EPIX Pharmaceuticals, Inc.
Form 10-K
March 17, 2008

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

Form 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2007

OR

o **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: 0-21863

EPIX PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**04-3030815**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*
4 Maguire Road, Lexington, Massachusetts	**02421**
(Address of principal executive offices)	*(Zip Code)*

Registrant s telephone number, including area code:
(781) 761-7600
Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.01 par value per share	The NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Exchange 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 o No þ

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

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 þ No o

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. o

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

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

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

The aggregate market value of the registrant s voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold as of the last business day of the registrant s most recently completed second fiscal quarter was $127,091,000.

As of March 14, 2008, the registrant had 41,355,575 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The following documents (or parts thereof) are incorporated by reference into the following parts of this Form 10-K: Certain information required in Part III of this Annual Report on Form 10-K is incorporated from the Registrant s Proxy Statement for the 2008 Annual Meeting of Stockholders.

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PART I

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and are subject to the safe harbor created by those sections. These statements relate to, among other things, our expectations concerning our research and development efforts, regulatory compliance, commercial strategy, strategic alliances and collaborative efforts, sales and reimbursement efforts and their likely future success. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Some of the forward-looking statements can be identified by the use of forward-looking terms such as believes, expects, may, will, should, seek, intends, plans, estimates, anticipates, or other c Accordingly, these statements involve estimates, assumptions and uncertainties that could cause actual results to differ materially from those expressed in them. Our actual results may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those set forth in Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. We have no plans to update our forward-looking statements to reflect events or circumstances after the date of this report. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made.

ITEM 1. *BUSINESS*

OVERVIEW

We are a biopharmaceutical company focused on discovering, developing and commercializing novel pharmaceutical products through the use of proprietary technology to better diagnose, treat and manage patients. We have four internally discovered therapeutic product candidates in clinical trials. These drug candidates are targeting conditions such as depression, Alzheimer s disease, cardiovascular disease and cognitive impairment. Our blood-pool imaging agent, Vasovist, is approved for marketing in more than 30 countries outside of the United States. We also have collaborations with SmithKline Beecham Corporation (GlaxoSmithKline), Amgen Inc., Cystic Fibrosis Foundation Therapeutics, Incorporated, and Bayer Schering Pharma AG, Germany. Our business strategy is to develop our internally discovered, novel pharmaceutical products through the point of proof of clinical concept, typically completion of Phase 2 clinical trials and then to seek pharmaceutical partnerships for the continued development, regulatory approvals and world-wide commercialization of the product candidates. In certain disease areas, such as pulmonary hypertension, where we believe we can efficiently obtain regulatory approval and effectively market the product through a specialty sales force, we may seek to retain commercialization rights in the United States.

The focus of our therapeutic drug discovery and development efforts is on the two classes of drug targets known as G-protein Coupled Receptors, or GPCRs, and ion channels. GPCRs and ion channels are classes of proteins embedded in the surface membrane of all cells and are responsible for mediating much of the biological signaling at the cellular level. We believe that our proprietary drug discovery technology and approach addresses many of the inefficiencies associated with traditional GPCR and ion channel-targeted drug discovery. By integrating computer-based, or in silico, technology with in-house medicinal chemistry, we believe that we can rapidly identify and optimize highly selective drug candidates. We focus on GPCR and ion channel drug targets whose role in disease has already been demonstrated in clinical trials or in preclinical studies. In each of our four clinical-stage therapeutic programs, we used our drug discovery technology and approach to optimize a lead compound into a clinical drug candidate in less than ten months, synthesizing fewer than 80 compounds per program. We moved each of these drug candidates into clinical trials in less than 18 months from lead identification. We believe our drug discovery technology and approach enables us to efficiently and cost-effectively discover and develop GPCR and ion channel-targeted drugs.

We expanded into the development of therapeutic drug products through our acquisition of Predix Pharmaceuticals Holdings, Inc., or Predix, in August 2006. Predix was incorporated in Delaware on November 2, 1994. Throughout this Annual Report on Form 10-K, except where otherwise stated or indicated by the context, we, us, or our means EPIX Pharmaceuticals, Inc. and its consolidated subsidiaries and their predecessors (including Predix).

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OUR PRODUCT CANDIDATES

The following chart summarizes the status of our clinical drug development programs as of March 14, 2008:

* Vasovist is approved for marketing in more than 30 countries outside of the United States. For a description of the collaboration agreement with Bayer Schering Pharma AG, Germany, see Business Strategic Alliances and Collaborations below.

THERAPEUTICS

Through the application of our GPCR and ion channel drug discovery expertise, over the past five years we have created a pipeline of drug candidates designed to address diseases with significant unmet medical needs and commercial potential across a range of therapeutic areas.

PRX-00023 for Depression

We are currently developing PRX-00023, a novel, highly selective, small-molecule 5-HT1A agonist for the treatment of depression. In March 2007, we initiated a Phase 2b clinical trial to evaluate the efficacy of PRX-00023 in patients with a primary diagnosis of Major Depressive Disorder (MDD) who also have concurrent anxiety. The randomized, double-blind, placebo-controlled trial completed enrollment in October 2007, enrolling 362 adult patients with MDD, and is designed to evaluate the effect of treatment with up to 120 mg of PRX-00023 twice-daily for eight weeks as determined by the change from baseline in the Montgomery Asberg Depression Rating Scale (MADRS) compared with placebo. All patients randomized to the drug treatment began with 40 mg PRX-00023 twice daily, and would increase the dose, if tolerated, to a maximum of 120 mg twice daily within the first week. Changes in the Hamilton Anxiety Score (HAM-A), Clinical Global Impressions Improvement Scale (CGI-I) and Clinical Global Severity of Illness Scale (CGI-S) were also measured. Results of the study are expected to be reported in March 2008. To date, there have been no serious adverse events associated with treatment in more than 300 subjects who have received PRX-00023.

During the fourth quarter of 2006, we completed a dose escalating study of PRX-00023 in healthy volunteers where we explored doses up to 320 mg, either as a single daily dose or as 160 mg given twice per day for three weeks. PRX-00023 was well tolerated with no serious adverse events or discontinuations. This study indicated that PRX-00023 at doses up to 320 mg per day may be well tolerated.

In September 2006, we completed a 310 patient, Phase 3 double-blind, placebo controlled, multi-center clinical trial for the treatment of generalized anxiety disorder with PRX-00023. Results from this trial demonstrated that PRX-00023 did not achieve a statistically significant improvement over placebo for the primary endpoint of efficacy with respect to generalized anxiety disorder at the dose tested (80 mg once daily). The mean HAM-A score change from baseline to week eight with PRX-00023 treatment was 9.8, compared to

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a mean HAM-A change of 8.5 from baseline to week eight with placebo (p=0.116). A p-value represents the probability that a difference observed between groups during an experiment happened by chance. For example, a p-value of p=0.05 means there is a 5% probability that the result occurred by chance. In general, clinical scientists regard p-values of less than 0.05 to be statistically significant, and p-values greater than 0.05 to be insignificant. Effects of PRX-00023 on symptoms of depression, which was a secondary endpoint of the Phase 3 clinical trial, were assessed using the MADRS, an FDA-recommended assessment for depression. The data from this trial showed a statistically significant (p=0.009) improvement from baseline with PRX-00023 treatment compared to placebo in the MADRS score, indicating that PRX-00023 reduced symptoms of depression present in the patients in this trial. In this Phase 3 trial, PRX-00023 was well tolerated, and the rate of discontinuation due to adverse events was very low (1.4% with PRX-00023 vs. 2.9% with placebo). Based on the Phase 3 trial results, we have discontinued clinical development of PRX-00023 at a dose of 80 mg once daily in generalized anxiety disorder. We are currently focusing our development efforts for this drug candidate on depression.

PRX-03140 for Alzheimer s disease

PRX-03140 is a novel, highly selective, small-molecule 5-HT4 agonist that we are developing for the treatment of Alzheimer s disease. PRX-03140 is being developed to provide improved cognition and to potentially slow Alzheimer s disease progression. We completed a Phase 2 trial of PRX-03140 alone and in combination with an approved drug for Alzheimer s disease (the cholinesterase inhibitor Aricept (donepezil)) in patients with Alzheimer s disease in the fourth quarter of 2007. This randomized, double-blind, placebo-controlled, multiple ascending dose trial enrolled 80 patients with mild Alzheimer s disease. Patients were studied on PRX-03140 across three dose groups of 10 patients each: 50 mg once-daily, 150 mg once-daily and placebo, or in a placebo-controlled combination across five dose arms of 10 patients each: PRX-03140 at 5, 25, 50, 100 and 200 mg with Aricept 10 mg once-daily.

The two primary endpoints of the trial were: (1) to assess the safety and tolerability of PRX-03140 in patients with Alzheimer s disease when dosed orally once-daily for 14 days alone and in combination with donepezil, and (2) to assess the effect of PRX-03140 on brain wave activity, as was performed in the Phase 1b clinical trial. Secondary endpoints of the trial included evaluating the pharmacokinetic effect of PRX-03140 on Aricept concentrations in patients with mild Alzheimer s disease and assessing the effects of repeat doses of PRX-03140 on a battery of standardized cognitive function tests, such as the Alzheimer s Disease Assessment Scale cognitive subscale (ADAS-cog). ADAS-cog is the current standard for evaluating drug efficacy for cognition in Alzheimer s disease and is an established and accepted FDA registration endpoint.

Efficacy results show that patients receiving 150 mg of PRX-03140 orally once daily as monotherapy achieved a mean 3.6 point improvement on the ADAS-cog versus a 0.9 point worsening in patients on placebo. This result corresponds to a p-value of 0.021, which is statistically significant. Data for the patients on a 50 mg dose of PRX-03140 showed a 1.0 point improvement on the ADAS-cog. The monotherapy dose response (150 mg versus 50 mg versus placebo) was also statistically significant (p=0.026). ADAS-cog changes in the combination arms of the trial were not statistically significant.

This trial also used Mindstreams, an automated battery of computerized cognitive function tests, as a secondary endpoint. Patients on PRX-03140 monotherapy demonstrated statistically significant (p<0.04) improvements in memory and visual-spatial indices as measured using Mindstreams when compared with placebo. PRX-03140 also produced positive trends in the alteration in brain wave activity in the 150 mg dose group versus placebo, similar to the changes observed with currently approved drugs for Alzheimer s disease.

Based upon the improvements in cognition demonstrated over 14 days of dosing, we received requests from certain patients, caregivers and clinical trial investigators for continued access to PRX-03140. We have accommodated such requests on a case-by-case basis by extending the study to allow these patients to continue on PRX-03140.

PRX-03140 appeared to be well tolerated in this trial, both alone and in combination with Aricept. No serious drug-related adverse events occurred during the trial.

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Pursuant to a development and license agreement entered into on December 11, 2006, we granted GlaxoSmithKline an option to obtain exclusive, worldwide license rights to complete the development of, and commercialize, PRX-03140. For a description of the collaboration agreement with GlaxoSmithKline, see Business Strategic Alliances And Collaborations below.

PRX-08066 for Pulmonary Hypertension

PRX-08066 is a novel, highly selective, small-molecule inhibitor, or antagonist, of a specific GPCR known as 5-HT2B. We are developing PRX-08066 for the treatment of two types of pulmonary hypertension: pulmonary arterial hypertension; and pulmonary hypertension associated with chronic obstructive pulmonary disease. Pulmonary hypertension, or PH, in general is a serious, often fatal cardiovascular disease characterized by elevation of pulmonary blood pressure and progressive thickening and narrowing of the blood vessels of the lungs, often leading to heart failure. We completed a Phase 2 trial of PRX-08066 in pulmonary hypertension associated with chronic obstructive pulmonary disease, or COPD, in August 2007. This randomized, double-blind, placebo-controlled Phase 2 trial enrolled 71 patients with PH associated with COPD. Patients were randomized to one of three arms; 200 mg of PRX-08066 once-daily; 400 mg of PRX-08066 once-daily; or placebo. The two-week double-blind phase of the study was followed by an open label extension in which 10 patients received 200 mg daily for six weeks. The primary endpoints of the trial were safety and tolerability of PRX-08066.

Efficacy was measured by the effect of PRX-08066 compared to placebo on systolic pulmonary artery pressure, or SPAP, and included 62 evaluable patients who completed the double-blind portion of the study. In a population where decreases of 3 mmHg to 4 mmHg in a post-exercise SPAP are considered clinically significant, the results showed a statistically significant dose-response for the patients that demonstrated a decrease of 4 mmHg or more. In the 400 mg dose group, 45% of the patients had a reduction in post-exercise SPAP of 4 mmHg or more versus 14% on placebo (p=0.043). An analysis of SPAP changes in all subjects revealed a dose trend with median reductions of 1.2 mmHg and 3.38 mmHg in the 200 mg and 400 mg dose groups, respectively, compared with no change on placebo. PRX-08066 was generally well-tolerated. There were no serious adverse events considered related to PRX-08066, and the majority of adverse events were mild or moderate in nature. One subject in the 200 mg dose group who then continued into the six-week open-label extension experienced a modest increase in liver enzyme levels at the end of the extension that was believed to be drug-related. These values returned to normal within two weeks and the subject remained asymptomatic.

We have completed three Phase 1 clinical trials of PRX-08066 in healthy volunteers, including a Phase 1b clinical trial in athletes conditioned to exercise at high altitudes. Results from the Phase 1b trial showed that, compared with placebo, PRX-08066 caused a statistically significant reduction in the increase in systolic pulmonary blood pressure observed during exercise in volunteers breathing low oxygen. In the two earlier Phase 1 trials as well as the Phase 1b trial, PRX-08066 was well-tolerated, with a half-life of approximately 16 hours, supporting once daily oral dosing. To date, there have been no serious adverse events associated with treatment with PRX-08066.

PRX-07034 for Cognitive Impairment associated with Schizophrenia and Alzheimer s disease

PRX-07034 is a novel, highly selective, small-molecule antagonist of a specific GPCR known as 5-HT6. PRX-07034 is being developed for the treatment of cognitive impairment associated with schizophrenia and Alzheimer s disease. We are also working on back-up compounds for use in other indications such as obesity.

In April 2007, we completed a Phase 1 multiple ascending dose clinical trial studying the safety, tolerability, pharmacokinetics, and pharmacodynamics of PRX-07034 administered once-daily for 28 days in a population of 33 otherwise healthy obese adults with body mass indices, or BMI, between 30 and 42 kg/m2. Normal BMI is less than 25 kg/m2. PRX-07034 demonstrated predictable pharmacokinetics with dose proportional increases in exposures, and

a half-life supporting once-daily dosing. Signals suggestive of pharmacologic activity were observed for obesity with a greater proportion of subjects on drug experiencing weight loss during the one month period than subjects on placebo. Overall results on cognitive function as

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measured by the CogScreen test battery, showed a dose dependent trend for improvement. For the predetermined cognitive endpoint that combines speed and accuracy, there was a statistically significant improvement at the 600 mg dose once daily. Subsequently, an independent external analysis of the CogScreen test battery results confirmed a significant drug effect on cognition but was not able to confirm the dose-dependent trend. No dose limiting toxicity was identified, and no serious adverse events were reported.

In October 2007, we completed a randomized, double-blind, placebo-controlled Phase 1 trial of 21 obese, but otherwise healthy, adults. Findings from this study demonstrated that adults taking 600 mg of PRX-07034 twice-daily for 28 days had a weight reduction of an average of 0.45 kg (approximately 1 pound), while adults on placebo gained 1.37 kg (approximately 3 pounds) during the same period, which was statistically significant ($p<0.005$). Subjects in the study were not required to follow any pre-specified diet or exercise program. PRX-07034 was associated with a statistically significant ($p=0.036$) reduction in serum leptin levels, a marker of fat stores in the body. Overall, only one of the subjects (approximately 10%) on placebo lost any weight during the trial, while 7 of the 11 subjects (approximately 64%) on PRX-07034 lost weight. PRX-07034 appeared well-tolerated and there were no serious adverse events reported. An increase in corrected QT interval, or QTc, was apparent at the dose tested, however, with a mean increase over the duration of the study of 10.7 milliseconds for the drug group versus a decrease of 1.7 milliseconds for the placebo group. The corrected QTc is a measurement of the QT interval, which is corrected for heart rate. Prolongations of the QTc are associated with an increased risk for potentially life-threatening heart rhythms and so this measurement is an important index to measure during the development of new drugs. In addition, of the population of 21 adults, one patient on drug discontinued due to a rash that resolved rapidly. There were no discontinuations on placebo. In the prior Phase 1 trial where doses up to 600 mg once daily were studied for 28 days, no clinically meaningful prolongations of the QTc were noted.

The 21-person trial, which was conducted in an outpatient setting (subjects spent three nights of the total 28-day trial as inpatients to accommodate measurements and physical examinations), included secondary endpoint measures to assess potential effects on body weight, hunger, satiety and exploratory endpoint measures of cognitive function. An analysis of cognitive data in this study showed no difference between drug and placebo at a dose of 600 mg twice daily. Accordingly, future studies in cognitive impairment are expected to utilize doses less than 600 mg twice daily based on the study results and the positive data in cognition previously demonstrated in lower doses.

Safety and tolerability data from an earlier single ascending dose Phase 1 trial completed in healthy adult male and female volunteers indicated that single doses of PRX-07034 were well tolerated up to 2500 mg, the highest dose tested. In addition, PRX-07034 demonstrated adequate absorption, with drug exposures increasing with increasing doses and a half-life of 14 to 24 hours. Preclinical animal models of obesity suggested that this drug candidate may reduce both food intake and body weight. In addition, preclinical animal models of memory impairment suggest that PRX-07034 may have cognitive-enhancing properties.

IMAGING AGENT

Vasovist

Vasovist is an internally discovered, injectable intravascular contrast agent that is designed to provide improved imaging of the vascular system using magnetic resonance angiography or MRA. Our target indication for Vasovist is for use in MRA imaging of peripheral vascular disease, with a goal of improving the physician s ability to visualize the human vascular system and thereby enhance disease diagnosis and treatment. As of December 31, 2007, Vasovist has been approved for marketing in more than 30 countries outside of the United States.

Vasovist reversibly binds to the human blood protein albumin, allowing imaging of the blood vessels for approximately an hour after administration. With a single injection, Vasovist enables the capture of three-dimensional

images of arteries and veins in the body. Vasovist may make it possible for physicians to detect vascular disease earlier, more safely and less invasively than with X-ray angiography, and for physicians to provide an improved evaluation of potential therapeutic options including percutaneous intervention and vascular surgery.

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In December 2003, we submitted a New Drug Application, or NDA, to the FDA for the use of Vasovist in detection of vascular disease. In January 2005 and November 2005, we received approvable letters from the FDA for Vasovist pending additional clinical trials. After considering the parameters of the additional clinical trials requested by the FDA, we filed a formal appeal with the FDA requesting approval of Vasovist, as well as the use of an advisory committee as part of the appeal process, which was denied in August 2006. We met with the FDA after receiving the August 2006 response letter and in February 2007 we filed a second formal appeal with the FDA requesting approval of Vasovist, as well as the use of an advisory committee as part of the appeal process. In June 2007, we received a response letter from the FDA on our second formal appeal. While denying the immediate approval of Vasovist, the FDA indicated that a blinded re-read of the images obtained from the previously completed Phase 3 clinical trials of Vasovist could support approval of Vasovist if the results are positive. In January 2008, we initiated the re-read of the images obtained in prior Phase 3 studies conducted for Vasovist. We expect to complete the re-read of the prior Phase 3 studies in the first half of 2008 and plan to submit the results to the FDA in mid 2008.

OUR THERAPEUTIC DRUG DISCOVERY TECHNOLOGY AND APPROACH

We have developed a novel and proprietary in silico protein structure-based approach to GPCR and ion channel-targeted drug discovery that allows us to benefit from the structure-based approach in the absence of experimentally-determined structures for these targets. Our PREDICT technology combines genomic information (the amino acid sequence of the target protein) with physical and chemical properties of the cell membrane environment to determine the most stable 3D structure of a membrane-bound protein. The use of our PREDICT technology to determine a 3D structure of the target protein is the foundation and first step in our novel system of discovery and optimization for GPCR and ion channel-targeted drugs. We maintain our GPCR and ion channel structures as trade secrets, which, when combined with our proprietary software and the know-how required to use the PREDICT technology, we believe creates a strong barrier to entry for our competitors.

Using our proprietary drug discovery technology and approach requires the successive application of the following five steps: (1) using our PREDICT technology to identify the most stable 3D structure of the desired GPCR or ion channel drug target, bypassing the need for X-ray crystallography, (2) analyzing the resulting 3D structure and identifying a potential binding site on the target structure for drug interaction, (3) performing in silico screening using the computer to virtually fit more than two million drug-like compounds into this drug site, ensuring that both the shape and chemical properties of the binding site and the compound match, (4) selecting the approximately 100-200 compounds that best match the binding site on the target and testing their activity in vitro in the laboratory and (5) identifying the most active and novel chemical compounds, referred to as lead compounds, and then subjecting these lead compounds to an integrated structure-based lead optimization process. The PREDICT-generated 3D structure of the target protein as well as other 3D protein structures (many of which are also generated by PREDICT) and more traditional medicinal chemistry efforts are used to steer lead optimization along the most efficient path, transforming lead compounds into drug candidates expeditiously. Our discovery and optimization process is outlined in the following steps:

PREDICT-3D in silico modeling. We have developed novel proprietary algorithms which we use in our PREDICT technology to model the 3D structure of targets of interest (GPCRs and ion channel proteins) from their primary amino acid sequence. PREDICT uses algorithms that explore a large number of possible structures of the target and then selects the biologically relevant one. It takes into account specific interactions between the target protein and the membrane, specific interactions within the target protein itself, and addresses the limitations that hamper homology-based modeling of GPCRs and ion channel proteins. The PREDICT software code and many of its algorithms are kept as trade secrets, making it difficult to copy or reverse engineer. We filed patent applications for PREDICT version 1.0 in 2000. The current version of PREDICT has evolved considerably from the original version and includes numerous new algorithms and capabilities. PREDICT bypasses the need for X-ray crystallography structures of the GPCR or ion channel

protein target to initiate a structure-based (so-called rational) drug discovery program.

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Virtual libraries. Our libraries consist of in silico versions of four million drug-like compounds which are available for purchase from commercial vendors worldwide. These virtual libraries reduce the need for us to synthesize or purchase, store and maintain tens or hundreds of thousands of actual compounds for the initial screening.

Rapid in silico screening. The process of in silico screening requires the computer to perform trillions of operations in trying to fit numerous drug-like compounds into the binding site of the target protein, matching both shape and chemical properties. We perform high-throughput in silico screening with a combination of proprietary and commercially available public software to identify compounds that may bind to a target GPCR or ion channel protein.

Ranking of screening results. We have developed proprietary algorithms for ranking our in silico screening results using internally developed tools, which we believe enables us to select the 100-200 most promising compounds for in vitro testing.

Integrated structure-based lead optimization. The most promising novel lead compounds, identified in silico and shown to have binding affinity and functionality in vitro, are optimized into drug candidates using an integrated structure-based approach. This process makes use of the PREDICT 3D structures (of the drug target and related off-target proteins) as well as many other in silico tools that we have created or acquired to enable efficient structure-based lead optimization, leading to highly selective drug candidates. These tools allow us to overcome challenges frequently encountered during lead optimization, such as selectivity, blood-brain barrier penetration and hERG ion channel binding, in a fraction of the time and cost compared to traditional lead optimization efforts. Using these in silico tools, our computational and medicinal chemists are able to select for actual synthesis the most promising subset of suggested compounds for further optimization. In each of our clinical-stage programs, this approach has allowed us to synthesize fewer than 10% of the compounds that we believe would have been synthesized if we were to follow the traditional methods of lead optimization.

STRATEGIC ALLIANCES AND COLLABORATIONS

GlaxoSmithKline

On December 11, 2006, we entered into a development and license agreement with SmithKline Beecham Corporation, doing business as GlaxoSmithKline, and Glaxo Group Limited to develop and commercialize medicines targeting four G-protein coupled receptors, or GPCRs, for the treatment of a variety of diseases, including an option to license our 5-HT4 partial agonist, PRX-03140. The other three GPCR targets identified under the collaboration are new discovery programs. GlaxoSmithKline does not have options to any of our other clinical programs besides PRX-03140. Our collaboration with GlaxoSmithKline is being conducted through its Center of Excellence for External Drug Discovery.

Pursuant to the collaboration agreement, we granted GlaxoSmithKline an exclusive option to obtain exclusive, worldwide license rights to complete the development and to commercialize the products initially developed under each of our four research programs under the collaboration agreement. In return for those options and in consideration of the development work to be performed by us under the collaboration agreement, GlaxoSmithKline paid us an initial payment of $17.5 million. Additionally, as part of the collaboration, on December 11, 2006, we entered into a stock purchase agreement with GlaxoSmithKline providing for the issuance and sale to GlaxoSmithKline of 3,009,027 shares of our common stock for an aggregate purchase price of $17.5 million. In addition, we may be eligible for up to an aggregate of $1.2 billion in additional nonrefundable option fees and milestone payments relating to the achievement of certain development, regulatory and commercial milestones across the four research programs. To date, we have received an aggregate of $6 million in such milestone payments related to identifying a total of six

lead candidates, three from each of the first two discovery programs, to move forward into lead optimization. We are also eligible to receive tiered, double-digit royalties based on net sales by GlaxoSmithKline of any products developed under the collaboration agreement. The specific royalty rates will vary depending upon a number of factors, including the total annual net sales of the product and whether it is covered by one of our patents. GlaxoSmithKline s royalty obligation under the collaboration agreement generally terminates on a

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product-by-product and country-by-country basis upon the later of (i) the expiration of our last patent claiming the manufacture, use, sale or importation of the product in the relevant country and (ii) twelve years after the first commercial sale of the product in the relevant country. GlaxoSmithKline accounted for 53% of our revenue in the year ended December 31, 2007.

If GlaxoSmithKline does not exercise any of the four options, the collaboration agreement will expire upon the expiration of the last such option. Otherwise, the collaboration agreement will expire on a product-by-product and country-by-country basis upon the expiration of the royalty payment obligations for each product in each country.

Under the collaboration agreement, we have agreed to design, discover and develop, at our own cost, small molecule drug candidates targeting four GPCRs. The design, discovery and development efforts will be guided by a joint steering committee formed pursuant to the collaboration agreement. The first program is focused on the 5-HT4 receptor and will include our 5-HT4 partial agonist drug candidate, PRX-03140, which is currently in Phase 2 clinical development for the treatment of Alzheimer s disease. We have retained an option to co-promote products successfully developed from the 5-HT4 program in the United States. Under any such co-promotion arrangement, the collaboration agreement provides for GlaxoSmithKline to direct the promotional strategy and compensate us for our efforts in co-promoting the product. We have ongoing research activities for each of the three additional GPCR targets identified under the collaboration.

We have responsibility and control for filing, prosecution or maintenance of any of our patents that are the subject of an option to GlaxoSmithKline under the collaboration agreement, provided that in the event an option is exercised, responsibility and control of the patents subject to such option transfers to GlaxoSmithKline.

The parties each have the right to terminate the collaboration agreement if the other party becomes insolvent or commits an uncured material breach of the collaboration agreement. In addition, GlaxoSmithKline has the right to terminate the collaboration agreement in its entirety, and to terminate its rights to any program developed under the collaboration agreement on a regional or worldwide basis, in each case without cause. Upon a termination of the collaboration agreement, depending upon the circumstances, the parties have varying rights and obligations with respect to the grant of continuing license rights, continued commercialization rights and continuing royalty obligations.

Amgen

On July 31, 2006, we entered into an exclusive license agreement with Amgen Inc. to develop and commercialize products based on our preclinical compounds that modulate the S1P1 receptor and compounds and products that may be identified by or acquired by Amgen and that modulate the S1P1 receptor. The S1P1 receptor is a cell surface GPCR found on white blood cells and in other tissues that is associated with certain autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis.

Pursuant to the license agreement, we granted Amgen an exclusive worldwide license to our intellectual property and know-how related to the compounds in our S1P1 program that modulate the S1P1 receptor, for the development and commercialization of those compounds and other compounds and products that modulate the S1P1 receptor. Amgen has limited rights to sublicense its rights under the license. In return for the license, Amgen paid us a nonrefundable, up-front payment of $20 million and is obligated to pay us royalties based on aggregate annual net sales of all S1P1-receptor-modulating products developed by Amgen under the license agreement. In addition, we may be eligible for up to an aggregate of $287.5 million of nonrefundable milestone payments that relate to milestones associated with the commencement of clinical trials, regulatory approvals and annual net sales thresholds of the products under the license agreement. These royalty rates and milestone amounts are subject to reduction in the event that, among other things:

Amgen is required to obtain third-party rights to develop and commercialize a product that incorporates an EPIX compound; and

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Amgen develops and commercializes products that are not covered by the intellectual property rights we licensed to Amgen, such as for example, S1P1-modulating products that may be acquired by Amgen from a third-party.

Generally, Amgen s royalty obligation under the agreement terminates on a product-by-product and country-by-country basis upon the later of (a) the expiration or termination of the last claim within the patents (whether such patents are patents EPIX licensed to Amgen or are patents owned or in-licensed by Amgen) covering such product and (b) ten years following the first commercial sale of the product. The agreement expires when all of Amgen s royalty obligations have terminated.

We have the option to co-promote one product from the collaboration in the United States for one indication to be jointly selected by EPIX and Amgen. During the first 15 months of the agreement, we were required to design, discover and develop, at our own cost, additional compounds that modulate the S1P1 receptor and that are within the same family of compounds as those identified in our patent applications licensed to Amgen under the agreement. The collaboration agreement provides Amgen with a license to these additional compounds to further its development efforts. We may undertake additional research under the agreement, at our own expense, as approved by a joint steering committee formed pursuant to the agreement. We have responsibility and control for filing, prosecution or maintenance for any of our patents licensed to Amgen for 24 months or until the start of Phase 1 clinical trials for the first product developed under the agreement, at which time, responsibility and control of such patents transfers to Amgen. Amgen has responsibility and control for filing, prosecution or maintenance for all other patents covered by the agreement, including patents jointly developed under the agreement. Amgen will have final decision making authority on all other research matters and will be responsible for non-clinical and clinical development, manufacturing, regulatory activities and commercialization of the compounds and products developed under the license agreement, at its own expense.

The parties each have the right to terminate the agreement (in whole or for specified products or countries, depending upon the circumstances) upon a material uncured breach by the other party and Amgen has the right to terminate the agreement for convenience upon varying periods of at least three months advance notice. Upon a termination of the agreement, depending upon the circumstances, the parties have varying rights and obligations with respect to the grant of continuing license rights, continued commercialization rights and continuing royalty obligations.

Bayer Schering Pharma AG, Germany

In June 2000, we entered into a strategic collaboration agreement with Bayer Schering Pharma AG, Germany pursuant to which we granted Bayer Schering Pharma AG, Germany an exclusive license to co-develop and market Vasovist worldwide, excluding Japan. In December 2000, we amended this strategic collaboration agreement to grant to Bayer Schering Pharma AG, Germany the exclusive rights to develop and market Vasovist in Japan. Generally, each party to the agreement will share equally in Vasovist costs and profits in the United States. Under the agreement, we retained responsibility for completing clinical trials and filing for FDA approval in the United States and Bayer Schering Pharma AG, Germany is responsible for clinical and regulatory activities for the product outside the United States. In addition, we granted Bayer Schering Pharma AG, Germany an exclusive option to develop and market an unspecified vascular MRI blood pool agent from our product pipeline. In connection with this strategic collaboration and the amendment to our strategic collaboration agreement with Covidien (formerly Tyco International Ltd.), as described under Intellectual Property below, Bayer Schering Pharma AG, Germany paid us an up-front fee of $10 million, which we then paid to Covidien. Under the agreement, Bayer Schering Pharma AG, Germany also paid us $20 million in exchange for shares of our common stock. We may be eligible for up to an additional $23.2 million upon the achievement of certain milestones, including $1.3 million that may be earned if Vasovist is approved in the United States. We also are entitled to receive a royalty on products sold outside the United States and, if Vasovist is approved

and launched in the United States, a percentage of Bayer Schering Pharma AG, Germany s operating profit margin on products sold in the United States.

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Under the terms of the strategic collaboration agreement with Bayer Schering Pharma AG, Germany, either party may terminate the agreement upon thirty days notice if there is a material breach of the contract. In addition, Bayer Schering Pharma AG, Germany may terminate the agreement at any time on a region-by-region basis or in its entirety, upon six months written notice to us.

In May 2003, we entered into a broad alliance with Bayer Schering Pharma AG, Germany for the discovery, development and commercialization of molecularly-targeted contrast agents for MRI. The alliance was composed of two areas of collaboration, with one agreement generally providing for exclusive development and commercialization collaboration for EP-2104R, our product candidate for the detection of thrombus, and the second agreement covering an exclusive research collaboration to discover novel compounds for diagnosing human disease using MRI. Under the first agreement, Bayer Schering Pharma AG, Germany had an option to the late stage development and worldwide marketing rights for EP-2104R. On July 12, 2006, Bayer Schering Pharma AG, Germany notified us that it declined to exercise this option. As a result, we retained commercial rights to EP-2104R. In the event EP-2104R is commercialized, we are obligated to pay Bayer Schering Pharma AG, Germany a royalty which is limited to a portion of the funding we received for this program from Bayer Schering Pharma AG, Germany. The second agreement related to a broader research collaboration under which the research jointly pursued under the agreement concluded in May 2006.

On May 8, 2000, we granted to Bayer Schering Pharma AG, Germany a worldwide, royalty-bearing license to patents covering Bayer Schering Pharma AG, Germany s development project, Primovist, an MRI contrast agent for imaging the liver, which was approved in the European Union in 2004. Under this agreement, Bayer Schering Pharma AG, Germany is required to pay us royalties based on sales of products covered by this agreement. This agreement expires upon the last-to-expire patent covered by the agreement unless terminated earlier by either party because of the material breach of the agreement by the other party. Also on May 8, 2000, Bayer Schering Pharma AG, Germany granted us a non-exclusive, royalty-bearing license to certain of its Japanese patents. Under this agreement, we are required to pay Bayer Schering Pharma AG, Germany royalties based on sales of products covered by this agreement. This agreement expires upon the last-to-expire patent covered by the agreement unless terminated earlier by either party because of the material breach of the agreement by the other party.

Cystic Fibrosis Foundation Therapeutics, Incorporated

In March 2005, we entered into a research, development and commercialization agreement with Cystic Fibrosis Foundation Therapeutics, Incorporated, or CFFT, the drug discovery and development affiliate of the Cystic Fibrosis Foundation. In August 2006, we expanded the research, development and commercialization agreement with CFFT. In November 2007, the agreement was further amended to provide for approximately $1.1 million of research funding for the Cystic Fibrosis Transmembrane conductance Regulator, or CFTR, program until the parties negotiate a follow-on agreement for the further discovery and development of the CFTR program. As of December 31, 2007, we have received an aggregate of $11.9 million in payments under the agreement. The agreement originally consisted of two development programs as follows:

The first program is focused on correcting a malfunction of the CFTR ion channel protein. We are using our proprietary structure-based technologies to model the structure of this ion channel protein target and identify binding sites in the channel for therapeutic intervention. Once these sites are identified, we aim to use our drug discovery capabilities to discover a drug that restores proper functionality to the channel in patients with cystic fibrosis. Based upon the results of the program, we have agreed with the CFFT to negotiate towards a follow-on agreement under which we will explore a structure-based approach for the discovery and commercialization of a drug that will target CFTR, with the financial support of CFFT and subject to a royalty payable to CFFT.

The second program is focused on the discovery of a small-molecule agonist to the G-Protein Coupled Receptor known as P2Y(2), which plays a role in cystic fibrosis, using our proprietary structure-based drug design system. We retain the right to develop and commercialize any drug candidates discovered through this second program, and are obligated to make aggregate royalty payments of up to

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$15.0 million to CFFT for the first drug candidate that reaches particular regulatory and sales milestones.

The agreement expires with respect to the first program on August 2, 2009. The second program expired during 2007. CFFT may terminate the CFTR program without cause upon 120 days notice or if we suspend or discontinue our business. Either party may terminate the agreement for an uncured material breach. CFFT accounted for 25% of our revenue in the year ended December 31, 2007.

TECHNOLOGY AGREEMENTS

Covidien (formerly Tyco International Ltd.)

In August 1996, we entered into a strategic collaboration agreement with Mallinckrodt Inc. (subsequently acquired by Covidien Ltd.), involving research, development and marketing of MRI vascular contrast agents developed or in-licensed by either party. In June 2000, in connection with the exclusive license that we granted to Bayer Schering Pharma AG, Germany under our strategic collaboration agreement, we amended our strategic collaboration with Covidien. The amendment enabled us to sublicense certain technology from Covidien to Bayer Schering Pharma AG, Germany which allowed us to enter into the strategic collaboration agreement for Vasovist with Bayer Schering Pharma AG, Germany. Pursuant to that amendment, we also granted to Covidien a non-exclusive, worldwide license to manufacture Vasovist for clinical development and commercial use on behalf of Bayer Schering Pharma AG, Germany in accordance with a manufacturing agreement entered into in June 2000 between Covidien and Bayer Schering Pharma AG, Germany. In connection with this amendment, we paid Covidien an up-front fee of $10.0 million and are obligated to pay up to an additional $5.0 million in milestone payments, of which $2.5 million was paid following the NDA filing in February 2004 and $2.5 million is required to be paid upon any U.S. product approval. We are also required to pay Covidien a share of our Vasovist operating profit margins in the United States and a percentage of the royalty that we receive from Bayer Schering Pharma AG, Germany on Vasovist gross profits outside the United States.

Bracco

In September 2001, pursuant to a settlement and release agreement and worldwide license agreement, we granted Bracco a worldwide, non-exclusive royalty bearing sub-license to certain of our patents. Under the terms of the license fee, we received $10.0 million in 2001 and are entitled to receive royalty payments from Bracco on their sales of MultiHance. The royalty on sales of MultiHance expired on the patent expiration date in each country in which MultiHance is sold. We received our final royalty payment from Bracco in the second quarter of 2007.

COMPETITION

We face, and will continue to face, intense competition from pharmaceutical and biotechnology companies, as well as numerous academic and research institutions and governmental agencies engaged in drug discovery activities or funding, both in the United States and abroad. Some of these competitors are pursuing the development of product candidates that target the same indications that we are targeting for our clinical and preclinical programs. Even if we and our collaborators are successful in developing our clinical-stage candidates, the resulting products will compete with a variety of established products.

Significant competitors in the area of GPCR-focused drug discovery include Arena Pharmaceuticals, Acadia Pharmaceuticals, Addex Pharmaceuticals and 7TM Pharma, and for ion channels our competitors include Vertex Pharmaceuticals and Sucampo Pharmaceuticals. In addition, most large pharmaceutical companies have drug discovery programs that target GPCRs and ion channels.

Many of our competitors have significantly greater financial, manufacturing, marketing and product development experience and resources than we do. These companies also have significantly greater research and development capabilities than we do, and have significantly greater experience than we do in preclinical and clinical trials of potential pharmaceutical products, and in obtaining FDA and other regulatory clearances.

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Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects or are less expensive than any products that we may develop.

If our clinical-stage drug candidates are approved, they will compete with currently approved drugs and potentially with drug candidates currently in development for the same indications, including the following:

PRX-00023. If approved, PRX-00023, the drug candidate we are developing for the treatment of depression, may compete with approved products from such pharmaceutical companies as Forest Laboratories, Inc., GlaxoSmithKline plc, Eli Lilly & Co., Pfizer Inc. and Wyeth, and may compete with drug candidates in clinical development from other companies, including Sanofi-Aventis.

PRX-03140. If approved, PRX-03140, the drug candidate we are developing for the treatment of Alzheimer s disease, may compete with approved products from such pharmaceutical companies as Forest Laboratories, Inc., Johnson & Johnson, Novartis AG and Pfizer, Inc., and may compete with drug candidates in clinical development from other companies, including Myriad Genetics, Inc., GlaxoSmithKline plc and Neurochem Inc. We are studying PRX-03140 both as monotherapy and in combination with approved products, such as Aricept which is marketed by Pfizer Inc.

PRX-08066. If approved, PRX-08066, the drug candidate we are developing for the treatment of pulmonary arterial hypertension (PAH), may compete with approved products from such pharmaceutical companies as Actelion Pharmaceuticals Ltd., GlaxoSmithKline plc, Pfizer Inc., Gilead Sciences Inc., and United Therapeutics Corporation, and may compete with drug candidates in clinical development by other companies, such as Encysive Pharmaceuticals Inc. and Bayer Schering Pharma AG.

PRX-07034. If approved for the treatment of cognitive impairment (associated with schizophrenia or Alzheimer s disease), PRX-07034 may compete with approved products from such pharmaceutical companies as Forest Laboratories, Johnson & Johnson, Novartis AG and Pfizer, Inc., and may compete with several therapeutic product candidates in clinical development from other companies, including GlaxoSmithKline plc, AstraZeneca and Memory Pharmaceuticals Corp. If approved for the treatment of obesity, PRX-07034 may compete with approved products from such pharmaceutical companies as Abbott Laboratories and Roche Holding Ltd., and may compete with several therapeutic product candidates in clinical development by other companies, such as Sanofi-Aventis and Arena Pharmaceuticals, Inc.

Vasovist. There are a number of general use MRI agents approved for marketing in the United States and in certain foreign markets that, if used or developed for MR angiography, are likely to compete with Vasovist. Such products include Magnevist and Gadovist by Bayer Schering Pharma AG, Germany, Dotarem by Guerbet, S.A., Omniscan by GE Healthcare, ProHance and MultiHance by Bracco and OptiMARK by Covidien Ltd. We are aware of certain agents under clinical development that have been or are being evaluated for use in MRA: Bayer Schering Pharma AG, Germany s Gadomer and SHU555C, Guerbet, S.A. s Vistarem, Bracco s B-22956/1, Ferropharm GmbH s Code VSOP-C184, and Advanced Magnetics, Inc. s Ferumoxytol. In addition to competition within the MRI field, we also face competition from other imaging technologies, including CT scans, ultrasounds, and X-ray scans.

INTELLECTUAL PROPERTY

We actively seek to protect the proprietary technology that we consider important to our business, including chemical species, compositions and formulations, their methods of use and processes for their manufacture, as new intellectual property is developed. In addition to seeking patent protection in the United States, we plan to selectively file patent applications in certain additional foreign countries in order to further protect the inventions that we consider important

to the development of our foreign business. We also rely upon trade secrets and contracts to protect our proprietary information.

As of February 28, 2008, our patent portfolio included a total of 16 issued U.S. patents, 117 issued foreign patents and 277 pending patent applications in the United States and other countries with claims covering the composition of matter and methods of use for all of our clinical-stage candidates and Vasovist. In addition to patents, we rely where necessary upon unpatented trade secrets and know-how and continuing

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technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, employees and consultants and invention assignment agreements with our employees. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

In addition, we license, and expect to continue to license, third-party technologies and other intellectual property rights that are incorporated into some elements of our drug discovery and development efforts. Set forth below are our significant license agreements.

Ramot

Our proprietary drug discovery technology and approach is in part embodied in technology that we license from Ramot at Tel Aviv University Ltd., the technology transfer company of Tel Aviv University. Pursuant to this license, we have exclusive, worldwide rights to certain technology developed at Tel Aviv University to develop, commercialize and sell products for the treatment of diseases or conditions in humans and animals. The licensed technology, as continually modified, added to and enhanced by us, consists in large part of computer-based models of biological receptors and methods of designing drugs to bind to those receptors.

All of our current clinical-stage therapeutic drug candidates, PRX-00023, PRX-03140, PRX-08066 and PRX-07034, were, at least in part, identified, characterized or developed using the licensed technology, and we would be required to make payments to Ramot, as described below, if and when rights to any such drug candidates are ever sublicensed or any such drug candidates are commercialized. In addition, we have used the licensed technology in all of our preclinical-stage programs and would expect to make payments to Ramot if rights to any drug candidates were ever commercialized from any of these programs. One of our employees, Sharon Shacham, Senior Vice President of Drug Development, was one of the inventors of the technology that we license from Ramot. We believe that Ramot shares a portion of any royalty income received with the respective inventors and, accordingly, Dr. Shacham receives a portion of the amounts we pay Ramot.

We paid Ramot an upfront fee of $40,000 upon the grant of the license. Under the license, we have an obligation to make royalty payments to Ramot on our net sales of products that are identified, characterized or developed through the use of the licensed technology that are either 1.5% or 2.5% of such net sales (depending upon the degree to which the product needed to be modified after being identified, characterized or developed through the use of the licensed technology) and decrease as the volume of sales increases. The royalty obligation for each product expires on a country-by-country basis twelve years after the first commercial sale. There is also an annual minimum royalty payment obligation of $10,000 per year.

We also are required to share between 5% and 10% of the consideration we receive from parties to whom we grant sublicenses of rights in the Ramot technology or sublicenses of rights in products identified, characterized or developed with the use of such technology and between 2% and 4% of consideration we receive from performing services using such technology. In connection with our collaborations with GlaxoSmithKline, Amgen and Cystic Fibrosis Foundation Therapeutics, Incorporated, we have to date paid $2.6 million in total royalties to Ramot primarily for the total payments received to date for the upfront payments and milestone payments received under these license agreements.

The license may be terminated by either party upon a material breach by the other party unless cured within 30 days, in the case of a payment breach, and 90 days in the case of any other breach. The license may also be terminated by either party in connection with the bankruptcy or insolvency of the other party. The license expires upon the

expiration of our obligation to make payments to Ramot. Therefore, since we have an ongoing obligation to pay annual minimum royalties to Ramot as described above, the license may not expire and may only terminate upon a breach by, or bankruptcy of, a party.

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