AGIOS PHARMACEUTICALS INC
Form 10-K
February 26, 2016
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, DC 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, 2015

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
Commission File Number:

001-36014

AGIOS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**26-0662915**
(State or other jurisdiction of incorporation or organization)	*(IRS Employer Identification No.)*
88 Sidney Street, Cambridge, MA	**02139**
(Address of principal executive offices)	*(Zip Code)*

Registrant s telephone number, including area code:

(617) 649-8600

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

Title of Class	Name of Exchange on Which Registered
Common Stock, Par Value $0.001 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 Section 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 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 definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

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

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

The aggregate market value of the voting and non-voting Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant s Common Stock as of June 30, 2015 (based on the last reported sale price on the NASDAQ Global Select Market as of such date) was $3,085,361,874.

As of February 23, 2016, there were 37,850,561 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement for its 2016 Annual Meeting of Stockholders to be filed pursuant to Regulation 14A within 120 days of the end of the registrant s fiscal year ended December 31, 2015 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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PART I

References to Agios

Throughout this Annual Report on Form 10-K, the Company, Agios, we, us, and our, and similar expressions, e
where the context requires otherwise, refer to Agios Pharmaceuticals, Inc. and its consolidated subsidiaries, and our board of directors refers to the board of directors of Agios Pharmaceuticals, Inc.

Forward-looking Information

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements regarding:

- the initiation, timing, progress and results of current and future preclinical studies and clinical trials, and our research and development programs;
- the potential of IDH1/IDH2 and pyruvate kinase-R mutations as therapeutic targets;
- the potential benefits of our product candidates targeting IDH1/IDH2 or pyruvate kinase-R mutations, including AG-120, AG-221, AG-881, AG-348 and AG-519;
- our plans to develop and commercialize our product candidates;
- our collaborations with Celgene Corporation, or Celgene;
- our ability to establish and maintain additional collaborations or obtain additional funding;
- the timing or likelihood of regulatory filings and approvals;
- the implementation of our business model, strategic plans for our business, product candidates and technology;

our commercialization, marketing and manufacturing capabilities and strategy;

the rate and degree of market acceptance and clinical utility of our products;

our competitive position;

our intellectual property position;

developments and projections relating to our competitors and our industry; and

our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the Risk Factors section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

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You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Item 1. Business

We are a biopharmaceutical company committed to applying our scientific leadership in the field of cellular metabolism to transform the lives of patients with cancer and rare genetic metabolic disorders, or RGDs, which are a subset of orphan genetic metabolic diseases. Metabolism is a complex biological process involving the uptake and assimilation of nutrients in cells to produce energy and facilitate many of the processes required for cellular division and growth. We focus our efforts on using cellular metabolism, an unexploited area of biological research with disruptive potential, as a platform for developing potentially transformative small molecule medicines. Our most advanced cancer product candidates are AG-221 and AG-120, which target mutated isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, and AG-881, which targets both mutated IDH1 and mutated IDH2. These mutations are found in a wide range of hematological malignancies and solid tumors. The lead product candidate in our RGD programs, AG-348, targets pyruvate kinase-R for the treatment of pyruvate kinase deficiency. Pyruvate kinase deficiency is a rare disorder that often results in severe hemolytic anemia due to inherited mutations in the pyruvate kinase enzyme within red blood cells.

The clinical development strategy for all of our product candidates includes a precision approach with initial study designs that allow for genetically or biomarker defined patient populations, enabling the potential for proof of concept early in clinical development, along with the potential for accelerated approval. Our ability to identify, validate and drug novel targets is enabled by a set of core capabilities. Key proprietary aspects of our core capabilities in cellular metabolism include our ability to measure the activities of numerous metabolic pathways in cells or tissues in a high throughput fashion and our expertise in flux biochemistry. This refers to the dynamic analysis of how metabolites, which are intermediates or small molecule products of metabolism, accumulate or diminish as they are created or chemically altered by multiple networks of metabolic enzymes. Complex mathematical modeling of metabolic pathways, enzymatic activity and the flux of metabolites through metabolic enzymatic reactions within diseased tissues allow us to identify novel biological parameters that can be measured to characterize a disease state or the effect of therapy, or biomarkers, and targets for drug discovery.

Our Strategy

We aim to build a multi-product company, based on our expertise in cellular metabolism, that discovers, develops and commercializes first- and best-in-class medicines to treat cancer and RGDs. Key elements of our strategy include:

- Aggressively pursuing the development of novel medicines to transform the lives of patients with cancer and RGDs.
- Maintaining our competitive advantage and focus in the field of cellular metabolism.
- Continuing to build a product engine for cancer and RGDs to generate novel and important medicines.

Building a preeminent independent biopharmaceutical company by engaging in discovery, development and commercialization of our medicines.

Maintaining a commitment to precision medicine in drug development.

Our Guiding Principles

We aim to build a long-term company with a disciplined focus on developing medicines that transform the lives of patients with cancer and RGDs. We maintain a culture of high integrity that embraces the following guiding principles, which we believe will provide long-term benefits for all our stakeholders:

Follow the science and do what is right for patients.

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Maintain a culture of incisive decision-making driven by deep scientific interrogation and respectful irreverence.

Foster collaborative spirit that includes all employees regardless of function or level.

Leverage deep strategic relationships with our academic and commercial partners to improve the quality of our discovery and development efforts.

Cellular Metabolism

Cellular metabolism refers to the set of life-sustaining chemical transformations within the cells of living organisms. The conversion of nutrients into energy via enzyme-catalyzed reactions allows organisms to grow and reproduce, maintain their structures, and respond to their environments. The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes catalyze quick and efficient reactions, serve as key regulators of metabolic pathways, and respond to changes in the cell s environment or signals from other cells. We believe our deep understanding of metabolic pathways within normal cells enables us to identify altered metabolic pathways within abnormal cells such as in rapidly proliferating cancers and RGDs.

Fundamental differences in the metabolism of normal cells and rapidly proliferating cancer cells were first discovered by Otto Warburg more than 80 years ago an observation that earned him the Nobel Prize. Warburg demonstrated that in contrast to normal cells, which convert nutrients, such as sugar, into energy via a process known as the Krebs cycle, cancer cells ferment their sugar into lactic acid a process known as aerobic glycolysis. It is now known that this allows the cancer cells to generate the building blocks they need to grow rapidly. The ability of the cancer cell to rewire its metabolic pathways to fuel its growth and survival has spawned an entirely new field of cancer biology known as cancer metabolism or tumor metabolism.

Cancer and cancer metabolism

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when the repair of genetic material in normal cells begins to fail and genes that regulate cell growth become disrupted. Carcinogens, or cancer causing agents, such as radiation, chemicals and hormones, can trigger changes to the genetic material of a cell, and typically prompt this disruption. Cells that have been disrupted may become cancerous, leading to changes in the cells DNA, and ultimately uncontrolled growth. Cancer cells can spread to other areas of the body, or metastasize, and form tumors, which can destroy normal tissue or organs. Risk factors for cancer include family history, age, diet, and exogenous factors, such as exposure to ultraviolet sunlight and smoking. Cancers can be classified in stages to document disease severity, measured in stages of I to IV, generally based on tumor size, involvement of lymph nodes, and metastases.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. These treatment regimens are often associated with side effects, including fatigue, infection, nausea and vomiting and pain. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. The goal of drug therapy is to kill cancer cells or to damage cellular components required for rapid growth and survival of cancer cells. In many cases, drug therapy entails the administration of several different drugs in combination. Over the past several decades, drug therapy has evolved from non-specific drugs that kill both healthy and cancerous cells to drugs that

target specific molecular pathways involved in cancer.

Cytotoxic chemotherapies

The earliest approach to cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific mechanisms, such as disrupting cell metabolism or causing damage to cellular components required for survival and rapid growth. While these drugs, (e.g., CYTOXAN®,

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Adriamycin®) have been effective in the treatment of some cancers they act in an indiscriminate manner, killing healthy as well as cancerous cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not effective in eradicating cancer cells.

Targeted therapies

The next approach to pharmacological cancer treatment was to develop drugs, referred to as targeted therapeutics, that target specific biological molecules in the human body that play a role in rapid cell growth and the spread of cancer. Targeted therapeutics are designed to preferentially kill cancer cells and spare normal cells, to improve efficacy and minimize side effects. The drugs are designed to either attack a target that causes uncontrolled growth of cancer cells because of either a specific genetic alteration primarily found in cancer cells but not in normal cells or a target that cancer cells are more dependent on for their growth in comparison to normal cells. Examples of effective targeted therapies include Herceptin®, Avastin® and Zelboraf®.

Emerging areas

Several new approaches to develop novel cancer treatments are underway. They include: treatment with drugs or other methods that stimulate the normal immune system to attack the cancer (immuno-oncology); antibody drug conjugates (e.g., Kadcyla®) that carry a powerful chemotherapy payload that is only released into the cancer cell; and drugs that target the changes in gene activity that occurs in cancer cells (epigenetics).

Cancer metabolism is a new and exciting field of biology that provides a fundamentally different approach to treating cancer. Cancers become addicted to certain fuel sources and inherently alter their cellular machinery to change how they consume and utilize nutrients. Cancer cells increase the transport of nutrients into the cell by 200-400 fold compared to normal cells while also mutating metabolic enzymes to generate metabolites that fuel growth and altering gene expression of enzymes to divert energy production. Collectively, these changes afford cancer cells the ability to generate the building blocks that drive tumor growth. Inhibiting key enzymes in cancer cell specific metabolic pathways has the potential to disrupt tumor cell proliferation and survival without affecting normal cells, thus providing a powerful new intervention point for discovery and development of novel targeted cancer therapeutics. Our research is directed at identifying such metabolic targets and discovering medicines against them.

Validation of the concept of cancer cell metabolic rewiring and excessive nutrient uptake comes from the widespread use of positron emission tomography, or PET, to detect cancers. This medical imaging technology relies on the uptake of nutrients, namely sugar, into cells. Patients are injected with a radioactively labeled form of sugar, which is more rapidly consumed by cancer cells given their profound requirement for nutrients relative to normal tissues. PET imaging precisely locates cancerous areas throughout the body and provides for both a diagnostic and prognostic tool throughout cancer therapy.

The metabolic rewiring of cancer cells can also be linked to specific genetic alterations in oncogenes (which are genes that transform normal cells into tumor cells) and tumor suppressor genes (which are genes that are anti-oncogenic) responsible for cell signaling. These mutations in signaling pathways can drive excessive uptake of nutrients and altered metabolic pathways, thereby causing cancer formation. This cross talk between cell signaling and metabolism offers multiple opportunities to treat cancer by combining our therapies directed against metabolic enzymes with existing or emerging standards of care.

Rare genetic metabolic disorders

Rare genetic metabolic disorders, a subset of orphan genetic metabolic diseases, are a broad group of more than 600 orphan genetic diseases caused by mutations of single metabolic genes. In these disorders, the defect of a single metabolic enzyme disrupts the normal functioning of a metabolic pathway, leading to either aberrant accumulation of upstream metabolites which may be toxic or interfere with normal function or reduced ability to synthesize essential downstream metabolites or other critical cellular components. RGDs are also referred to as congenital metabolic diseases or rare genetic disorders of metabolism.

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Most of these diseases are rare or ultra-rare orphan diseases, often with severe or life-threatening features. A disorder is considered orphan if it affects fewer than 200,000 people in the United States, or fewer than five per 10,000 people in the European Union. In a study in British Columbia, the overall incidence of RGDs was estimated to be 70 per 100,000 live births or one in 1,400 births, overall representing more than approximately 15% of single gene disorders in the population. Incidence of a single RGD can vary widely but is generally rare, usually equal to or less than one per 100,000 births. Many RGDs are likely to be under-diagnosed given the lack of available therapies or diagnostics and the rarity of the condition.

Current treatment options for these disorders are limited. Diet modification or nutrient supplementation can be beneficial in some RGDs. Several of these disorders, from a group known as lysosomal storage diseases, have been treated successfully with enzyme replacement therapy, or ERT, the therapeutic administration of a functional version of the defective enzyme. Examples of ERTs for lysosomal storage disorders include Fabrazyme® for Fabry disease, Myozome® for Pompe disease, Cerezyme® for Gaucher disease, and Elaprase® for Hunter syndrome.

Unfortunately, most mutations driving RGDs are intracellular and not amenable for treatment with enzyme replacement therapies. As a result, despite the promising progress made for patients with a small group of these diseases, the vast majority of patients with RGDs have few therapeutic options available, and the standard of care is palliative, meaning treatment of symptoms with no effect on underlying disease mechanisms. We are taking a novel small molecule approach to correct the metabolic defects within diseased cells with a goal of developing transformative medicines for patients.

We focus on RGDs that share the following common set of features:

- single gene defect;
- severe clinical presentation with evidence that disease damage is progressive but potentially reversible;
- adequate number of patients for prospective clinical trials; and
- an assessment of the target, based upon a detailed mutational, structural, and metabolomic analysis, to determine if a small molecule approach to correcting the disease is possible.

Precision Medicine Approach

Our understanding of cellular metabolism within diseased tissues enables the development of methods to measure the effect of a drug on the target of interest and the patient, or pharmacodynamic markers, and patient selection strategies for clinical development. Utilizing our approach we identify altered metabolic pathways within abnormal cells. Altered metabolic pathways generate disease-specific metabolic fingerprints, comprising patterns of metabolite levels, which are the amounts of particular metabolites, that can be exploited in both discovery and development of novel therapeutics. Metabolites make ideal biomarkers because they are readily measured in the target tissues and blood. Metabolic biomarkers can identify appropriate patients for clinical trials, serve as pharmacodynamics markers to characterize medicine/target engagement in patients, and permit the monitoring of patient response to therapy.

We will only progress our drug candidates forward into phase 1 clinical trials if we have the ability to select patients who are most likely to respond to a given therapy based on biomarkers, for example, genetic or metabolic markers. While many factors are considered critical to maximize the probability of technical success in the drug development process, perhaps none is more important than identifying highly specific and selective molecules aimed at the best possible targets for therapy coupled with the patients most likely to respond to that therapy. Our goal is to develop increasing confidence in the target and the patient population prior to entering human clinical trials and then initiate those first human trials in a patient population that has been selected based on target dependence using a biomarker. This approach, known as personalized or precision medicine, is used in the industry to lead to the potential for clear proof of concept in early human trials, along with the potential for accelerated approval.

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Our Development Programs

We believe that leveraging our core capabilities in cellular metabolism combined with a precision medicine approach has significantly enhanced our ability to build a research and development engine that is focused in the therapeutic areas of cancer and RGDs. This engine has permitted us to discover proprietary first-in-class orally available small molecules as potential lead product candidates for each of several novel programs in development. All of our lead programs focus on diagnostically identified patient populations with the potential for early clinical proof of concept and accelerated approval paths.

The following table summarizes key information about our most advanced product candidates as of February 1, 2016, each of which is described and discussed in further detail below:

Product Candidate	Biomarker(s)	Initial Indications	Stage of Development	Commercial Rights
Cancer metabolism:				
AG-221 (IDH2 mutant inhibitor)	Genotyping of IDH2 mutation; 2HG	IDH2 mutant positive hematologic malignancies	Phase 1/2 clinical trial on-going; phase 1b combination clinical trial on-going; phase 3 IDHENTIFY clinical trial on-going	Agios: milestones and royalties
		IDH2 mutant positive solid tumors including AITL	Phase 1/2 clinical trial on-going	Celgene: worldwide
AG-120 (IDH1 mutant inhibitor)	Genotyping of IDH1 mutation; 2HG	IDH1 mutant positive hematologic malignancies	Phase 1 clinical trial on-going; phase 1b combination clinical trial on-going	Agios: Milestones, cross-royalties, and U.S. rights
		IDH1 mutant positive solid tumors	Phase 1 clinical trial on-going	Celgene: ex-U.S. rights, cross-royalties
AG-881 (pan-IDH mutant inhibitor)	Genotyping of pan-IDH mutation; 2HG	Pan-IDH mutant positive hematologic malignancies	Phase 1 clinical trial on-going	Agios: Milestones Agios and Celgene:
		Pan-IDH mutant positive solid tumors	Phase 1 clinical trial on-going	Joint worldwide collaboration
Rare genetic metabolic disorders:				
AG-348				Agios: worldwide

(Pyruvate kinase- R activator)	Genetic testing for mutation in the pyruvate kinase-R gene	Patients with pyruvate kinase deficiency	Phase 2 DRIVE PK clinical trial on-going	
AG-519 (Pyruvate kinase-R activator)	Genetic testing for mutation in the pyruvate kinase-R gene	Patients with pyruvate kinase deficiency	Phase 1 clinical trial in healthy volunteers on-going	Agios: worldwide

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Targeting Mutated Isocitrate Dehydrogenase (IDH) for the Treatment of Cancer

The isocitrate dehydrogenase, or IDH, protein is a critical enzyme in the citric acid cycle, also known as the tricarboxylic acid, or Krebs, cycle. The Krebs cycle is centrally important to many biochemical pathways and is one of the earliest established components of cellular metabolism. The Krebs cycle converts an essential cellular metabolite called isocitrate into another metabolite, alpha-ketoglutarate (a-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In humans, there are three forms of the IDH enzyme, IDH1, IDH2, and IDH3, but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the same reaction but in different cellular compartments: IDH1 is found in the cytoplasm of the cell and IDH2 in the mitochondria. Tumor cells are generally observed to carry either an IDH1 or IDH2 mutation, but not both.

Using our proprietary metabolic platform, we and our collaborators examined the mutated pathway and discovered that the mutated IDH enzymes had adopted a novel gain of function activity that allows only the mutated IDH enzyme to produce large amounts of a metabolite called 2-hydroxygluturate, or 2HG. We believe that the excessive levels of the metabolite 2HG produced by the tumor fuel cancer growth and survival via multiple cellular changes that lead to a block in cell maturation, or differentiation. We believe that inhibition of these mutated proteins will lead to clinical benefit for the subset of cancer patients whose tumors carry these mutations. We have identified selective development candidates that target and inhibit the mutated forms of IDH1 and IDH2. To date, our early clinical data of AG-221 and AG-120, our lead inhibitors of mutant IDH2 and IDH1, respectively, demonstrate a mechanism of response that is consistent with preclinical studies, including substantial reduction of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat acute myeloid leukemia, or AML.

To date, IDH1 and IDH2 mutations have been found to be prevalent in a broad range of advanced hematologic and solid tumors. The following tables summarize our current initial estimates on the occurrence of IDH2 and IDH1 mutations in hematologic and solid tumors. We believe our estimates may expand as more cancer treatment centers screen for these IDH mutations.

Mutation	Indications	% with IDH mutations
IDH1	Low grade glioma & 2^{ary} Glioblastomas (GBM)	68-74
	Chondrosarcoma	40-52
	Acute Myeloid Leukemia (AML)	6-10
	Myelodysplastic Syndromes (MDS) / Myeloproliferative neoplasms (MPN)	3
	Intrahepatic Cholangiocarcinoma	11-24
	Ollier/Maffucci	80
	Others* (colon, melanoma, lung, prostate)	1-3
IDH2	Acute Myeloid Leukemia (AML)	9-13
	MDS/MPN	3-6
	Angio-immunoblastic non-Hodgkin lymphoma (NHL)	30
	Intrahepatic Cholangiocarcinoma	2-6
	Giant Cell Tumor of the Bone	80
	D-2-hydroxyglutarate (D2HG) Aciduria	50
	Others* (melanoma, glioma)	3-5

Based on literature analysis; estimates will continue to evolve with additional future data.

* Includes basket of emerging unconfirmed indications

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AG-221: lead IDH2 program

AG-221 is an orally available, selective, potent inhibitor of the mutated IDH2 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH2 mutations, including those with acute myeloid leukemia, or AML, who have a historically poor prognosis. In June 2014, the U.S. Food and Drug Administration (FDA) granted us orphan drug designation for AG-221 for treatment of patients with AML. In August 2014, we announced that the FDA granted fast track designation to AG-221 for treatment of patients with AML that harbor an IDH2 mutation. We have been evaluating AG-221 in several clinical trials evaluating both hematological and solid tumor cancers with IDH2 mutations. To date, all clinical data reported by us in hematological cancers highlights that the mechanism of response is consistent with preclinical studies, including substantial reduction of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML.

In September 2013, we initiated our first phase 1 multicenter, open-label, dose-escalation clinical trial to assess the safety, clinical activity, and tolerability of AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation. In June 2014, Celgene exercised its option to an exclusive global license for development and commercialization of AG-221 under a collaboration agreement between us and Celgene, which focuses on cancer metabolism, or the 2010 Agreement. Under the 2010 Agreement, Celgene is responsible for all development costs for AG-221. We are eligible to receive up to $120.0 million in milestone payments and a tiered royalty on any net sales of products containing AG-221. In January 2016, in conjunction with the initiation of AG-221 phase 3 trials we received a milestone payment of $25.0 million. We also have the right to conduct a portion of any commercialization activities for AG-221 in the United States. In addition to contributing our scientific and translational expertise, we will continue to conduct some clinical development and regulatory activities within the AG-221 development program in collaboration with Celgene.

In October 2014, we initiated four expansion cohorts in our ongoing phase 1 clinical trial of AG-221 in patients with IDH2 mutant-positive hematologic malignancies to assess the safety and tolerability of AG-221 at 100 mg once daily oral dose in approximately 100 patients with IDH2 mutant-positive hematologic malignancies, including AML. In the expansion cohorts, we evaluated relapsed or refractory AML patients 60 years of age and older, relapsed or refractory AML patients under age 60, untreated AML patients who decline standard of care chemotherapy and patients with other IDH2 mutant-positive advanced hematologic malignancies.

In May 2015, we announced that our ongoing phase 1 clinical trial of AG-221 had been expanded to add an additional more homogenous cohort of 125 patients with IDH2 mutant-positive AML who are in second or later relapse, are refractory to second-line induction or reinduction treatment, or have relapsed after allogeneic transplantation. Consistent with the previous expansion cohorts, AG-221 is administered at a dose of 100 mg once daily. The primary objectives of the trial are to confirm the safety and clinical activity of AG-221 in a select, highly resistant AML population.

In October 2015, Celgene, in collaboration with us, initiated IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial designed to compare the efficacy and safety of AG-221 versus conventional care regimens in patients 60 years or older with IDH2 mutant-positive AML that is refractory to or relapsed after second- or third-line therapy.

In December 2015, we reported additional clinical data, as of September 1, 2015, from the dose escalation phase and expansion cohorts of the ongoing phase 1 clinical trial, which was transitioned to a phase 1/2 trial in May 2015, evaluating single agent AG-221, which included 209 response-evaluable enrolled patients with IDH2 mutant-positive

AML. The new data were presented at the 2015 American Society of Hematology (ASH) Annual Meeting and Exposition in Orlando, Florida and showed investigator-assessed objective responses in 79 out of 209 response-evaluable patients. Of the 79 patients who achieved an objective response, there were 37 complete remissions (CR), three complete remissions with incomplete platelet recovery (CRp), 14 marrow complete remissions (mCR), three complete remissions with incomplete hematologic recovery (CRi) and 22 partial

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remissions (PR). A CR is determined by using well-established criteria, which requires no evidence of leukemia in the bone marrow and blood accompanied by full restoration of all blood counts to normal ranges. A CRp means all the criteria for CR are met except that platelet counts are outside of the normal range. Platelets are one of the three major types of blood cells. A mCR means that there is no evidence for leukemia in the marrow but the blood counts have not fully restored. A CRi means there is no evidence for leukemia in the marrow but the neutrophils, a subset of white blood cells responsible for fighting bacterial infections, are outside the normal range. A partial response means all the criteria for CR are met except that the immature defective blood cells, or leukemia, in the bone marrow are in the 5% to 25% range and have been decreased by at least 50% over pretreatment. Of the 159 patients with relapsed or refractory AML, 59 achieved an objective response, including 29 CRs, one CRp, nine mCRs, three CRis and 17 PRs. Of the 24 patients with AML who declined standard of care chemotherapy, 10 achieved an objective response, including four CRs, one CRp, one mCR and four PRs. Of the 14 patients with MDS, seven achieved an objective response, including three CRs, one CRp and three mCRs. Responding relapsed or refractory AML patients were on the trial for up to 18 months with a median duration of treatment of 6.8 months, ranging from 1.8 to 18 months. Responses were durable, with median response duration of 6.9 months in patients with relapsed or refractory AML. A safety analysis was conducted for all 231 treated patients. The majority of adverse events reported by investigators were mild to moderate, with the most common being nausea, diarrhea, fatigue and febrile neutropenia. The serious adverse events, or SAEs, observed during the trial were mainly disease related. Twenty-three percent of patients had treatment-related SAEs, including notably differentiation syndrome (4 percent), leukocytosis (4 percent) and nausea (2 percent). Drug-related Grade 5 SAEs included atrial flutter (one patient), cardiac tamponade (one patient), pericardial effusion (one patient) and respiratory failure (one patient). Dose escalation has been completed and a maximum tolerated dose, or MTD, has not been reached. The first four expansion cohorts have completed enrollment. AG-221 continued to show favorable drug exposure and pharmacokinetics at all doses tested with substantial reductions in plasma levels of 2HG, which is produced by the mutated IDH2 and IDH1 proteins, to the level observed in healthy volunteers. In 2016, Celgene, in collaboration with us, intends to initiate an expansion arm of our phase 1/2 clinical trial, evaluating AG-221 in high-risk MDS patients.

Also in December 2015, we announced the initiation of a phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of AG-221 or AG-120 in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH2 or IDH2 mutation who are eligible for intensive chemotherapy. The trial will evaluate continuous dosing for up to one year with AG-221 administered at an initial oral dose of 100 mg once daily in patients with an IDH2 mutation or AG-120 administered at an initial oral dose of 500 mg once daily in patients with an IDH1 mutation. AG-221 or AG-120 will be administered with two types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and two types of AML consolidation therapies (mitoxantrone with etoposide [ME] or cytarabine).

In the first quarter of 2016, Celgene, in collaboration with us, intends to initiate a phase 1/2 frontline combination clinical trial, to be conducted by Celgene, of either AG-221 or AG-120 in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy, with a phase 1 component to determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate.

In October 2014, we announced the initiation of a phase 1/2 multicenter clinical trial of AG-221 in patients with advanced solid tumors, including gliomas, as well as angioimmunoblastic T-cell lymphoma, including AITL, in each case that carry an IDH2 mutation. This phase 1/2 multicenter, open-label, dose-escalation clinical trial of AG-221, conducted in collaboration with Celgene, is designed to assess the safety, clinical activity, and tolerability of AG-221 among patients who have an IDH2 mutant-positive advanced solid tumor or AITL. The phase 1/2 clinical trial includes a dose expansion phase where three cohorts of patients with glioma, AITL and other solid tumors that are IDH2 mutant-positive are receiving AG-221 to further evaluate safety, tolerability and clinical activity in advanced

solid tumors.

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AG-120: lead IDH1 program

AG-120 is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH1 mutations. Mutations in IDH1 have been identified in difficult to treat hematologic and solid tumor cancers, including AML, chondrosarcoma and cholangiocarcinoma where both the treatment options and prognosis for patients are poor. In March 2014, we initiated two phase 1, multicenter, open-label, dose-escalation and expansion clinical trials for AG-120, one designed to assess the safety, clinical activity and tolerability of AG-120 in patients with advanced hematologic malignancies and the second designed to evaluate the safety, clinical activity and tolerability of AG-120 in patients with advanced solid tumors, each as a single agent. Both trials are only enrolling patients that carry an IDH1 mutation. On May 18, 2015, we announced that the FDA granted fast track designation to AG-120 for treatment of patients with AML that harbor an IDH1 mutation. On June 10, 2015, the FDA granted us orphan drug designation for AG-120 for treatment of patients with AML.

Four expansion cohorts have been added to the ongoing phase 1 clinical trial of AG-120 in patients with advanced hematologic malignancies. These four expansion cohorts will evaluate AG-120 in 200 patients with IDH1 mutant-positive advanced hematologic malignancies. The first cohort will evaluate a more homogenous population of 125 AML patients who are in second or later relapse, are refractory to second-line induction or reinduction treatment, or have relapsed after allogeneic transplantation. The second cohort will evaluate 25 untreated AML patients. The third cohort will evaluate 25 patients with other non-AML IDH1 mutant-positive relapsed or refractory advanced hematologic malignancies. The fourth cohort will evaluate patients with relapsed IDH1 mutant-positive AML not eligible for the first arm or standard of care chemotherapy. AG-120 is administered at a 500 mg once daily oral dose, in 28-day cycles. The trial s primary objectives are to confirm the safety and clinical activity of AG-120.

In November 2015, we reported clinical data from the dose-escalation portion of our ongoing phase 1 clinical trial evaluating AG-120 in patients with IDH1 mutant-positive advanced solid tumors, including glioma, intrahepatic cholangiocarcinoma, or IHCC, and chondrosarcomas who received AG-210 administered from 200 mg to 1200 mg total daily doses. The data were presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston. As of the September 3, 2015 data cut-off, 62 patients had been treated with single agent AG-120, of which 55 were response-evaluable. Seven of the 11 response-evaluable patients with IDH1 mutant-positive chondrosarcoma had stable disease, with five of these patients maintaining stable disease for six months or more. One of the 20 patients with IDH1 mutant-positive IHCC had a partial response and 11 patients had stable disease, with six such patients maintaining stable disease for six months or more. Ten of the 20 patients with IDH1 mutant-positive glioma had stable disease, with four of these patients maintaining stable disease for six months or more. One of the four patients with other IDH1 mutant-positive solid tumors had stable disease. Treatment with AG-120 showed substantial reduction of 2HG in plasma and tumor tissue, and imaging results suggest that AG-120 can lower 2HG levels in the brain. AG-120 was well tolerated, with the majority of adverse events reported by investigators being mild to moderate. The most common investigator-reported adverse events were nausea, diarrhea, vomiting, anemia and QT prolongation. The majority of reported SAEs were disease related. A MTD has not been reached. We are currently enrolling four expansion cohorts of 25 patients each in (i) low grade glioma with at least six months of prior scans to assess volumetric changes, (ii) second-line cholangiocarcinoma, (iii) high grade, or metastatic, chondrosarcoma, and (iv) other solid tumors with an IDH1 mutation, who will receive the recommended dose of 500 mg of AG-120 once daily.

In December 2015, we reported new data, as of October 1, 2015, from the ongoing phase 1 clinical trial evaluating single agent AG-120, which included 87 enrolled patients with IDH1 mutant-positive advanced hematologic malignancies, of which 78 were from the dose-escalation phase and nine were from the expansion phase. The data were presented at the 2015 ASH Annual Meeting and Exposition in Orlando, Florida and showed

investigator-assessed objective responses in 27 out of 78 response-evaluable patients on AG-120. Of the 27 patients who achieved an objective response, there were 12 CRs, seven CRps, six mCRs, one CRi and one PR.

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Patients were on the trial treatment for up to 14.1 months, with a median duration of treatment of 2.9 months, ranging from 0.1 to 14.1 months. Data continued to show durable clinical activity for AG-120, with responses maintained for up to 12.5 months and a median duration of response of 5.6 months. AG-120 continued to show favorable drug exposure and pharmacokinetics at all doses tested and also substantially reduced plasma levels of 2HG to the level observed in healthy volunteers. The mechanism of response is consistent with differentiation, as evidenced by the maturation of the leukemic cells into infection fighting white blood cells, or neutrophils. The majority of adverse events reported by investigators were mild to moderate, with the most common being fatigue, diarrhea, pyrexia and nausea. A MTD has not been reached, and dose escalation is now complete.

As described above, in December 2015, we announced the initiation of a phase 1b, multicenter, international, open-label clinical trial of AG-221 or AG-120 in combination with induction and consolidation therapy in patients with newly diagnosed AML with an isocitrate dehydrogenase (IDH) mutation who are eligible for intensive chemotherapy.

Together with Celgene, we intend to initiate a global registration-enabling phase 3 clinical trial in frontline AML patients who harbor an IDH1 mutation in the second half of 2016. In addition, we intend to (i) initiate a randomized phase 2 clinical trial of AG-120 in patients with IDH1 mutant-positive cholangiocarcinoma in the second half of 2016 and (ii) as described above, initiate a phase 1/2 frontline combination clinical trial, to be conducted by Celgene, of either AG-221 or AG-120 in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy in the first quarter of 2016, with a phase 1 component to determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate.

Celgene exercised its exclusive option to license development and commercialization rights to AG-120 outside the United States in January 2015. We had previously elected to exercise our option to retain development and commercialization rights to AG-120 in the United States in January 2014. Upon Celgene s exercise of its exclusive option under the terms of our 2010 Agreement, Celgene leads development and commercialization outside the United States, and we lead development and commercialization in the United States. Celgene is responsible for future development and commercialization costs specific to countries outside the United States, we are responsible for future development and commercialization costs specific to the United States, and we and Celgene will equally fund the future global development costs of AG-120 that are not specific to any particular region or country. Celgene is eligible to receive tiered royalties on any net sales in the United States. We are eligible to receive tiered royalties on any net sales outside the United States and up to $120.0 million in payments on achievement of certain milestones. We also are eligible to receive an additional one-time payment of $25.0 million upon the dosing of the last patient in an Agios-sponsored phase 2 clinical trial for AG-120.

AG-881: lead pan-IDH program

AG-881 is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor, which provides added flexibility to our current portfolio of IDH mutant inhibitors. AG-881 successfully completed IND-enabling studies in April 2015. We and Celgene are jointly collaborating on a worldwide development program, wherein we share worldwide development costs and profits and Celgene would book any worldwide commercial sales. We will lead commercialization in the United States with both companies sharing equally in field-based commercial activities, and Celgene will lead commercialization outside of the United States with us providing one third of field-based commercial activities in the major EU markets. In June 2015, we initiated a phase 1 clinical trial for AG-881 in patients with advanced solid tumors. This phase 1 multi-center, open-label clinical trial is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-881 in advanced solid tumors, including gliomas. AG-881 will be administered continuously as a single agent dosed orally in a 28-day cycle. The first portion of the

trial includes a dose-escalation phase in which cohorts of patients will receive ascending oral doses of AG-881 to determine the maximum tolerated dose and/or the recommended phase 2 dose based on safety and tolerability. The second portion of the trial is a dose expansion phase where patients will receive AG-881 to further evaluate the safety, tolerability and clinical activity of the recommended phase 2 dose.

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In August 2015, we initiated a second dose escalation and expansion phase 1 clinical trial for AG-881 in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies whose cancer has progressed on a prior IDH inhibitor therapy. This phase 1 multi-center, open-label clinical trial is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-881 in advanced hematological malignancies. AG-881 will be administered continuously as a single agent dosed orally in a 28-day cycle. The first portion of the trial includes a dose-escalation phase in which cohorts of patients will receive ascending oral doses of AG-881 to determine the maximum tolerated dose and/or the recommended phase 2 dose based on safety and tolerability. The second portion of the trial is a dose expansion phase where patients will receive AG-881 to further evaluate the safety, tolerability and clinical activity of the recommended phase 2 dose.

Pyruvate Kinase Deficiency Program

Pyruvate kinase, or PK, is the enzyme involved in the second to last reaction in glycolysis the conversion of glucose into lactic acid. This enzyme is critical for the survival of the cell and has several tissue-specific isoforms (PKR, PKL, PKM1 and PKM2). PKR is the isoform of pyruvate kinase that is present in red blood cells. Mutations in PKR cause defects in red cell glycolysis and lead to a hematological RGD known as pyruvate kinase deficiency, or PK deficiency. Glycolysis is the only pathway available for red blood cells to maintain the production of ATP, or Adenosine-5 -triphosphate, which transports chemical energy within cells for metabolism. Accordingly, total absence of the PKR gene is not compatible with life. PK deficiency leads to a shortened life span for red blood cells and is the most common form of non-spherocytic hemolytic anemia in humans. The disease is autosomal recessive, meaning children inherit one mutated form of PKR from one parent and the second mutated form from the other parent. Children with the disease produce PKR enzyme that has only a fraction of the normal level of activity (generally <50%). Parents of affected children have only one copy of the mutated PKR enzyme and are clinically normal.

PK deficiency is a rare genetic disorder and disease understanding is still evolving. Several published epidemiology studies estimated prevalence of PK deficiency between three to nine affected patients per million. We estimate that there are approximately 2,400 diagnosed patients in the United States and EU5 countries (United Kingdom, France, Germany, Italy, Spain), and we believe that the disease is likely under-diagnosed. There is no unique ethnic or geographic representation of the disease. The disease manifests by mild to severe forms of anemia caused by the excessive premature destruction of red blood cells. The precise mechanism for the destruction is not well understood but is thought to result from membrane instability secondary to the metabolic defect caused by the low level of PKR enzyme. The hemolysis is extra-vascular in that the red blood cells are destroyed in small capillaries or organs and not spontaneously breaking open in the circulation.

AG-348: lead pyruvate kinase (PK) deficiency program

AG-348 is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzyme, which has resulted in restoration of ATP levels and a decrease in 2,3-DPG levels in blood sampled from patients with PK deficiency in nonclinical studies. The wild-type PKR activity of AG-348 allowed the study of enzyme activation in healthy volunteers, providing an opportunity to understand the safety, dosing and pharmacodynamic activity of AG-348 prior to entering a proof-of-concept study in patients. On March 24, 2015, the FDA granted us orphan drug designation for AG-348 for treatment of patients with PK deficiency.

In April 2014, we initiated a single ascending dose, or SAD, escalation phase 1 clinical trial for AG-348 in healthy volunteers and in June 2014, we initiated a multiple ascending dose, or MAD, escalation phase 1 clinical trial for healthy volunteers. In late 2014, we reported the SAD trial was completed and met its primary endpoint. The MAD trial completed dosing in early 2015 and has also met its primary endpoint. The primary endpoint is defined in the protocol to identify a safe and pharmacodynamically active dose and dosing schedule for AG-348 to be used in

subsequent clinical studies in patients with pyruvate kinase deficiency.

In December 2014, during a poster session at ASH 2014, we reported the first clinical data from the phase 1 SAD and MAD clinical trials of AG-348 in healthy volunteers. These results provided early proof-of-mechanism for

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AG-348 as a novel, first-in-class, oral activator of both wild-type and mutated PKR enzymes. In these phase 1 clinical trials, dosing of AG-348 over 14-days in healthy volunteers resulted in a dose-dependent activation of the PKR pathway as evidenced by a substantial increase in ATP and decrease in 2,3-DPG levels, which are key biomarkers of PKR activity and primary indicators of PK deficiency. These data support the hypothesis that AG-348 treatment may similarly enhance PKR activity in patients with PK deficiency and thus correct the underlying defect of the disease. Results presented were from 64 healthy volunteers who received either AG-348 or placebo, which included 48 people from the completed SAD trial and 16 people in the first two cohorts of the MAD trial, which recently completed dosing. Complete safety results were reported from the SAD phase 1 clinical trial and showed that AG-348 was well tolerated. Although the MAD trial remained blinded, no serious adverse events had been reported in the first two analyzed cohorts. AG-348 also showed a favorable pharmacokinetic profile with rapid absorption, low variability and dose-proportional increase in exposure following both single and multiple doses. The observed dose-dependent changes in 2,3-DPG and ATP blood levels seen are consistent with a substantial increase in PKR enzymatic activity.

On June 12, 2015, we reported final clinical data from the phase 1 MAD clinical trial of AG-348 in healthy volunteers and the first data from a natural history study of PK deficiency. The data were presented at the 20th Congress of the European Hematology Association (EHA) in Vienna, Austria. Results presented were from 48 healthy volunteers who received either AG-348 or placebo for fourteen days at 15 mg, 60 mg, 120 mg, 360 mg or 700 mg twice daily or 120 mg once daily in six sequential cohorts. The study showed that AG-348 was well tolerated, with most adverse events occurring in the highest dose group (700 mg), with all but one being mild to moderate. Thirty-two of 36 healthy volunteers receiving AG-348 completed the study. Two volunteers receiving AG-348 withdrew due to adverse events, including drug eruption (60 mg) and Grade 3 liver function test abnormalities (700 mg), which resolved after treatment discontinuation. Two additional AG-348 volunteers (both 700 mg) withdrew consent due to nausea or vomiting. Serum hormone changes consistent with reversible aromatase inhibition were observed. AG-348 also showed a favorable pharmacokinetic profile with rapid absorption, low to moderate variability and a dose-proportional increase in exposure following multiple doses.

As predicted by the mechanism of action of AG-348, there was a robust activation of pyruvate kinase as evidenced by a decrease in 2,3-DPG (2,3-diphosphoglycerate) and increase in ATP (adenosine triphosphate) in blood of healthy volunteers. The decrease in 2,3-DPG was approximately 50 percent for doses 120 mg and higher with levels returning back to baseline approximately 72 hours after AG-348 was discontinued. There was also an approximately 50 percent increase in ATP in blood with AG-348 at doses 60 mg and higher in healthy volunteers.

In June 2015, we initiated DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial of AG-348 in adult, transfusion-independent patients with PK deficiency. The multi-center, randomized trial will include two arms with 25 patients each. The patients in the first arm will receive 50 mg twice daily, and the patients in the second arm will receive 300 mg twice daily. The trial will include a six-month dosing period with the opportunity for continued treatment beyond six months based on safety and clinical activity. In July 2015, we dosed the first-patient in this phase 2 clinical trial, and we expect to present the first data from the trial in the first half of 2016.

We have worldwide development and commercial rights to AG-348 and expect to fund the future development and commercialization costs related to this program.

AG-519: a second novel PKR activator

AG-519 is an orally available small molecule and our second product candidate that is a potent activator of the PKR enzyme. We initiated a placebo-controlled phase 1 clinical trial of AG-519 in healthy volunteers in the first quarter of 2016. This trial will be an integrated single ascending dose and multiple ascending dose trial. We expect to present data from this trial in the first half of 2016. We have worldwide development and commercial rights to AG-519 and

expect to fund the future development and commercialization costs related to this program.

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Collaboration with Celgene

2010 Agreement and amendments

In April 2010, we entered into the 2010 Agreement with Celgene, a related party through ownership of the Company s common stock. The agreement was amended in October 2011 and July 2014, as described below. The goal of the collaboration is to discover, develop and commercialize disease-altering therapies in oncology based on the Company s cancer metabolism research platform. We will initially lead discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration.

The discovery phase of the 2010 Agreement was scheduled to expire in April 2014, subject to Celgene s option to extend the discovery phase for up to an additional two years with additional funding made to us. In December 2013, Celgene elected to extend the term of the initial discovery phase from four years to five years, to April 2015, in exchange for the payment of a $20.0 million extension fee which we received in May 2014. In December 2014, Celgene elected to exercise its final option to extend the term of the initial discovery phase one additional year, to April 2016, in exchange for the payment of a $20.0 million extension fee which was received in May 2015.

Pursuant to the 2010 Agreement, we are responsible for nominating development candidates, of which two required confirmation by the Joint Research Committee, or JRC, during the discovery phase. During the year ended December 31, 2012 we nominated our first development candidate (AG-221) and during the year ended December 31, 2013 we nominated our second development candidate (AG-120), both of which have been confirmed by the JRC pursuant to the 2010 Agreement. For each development candidate, Celgene elected to progress such development candidate into preclinical development requiring us to conduct studies to meet the requirements for filing an Investigational New Drug application, or IND, or IND-enabling studies. Subsequently, we were required to file an IND for each of the two development candidates and, upon the FDA s acceptance of the INDs, Celgene requested that we conduct an initial phase 1 clinical trial.

Discovery programs with development candidates. Celgene may elect to progress into preclinical development each discovery program for which we nominate and the JRC confirms a development candidate during the discovery phase. If Celgene makes such an election, we will, at our expense, conduct studies required to meet the requirements for filing an IND, or IND-enabling studies, and, following their successful completion as confirmed by the JRC, we will file an IND to commence clinical studies of such development candidate. If the FDA accepts the IND, Celgene may request that we conduct an initial phase 1 clinical trial at our expense, for which Celgene will pay us at least $5.0 million upon the earlier of the determination of the maximum tolerated dose or Celgene s election to license the program, unless such program becomes a split licensed program, as described below.

Celgene may elect to convert each discovery program for which we have nominated a development candidate into a co-commercialized licensed program, the attributes of which are described below. We have the right, exercisable during a specified period following FDA acceptance of the applicable IND, to convert one of every three co-commercialized licensed programs into a split licensed program, for which we will retain the United States rights, other attributes of which are further described below. We may elect to opt out of any split licensed program, after which such split licensed program will revert to a co-commercialized licensed program, and Celgene will have the right, but not the obligation, to commercialize medicines from such program in the United States. Our IDH2 program is a co-commercialized licensed program and not a split licensed program. In June 2014, Celgene exercised its option to an exclusive global license for the development and commercialization of our IDH2 program, AG-221. We elected to retain U.S. rights to our IDH1 program, AG-120, in January 2014. Celgene exercised its rights to this program in during the three months ended March 31, 2015. In addition, Celgene may license certain discovery programs that we do not nominate or the JRC does not confirm as a development candidate and for which Celgene will lead and fund

global development and commercialization.

We will retain our rights to the development candidates and certain other compounds from any discovery program for which we nominate and the JRC confirms a development candidate but that Celgene does not elect

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to progress into preclinical development or convert into a co-commercialized licensed program. In addition, if the JRC or Celgene elects not to continue collaboration activities with respect to a particular target, either we or Celgene would have the right to independently undertake a discovery program on such target and would have rights to specified compounds from such program, subject to certain buy-in rights granted to the other party.

Further development and commercialization of programs. The agreement provides for three types of licensed programs discussed above: co-commercialized licensed programs, split licensed programs, and buy-in programs. Celgene s and our rights and obligations under each licensed program vary depending on the type of licensed program, as described below.

Co-commercialized licensed programs: Celgene will lead and, following either IND acceptance by the FDA or, if Celgene requests us to conduct the initial phase 1 clinical trial, upon completion of such phase 1 clinical trial, will fund global development and commercialization of each co-commercialized licensed program. We have the right to participate in a portion of commercialization activities in the United States for medicines from co-commercialized programs in accordance with the applicable commercialization plan.

Split licensed programs: Celgene will lead development and commercialization outside the United States, and we will lead development and commercialization in the United States, for each split licensed program. We and Celgene will equally fund the global development costs of each split licensed program that are not specific to any particular region or country, Celgein;width:14.94%;">

		175,000	5,895,750
Schlumberger Ltd.		85,000	5,721,350
Tidewater, Inc.		176,000	5,728,800
			17,345,900

COMMON STOCKS (99.4%)	SHARES	MARKET VALUE
Oil & Gas (1.9%)		
BP p.l.c. (b)	158,775	$ 9,134,326
ConocoPhillips	104,600	8,666,110
Premcor, Inc. (a)	134,650	5,184,025
		22,984,461
FINANCIALS (21.9%)		
Capital Markets (3.6%)		
The Charles Schwab Corp.	535,265	4,919,085
The Goldman Sachs Group, Inc.	60,000	5,594,400
Merrill Lynch & Co., Inc.	269,000	13,374,680
Morgan Stanley	417,775	20,596,308
		44,484,473
Commercial Banks (2.3%)		
Bank of America Corp. (c)	373,860	16,199,354
Bank of New York Co., Inc.	266,000	7,759,220
Comerica, Inc.	66,675	3,957,161
		27,915,735
Diversified Financial Services (3.4%)		
CIT Group, Inc.	314,400	11,755,416
Citigroup, Inc.	395,250	17,438,430
J.P. Morgan Chase & Co.	302,625	12,023,291
		41,217,137
Insurance (9.3%)		
AFLAC, Inc.	191,300	7,500,873
Allstate Corp.	141,525	6,791,785
American International Group, Inc.	191,450	13,016,685
Aon Corp.	413,175	11,874,649
Genworth Financial, Inc., Class A (a)	176,650	4,115,945
Loews Corp.	226,200	13,232,700
Marsh & McLennan Companies, Inc.	136,700	6,255,392
MBIA, Inc.	109,275	6,360,898
MetLife, Inc.	330,900	12,789,285
The Progressive Corp.	232,105	19,670,899
Torchmark Corp.	97,575	5,189,039
XL Capital Ltd., Class A	95,300	7,051,247
		113,849,397

COMMON STOCKS (99.4%)	SHARES	MARKET VALUE
Real Estate (1.0%)		
CB Richard Ellis Group, Inc., Class A (a)	164,275	$ 3,794,752
Crescent Real Estate Equities Co.	136,975	2,155,987
The St. Joe Co.	99,900	4,772,223
Trizec Properties, Inc.	70,800	1,130,676
		11,853,638
Thrifts & Mortgage Finance (2.3%)		
Fannie Mae	151,350	9,595,590
Freddie Mac	205,425	13,401,927
The PMI Group, Inc.	74,350	3,017,123
Radian Group, Inc.	51,525	2,382,001
		28,396,641
HEALTH CARE (15.3%)		
Biotechnology (6.2%)		
Affymetrix, Inc. (a)	177,000	5,435,670
Amgen, Inc. (a)	268,100	15,195,908
Biogen Idec, Inc. (a)	112,000	6,851,040
Cephalon Inc. (a)	110,000	5,269,000
Genentech, Inc. (a)	410,400	21,513,168
Genzyme Corp. (a)	138,000	7,508,580
Invitrogen Corp. (a)	87,000	4,784,130
MedImmune, Inc. (a)	381,750	9,047,475
		75,604,971
Health Care Equipment & Supplies (2.8%)		
Alcon, Inc.	74,000	5,934,800
Baxter International, Inc.	355,575	11,435,292
Fisher Scientific International, Inc. (a)	120,000	6,999,600
Guidant Corp.	146,000	9,641,840
		34,011,532
Health Care Providers & Services (2.2%)		
Aetna, Inc.	24,750	2,473,267
AmerisourceBergen Corp.	68,775	3,693,905
CIGNA Corp.	105,175	7,323,335
HCA, Inc.	122,250	4,663,838
McKesson Corp.	178,525	4,579,166
Tenet Healthcare Corp. (a)	410,150	4,425,519
		27,159,030

COMMON STOCKS (99.4%)	SHARES	MARKET VALUE
Pharmaceuticals (4.1%)		
Bristol-Myers Squibb Co.	628,500	$ 14,876,595
Eli Lilly & Co.	90,740	5,448,937
Johnson & Johnson	90,000	5,069,700
Merck & Co., Inc.	169,000	5,577,000
Pfizer, Inc.	250,000	7,650,000
Teva Pharmaceutical Industries Ltd. (b)	165,000	4,281,750
Wyeth	216,000	8,078,400
		50,982,382
INDUSTRIALS (11.3%)		
Aerospace & Defense (2.4%)		
The Boeing Co.	516,625	26,668,182
Bombardier, Inc., Class B	927,850	2,141,447
		28,809,629
Air Freight & Logistics (1.0%)		
FedEx Corp.	71,000	6,083,990
Ryder System, Inc.	136,000	6,397,440
		12,481,430
Airlines (0.3%)		
Southwest Airlines Co.	310,000	4,222,200
Commercial Services & Supplies (0.9%)		
Apollo Group, Inc., Class A (a)	68,300	5,011,171
Cendant Corp.	275,825	5,957,820
		10,968,991
Electrical Equipment (1.1%)		
American Power Conversion Corp.	415,000	7,216,850
Emerson Electric Co.	92,000	5,693,880
		12,910,730
Industrial Conglomerates (2.2%)		
General Electric Co.	421,200	14,143,896
Tyco International Ltd.	412,100	12,634,986
		26,778,882
Machinery (1.5%)		
Danaher Corp.	110,000	5,640,800
Illinois Tool Works, Inc.	63,000	5,869,710
Navistar International Corp. (a)	194,625	7,238,104
		18,748,614

COMMON STOCKS (99.4%)	SHARES	MARKET VALUE
Road & Rail (1.9%)		
CSX Corp.	191,375	$ 6,353,650
Norfolk Southern Corp.	175,000	5,204,500
Swift Transportation Co., Inc. (a)	103,575	1,742,131
Union Pacific Corp.	127,600	7,477,360
Werner Enterprises, Inc.	158,050	3,051,946
		23,829,587
INFORMATION TECHNOLOGY (21.7%)		
Communications Equipment (2.5%)		
Cisco Systems, Inc. (a)	647,100	11,712,510
Nokia Oyj (b)	410,000	5,625,200
QUALCOMM, Inc.	354,400	13,835,776
		31,173,486
Computers & Peripherals (4.0%)		
Adaptec, Inc. (a)	475,000	3,610,000
Dell, Inc. (a)	268,900	9,572,840
EMC Corp. (a)	547,500	6,318,150
Hewlett-Packard Co.	606,775	11,377,031
Network Appliance, Inc. (a)	627,200	14,425,600
Sun Microsystems, Inc. (a)	931,200	3,762,048
		49,065,669
Electronic Equipment & Instruments (2.9%)		
Agilent Technologies, Inc. (a)	341,850	7,373,704
Avnet, Inc. (a)	264,975	4,536,372
Ingram Micro, Inc. (a)	87,475	1,408,347
Sanmina-SCI Corp. (a)	1,089,675	7,682,209
Symbol Technologies, Inc.	620,000	7,836,800
Vishay Intertechnology, Inc. (a)	540,825	6,976,643
		35,814,075
Internet Software & Services (1.4%)		
Yahoo! Inc. (a)	498,100	16,890,571
IT Services (0.7%)		
BearingPoint, Inc. (a)	419,780	3,752,833
Electronic Data Systems Corp.	215,375	4,176,121
		7,928,954

COMMON STOCKS (99.4%)	SHARES	MARKET VALUE
Semiconductors & Semiconductor Equipment (5.4%)		
Analog Devices, Inc.	155,000	$ 6,010,900
Applied Materials, Inc. (a)	628,990	10,372,045
Intel Corp.	586,000	11,755,160
Maxim Integrated Products, Inc.	259,900	10,991,171
Novellus Systems, Inc. (a)	457,300	12,159,607
ON Semiconductor Corp. (a)	32,150	100,630
Teradyne, Inc. (a)	88,950	1,191,930
Texas Instruments, Inc.	240,000	5,107,200
Xilinx, Inc.	297,900	8,043,300
		65,731,943
Software (4.8%)		
Adobe Systems, Inc.	135,000	6,678,450
Computer Associates International, Inc.	515,725	13,563,568
Electronic Arts, Inc. (a)	99,800	4,589,802
Microsoft Corp.	296,800	8,206,520
Oracle Corp. (a)	550,000	6,204,000
Symantec Corp. (a)	279,800	15,355,424
VERITAS Software Corp. (a)	264,000	4,699,200
		59,296,964
MATERIALS (2.6%)		
Chemicals (1.2%)		
Bayer AG (b)	102,985	2,824,879
Dow Chemical Co.	65,375	2,953,642
IMC Global, Inc. (a)	534,175	9,289,303
		15,067,824
Metals & Mining (0.7%)		
Alcan, Inc.	94,575	4,520,685
Freeport-McMoRan Copper & Gold, Inc., Class B	87,486	3,543,183
		8,063,868
Paper & Forest Products (0.7%)		
Abitibi Consolidated, Inc.	391,250	2,468,788
Domtar, Inc.	247,675	2,982,007
International Paper Co.	85,240	3,444,548
		8,895,343

COMMON STOCKS (99.4%)	SHARES	MARKET VALUE
TELECOMMUNICATION SERVICES (0.6%)		
Wireless Telecommunication Services (0.6%)		
AT&T Wireless Services, Inc. (a)	248,275	$ 3,669,505
Nextel Communications, Inc., Class A (a)	42,775	1,019,756
Telephone and Data Systems, Inc.	36,600	3,080,622
		7,769,883
UTILITIES (2.4%)		
Electric Utilities (1.2%)		
FirstEnergy Corp.	53,375	2,192,645
PG&E Corp. (a)	146,300	4,447,520
Wisconsin Energy Corp.	234,475	7,479,752
		14,119,917
Multi-Utilities & Unregulated Power (1.2%)		
NRG Energy, Inc. (a)	199,200	5,366,448
Reliant Energy, Inc. (a)	776,275	7,242,646
SCANA Corp.	67,725	2,528,852
		15,137,946
TOTAL COMMON STOCKS (COST OF $1,169,628,168)		1,218,026,208

CONVERTIBLE BONDS (0.0%)	INTEREST RATE	MATURITY DATE		PAR VALUE	
INDUSTRIALS (0.0%)					
Airlines (0.0%)					
Delta Air Lines, Inc. (Cost of $1,335,173)	8.00%	06/03/23	$	1,808,000	566,248

SHORT-TERM INVESTMENT (2.5%)		PAR VALUE		MARKET VALUE
REPURCHASE AGREEMENT (2.5%)				
Repurchase agreement with State Street Bank & Trust Co., dated 09/30/04, due 10/01/04 at 1.58%, collateralized by a U.S. Treasury Bond maturing 02/15/31, market value $30,651,748 (repurchase proceeds $30,036,318) (cost of $30,035,000)	$	30,035,000	$	30,035,000
TOTAL INVESTMENTS (101.9%) (COST OF $1,200,998,341)				1,248,627,456
OTHER ASSETS & LIABILITIES, NET (-1.9%)				(23,826,078)
NET ASSETS (100.0%)			$	1,224,801,378
NET ASSET VALUE PER SHARE (144,148,727 SHARES OUTSTANDING)			$	8.50

NOTES TO SCHEDULE OF INVESTMENTS:

(a) Non-income producing security.

(b) Represents an American Depositary Receipt.

(c) Investments in affiliates during the nine months ended September 30, 2004:

Security Name: FleetBoston Financial Corp., the parent company of the Investment Advisor prior to April 1, 2004:

Shares as of 12/31/03:		200,000
Shares purchased:		
Shares converted:		(200,000)
Shares as of 09/30/04:		
Net realized gain (loss):		
Dividend income earned:	$	50,111
Value at end of period:		

Security Name: Bank of America Corp. (As a result of the acquisition of FleetBoston Financial Corp. effective April 1, 2004, Bank of America Corp. became the parent company of the Fund Manager.)

Shares as of 12/31/03:	
Shares purchased:	161,800*
Shares sold:	70,750
Shares acquired through acquisition:	79,505
Shares acquired through two for one stock split:	203,305
Shares as of 09/30/04:	373,860

Net realized gain (loss):		355,986
Dividend income earned:	$	437,276**
Value at end of period:	$	16,199,354

*Occurred prior to April 1, 2004.

**Represents activity for the period April 1, 2004 through September 30, 2004.

Gross unrealized appreciation and depreciation of investments at September 30, 2004 is as follows:

Gross unrealized appreciation	$	168,704,509
Gross unrealized depreciation		(121,075,394)
Net unrealized appreciation	$	47,629,115

Item 2. Controls and Procedures.

(a) The registrant s principal executive officer and principal financial officer, based on their evaluation of the registrant s disclosure controls and procedures as of a date within 90 days of the filing of this report, have concluded that such controls and procedures are adequately designed to ensure that information required to be disclosed by the registrant in Form N-Q is accumulated and communicated to the registrant s management, including the principal executive officer and principal financial officer, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

(b) There were no changes in the registrant s internal control over financial reporting that occurred during the registrant s last fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant s internal control over financial reporting.

Item 3. Exhibits.

Certifications pursuant to Rule 30a-2(a) under the Investment Company Act of 1940 (17 CFR 270.30a-2(a)) attached hereto as Exhibit 99.CERT.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934 and the Investment Company Act of 1940, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

(registrant)	Liberty All-Star Equity Fund
By (Signature and Title)	/s/ William R. Parmentier, Jr. William R. Parmentier, Jr., President
Date	November 22, 2004

Pursuant to the requirements of the Securities Exchange Act of 1934 and the Investment Company Act of 1940, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

By (Signature and Title)	/s/ William R. Parmentier, Jr. William R. Parmentier, Jr., President
Date	November 22, 2004
By (Signature and Title)	/s/ J. Kevin Connaughton J. Kevin Connaughton, Treasurer
Date	November 22, 2004