction (the so-called "service provider" exemption). There can be no assurance that any of these class or statutory exemptions will be available with respect to transactions involving the Buffered PLUS.

Because we may be considered a party in interest with respect to many Plans, the Buffered PLUS may not be purchased, held or disposed of by any Plan, any entity whose underlying assets include "plan assets" by reason of any Plan's investment in the entity (a "Plan Asset Entity") or any person investing "plan assets" of any Plan, unless such purchase, holding or disposition is eligible for exemptive relief, including relief available under PTCEs 96-23, 95-60, 91-38, 90-1, 84-14 or the service provider exemption or such purchase, holding or disposition is otherwise not prohibited. Any purchaser, including any fiduciary purchasing on behalf of a Plan, transferee or holder of the Buffered PLUS will be deemed to have represented, in its corporate and its fiduciary capacity, by its purchase and holding of the Buffered PLUS that either (a) it is not a Plan or a Plan Asset Entity and is not purchasing such Buffered PLUS on behalf of or with "plan assets" of any Plan or with any assets of a governmental, non-U.S. or church plan that is subject to any federal, state, local or non-U.S. law that is substantially similar to the provisions of Section 406 of ERISA or Section 4975 of the Code ("Similar Law") or (b) its purchase, holding and disposition of these Buffered PLUS will not constitute or result in a non-exempt prohibited transaction under Section 406 of ERISA or Section 4975 of the Code or violate any Similar Law.

Due to the complexity of these rules and the penalties that may be imposed upon persons involved in non-exempt prohibited transactions, it is particularly important that fiduciaries or other persons considering

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purchasing the Buffered PLUS on behalf of or with "plan assets" of any Plan consult with their counsel regarding the availability of exemptive relief.

The Buffered PLUS are contractual financial instruments. The financial exposure provided by the Buffered PLUS is not a substitute or proxy for, and is not intended as a substitute or proxy for, individualized investment management or advice for the benefit of any purchaser or holder of the Buffered PLUS. The Buffered PLUS have not been designed and will not be administered in a manner intended to reflect the individualized needs and objectives of any purchaser or holder of the Buffered PLUS.

Each purchaser or holder of any Buffered PLUS acknowledges and agrees that:

(i) the purchaser or holder or its fiduciary has made and shall make all investment decisions for the purchaser or holder and the purchaser or holder has not relied and shall not rely in any way upon us or our affiliates to act as a fiduciary or adviser of the purchaser or holder with respect to (A) the design and terms of the Buffered PLUS, (B) the purchaser or holder's investment in the Buffered PLUS, or (C) the exercise of or failure to exercise any rights we have under or with respect to the Buffered PLUS;

(ii) we and our affiliates have acted and will act solely for our own account in connection with (A) all transactions relating to the Buffered PLUS and (B) all hedging transactions in connection with our obligations under the Buffered PLUS;

(iii) any and all assets and positions relating to hedging transactions by us or our affiliates are assets and positions of those entities and are not assets and positions held for the benefit of the purchaser or holder;

(iv) our interests are adverse to the interests of the purchaser or holder; and

(v) neither we nor any of our affiliates is a fiduciary or adviser of the purchaser or holder in connection with any such assets, positions or transactions, and any information that we or any of our affiliates may provide is not intended to be impartial investment advice.

Each purchaser and holder of the Buffered PLUS has exclusive responsibility for ensuring that its purchase, holding and disposition of the Buffered PLUS do not violate the prohibited transaction rules of ERISA or the Code or any Similar Law. The sale of any Buffered PLUS to any Plan or plan subject to Similar Law is in no respect a representation by us or any of our affiliates or representatives that such an investment meets all relevant legal requirements with respect to investments by plans generally or any particular plan, or that such an investment is appropriate for plans generally or any particular plan. In this regard, neither this discussion nor anything provided in this document is or is intended to be investment advice directed at any potential Plan purchaser or at Plan purchasers generally and such purchasers of the Buffered PLUS should consult and rely on their own counsel and advisers as to whether an investment in the Buffered PLUS is suitable.

Additional considerations:

However, individual retirement accounts, individual retirement annuities and Keogh plans, as well as employee benefit plans that permit participants to direct the investment of their accounts, will not be permitted to purchase or hold the Buffered PLUS if the account, plan or annuity is for the benefit of an employee of Morgan Stanley or Morgan Stanley Wealth Management or a family member and the employee receives any compensation (such as, for example, an addition to bonus) based on the purchase of the Buffered PLUS by the account, plan or annuity.

Client accounts over which Morgan Stanley, Morgan Stanley Wealth Management or any of their respective subsidiaries have investment discretion are not permitted to purchase the Buffered PLUS, either directly or indirectly.

Supplemental information regarding plan of distribution; conflicts of interest:

MS & Co. expects to sell all of the Buffered PLUS that it purchases from us to an unaffiliated dealer at a price of $992.50 per Buffered PLUS, for further sale to certain fee-based advisory accounts at the price to public of $1,000 per Buffered PLUS. MS & Co. will not receive a sales commission with respect to the Buffered PLUS.

MS & Co. is an affiliate of MSFL and a wholly owned subsidiary of Morgan Stanley, and it and other affiliates of ours expect to make a profit by selling, structuring and, when applicable, hedging the Buffered PLUS.

MS & Co. will conduct this offering in compliance with the requirements of FINRA Rule 5121 of the Financial Industry Regulatory Authority, Inc., which is commonly referred to as FINRA, regarding a FINRA member firm's distribution of the securities of an affiliate and related conflicts of interest. MS & Co. or any of our other affiliates may not make sales in this offering

	to any discretionary account. See “Plan of Distribution (Conflicts of Interest)” and “Use of Proceeds and Hedging” in the accompanying product supplement for PLUS.
Validity of the Buffered PLUS:	In the opinion of Davis Polk & Wardwell LLP, as special counsel to MSFL and Morgan Stanley, when the Buffered PLUS offered by this pricing supplement have been executed and issued by MSFL, authenticated by the trustee pursuant to the MSFL Senior Debt Indenture (as defined in the accompanying prospectus) and delivered against payment as contemplated herein, such Buffered PLUS will be valid and binding obligations of MSFL and the related guarantee will be a valid and binding obligation of Morgan Stanley, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency and similar laws affecting creditors’ rights generally, concepts of reasonableness and equitable principles of general applicability (including, without

Morgan Stanley Finance LLC

Buffered PLUS Based on the Value of the S&P 500® Index due December 31, 2020

Buffered Performance Leveraged Upside Securities℠

Principal at Risk Securities

limitation, concepts of good faith, fair dealing and the lack of bad faith), *provided* that such counsel expresses no opinion as to (i) the effect of fraudulent conveyance, fraudulent transfer or similar provision of applicable law on the conclusions expressed above and (ii) any provision of the MSFL Senior Debt Indenture that purports to avoid the effect of fraudulent conveyance, fraudulent transfer or similar provision of applicable law by limiting the amount of Morgan Stanley's obligation under the related guarantee. This opinion is given as of the date hereof and is limited to the laws of the State of New York, the General Corporation Law of the State of Delaware and the Delaware Limited Liability Company Act. In addition, this opinion is subject to customary assumptions about the trustee's authorization, execution and delivery of the MSFL Senior Debt Indenture and its authentication of the Buffered PLUS and the validity, binding nature and enforceability of the MSFL Senior Debt Indenture with respect to the trustee, all as stated in the letter of such counsel dated November 16, 2017, which is Exhibit 5-a to the Registration Statement on Form S-3 filed by Morgan Stanley on November 16, 2017.

Contact: Morgan Stanley Wealth Management clients may contact their local Morgan Stanley branch office or our principal executive offices at 1585 Broadway, New York, New York 10036 (telephone number (866) 477-4776). All other clients may contact their local brokerage representative. Third-party distributors may contact Morgan Stanley Structured Investment Sales at (800) 233-1087.

Where you can find more information: Morgan Stanley and MSFL have filed a registration statement (including a prospectus, as supplemented by the product supplement for PLUS and the index supplement) with the Securities and Exchange Commission, or SEC, for the offering to which this communication relates. You should read the prospectus in that registration statement, the product supplement for PLUS, the index supplement and any other documents relating to this offering that Morgan Stanley and MSFL have filed with the SEC for more complete information about Morgan Stanley, MSFL and this offering. You may get these documents without cost by visiting EDGAR on the SEC web site at.www.sec.gov. Alternatively, Morgan Stanley, MSFL, any underwriter or any dealer participating in the offering will arrange to send you the product supplement for PLUS, index supplement and prospectus if you so request by calling toll-free 1-(800)-584-6837.

You may access these documents on the SEC web site at.www.sec.gov as follows:

Product Supplement for PLUS dated November 16, 2017

Index Supplement dated November 16, 2017

Prospectus dated November 16, 2017

Terms used but not defined in this document are defined in the product supplement for PLUS, in the index supplement or in the prospectus.

"Performance Leveraged Upside Securities℠" and "PLUS℠" are our service marks.