REGENERON PHARMACEUTICALS INC
Form 10-K
February 17, 2011

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

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2010

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 0-19034

REGENERON PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

New York	13-3444607
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No)
777 Old Saw Mill River Road, Tarrytown, NewYork	10591-6707
(Address of principal executive offices)	(Zip code)

(914) 347-7000
(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 - par value $.001 per share	NASDAQ Global Select Market

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 þ 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 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 ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the

registrant was required to submit and post such files). Yes þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) 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, 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.

Large accelerated filer þ	Accelerated filer ¨	Non-accelerated filer ¨	Smaller reporting company ¨

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

The aggregate market value of the common stock held by non-affiliates of the registrant was approximately $1,726,149,000, computed by reference to the closing sales price of the stock on NASDAQ on June 30, 2010, the last trading day of the registrant's most recently completed second fiscal quarter.

The number of shares outstanding of each of the registrant's classes of common stock as of February 11, 2011:

Class of Common Stock	Number of Shares
Class A Stock, $.001 par value	2,182,036
Common Stock, $.001 par value	87,777,008

DOCUMENTS INCORPORATED BY REFERENCE:

Specified portions of the Registrant's definitive proxy statement to be filed in connection with solicitation of proxies for its 2011 Annual Meeting of Shareholders are incorporated by reference into Part III of this Form 10-K. Exhibit index is located on pages 67 to 71 of this filing.

PART I

ITEM 1. BUSINESS

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties relating to future events and the future financial performance of Regeneron Pharmaceuticals, Inc., and actual events or results may differ materially. These statements concern, among other things, the nature, timing, and possible success and therapeutic applications of our product candidates and research programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of our late-stage product candidates, the commercial success of our marketed product, and the future sources and uses of capital and our financial needs. These statements are made by us based on management's current beliefs and judgment. In evaluating such statements, shareholders and potential investors should specifically consider the various factors identified under the caption "Risk Factors" which could cause actual events and results to differ materially from those indicated by such forward-looking statements. We do not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, except as required by law.

General

Regeneron Pharmaceuticals, Inc. is a biopharmaceutical company that discovers, develops, and commercializes pharmaceutical products for the treatment of serious medical conditions. We currently have one marketed product: ARCALYST® (rilonacept) Injection for Subcutaneous Use, which is available for prescription in the United States for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

We have 11 product candidates in clinical development, including three that are in late-stage, (Phase 3). All of these product candidates were discovered in our research laboratories. Our late-stage programs are VEGF Trap-Eye (aflibercept ophthalmic solution), which is being developed using intraocular delivery for the treatment of serious eye diseases; ARCALYST®, which is being developed for the prevention of gout flares in patients initiating uric acid-lowering treatment; and aflibercept (VEGF Trap), which is being developed in oncology in collaboration with the sanofi-aventis Group. Our earlier stage clinical programs include the following fully human antibodies, which are being developed in collaboration with sanofi-aventis:

- REGN727, an antibody to Proprotein Convertase Substilisin/Kexin type 9 (PCSK9) for low-density lipoprotein (LDL) cholesterol reduction;
- REGN88, an antibody to the interleukin-6 receptor (IL-6R), which is being developed in rheumatoid arthritis and ankylosing spondylitis;
- REGN668, an antibody to the interleukin-4 receptor (IL-4R), which is being developed in atopic dermatitis and asthma;
- REGN421, an antibody to Delta-like ligand-4 (Dll4), a novel angiogenesis target, which is being developed in oncology,
- REGN910, an antibody to Angiopoietin-2 (ANG2), another novel angiogenesis target, which is being developed in oncology;
- REGN475, an antibody to Nerve Growth Factor (NGF), which is being developed for the treatment of pain (currently on clinical hold); and
- REGN728 and REGN846, two antibodies in clinical development against undisclosed targets.

Our core business strategy is to maintain a strong foundation in basic scientific research and discovery-enabling technologies, to combine that foundation with our clinical development and manufacturing capabilities, and to continue to expand our commercialization capabilities in anticipation of possible regulatory approval and launch of one or more of our late-stage product candidates. Our long-term objective is to build a successful, integrated, multi-product biopharmaceutical company that provides patients and medical professionals with innovative options for preventing and treating human diseases.

We believe that our ability to develop product candidates is enhanced by the application of our VelociSuite™ technology platforms. Our discovery platforms are designed to identify specific proteins of therapeutic interest for a particular disease or cell type and validate these targets through high-throughput production of genetically modified mice using our VelociGene® technology to understand the role of these proteins in normal physiology, as well as in models of disease. Our human monoclonal antibody technology (VelocImmune®) and cell line expression technologies (VelociMab®) may then be utilized to discover and produce new product candidates directed against the disease target. Our antibody product candidates currently in clinical trials were developed using VelocImmune®. Under the terms of our antibody collaboration with sanofi-aventis, which was expanded during 2009, we plan to advance an average of four to five new antibody product candidates into clinical development each year, for an anticipated total of 30-40 candidates from 2010 through 2017. We continue to invest in the development of enabling technologies to assist in our efforts to identify, develop, manufacture, and commercialize new product candidates.

Commercial Product:

ARCALYST® – CAPS

Net product sales of ARCALYST® in 2010 were $25.3 million, which included $20.5 million of ARCALYST® net product sales made in 2010 and $4.8 million of previously deferred net product sales, as described below under Item 7. “Management’s Discussion and Analysis of Financial Condition and Results of Operations – Results of Operations.” In 2009, we recognized $18.4 million of ARCALYST® net product sales.

ARCALYST® is a protein-based product designed to bind the interleukin-1 (called IL-1) cytokine and prevent its interaction with cell surface receptors. ARCALYST® is available for prescription in the United States for the treatment of CAPS, including FCAS and MWS in adults and children 12 and older. CAPS are a group of rare, inherited, auto-inflammatory conditions characterized by life-long, recurrent symptoms of rash, fever/chills, joint pain, eye redness/pain, and fatigue. Intermittent, disruptive exacerbations or flares can be triggered at any time by exposure to cooling temperatures, stress, exercise, or other unknown stimuli.

Clinical Programs:

1. VEGF Trap-Eye – Ophthalmologic Diseases

VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap, which is being developed for use in intraocular applications. We, together with our ex-U.S. collaborator Bayer HealthCare LLC, are evaluating VEGF Trap-Eye in Phase 3 programs in patients with the neovascular form of age-related macular degeneration (wet AMD), central retinal vein occlusion (CRVO), and choroidal neovascularisation (CNV) of the retina as a result of pathologic myopia. We and Bayer HealthCare conducted a Phase 2 study of VEGF Trap-Eye in patients with diabetic macular edema (DME) and are discussing plans to initiate Phase 3 studies in DME. Wet AMD, diabetic retinopathy (which includes DME), and retinal vein occlusion are three of the leading causes of adult blindness in the developed world. In these conditions, severe visual loss is caused by a combination of retinal edema and neovascular proliferation.

The Phase 3 trials in wet AMD, known as VIEW 1 and VIEW 2 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), compared VEGF Trap-Eye and Lucentis® (ranibizumab injection), a registered trademark of Genentech, Inc. Lucentis® is an anti-angiogenic agent approved for use and the current standard of care in wet AMD. VIEW 1 was conducted in North America and VIEW 2 was conducted in Europe, Asia Pacific, Japan, and Latin America. The VIEW 1 and VIEW 2 trials both evaluated VEGF Trap-Eye doses of 0.5 milligrams (mg) and 2.0 mg at dosing intervals of four weeks and 2.0 mg at a dosing interval of eight weeks (after three monthly loading doses), compared with Lucentis® dosed according to its U.S. label, which specifies doses of 0.5 mg administered every four weeks over the first year. As-needed dosing (PRN) with both agents is being evaluated in the second year of the studies, although patients will be dosed no less frequently than every 12 weeks.

The primary endpoint of these non-inferiority studies was the proportion of patients treated with VEGF Trap-Eye who maintain visual acuity at the end of one year compared to patients dosed monthly with Lucentis®. Visual acuity is defined as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, a standard research tool for measuring visual acuity. Maintenance of vision is defined as losing

fewer than three lines (equivalent to 15 letters) on the ETDRS chart. Secondary endpoints included the mean change from baseline in visual acuity as measured by ETDRS, the proportion of patients who gained at least 15 letters of vision at week 52, and the amount of fluid under the retina.

We and Bayer HealthCare announced week 52 results from the VIEW 1 and VIEW 2 studies in November 2010. In these studies, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint of statistical non-inferiority compared to Lucentis® dosed every month. In the North American VIEW 1 study, 96% of patients receiving VEGF Trap-Eye 0.5 mg monthly, 95% of patients receiving VEGF Trap-Eye 2.0 mg monthly, and 95% of patients receiving VEGF Trap-Eye 2.0 mg every two months achieved maintenance of vision compared to 94% of patients receiving Lucentis® 0.5 mg dosed every month. In the international VIEW 2 study, 96% of patients receiving VEGF Trap-Eye 0.5 mg monthly, 96% of patients receiving VEGF Trap-Eye 2.0 mg monthly, and 96% of patients receiving VEGF Trap-Eye 2.0 mg every two months achieved maintenance of vision compared to 94% of patients receiving Lucentis® 0.5 mg dosed every month.

A generally favorable safety profile was observed for both VEGF Trap-Eye and Lucentis®. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation, breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

Based on these positive results, we plan to submit a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) in the first half of 2011 for marketing approval of VEGF Trap-Eye in wet AMD in the U.S. In addition, Bayer HealthCare intends to submit regulatory applications in the first half of 2011 for marketing approval of VEGF Trap-Eye in wet AMD in Europe.

VEGF Trap-Eye is also in Phase 3 development for the treatment of CRVO, another cause of visual impairment. We are leading the COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study, and Bayer HealthCare is leading the GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study. Patients in both studies receive six monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2.0 mg or sham control injections. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. At the end of the initial six months, patients are dosed on a PRN basis for another six months. All patients are eligible for rescue laser treatment.

We and Bayer HealthCare announced in December 2010 that in the COPERNICUS study, VEGF Trap-Eye met the primary endpoint of a statistically significant improvement in visual acuity at six months compared to sham injections. In this trial, 56.1% of patients receiving VEGF Trap-Eye gained at least 15 letters of vision from baseline, compared to 12.3% of patients receiving sham injections ($p<0.0001$). Patients receiving VEGF Trap-Eye on average gained 17.3 letters of vision, compared to a mean loss of 4.0 letters with sham injections ($p<0.001$), a secondary endpoint.

In the COPERNICUS study, VEGF Trap-Eye was generally well tolerated. The most common adverse events were those typically associated with intravitreal injections or the underlying disease. Serious ocular adverse events in the VEGF Trap-Eye group were uncommon (3.5%) and were more frequent in the control group (13.5%). The incidence of non-ocular serious adverse events was generally well-balanced between the treatment arms. There were no deaths among the 114 patients treated with VEGF Trap-Eye and two (2.7%) in the 73 patients treated with sham injections.

GALILEO study data are expected in the first half of 2011.

The Phase 2 DME study, known as DA VINCI (DME And VEGF Trap-Eye: INvestigation of Clinical Impact), was a double-masked, randomized, controlled trial that evaluated four different dosing regimens of VEGF Trap-Eye versus focal laser treatment. In February 2010, we and Bayer HealthCare announced that treatment with VEGF Trap-Eye demonstrated a statistically significant improvement in visual acuity compared to focal laser therapy at 24 weeks, the primary endpoint of the study. Visual acuity was measured by the mean number of letters gained.

Patients in each of the four dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean improvements in visual acuity (8.5 to 11.4 letters of vision gained) compared to patients receiving focal laser therapy (2.5 letters gained) at week 24 ($p< 0.01$ for each VEGF Trap-Eye group versus focal laser). VEGF Trap-Eye was generally well-tolerated, and no ocular or non-ocular drug-related serious adverse events were reported. The adverse events reported were those typically associated with intravitreal injections or the underlying disease.

In December 2010, we and Bayer HealthCare reported that the mean visual acuity gains seen in the DA VINCI study at 24 weeks were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including the group receiving a 2.0 mg dose every two months. At week 52, all VEGF Trap-Eye dose groups reported mean gains in visual acuity of 9.7 to 13.1 letters, compared to a mean loss of 1.3 letters for patients receiving focal laser therapy ($p<0.01$ for each VEGF Trap-Eye dose group versus focal laser). VEGF Trap-Eye was generally well tolerated during the study and no patients experienced ocular drug-related serious adverse events. There were no patients with non-ocular serious adverse events judged by investigators to be drug-related during the first six months of the study and one in the second six months. The most common adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent ocular adverse events reported among patients receiving VEGF Trap-Eye were conjunctival hemorrhage, eye pain, ocular redness (hyperemia), and increased intraocular pressure. The incidence of non-ocular serious adverse events was generally well balanced between all treatment arms. There were six deaths (3.4%) among the 175 patients treated with VEGF Trap-Eye and one (2.3%) in the 44 patients treated with focal laser over 12 months. Based on these positive results, Regeneron and Bayer HealthCare are discussing plans to initiate Phase 3 studies of VEGF Trap-Eye in DME.

In January 2011, we and Bayer HealthCare initiated a new Phase 3 clinical trial in Asia in collaboration with the Singapore Eye Research Institute (SERI) investigating the efficacy and safety of VEGF Trap-Eye in patients with CNV of the retina as a result of pathologic myopia. The study, which will enroll approximately 250 patients, has started in Japan and is scheduled to run until June 2013.

Collaboration with Bayer HealthCare

In October 2006, we entered into a license and collaboration agreement with Bayer HealthCare for the global development and commercialization outside the United States of VEGF Trap-Eye. Under the agreement, we and Bayer HealthCare collaborate on, and share the costs of, the development of VEGF Trap-Eye through an integrated global plan. Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. If VEGF Trap-Eye is granted marketing authorization in a major market country outside the United States, we will be obligated to reimburse Bayer HealthCare for 50% of the development costs that it has incurred under the agreement from our share of the collaboration profits. Within the United States, we retain exclusive commercialization rights to VEGF Trap-Eye and are entitled to all profits from any such sales. We have received $60 million in development milestone payments and can earn up to $50 million in future milestone payments related to marketing approvals of VEGF Trap-Eye in major market countries outside the United States. We can also earn up to $135 million in sales milestone payments if total annual sales of VEGF Trap-Eye outside the United States achieve certain specified levels starting at $200 million.

2. ARCALYST® – Inflammatory Diseases

ARCALYST® is being developed for the prevention of gout flares in patients initiating uric acid-lowering therapy. Gout, a disease in which IL-1 may play an important role in pain and inflammation, is a very painful and common form of arthritis that results from high levels of uric acid, a bodily waste product normally excreted by the kidneys. The elevated uric acid can lead to formation of urate crystals in the joints of the toes, ankles, knees, wrists, fingers, and elbows. Uric acid-lowering therapy, most commonly allopurinol, is prescribed to eliminate the urate crystals and prevent them from reforming. Paradoxically, the initiation of uric acid-lowering therapy often triggers an increase in the frequency of gout attacks in the first several months of treatment, which may lead to discontinuation of therapy. The break up of the urate crystals can result in stimulation of inflammatory mediators, including IL-1, resulting in acute flares of joint pain and inflammation. These painful flares generally persist for at least five days.

We are conducting a Phase 3 clinical development program with ARCALYST® in gout patients initiating uric acid-lowering therapy. The program currently consists of PRE-SURGE 1 (PREvention Study against URate-lowering drug-induced Gout Exacerbations), PRE-SURGE 2, and RE-SURGE (REview of Safety Utilizing Rilonacept in Gout Exacerbations), each of which are described below.

In June 2010, we announced that results from PRE-SURGE 1, a North America-based double-blind, placebo-controlled study, showed that ARCALYST® prevented gout attacks, as measured by the primary study endpoint of the number of gout flares per patient over the 16 week treatment period. Patients initiating uric acid-lowering therapy who received ARCALYST® at a weekly, self-administered, subcutaneous dose of 160 mg had an 80% decrease in mean number of gout flares compared to the placebo group over the 16 week treatment period (0.21 flares vs. 1.06 flares, p<0.0001). Patients who received ARCALYST® at a weekly dose of 80 mg had a 73% decrease compared to the placebo group (0.29 flares vs. 1.06 flares, p<0.0001).

All secondary endpoints of the study were highly positive (p<0.001 vs. placebo). Among these endpoints, treatment with ARCALYST® reduced the proportion of patients who experienced two or more flares during the study period by up to 88% (3.7% with ARCALYST® 160 mg, 5.0% with ARCALYST® 80 mg, and 31.6% with placebo, p<0.0001). In addition, treatment with ARCALYST® reduced the proportion of patients who experienced at least one gout flare during the study period by up to 65% (16.3% with ARCALYST® 160 mg, 18.8% with ARCALYST® 80 mg, and 46.8% with placebo, p<0.001).

A total of 241 patients were randomized in PRE-SURGE 1. ARCALYST® was generally well tolerated with no reported drug-related serious adverse events. Adverse events that occurred at a frequency of at least 5% in any study group were: injection site reaction (19.8% with ARCALYST® 160 mg, 8.8% with ARCALYST® 80 mg, and 1.3% with placebo), upper respiratory tract infection (9.9% with ARCALYST® 160 mg, 8.8% with ARCALYST® 80 mg, and 7.6% with placebo), lower respiratory tract infection (0% with ARCALYST® 160 mg, 5.0% with ARCALYST® 80 mg, and 2.5% with placebo), musculoskeletal pain/discomfort (6.2% with ARCALYST® 160 mg, 7.5% with ARCALYST® 80 mg, and 8.9% with placebo), and headache, (3.7% with ARCALYST® 160 mg, 6.3% with ARCALYST® 80 mg, and 1.3% with placebo).

In addition, in June 2010, we reported results from a placebo-controlled, Phase 3 study evaluating pain in patients presenting with an acute gout flare. The results of this study showed that there was no significant benefit from combining ARCALYST® with indomethacin (a non-steroidal anti-inflammatory drug (NSAID) considered the standard of care), as measured by the primary study endpoint, which was the average intensity of gout pain from 24 to 72 hours after initiation of treatment.

There are two ongoing studies in the Phase 3 program with ARCALYST® in the prevention of gout flares in patients initiating uric acid-lowering therapy. The global PRE-SURGE 2 study, which has a similar trial design as PRE-SURGE 1, is evaluating the number of gout flares per patient over the first 16 weeks of initiation of allopurinol therapy. The global RE-SURGE study is evaluating the safety of ARCALYST® versus placebo over 16 weeks in patients who are at risk for gout flares because they are taking uric acid-lowering drug treatment. PRE-SURGE 2 and RE-SURGE are fully enrolled, and we expect to have initial data from both studies during the first quarter of 2011. We own worldwide rights to ARCALYST®.

3. Aflibercept – Oncology

Aflibercept is a protein-based product candidate designed to bind all forms of Vascular Endothelial Growth Factor-A (called VEGF-A), VEGF-B, and the related Placental Growth Factor (called PlGF), and prevent their interaction with cell surface receptors. VEGF-A (and to a lesser degree, PlGF) is required for the growth of new blood vessels (a process known as angiogenesis) that are needed for tumors to grow.

Aflibercept is being developed globally in cancer indications in collaboration with sanofi-aventis. We and sanofi-aventis are conducting three randomized, double-blind Phase 3 trials, all of which are fully enrolled, that are evaluating combinations of standard chemotherapy regimens with either aflibercept or placebo for the treatment of cancer. One trial (VELOUR) is evaluating aflibercept as a 2nd-line treatment for metastatic colorectal cancer in combination with FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan). A second trial (VITAL) is evaluating aflibercept as a 2nd-line treatment for locally advanced or metastatic non-small cell lung cancer in combination with docetaxel. A third trial (VENICE) is evaluating aflibercept as a 1st-line treatment for hormone-refractory metastatic prostate cancer in combination with docetaxel/prednisone. In addition, a Phase 2 study (AFFIRM) of aflibercept in 1st-line metastatic colorectal cancer in combination with FOLFOX (folinic acid [leucovorin], 5-fluorouracil, and oxaliplatin) is also fully enrolled.

Each of the Phase 3 studies is monitored by an Independent Data Monitoring Committee (IDMC), a body of independent clinical and statistical experts. The IDMCs meet periodically to evaluate data from the studies and may recommend changes in study design or study discontinuation. Both interim and final analyses will be conducted when a pre-specified number of events have occurred in each trial. In September 2010, we and sanofi-aventis announced that, following a planned interim analysis, the VELOUR study's IDMC recommended that the VELOUR study continue to completion as planned, with no modifications due to efficacy or safety concerns. Both sanofi-aventis and our management and staff remain blinded to the interim study results. Final results from the VITAL and VELOUR studies are anticipated in the first half of 2011. Based on projected event rates, an interim analysis of the VENICE study is expected to be conducted by an IDMC in mid-2011, with final results anticipated in 2012. Initial data from the AFFIRM study are anticipated in the second half of 2011.

Aflibercept Collaboration with sanofi-aventis

We and sanofi-aventis globally collaborate on the development and commercialization of aflibercept. Under the terms of our September 2003 collaboration agreement, as amended, we and sanofi-aventis will share co-promotion rights and profits on sales, if any, of aflibercept outside of Japan for disease indications included in our collaboration. In Japan, we are entitled to a royalty of approximately 35% on annual sales of aflibercept, subject to certain potential adjustments. We may also receive up to $400 million in milestone payments upon receipt of specified marketing approvals, including up to $360 million related to the receipt of marketing approvals for up to eight aflibercept oncology and other indications in the United States or the European Union and up to $40 million related to the receipt of marketing approvals for up to five oncology indications in Japan.

Under the aflibercept collaboration agreement, as amended, agreed upon worldwide development expenses incurred by both companies during the term of the agreement will be funded by sanofi-aventis. If the collaboration becomes profitable, we will be obligated to reimburse sanofi-aventis for 50% of aflibercept development expenses in accordance with a formula based on the amount of development expenses and our share of the collaboration profits and Japan royalties, or at a faster rate at our option.

4. REGN727 (PCSK9 Antibody) for LDL cholesterol reduction

Elevated LDL cholesterol ("bad cholesterol") level is a validated risk factor leading to cardiovascular disease. Statins are a class of drugs that lower LDL cholesterol by upregulating the expression of the LDL receptor (LDLR), which removes LDL from circulation. PCSK9 is a naturally occurring secreted protein that also modulates LDL cholesterol levels through its interaction with the LDL receptor. In a landmark study published in the New England Journal of Medicine in March 2006, patients with lower than normal PCSK9 levels due to a genetic abnormality not only had significantly lower levels of LDL cholesterol, but also a significant reduction in the risk of coronary heart disease. We used our VelocImmune® technology to generate a fully human monoclonal antibody inhibitor of PCSK9, called REGN727, that is intended to robustly lower LDL cholesterol.

In May 2010, we announced that in an interim efficacy analysis of a dose-escalating, randomized, double-blind, placebo-controlled, Phase 1 trial in healthy volunteers, REGN727 achieved substantial, dose dependent decreases of LDL cholesterol. Each dosing cohort consisted of six treated and two placebo patients. In July 2010, we presented additional data from this Phase 1 program. At the highest intravenous dose tested, a single dose of REGN727 achieved a greater than 60% maximum mean reduction of LDL cholesterol from baseline that lasted for more than one month. At the highest subcutaneous dose tested, a single dose of REGN727 achieved a greater than 60% maximum mean reduction of LDL cholesterol from baseline that lasted for more than two weeks. No serious adverse events and no dose limiting toxicities have been reported. Dose escalation is ongoing in both studies.

In July 2010, we also presented the results of an interim efficacy analysis of a dose escalating, randomized, double-blind, placebo-controlled Phase 1 trial of subcutaneously delivered REGN727 in hyperlipidemic patients (familial hypercholesterolemia and non-familial hypercholesterolemia) on stable doses of statins whose LDL levels were greater than 100 milligrams per deciliter (mg/dL). At the highest dose tested at that time, in eleven patients, a single dose of REGN727 achieved an approximately 40% maximum mean additional reduction of LDL cholesterol from baseline. No serious adverse events and no dose limiting toxicities were reported. Dose escalation in this study is ongoing. In early 2011, we initiated Phase 2 studies of REGN727 in patients with hypercholesterolemia. REGN727 is being developed in collaboration with sanofi-aventis.

5. REGN88 (IL-6R Antibody) for inflammatory diseases

IL-6 is a key cytokine involved in the pathogenesis of rheumatoid arthritis, causing inflammation and joint destruction. A therapeutic antibody to IL-6R, Actemra® (tocilizumab), a registered trademark of Genentech, has been approved for the treatment of rheumatoid arthritis.

REGN88 is a fully human monoclonal antibody to IL-6R generated using our VelocImmune® technology that has completed Phase 1 studies, the results of which were presented at the annual meetings of the European League Against Rheumatism (EULAR) in June 2010 and the American College of Rheumatology in October 2010. REGN88 was well tolerated by patients with rheumatoid arthritis, and no dose-limiting toxicities were reported. Treatment with REGN88 resulted in dose-related reductions in biomarkers of inflammation. REGN88 is currently in a Phase 2/3 double-blind, placebo-controlled, dose-ranging study in patients with active rheumatoid arthritis and a Phase 2 double-blind, placebo-controlled, dose-ranging study in ankylosing spondylitis, a form of arthritis that primarily affects the spine. Both studies are enrolling patients, and initial Phase 2 results are expected in 2011. REGN88 is being developed in collaboration with sanofi-aventis.

6. REGN668 (IL-4R Antibody) for allergic and immune conditions

IL-4R is required for signaling by the cytokines IL-4 and IL-13. Both of these cytokines are critical mediators of immune response, which, in turn, drives the formation of Immunoglobulin E (IgE) antibodies and the development of allergic responses, as well as the atopic state that underlies asthma and atopic dermatitis.

REGN668 is a fully human monoclonal antibody generated using our VelocImmune® technology that is designed to bind to IL-4R. A Phase 1 trial of REGN668 in healthy volunteers has been completed. A Phase 1b study in patients with atopic dermatitis is underway and a Phase 2 study in asthma is planned. REGN668 is being developed in collaboration with sanofi-aventis.

7. REGN421 (Dll4 Antibody) for advanced malignancies

In many clinical settings, positively or negatively regulating blood vessel growth could have important therapeutic benefits, as could the repair of damaged and leaky vessels. VEGF was the first growth factor shown to be specific for blood vessels, by virtue of having its receptor primarily expressed on blood vessel cells. In the December 21, 2006 issue of the journal Nature, we reported data from a preclinical study demonstrating that blocking an important cell signaling molecule, known as Dll4, inhibited the growth of experimental tumors by interfering with their ability to produce a functional blood supply. The inhibition of tumor growth was seen in a variety of tumor types, including those that were resistant to blockade of VEGF, suggesting a novel anti-angiogenesis therapeutic approach. Moreover, inhibition of tumor growth is enhanced by the combination of Dll4 and VEGF blockade in many preclinical tumor models.

REGN421 is a fully human monoclonal antibody to Dll4 generated using our VelocImmune® technology. REGN421, which is being developed in collaboration with sanofi-aventis, is in Phase 1 clinical development.

8. REGN910 (ANG2 Antibody) for oncology

In the fourth quarter of 2010, we initiated a phase 1 study in the oncology setting of REGN910, an antibody that specifically blocks ANG2. The angiopoietins, which were discovered at Regeneron, are ligands for the endothelial cell receptor Tie2 and are essential for vascular development and angiogenesis. Unlike other family members, ANG2 is strongly upregulated by endothelial cells at sites of angiogenesis and vascular remodeling, including tumors. REGN910 is being developed for cancer indications in collaboration with sanofi-aventis.

9. REGN475 (NGF Antibody) for pain

REGN475 is a fully human monoclonal antibody to NGF, generated using our VelocImmune® technology, which is designed to block pain sensitization in neurons. Preclinical experiments indicate that REGN475 specifically binds to and blocks NGF activity and does not bind to or block cell signaling for closely related neurotrophins such as NT-3, NT-4, or BDNF. REGN475 is being developed in collaboration with sanofi-aventis.

In May 2010, we announced an interim analysis of a randomized, double-blind, four-arm, placebo-controlled Phase 2 trial in 217 patients with osteoarthritis of the knee. In July 2010, we presented additional results from this trial through 16 weeks.

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The primary endpoint of this study was safety, and REGN475 was generally well tolerated through 16 weeks. Serious treatment emergent adverse events were rare and balanced between placebo and drug arms with three events (5.5%) in the placebo group and four events (2.5%) in the combined REGN475 groups. The most frequent adverse events reported among patients receiving REGN475 included sensory abnormalities, arthralgias, hyper/hypo-reflexia, peripheral edema, and injection site reactions. The types and frequencies of adverse events reported were similar to those previously reported from other investigational studies involving an anti-NGF antibody.

In the first interim efficacy analysis, REGN475 demonstrated significant improvements at the two highest doses tested as compared to placebo in average walking pain scores over 8 weeks following a single intravenous infusion ($p<0.01$). In July 2010, we reported that REGN475 demonstrated significant improvements at the two highest doses tested as compared to placebo in average walking pain scores over 16 weeks following a second intravenous infusion at week 8 ($p<0.01$). Pain was measured by the Numeric Rating Scale (NRS), as well as the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain and function subscales.

Analysis of efficacy data from a Phase 2 trial in the acute setting of nerve root compression induced pain (acute sciatica) suggested that REGN475 therapy would not be effective in that setting. Studies in burn pain, vertebral compression fracture, and pancreatitis pain have been terminated due to low enrollment.

In December 2010, the Company was informed by the FDA that a case confirmed as avascular necrosis of a joint was seen in another company's anti-NGF program. The FDA believes this case, which follows previously-reported cases of joint replacements in patients on an anti-NGF drug candidate being developed by another pharmaceutical company, provides evidence to suggest a class-effect and has placed REGN475 on clinical hold. There are currently no ongoing trials with REGN475 that are either enrolling or treating patients. REGN475 is being developed in collaboration with sanofi-aventis.

10. REGN728 and REGN846

In the fourth quarter of 2010, clinical trials began with two additional antibodies that are part of the sanofi-aventis collaboration, REGN728 and REGN846. The targets of these antibodies have not been disclosed.

Research and Development Technologies:

Many proteins that are either on the surface of or secreted by cells play important roles in biology and disease. One way that a cell communicates with other cells is by releasing specific signaling proteins, either locally or into the bloodstream. These proteins have distinct functions, and are classified into different "families" of molecules, such as peptide hormones, growth factors, and cytokines. All of these secreted (or signaling) proteins travel to and are recognized by another set of proteins, called "receptors," which reside on the surface of responding cells. These secreted proteins impact many critical cellular and biological processes, causing diverse effects ranging from the regulation of growth of particular cell types, to inflammation mediated by white blood cells. Secreted proteins can at times be overactive and thus result in a variety of diseases. In these disease settings, blocking the action of specific secreted proteins can have clinical benefit. In other cases, proteins on the cell-surface can mediate the interaction between cells, such as the processes that give rise to inflammation and autoimmunity.

Our scientists have developed two different technologies to design protein therapeutics to block the action of specific cell surface or secreted proteins. The first technology, termed the "Trap" technology, was used to generate our first approved product, ARCALYST®, as well as aflibercept and VEGF Trap-Eye, all of which are in Phase 3 clinical trials. These novel "Traps" are composed of fusions between two distinct receptor components and the constant region of an antibody molecule called the "Fc region", resulting in high affinity product candidates. VelociSuiteTM is our second technology platform; it is used for discovering, developing, and producing fully human monoclonal antibodies that can address both secreted and cell-surface targets.

VelociSuiteTM

VelociSuiteTM consists of VelocImmune®, VelociGene®, VelociMouse®, and VelociMab® The VelocImmune® mouse platform is utilized to produce fully human monoclonal antibodies. VelocImmune® was generated by exploiting our VelociGene® technology (see below), in a process in which six megabases of mouse immune gene loci were replaced, or "humanized," with corresponding human immune gene loci. VelocImmune® mice can be

used to generate efficiently fully human monoclonal antibodies to targets of therapeutic interest. VelocImmune® and our entire VelociSuiteTM offer the potential to increase the speed and efficiency through which human monoclonal antibody therapeutics may be discovered and validated, thereby improving the overall efficiency of our early stage drug development activities. We are utilizing the VelocImmune® technology to produce our next generation of drug candidates for preclinical and clinical development.

Our VelociGene® platform allows custom and precise manipulation of very large sequences of DNA to produce highly customized alterations of a specified target gene, or genes, and accelerates the production of knock-out and transgenic expression models without using either positive/negative selection or isogenic DNA. In producing knockout models, a color or fluorescent marker may be substituted in place of the actual gene sequence, allowing for high-resolution visualization of precisely where the gene is active in the body during normal body functioning as well as in disease processes. For the optimization of preclinical development and pharmacology programs, VelociGene® offers the opportunity to humanize targets by replacing the mouse gene with the human homolog. Thus, VelociGene® allows scientists to rapidly identify the physical and biological effects of deleting or over-expressing the target gene, as well as to characterize and test potential therapeutic molecules.

Our VelociMouse® technology platform allows for the direct and immediate generation of genetically altered mice from embryonic stem cells (ES cells), thereby avoiding the lengthy process involved in generating and breeding knockout mice from chimeras. Mice generated through this method are normal and healthy and exhibit a 100% germ-line transmission. Furthermore, mice developed using our VelociMouse® technology are suitable for direct phenotyping or other studies. We have also developed our VelociMab® platform for the rapid screening of antibodies and rapid generation of expression cell lines for our Traps and our VelocImmune® human monoclonal antibodies.

Antibody Collaboration and License Agreements

sanofi-aventis. In November 2007, we and sanofi-aventis entered into a global, strategic collaboration to discover, develop, and commercialize fully human monoclonal antibodies. The collaboration is governed by a Discovery and Preclinical Development Agreement and a License and Collaboration Agreement. In connection with the execution of the discovery agreement in 2007, we received a non-refundable, up-front payment of $85.0 million from sanofi-aventis. Pursuant to the collaboration, sanofi-aventis is funding our research to identify and validate potential drug discovery targets and develop fully human monoclonal antibodies against these targets. We lead the design and conduct of research activities under the collaboration, including target identification and validation, antibody development, research and preclinical activities through filing of an Investigational New Drug Application (IND) or its equivalent, toxicology studies, and manufacture of preclinical and clinical supplies.

For each drug candidate identified through discovery research under the discovery agreement, sanofi-aventis has the option to license rights to the candidate under the license agreement. If it elects to do so, sanofi-aventis will co-develop the drug candidate with us through product approval. Development costs for the drug candidate are shared between the companies, with sanofi-aventis generally funding these costs up front, except that following receipt of the first positive Phase 3 trial results for a co-developed drug candidate, subsequent Phase 3 trial-related costs for that drug candidate are shared 80% by sanofi-aventis and 20% by us. We are generally responsible for reimbursing sanofi-aventis for half of the total development costs for all collaboration antibody products from our share of profits from commercialization of collaboration products to the extent they are sufficient for this purpose. However, we are not required to apply more than 10% of our share of the profits from collaboration products in any calendar quarter towards reimbursing sanofi-aventis for these development costs.

Sanofi-aventis will lead commercialization activities for products developed under the license agreement, subject to our right to co-promote such products. The parties will equally share profits and losses from sales within the United States. The parties will share profits outside the United States on a sliding scale based on sales starting at 65% (sanofi-aventis)/35% (us) and ending at 55% (sanofi-aventis)/45% (us), and will share losses outside the United States at 55% (sanofi-aventis)/45% (us). In addition to profit sharing, we are entitled to receive up to $250 million in sales milestone payments, with milestone payments commencing after aggregate annual sales outside the United States exceed $1.0 billion on a rolling 12-month basis.

In November 2009, we and sanofi-aventis amended these agreements to expand and extend our antibody collaboration. The goal of the expanded collaboration is to advance an average of four to five new antibody product candidates into clinical development each year, for an anticipated total of 30-40 candidates from 2010 through 2017.

Under the amended discovery agreement, sanofi-aventis agreed to fund up to $160 million per year of our antibody discovery activities over the period from 2010-2017, subject to a one-time option for sanofi-aventis to adjust the maximum reimbursement amount down to $120 million per year commencing in 2014 if over the prior two years certain specified criteria were not satisfied. Sanofi-aventis has an option to extend the discovery program for up to an additional three years after 2017 for further antibody development and preclinical activities. Pursuant to the collaboration, sanofi-aventis is also obligated to fund up to $30 million of agreed-upon costs we incur to expand our manufacturing capacity at our Rensselaer, New York facilities.

In 2010, as we scaled up our capacity to conduct antibody discovery activities, sanofi-aventis funded $137.7 million of our preclinical research under the expanded collaboration. The balance between that amount and $160 million, or $22.3 million, has been added to the funding otherwise available to us in 2011-2012 under the amended discovery agreement. During 2010, sanofi-aventis also funded $138.3 million of our costs for clinical development of antibodies under the license agreement.

From the collaboration's inception in November 2007 through December 31, 2010, sanofi-aventis has funded a total of $312.7 million of our costs under the discovery agreement and a total of $263.0 million of our development costs under the license agreement, or a total of $575.7 million in funding for our antibody research and development activities during this approximate three-year period.

In August 2008, we entered into an agreement with sanofi-aventis to use our VelociGene® platform to supply sanofi-aventis with genetically modified mammalian models of gene function and disease. Under this agreement, sanofi-aventis is required to pay us a minimum of $21.5 million for the term of the agreement, which extends through December 2012, for knock-out and transgenic models of gene function for target genes identified by sanofi-aventis. Sanofi-aventis will use these models for its internal research programs that are outside of the scope of our antibody collaboration.

AstraZeneca UK Limited. In February 2007, we entered into a six-year, non-exclusive license agreement with AstraZeneca UK Limited to allow AstraZeneca to utilize our VelocImmune® technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, AstraZeneca made a $20.0 million annual, non-refundable payment to us in each of the first quarters of 2007, 2008, 2009, and 2010. In November 2010, as permitted by the agreement, MedImmune Limited (as successor by novation from AstraZeneca) gave written notice of voluntary termination of the agreement, effective in February 2011, thereby canceling its obligation to make either of the final two annual payments. We remain entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by MedImmune using our VelocImmune® technology.

Astellas Pharma Inc. In March 2007, we entered into a six-year, non-exclusive license agreement with Astellas Pharma Inc. to allow Astellas to utilize our VelocImmune® technology in its internal research programs to discover human monoclonal antibodies. Under the terms of the agreement, Astellas made a $20.0 million annual, non-refundable payment to us in each of the second quarters of 2007, 2008, 2009, and 2010. In July 2010, the license agreement with Astellas was amended and extended through June 2023. Under the terms of the amended agreement, Astellas made a $165.0 million up-front payment to us in August 2010. In addition, Astellas will make a $130.0 million second payment to us in June 2018 unless the license agreement has been terminated prior to that date. Astellas has the right to terminate the agreement at any time by providing 90 days' advance written notice. Under certain limited circumstances, such as our material breach of the agreement, Astellas may terminate the agreement and receive a refund of a portion of its up-front payment or, if such termination occurs after June 2018, a portion of its second payment, to us under the July 2010 amendment to the agreement. We are entitled to receive a mid-single-digit royalty on any future sales of antibody products discovered by Astellas using our VelocImmune® technology.

Royalty Agreement with Novartis Pharma AG

Under a June 2009 agreement with Novartis Pharma AG (that replaced a previous collaboration and license agreement), we receive royalties on worldwide sales of Novartis' canakinumab, a fully human anti-interleukin-IL1ß antibody. The royalty rates in the agreement start at 4% and reach 15% when annual sales exceed $1.5 billion. Canakinumab is marketed for the treatment of CAPS, has completed Phase 3 development for gout, and is in earlier stage development for atherosclerosis and other inflammatory diseases. While our royalties under this agreement

could be significant if canakinumab is approved and successfully commercialized for additional disease indications, to date these royalties have been minimal. Accordingly, we are unable to predict whether these royalties will ever contribute materially to our results of operations or financial condition.

National Institutes of Health Grant

In September 2006, we were awarded a five-year grant from the National Institutes of Health (NIH) as part of the NIH's Knockout Mouse Project. The goal of the Knockout Mouse Project is to build a comprehensive and broadly available resource of knockout mice to accelerate the understanding of gene function and human diseases. Under the NIH grant, as amended, we have received $21.6 million from the grant's inception through December 31, 2010 and are entitled to receive an additional $3.7 million through the remaining term of the grant.

Research Programs

Our preclinical research programs are in the areas of oncology and angiogenesis, ophthalmology, metabolic and related diseases, muscle diseases and disorders, inflammation and immune diseases, bone and cartilage, pain, cardiovascular diseases, and infectious diseases.

Sales and Marketing

We have established a small commercial organization to support sales of ARCALYST® for the treatment of CAPS in the United States. We have no sales or distribution personnel and distribute the product through third party service providers. We currently have no sales, marketing, commercial, or distribution organization outside the United States. We are currently expanding our commercial capabilities and increasing the number of commercial personnel in preparation for the potential commercialization of VEGF Trap-Eye and our other late-stage product candidates.

Manufacturing

Our manufacturing facilities are located in Rensselaer, New York and consist of three buildings totaling approximately 395,500 square feet of research, manufacturing, office, and warehouse space. We currently have approximately 54,000 liters of cell culture capacity at these facilities. At December 31, 2010, we employed 356 people at our Rensselaer facilities. There were no impairment losses associated with long-lived assets at these facilities as of December 31, 2010.

Among the conditions for regulatory marketing approval of a medicine is the requirement that the prospective manufacturer's quality control and manufacturing procedures conform to the good manufacturing practice (GMP) regulations of the health authority. In complying with standards set forth in these regulations, manufacturers must continue to expend time, money, and effort in the areas of production and quality control to ensure full technical compliance. Manufacturing establishments, both foreign and domestic, are also subject to inspections by or under the authority of the FDA and by other national, federal, state, and local agencies. If our manufacturing facilities fail to comply with FDA and other regulatory requirements, we will be required to suspend manufacturing. This would likely have a material adverse effect on our financial condition, results of operations, and cash flow.

Competition

We face substantial competition from pharmaceutical, biotechnology, and chemical companies (see Item 1A. "Risk Factors – Risks Related to Commercialization of Products – Even if our product candidates are approved for marketing, their commercial success is highly uncertain because our competitors have received approval for and may be marketing products with a similar mechanism of action, or may enter the marketplace with better or lower cost drugs."). Our competitors include Genentech/Roche, Novartis, Pfizer Inc., Bayer HealthCare, Onyx Pharmaceuticals, Inc., Eli Lilly and Company, Abbott Laboratories, sanofi-aventis, Merck & Co., Inc., Amgen Inc., AstraZeneca, BristolMyersSquibb, Johnson and Johnson, GlaxoSmithKline, and others. Many of our competitors have substantially greater research, preclinical, and clinical product development and manufacturing capabilities, and financial, marketing, and human resources than we do. Competition from smaller competitors may also be or become more significant if those competitors acquire or discover patentable inventions, form collaborative arrangements, or merge with large pharmaceutical companies. Even if we are able to commercialize additional product candidates, one or more of our competitors may have brought a competitive product to market earlier than us or may have obtained

or obtain patent protection that dominates or adversely affects our activities or products. Our ability to compete will depend, to a great extent, on how fast we can develop safe and effective product candidates, complete clinical testing and approval processes, and supply commercial quantities of the product to the market. Competition among product candidates approved for sale will also be based on efficacy, safety, reliability, availability, price, patent position, and other factors.

ARCALYST®. In 2009, Novartis received regulatory approval in the U.S. and Europe for canakinumab, a fully human anti-interleukin-IL1ß antibody, for the treatment of CAPS. In January 2011, Novartis announced that it had submitted an application to the EMA for approval of canakinumab in gout. Novartis has also announced that it plans to submit to the FDA in the first quarter of 2011 an application for approval of canakinumab in gout. Canakinumab is also in development for atherosclerosis and a number of other inflammatory diseases. In addition, there are both small molecules and antibodies in development by other third parties that are designed to block the synthesis of IL-1 or inhibit the signaling of IL-1. For example, Xoma Ltd., in collaboration with Servier, is developing an antibody to IL-1, and both Amgen and MedImmune are developing antibodies to the IL-1 receptor. These drug candidates could offer competitive advantages over ARCALYST®. The successful development and/or commercialization of these competing molecules could adversely affect sales of ARCALYST® for CAPS and delay or impair our ability to commercialize ARCALYST® for indications other than CAPS.

VEGF Trap-Eye. The market for eye disease products is also very competitive. Novartis and Genentech are collaborating on the commercialization and further development of a VEGF antibody fragment (Lucentis®) for the treatment of wet AMD, DME, and other eye indications. Lucentis® was approved by the FDA in June 2006 for the treatment of wet AMD and in June 2010 for the treatment of macular edema following retinal vein occlusion (RVO). Lucentis® was approved by the European Medicines Agency (EMA) for wet AMD in January 2007 and for the treatment of DME in January 2011. Many other companies are working on the development of product candidates for the potential treatment of wet AMD and DME including those that act by blocking VEGF and VEGF receptors as well as use of small interfering ribonucleic acids (siRNAs) that modulate gene expression. In addition, ophthalmologists are using off-label, with success for the treatment of wet AMD, DME, and RVO, a third-party repackaged version of Genentech's approved VEGF antagonist, Avastin® (bevacizumab). The relatively low cost of therapy with Avastin® in patients with wet AMD presents a significant competitive challenge in this indication. The National Eye Institute (NEI) initiated a Phase 3 trial to compare Lucentis® to Avastin® in the treatment of wet AMD. Data from this NEI study are expected to be published in 2011. Avastin® is also being evaluated in eye diseases in trials that have been initiated in the United Kingdom, Canada, Brazil, Mexico, Germany, Israel, and other areas.

Aflibercept. Many companies are developing therapeutic molecules designed to block the actions of VEGF specifically and angiogenesis in general. A variety of approaches have been employed, including antibodies to VEGF, antibodies to the VEGF receptor, small molecule antagonists to the VEGF receptor tyrosine kinase, and other anti-angiogenesis strategies. Many of these alternative approaches may offer competitive advantages to aflibercept in efficacy, side-effect profile, or method of delivery. Additionally, some of these molecules are either already approved for marketing or are at a more advanced stage of development than our product candidate.

In particular, Genentech has an approved VEGF antagonist, Avastin®, on the market for treating certain cancers and a number of pharmaceutical and biotechnology companies are working to develop competing VEGF antagonists, including Novartis, Amgen, Imclone LLC/Eli Lilly, Pfizer, AstraZeneca, and GlaxoSmithKline. Many of these molecules are further along in development than aflibercept and may offer competitive advantages over our molecule. Pfizer, Onyx (together with its partner Bayer Healthcare), and GlaxoSmithKline are selling and marketing oral medications that target tumor cell growth and new vasculature formation that fuels the growth of tumors.

Monoclonal Antibodies. Our early-stage clinical candidates in development are all fully human monoclonal antibodies which were generated using our VelocImmune® technology. Our antibody generation technologies and early-stage clinical candidates face competition from many pharmaceutical and biotechnology companies using various technologies.

Numerous other companies are developing therapeutic antibody products. Companies such as Pfizer, Johnson & Johnson, AstraZeneca, Amgen, Biogen Idec, Inc., Novartis, Genentech/Roche, Bristol-Myers Squib, Abbott, and GlaxoSmithKline have generated therapeutic products that are currently in development or on the market that are derived from recombinant DNA that comprise human antibody sequences. As noted above, AstraZeneca and Astellas have licensed our VelocImmune® technology as part of their internal antibody development programs.

We are aware of several pharmaceutical and biotechnology companies actively engaged in the research and development of antibody products against targets that are also the targets of our early-stage product candidates. For example, Pfizer, Johnson & Johnson, and Abbott are developing antibody product candidates against NGF. Genentech/Roche is marketing an antibody against IL-6R (tocilizumab) for the treatment of rheumatoid arthritis, and several other companies, including Centocor Ortho Biotech, Inc. and Bristol-Myers Squibb, have antibodies against IL-6 in clinical development for this disease. GlaxoSmithKline, in partnership with OncoMed Pharmaceuticals, Inc., has a Dll4 antibody in clinical development for the treatment of solid tumors. Aerovance has two formulations of a biologic directed against IL-4 in clinical development. Amgen previously had an antibody against IL-4R in clinical development for the treatment of asthma. We believe that several companies, including Amgen and Pfizer, have development programs for antibodies against PCSK9. Amgen, Pfizer, and AstraZeneca have development programs underway for antibodies against ANG2.

Other Areas. Many pharmaceutical and biotechnology companies are attempting to discover new therapeutics for indications in which we invest substantial time and resources. In these and related areas, intellectual property rights have been sought and certain rights have been granted to competitors and potential competitors of ours, and we may be at a substantial competitive disadvantage in such areas as a result of, among other things, our lack of experience, trained personnel, and expertise. A number of corporate and academic competitors are involved in the discovery and development of novel therapeutics that are the focus of other research or development programs we are now conducting. These competitors include Amgen and Genentech, as well as many others. Many firms and entities are engaged in research and development in the areas of cytokines, interleukins, angiogenesis, and muscle conditions. Some of these competitors are currently conducting advanced preclinical and clinical research programs in these areas. These and other competitors may have established substantial intellectual property and other competitive advantages.

If any of these or other competitors announces a successful clinical study involving a product that may be competitive with one of our product candidates or the grant of marketing approval by a regulatory agency for a competitive product, such developments may have an adverse effect on our operations or future prospects.

We also compete with academic institutions, governmental agencies, and other public or private research organizations, which conduct research, seek patent protection, and establish collaborative arrangements for the development and marketing of products that would provide royalties or other consideration for use of their technology. These institutions are becoming more active in seeking patent protection and licensing arrangements to collect royalties or other consideration for use of the technology they have developed. Products developed in this manner may compete directly with products we develop. We also compete with others in acquiring technology from these institutions, agencies, and organizations.

Patents, Trademarks, and Trade Secrets

Our success depends, in part, on our ability to obtain patents, maintain trade secret protection, and operate without infringing on the proprietary rights of third parties (see Item 1A. “Risk Factors – Risks Related to Intellectual Property – We may be restricted in our development and/or commercialization activities by, and could be subject to damage awards if we are found to have infringed, third party patents or other proprietary rights.”). Our policy is to file patent applications to protect technology, inventions, and improvements that we consider important to our business and operations. As of December 31, 2010, we held an ownership interest in a total of approximately 170 issued patents in the United States and approximately 590 issued patents in foreign countries with respect to our products and technologies. In addition, we hold an ownership interest in hundreds of patent applications in the United States and foreign countries.

Our patent portfolio includes granted patents and pending patent applications covering our VelociSuite™ technologies, including our VelocImmune® mouse platform which produces fully human monoclonal antibodies. Our issued patents covering these technologies generally expire between 2020 and 2030. However, we continue to file patent applications directed to improvements to these technology platforms.

Our patent portfolio also includes issued patents and pending applications relating to our marketed product, ARCALYST®, and our product candidates in clinical development. These patents cover the proteins and DNA encoding the proteins, manufacturing patents, method of use patents, and pharmaceutical compositions, as well as

various methods of using the products. For each of ARCALYST® and our late-stage product candidates, aflibercept and VEGF Trap-Eye, these patents generally expire between 2020 and 2028. However, the projected patent terms may be subject to extension based on potential patent term extensions in countries where such extensions are available.

We also are the nonexclusive licensee of a number of additional patents and patent applications. In July 2008 we entered into an Amended and Restated Non-Exclusive License Agreement with Cellectis S.A. pursuant to which we licensed certain patents and patent applications relating to a process for the specific replacement of a copy of a gene in the receiver genome by homologous recombination. Pursuant to this agreement, we agreed to pay Cellectis a low, single-digit royalty based on any future revenue received by us from any future licenses or sales of our VelociGene® or VelocImmune® products or services. No royalties are payable to Cellectis on any revenue from commercial sales of antibodies from our VelocImmune® technology, including antibodies developed under our collaboration with sanofi-aventis. We also have non-exclusive license agreements with Amgen and other organizations for patent rights related to ARCALYST®. In exchange for these licenses, we pay a mid-single digit royalty on net sales of ARCALYST®.

Patent law relating to the patentability and scope of claims in the biotechnology field is evolving and our patent rights are subject to this additional uncertainty. The degree of patent protection that will be afforded to our products in the United States and other important commercial markets is uncertain and is dependent upon the scope of protection decided upon by the patent offices, courts, and governments in these countries. There is no certainty that our existing patents or others, if obtained, will provide us protection from competition or provide commercial benefit.