Initiation
Overweight

BLUE, BLUE US
Price: $30.22

Price Target: $44.00

bluebird bio

You're My Boy BLUE…Initiating at OW

We are initiating coverage of BLUE with an Overweight rating and YE14 target of $44. Catchy titles aside, bluebird bio is anything but "Old School." Quite the contrary. In our view, BLUE – with its gene therapy platform – is one of the more potentially transformative and disruptive companies we've come across in some time. Importantly, however, this appears to be more than just a "big idea." bluebird has already established promising proof-of-concept for its two lead products and is going after orphan indications with a very high unmet medical need that could bolster the ultimate probability of success.

- **Developing one-time therapies for severe genetic and orphan diseases.** BLUE's cutting edge gene therapy platform has benefited from recent advances in the field including enhanced viral vectors and industrialized manufacturing potency as well as scale. The company's strategy is to pursue monogenic orphan diseases (where there's a single genetic defect) with a high unmet medical need, which we believe improves the probability of clinical, regulatory, and ultimately commercial success.
- **Two clinical programs with compelling proof-of-concept.** The company's most advanced asset is Lenti-D for CCALD, a rare and devastating neurological disorder in young boys. Impressively, a previous version of the product was able to arrest disease progression in 4/4 boys treated, and a pivotal Phase 2/3 trial is expected to begin in late 2013. There was also a striking response in 1 of 3 patients treated with the company's second product, LentiGlobin for beta-thalassemia, an inherited blood disorder that can lead to severe anemia. There's an ongoing Phase 1/2 for this indication (and sickle cell disease) in the EU and another poised to begin in the US.
- **Safety is a risk but one that's been successfully navigated thus far.** Importantly, there have not been adverse safety events during the now 6-year span of the CCALD and beta-thalassemia programs. We also believe the company's *ex vivo* (outside the body) approach to gene therapy provides added safety margins.
- **Upcoming news flow.** Following the recent IPO, the balance of 2013 will be about getting studies up and running. We anticipate interim data updates could begin in 2014.
- **Initiating at OW with a $44 target.** For the foreseeable future, we expect BLUE shares to trade more on the scientific, clinical, and regulatory progress of its gene therapy programs than any financial projections. Nevertheless, our PT is based on an average of three models (rNPV, SOTP, and DCF) and reflects a 50% probability of success for Lenti-D (~$250M in peak sales) and 25% for LentiGlobin (~$1B peak).

Biotechnology

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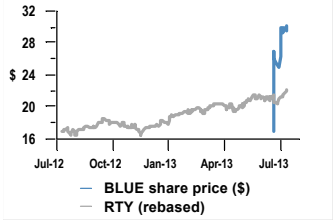
Price Performance



	YTD	1m	3m	12m
Abs	77.8%	77.8%	77.8%	77.8%
Rel	59.5%	72.5%	68.7%	47.4%

bluebird bio, Inc. (BLUE;BLUE US)

FYE Dec	2013E	2014E
EPS reported ($)		
Q1 (Mar)	-	-
Q2 (Jun)	(0.07)	-
Q3 (Sep)	(0.20)	-
Q4 (Dec)	(0.26)	-
FY	(0.82)	(1.07)

Source: Company data, Bloomberg, J.P. Morgan estimates.

Company Data	
Price ($)	30.22
Date Of Price	11 Jul 13
52-week Range ($)	31.14-17.00
Market Cap ($ mn)	689.31
Fiscal Year End	Dec
Shares O/S (mn)	23
Price Target ($)	44.00
Price Target End Date	31-Dec-14

See page 66 for analyst certification and important disclosures.

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Investment Thesis

bluebird bio (BLUE)

Overweight

The time really is now for gene therapy

We believe this is a very exciting time in the field of gene therapy. Through this still novel therapeutic approach, a functional copy of a mutated or aberrant gene is delivered to a patient in an attempt to correct an underlying genetic defect. Gene therapy has seen its fair share of setbacks over the years (including treatment-related cases of leukemia and even the death of a US teenager in 1999), but recently there has been a meaningful amount of progress on the technological (viral vectors, manufacturing), clinical (proof of concept data), and regulatory fronts. Indeed, we just witnessed the first approval of a gene therapy in the Western world (UniQure's Glybera was approved in Europe last November). With this progress has come renewed interest, and, in our opinion, bluebird is on the cutting edge of this exciting, if not entirely new, therapeutic modality.

bluebird's gene therapy platform may enable development of transformative, one-time therapies for severe genetic and orphan diseases

We are impressed by multiple facets of bluebird's platform, including its lentiviral vectors (evidence of sustained expression, a large carrying capacity, and encouraging safety to date), *ex vivo* transduction (further reduces the risk of adverse events by getting the product directly to the target cells outside of the body), and industrialized manufacturing potency and scale. Beyond the platform, we believe the initial proof-of-concept demonstrated by the company's two wholly-owned clinical assets (Lenti-D in CCALD, and LentiGlobin in beta-thalassemia) as well as the recent partnership with Celgene (rated OW by JPM Biotech analyst Geoff Meacham) provide strong support for its approach. bluebird's intent is to create one-time treatments with curative potential, which introduces a fundamentally new and transformative value proposition. In our view, the company's platform has the potential to generate a portfolio of promising products, and by pursuing monogenic diseases (where there's a single defective gene) within orphan indications, we see a relatively higher probability of ultimate success.

Two lead programs are advancing in the clinic…

A pivotal Phase 2/3 study (ALD-102) is set to begin in late 2013 for bluebird's lead asset, Lenti-D. This product is in development for childhood cerebral adrenoleukodystrophy (CCALD), a rare and devastating inherited disorder in young boys that's associated with rapid neurological deterioration (leading to a vegetative state and ultimately death) due to the breakdown of the protective myelin sheath in the brain. Lenti-D delivers a functional ABCD1 gene to these patients in an attempt to arrest disease progression. bluebird's next most advanced asset, LentiGlobin, is in development for both beta-thalassemia and sickle cell disease (as each is driven by a dysfunctional beta-globin gene). BLUE has an ongoing Phase 1/2 trial in France (HGB-205) and is poised to launch another in the US in mid-2013 (HGB-204).

…and both programs have demonstrated some compelling proof-of-concept

The proof-of-concept demonstrated to date for both Lenti-D and LentiGlobin are key tenets to our bullish investment thesis for BLUE, and the upcoming studies for both programs use new and improved vectors. For CCALD, results from a Phase 1/2 French trial using a product similar to Lenti-D show prolonged disease stabilization in all 4 patients treated (longest patient now out almost 7 years post transplant).

These efficacy results appear at least comparable to outcomes that would be anticipated following a successful allogeneic stem cell transplant (available to <30% of patients). Importantly, there have been no incidents of gene therapy-related adverse events so far in this study. The early results are admittedly not quite as compelling for beta-thalassemia, as just 1 of 3 patients responded to therapy. However, that patient had a remarkable response; he had been transfusion dependent since age 2, was transplanted with a LentiGlobin-like product at age 18, became transfusion independent 1 year later and remains as such 5 years later. This is not something that would likely spontaneously occur in a beta-thalassemia patient.

The opportunities don't end with CCALD and beta-thalassemia

In our view, the potential of bluebird's platform extends well beyond CCALD and beta-thalassemia and offers the possibility of long-tailed value creation. The company's strategy is to pursue indications with a high unmet medical need and a high probability of clinical, regulatory, and commercial success. So while we expect investors to focus near term on the CCALD and beta-thalassemia programs, there are a number of other monogenic diseases the company could ultimately target. We already know about LentiGlobin for sickle cell disease (SCD; being evaluated in the EU and an IND planned for 2014 in the US). In addition, bluebird just announced a three-year global strategic collaboration with Celgene to discover, develop, and commercialize novel, disease-altering gene therapies for oncology. A sample of other monogenic diseases include hemophilia A, cystic fibrosis, Tay sachs disease, Fragile X syndrome, and Huntington's disease (although bluebird has not specifically commented on any that may be amenable to its technology beyond SCD/oncology).

KOL feedback is supportive of bluebird's platform, products, and clinical data

We spoke with a half dozen key opinion leaders in the fields of gene therapy, ALD, and beta-thalassemia. Overall, these conversations reinforced our outlook for gene therapy in general and bluebird bio in particular. These physicians spoke to the substantial evolution in the field, especially around vectors (bluebird's lentiviral vector deemed superior than older retroviruses), safety margins, and regulatory interactions. There was a lot of enthusiasm for the company's approach and early proof-of-concept data with comments along the lines of "these types of results don't just happen" in these types of patients. In addition, the KOLs emphasized the unmet medical need of bluebird's initial target indications.

Balance sheet check: bluebird is relatively well positioned

As of the end of 1Q13, bluebird had a cash balance of ~$132M. Given this stable cash position, combined with net proceeds from the IPO offering of ~$108M (J.P. Morgan acted as joint book runner), bluebird should have sufficient capital to fund operations for at least several years.

We are initiating coverage of BLUE with an OW rating and YE14 target of $44

We are drawn to the transformative and disruptive potential of BLUE's technology but also reassured by the company's focus on orphan diseases of high unmet medical need, compelling proof-of-concept, and well articulated strategy. A strong management team and the recent Celgene collaboration further bolster the story, in our view. Our target is based on a blended average of our risk-adjusted NPV model, our proprietary scenario analysis, and a DCF model. We assume a 50% probability of success for Lenti-D for CCALD (with ~$250M in base peak sales potential), and 25% for LentiGlobin for beta-thalassemia (~$1B peak sales potential).

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Risks to Rating and Price Target

bluebird is susceptible to the standard risks that apply to the entire biotech industry, including development, regulatory, commercial, manufacturing, financing, and IP pitfalls. Risks more specific to bluebird are outlined below:

Clinical risk

A key risk is the emergence of serious adverse events (i.e., cases of leukemia) in upcoming trials with bluebird's products. If bluebird's vectors were to be associated with serious adverse events, the company may be required to halt or delay further clinical development of its product candidates. Another clinical risk is if results show a lack of efficacy in the ongoing trials. Further optimization of bluebird's vectors is also a risk for the upcoming studies, given that the new vectors have not been tested in patients to date. For instance, the ALD-102 study will be the first trial to use bluebird's current Lenti-D viral vector and product candidate, and both the HGB-205 and HGB-204 trials will use a new vector, not the one tested in the LG001 study. While designed to be better, there are no assurances that they will perform as such in these upcoming trials.

Regulatory risk

While we are seeing some regulatory maturity in the field of gene therapy, it remains a relatively new and novel therapeutic approach that is likely to encounter significant agency scrutiny. Only one gene therapy product has been approved in the Western world to date (UniQure's Glybera in Europe in November 2012), highlighting the relative immaturity of the field. There is risk that regulatory agencies do not view the ALD-102 study as being sufficient to act as a pivotal trial to gain approval for Lenti-D and that regulatory agencies may want to see additional, long-term data given past failures and safety issues (i.e., insertional oncogenesis leading to leukemia) with different gene therapies. Even if approved, it is possible that regulatory agencies could remove a gene therapy from the market if it shows severe adverse events in the real-world setting.

Commercial risk

If approved, the rate of uptake and/or pricing could limit sales of bluebird's products. bluebird does not currently have a therapy on the market, and it's possible that future uptake by physicians may be slower than expected. The insurance coverage and reimbursement status of newly approved products is uncertain, and there is difficulty in knowing how to price a potentially one-time curative therapy. Market uptake/ adoption will also be influenced by whether the gene therapies are deemed to be a better option vs. an allogeneic transplant. In addition, there is also risk around bluebird's ability to deliver gene therapies on a commercially viable scale.

Competitive risk

A number of other companies and academic institutions are also working on gene therapies. While none are currently targeting the same indications, it's possible that other approaches could ultimately prove superior to bluebird's. Regarding the current treatments for CCALD and beta-thalassemia, ongoing attempts to reduce the risk of GvHD with allogeneic HSCT also represent competing technologies, and various academic centers around the world are seeking to develop improvements to allogeneic HSCT.

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Company Description

bluebird bio is a clinical-stage biotech company focused on developing innovative next generation products based on the transformative potential of gene therapy for severe genetic and orphan diseases. bluebird bio has two clinical stage products in development for childhood cerebral adrenoleukodystrophy (CCALD) and beta-thalassemia/sickle cell disease in addition to a preclinical oncology program focusing on chimeric antigen receptor (CAR) T cells in partnership with Celgene and Baylor. bluebird was founded in 1992 (under the name Genetix Pharmaceuticals) and has operations located in Cambridge (MA), San Francisco (CA), and Paris (France). The company has ~50 employees.

Upcoming Events

While 2013 should be more about trial initiations and getting sites up and running, we could get an early read of some Phase 1/2 data for LentiGlobin in beta-thalassemia in 2014. Over the next couple of years, we expect investors to primarily focus on the progress of bluebird's two lead clinical programs – Lenti-D in CCALD (pivotal Phase 2/3 ALD-102 Study is expected to begin in late 2013) and LentiGlobin in beta-thalassemia and sickle cell disease (US Phase 1/2 HGB-204 Study is expected to begin in mid-2013, while the French Phase 1/2 HGB-205 Study is already underway). Importantly, we assume there could be interim reports from the 204/205 studies by 2H14. bluebird also expects to file an IND in the US for sickle cell disease in 2014. Lastly, there could also be various clinical data publications over the next 12-18 months that focus additional attention on bluebird's products and technology.

Figure 1: BLUE Upcoming Events

Program	Event	Expected Timing	Significance
Lenti-D	Initiate Ph 2/3 study (ALD-102) in CCALD in the US/EU	Late-2013	Medium
LentiGlobin	Initiate Phase 1/2 studiy (HGB-205) in beta-thalassemia in the US	Mid-2013	Medium
	File IND for SCD	2014	Medium
	Preliminary Phase 1/2 data for beta-thalassemia	2H14	High
CAR T-cells	Initiate Ph1 trial	2016	Low-Medium

Source: Company reports

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Pipeline

Figure 2: BLUE's Pipeline

Program	P/C	Ph1	Ph2	Ph3	FDA	Mkt.	Partner	Comments
Lenti-D								Grated Orphan Drug designation by FDA and EMA in 2012
Childhood Cerebral ALD								Pivotal study to begin in late 2013e
Adult Cerebral ALD								
LentiGlobin								
Beta-Thalassemia								Ph 1/2 ongoing in France, to begin in mid-2013e in US
Sickle Cell Disease								SCD pts in France study; SCD IND in 2014e
CAR T-cells							CELG	
Hematologic malignancies								
Solid tumors								

Source: Company reports

The major clinical products in bluebird's pipeline are:

- **Lenti-D.** bluebird's Lenti-D product candidate has the potential to be a one-time treatment to stabilize and prevent progression of CCALD. The company's approach involves the *ex vivo* insertion of a functional copy of the ABCD1 gene into a patient's own hematopoietic stem cells (HSCs). Early promising clinical proof-of-concept results have been presented for four patients (using a similar product to Lenti-D), with the safety and therapeutic benefits having been maintained for >6 years in one patient. bluebird is developing a next generation product, called Lenti-D, for which it plans to initiate a potentially pivotal Phase 2/3 study called the ALD-102 Study in CCALD in the US and Europe in late 2013.

- **LentiGlobin.** bluebird's LentiGlobin product development program aims to treat beta-thalassemia and sickle cell disease by inserting a fully functional human beta-globin gene into a patient's own hematopoietic stem cells (HSCs). Promising early clinical proof-of-concept data has been presented for one beta-thalassemia patient from a Phase 1/2 trial using a similar product to LentiGlobin (the patient remains transfusion-free for >5 years post-transplant). A Phase 1/2 trial, the HGB-205 Study, using the new LentiGlobin product is ongoing in France, and a second Phase 1/2 trial, the HGB-204 Study, is set to begin in the US in mid-2013.

- **CAR T-cells.** In March 2013, bluebird and Celgene announced the formation of a broad, global strategic collaboration to discover, develop and commercialize novel disease-altering gene therapies in oncology by utilizing a patient's own genetically modified T cells, known as chimeric antigen receptor (CAR) T cells, to selectively target and destroy cancer cells. T cells are extracted from a patient's blood and genetically modified to recognize and attack cancer cells prior to reinfusion. This is a preclinical program, and human studies are not expected to begin until 2016.

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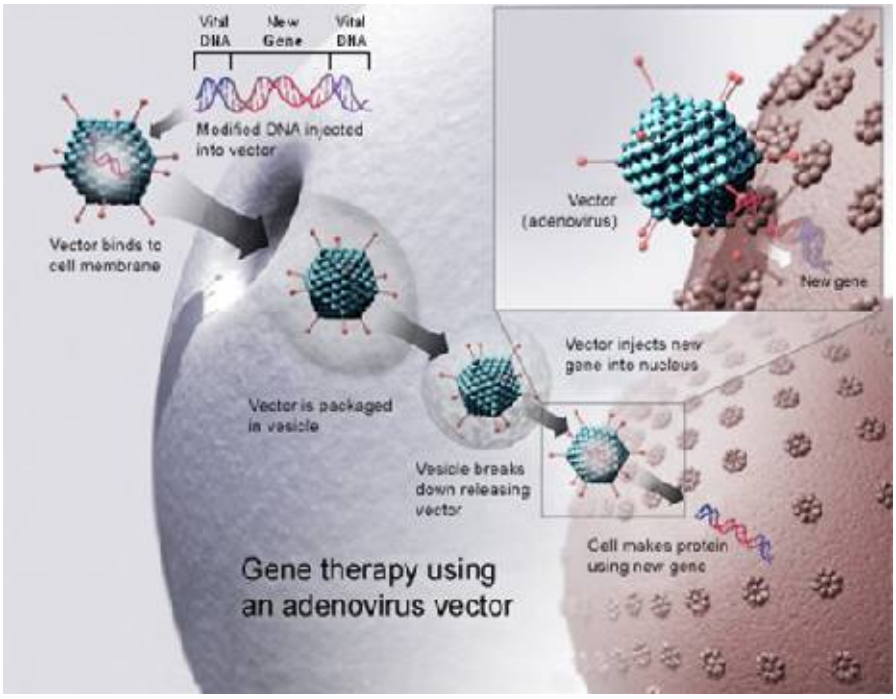
Gene Therapy Primer

What is gene therapy? Gene therapy is an approach to treating disease through the delivery of a functional copy of a desired, disease-associated gene or gene sequence (which is mutated/defective) into a patient's own cells (a process called gene transfer) to modulate or enhance the activity of cells that are causing the disease. The basic concept of gene therapy is to replace a defective gene or add in a functional copy to correct the underlying genetic defect that causes aberrant gene expression (and restore the natural function of the body).

The basic concept of gene therapy is to replace a defective gene or add in a functional copy to correct the underlying genetic defect

The gene transfer process relies on a "vector." In the gene transfer process, a functional gene is delivered and incorporated into a patient's cells through a delivery system (called a vector). The vector encloses a corrected DNA sequence and acts as a delivery vehicle to get the DNA inside affected somatic cells. The vector is most commonly based on a naturally occurring virus that has been modified to take advantage of the virus' natural ability to introduce genes into cells. However, for safety, the viruses are modified (or deactivated) so they are unable to replicate and infect other cells and cause disease. Unlike naturally occurring viruses, which replicate following infection of a target cell and have the ability to infect new cells, the viral vectors in gene therapy are modified to be non-replicating via deletion of the portion of the viral genome responsible for replication. The deactivated virus' job is to transport a gene into a cell's nucleus. The DNA is then expressed in the diseased cells, resulting in the production of therapeutic protein. Gene transfer using a viral vector is called transduction, and the resulting gene-modified cells are described as transduced cells. Both viral and non-viral gene transfer vectors have been studied in preclinical and clinical settings; however, a major focus has been on developing adeno-associated viruses and lentivirus vectors.

Figure 3: Gene Therapy Using an Adenovirus Vector



Source: http://ghr.nlm.nih.gov

A brief comparison of the most commonly used vectors can be seen in Figure 4.

Figure 4: Comparison of Commonly Used Vectors for Gene Therapy

	Adenovirus vector	Adeno-associated virus vector	Lentivirus vector	Retrovirus vector	Liposomes
Tropism	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing cells	Dividing and non-dividing cells
Host genome	No integration	No integration	Integration	Integration	No integration
Transgene expression	Transient	Stable	Stable	Stable	Transient
Packaging capacity	~ 8 kb	~ 5 kb	~ 8 kb	~ 8 kb	> 20 kb
Advantages	Large packaging capacity; High production yields	High production yields; Low immunogenicity; Long-term expression	Large packaging capacity; Long-term expression	Large packaging capacity; Long-term expression	Low immunogenicity
Disadvantage	High immunogenicity; Transient expression	Small packaging capacity	Insertional mutagenesis	High risk of insertional mutagenesis	Transient expression

Source: Gene Therapy Makes a Comeback (Limperis M., 2012)

Transduction can be accomplished either via *ex vivo* or *in vivo* delivery. In the *ex vivo* approach, cells are gene-modified outside of the patient's body and the modified cells are transplanted back into the patient. In the *in vivo* approach, vectors are introduced directly into the patient's body to deliver the desired gene to the target cell. bluebird uses the *ex vivo* approach with its lentivirus vectors.

Gene therapy offers the potential to permanently correct a disease and could potentially "cure" many single-gene defect conditions. Gene therapy represents an opportunity to change the way patients with severe genetic and orphan diseases are treated by correcting the underlying genetic defect (or by providing additional functionality that can at least lessen the disease burden). In this fashion, gene therapy has the potential to provide transformative disease modifying effects, with potentially life-long clinical benefits based on a single, one-time therapeutic administration. The ultimate goal is to cure lethal diseases by enabling normal genes to take over from defective ones.

Gene therapy has the potential to provide transformative disease modifying effects, with potentially life-long clinical benefits based on a single, one-time therapeutic administration

Gene therapy has the potential to treat a variety of diseases. As a versatile treatment option, gene therapy may be able to 1) replace missing or defective genes that can cause inherited or acquired disorders with a "corrected" version, 2) deliver genes that aid in the destruction of cancer cells, and 3) introduce genes that stimulate cell growth and heal damaged tissue.

A Brief History of Gene Therapy and Some Recent Developments in the Field

Gene therapy has come a long way over the last 20 years. The idea of gene therapy was formulated in the 1970s, after which early *in vitro* proof-of-concept studies followed in the 1980s. Gene therapy entered the clinic in 1990, where human gene transfer was tested in patients with adenosine deaminase deficiency (ADA; a severe combined immune-deficiency, or SCID) using retroviral vectors. This was the first successful study, and the field has seen significant interest and development since then, with over 1,700 trials ongoing worldwide for various indications including cancers, cardiovascular, neurological and inflammatory diseases. A vast

majority of research was in the form of proof-of-concept studies testing the feasibility of gene transfer and efficacy in preclinical models, which have not always translated into higher animal models and humans. Key challenges in replicating results have included species-specific differences in vector targeting, uptake and processing in affected cells and complex immune responses invoked in higher species. However, these challenges have helped to gain a better understanding of host-vector interactions and to help develop a gene therapy platform capable of coming up with novel vector approaches for clinical benefit.

The three main historical challenges for gene therapy have been related to potency, efficiency and safety:

- The ***potency*** of a gene therapy product is assessed by its effectiveness, which is based on introducing a gene into the target cells at a high enough frequency to achieve expression of the desired protein at a level sufficient to have a therapeutic benefit. For example, in the early 1980s scientists had some success with experimental gene therapies in mouse models, but the results were unable to be reproduced in humans. Researchers initially hoped that swapping a good gene for a bad gene could cure patients with cystic fibrosis, but scientists encountered many obstacles, including weak efficacy (as well as side effects). It has taken ~20 years to get to appropriate levels of clinical effectiveness.

- The ***efficiency*** of a gene therapy product is measured by the amount of product that is needed to have the desired effect, the amount of time it takes for the therapy to have an effect, and the length of time over which the therapy is effective for a given dose. For a long time, gene therapies were unable to produce sustained efficacy.

- ***Safety*** is assessed based on the nature and severity of any adverse events, complications, and conditions or diseases that may be caused from the introduction of foreign materials into a patient. For example, in some past clinical trials involving viral vectors for gene therapy, some patients experienced serious side effects, including the development of leukemia due to vector-related insertional oncogenesis.

Perhaps the most marked or widely publicized setback for gene therapy was the death of an 18-year-old US teenager in a study in 1999

Gene therapy has run into a host of clinical setbacks over the years. Perhaps the most marked or widely publicized setback for gene therapy was the death of an 18-year-old US teenager in a study in 1999 after receiving experimental gene therapy for a genetic condition. In addition, soon after this several children in two separate gene-therapy trials in Europe developed leukemia after receiving gene therapy. In one study, 4/10 children treated with gene therapy for severe combined immunodeficiency disease (SCID, or “bubble boy” syndrome) developed leukemia, as the corrected gene was inserted too close to a cancer-causing gene, which it activated. These results prompted the FDA to place a temporary halt on certain gene-therapy trials, derailing its development. While the FDA eased the ban in April 2003, these episodes prompted criticism that researchers had moved too quickly and there needed to be a rapid evaluation of the underlying technology. Moreover, in 2003, 20 patients treated for X-linked severe combined immunodeficiency in two gene therapy studies using a murine gamma-retroviral vector showed correction of the disease, but the studies were terminated after five patients developed leukemia (four of whom were subsequently cured). The cause of these side effects was shown to be insertional oncogenesis (a process in which the corrected gene inserts near a gene that is

important in a critical cellular process like growth or division, and the insertion results in the development of a cancer, often leukemia). Using molecular diagnostic techniques, it was determined that clones from these patients showed retrovirus insertion in close proximity to the promoter of the LMO2 proto-oncogene. Some of the early problems with gene therapies were also due to severe, or even deadly, immune reactions to the retroviral vector sparked by genomic changes induced by the viruses.

However, there have been several positive developments in the field of gene therapy in recent years that have led to heightened interest. The following developments all suggest that gene therapy could be on the verge of emerging as an important new therapeutic modality in the near future:

Over the last several years, several clinical studies of gene therapies have demonstrated promising efficacy and safety results

- **A growing body of promising gene therapy-based clinical data.** Over the last several years, several clinical studies of gene therapies have demonstrated promising efficacy and safety results in conditions such as retinal disease/congenital blindness, adrenoleukodystrophy (ALD), beta-thalassemia, chronic lymphoid leukemia (CLL), hemophilia B, immune deficiencies, and Parkinson's disease. Early confidence in gene therapy for treating cancers surfaced in 2006, when two patients were successfully treated for metastatic melanoma using genetically modified killer T-cells. The study results were published by the NIH in 2006. A similar treatment approach was reported to have cured two patients from CLL in 2011. An immunotherapy treatment of HIV using a lentiviral vector for the transfer of an antisense gene to disrupt the HIV envelope was also reported in late 2006. In 2011, researchers at University College London and St. Jude Children's Research Hospital in the US successfully used gene therapy to treat six patients with hemophilia B. In addition, encouraging results in patients with ALL were reported by the Memorial Sloan-Kettering Cancer Center in March 2013. Clinical proof-of-concept has now been reported in peer-reviewed and industry journals across several diseases. Renewed optimism for and investment in gene therapy has taken off in the last 10 years, and even more so in the last 5 years, due to these clinical successes.

- **Design, manufacturing, and process improvements.** In recent years, new viral vectors have been designed with safer profiles vs. earlier generation vectors. Well-publicized adverse events in past gene therapy trials has led to the development of new viral vectors, such as lentiviral vectors, with improved safety profiles. To date, lentiviral vectors have shown improved safety profiles vs. gamma-retroviral vectors, with no known events of gene therapy-related side effects having been observed so far. bluebird believes this is due to 1) lentiviral vectors tend to integrate within genes rather than in areas that control gene expression, and 2) their lack of strong viral enhancers. In addition, improvements in viral vector manufacturing processes and techniques have also enabled the production of more purified, concentrated, potent, and efficient viral vectors on a commercially viable scale. This is evidenced by the ~25-30-fold reduction in non-infectious viral particles vs. viral vectors used in previous clinical trials. Until recently, there has been a lack of manufacturing and transduction infrastructure that could enable the delivery of gene therapies in a reliable and reproducible manner and at a commercially viable scale. Now,

however, more companies are investing in the development of mid- to large-scale manufacturing systems designed to be both reproducible and sustainable.

- **In November 2012, the first gene therapy product was approved in the Western world, marking a significant regulatory milestone.** Europe's EMA approved Amsterdam-based UniQure's Glybera (alipogene tiparovec), a gene therapy product for a rare, fat-processing genetic disease called lipoprotein lipase deficiency (LPLD). Glybera thus becomes the first gene therapy product approved by regulatory authorities anywhere in the Western world (there is also a gene therapy for cancer on the market in China). Glybera introduces a normal version of a gene that helps the body produce an enzyme that breaks down harmful fats in the blood. Patients with LPLD have defective copies of the gene and are unable to process the fat particles, leading to significantly increased levels of fat in the blood, which can lead to potentially lethal inflammation of the pancreas as well as early onset of diabetes and cardiovascular disease. The genetic repair lowers blood fat concentration and reduces the frequency of pancreatitis. The EMA initially rejected the drug three times, expressing doubts about its efficacy. However, the fourth time around, the agency changed its analysis and approved the use of the drug only in severe cases. This approval highlights the progress gene therapy is beginning to make after years of false starts and high profile troubles.

In November 2012, the first gene therapy product was approved in the Western world

- **Increasing support from regulatory agencies for gene therapies.** While the FDA has not yet approved a human gene therapy product, it has at least provided some guidance for their development (including draft guidance on considerations for the design of early-phase clinical trials of gene therapy products in July 2013). For instance, the FDA has established the Office of Cellular, Tissue and Gene Therapies (OCTGT) within CBER to consolidate the review of gene therapy products, and the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) to advise CBER. Moreover, the FDA has issued a growing body of clinical guidelines, chemical, manufacturing and control (CMC) guidelines intended to govern the industry's development and approval of gene therapy products.

- **Increasing investment from the pharmaceutical and biotechnology industries, as highlighted by the relatively recent Celgene/bluebird collaboration (among others).** Companies such as Novartis, GlaxoSmithKline, Sanofi/Genzyme, Baxter, and BioMarin Pharmaceutical are currently advancing programs in gene therapy. In addition, in 2012 Novartis AG announced a collaboration with the University of Pennsylvania to develop gene therapy products, and Celgene just recently partnered with bluebird to work on gene therapies in oncology.

Probably the single most important advancement in gene therapy in recent years has been the development and use of improved, next-generation viruses to transfer the genetic information

A key advancement in the field of gene therapy in recent years has been the use of lentiviral vectors. Probably the single most important advancement in gene therapy in recent years has been the development and use of improved, next-generation viruses to transfer the genetic information. Earlier generation mouse retroviruses used in the 1990s have been shown to preferentially integrate in regulatory regions of genes that control cell growth, which in some cases raised serious safety concerns (development of leukemia). Since then, two vectors have risen to the top of the gene therapy world; lentiviral vectors (i.e., HIV-1) and adeno-associated vectors (AAV), as researchers have found them to be safer viruses and

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offering improved techniques for getting the replacement genes into a patient's body. bluebird is working with HIV-based lentiviruses. These vectors appear to have improved potency, efficiency and safety compared to the vectors used historically. To date, safety has been much better with the lentiviruses. For instance, gene therapy cancers have only been associated with retroviruses, not lentiviruses so far. Retroviruses tend to integrate close to enhancers/promoters, leading to a greater tendency to activate adjacent genes, whereas lentiviruses often integrate in the middle of genes. Advantages of the lentiviruses are that they integrate into the target cell genome, have a larger payload capacity, and only a single viral genome is required for replication. By contrast, AAVs – another common modern day vector – are non-integrating, have a smaller payload, and many viral genomes are required for replication.

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bluebird's Gene Therapy Platform

bluebird believes it has developed proprietary, next generation lentiviral vectors with improved potency, efficiency, and safety using a reproducible, scalable manufacturing process

bluebird's gene therapy platform is based upon an *ex vivo* viral delivery system. *Ex vivo* gene therapy is performed with the genetic alterations of a patient's target cells occurring outside the body in a culture. A virus delivers a gene into a cell and then inserts this gene into the cell's existing DNA. bluebird's gene therapy platform is based on viral vectors that use a modified, non-replicating version of the Human Immunodeficiency Virus Type 1 (HIV-1) virus, which is part of the lentivirus family.

bluebird's vectors are lentiviral vectors, but, importantly, the HIV-1 virus has all of its components required for self-replication removed so that it cannot infect additional cells. bluebird's lentiviral construct design includes only the minimal viral components of the HIV-1 virus needed for the vector to undergo one round of replication within the cell during manufacturing. The lentiviral vectors are used to introduce a functional copy of a gene to a patient's own isolated hematopoietic stem cells (HSCs) from the patient's bone marrow. HSCs are capable of differentiating into a wide range of different cell types. As HSCs are dividing cells, this approach allows expression of the modified gene to be sustained, as bluebird can take advantage of replication of the gene-modified HSCs over a lifetime.

In addition, bluebird has developed a proprietary cell-based vector manufacturing process that is both reproducible and scalable. A gene therapy KOL we consulted with believes bluebird has the single best technology platform in the gene therapy field. A key aspect of bluebird's expertise is some semi-proprietary novel methods – something akin to "home cooking" – which may be non-patent related.

A gene therapy KOL we consulted with believes bluebird has the single best technology platform in the gene therapy field

bluebird's gene therapies utilize a four-step therapeutic approach. There are two main components in the process that results in the finished "drug product," including lentiviral vector production and target cell transduction. Overall, however, there are four key steps in bluebird administering a patient its gene therapy product:

1. **Produce a lentiviral vector carrying a functional gene sequence (the therapeutic gene "payload").** bluebird's lentiviral vectors are assembled using a human cell line called HEK293T. bluebird produces a lentiviral vector by co-transfecting the HEK293T cells (the "cellular manufacturing plant") with multiple plasmids (these include the capsid protein, rev protein, VSVG envelope protein, and the therapeutic transgene RNA, which encodes the broken gene) encoding all the genetic material required to assemble the lentiviral vector carrying the functional gene of interest. These plasmids separately encode the components of the virus as well as the functional gene sequence the viral vector will carry. These finished lentiviral vectors are what are ultimately used to transduce the target cells isolated from the patient. This step is known as transfection. The genetic material is delivered on multiple plasmids as an attempt to reduce the probability of generating a replication-competent virus (that could potentially cause infection) and improve the safety of this step of the procedure. Once the transfected HEK293T cells have assembled the lentiviral vectors packaged with the functional gene of interest, they bud off into the cell culture media. The media containing the assembled vectors is harvested, purified by a single chromatography step, concentrated, and then formulated prior to freezing for storage.

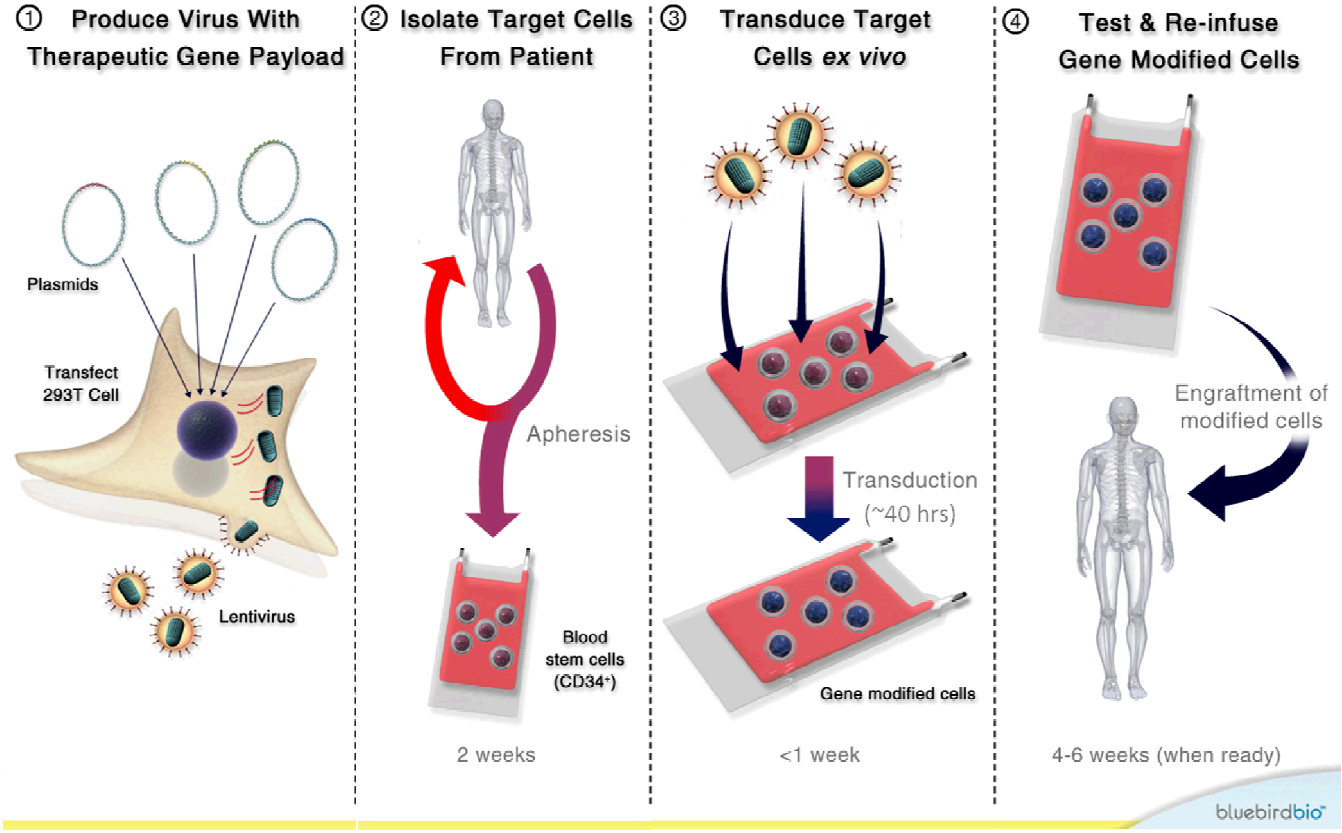
2. **Mobilize, extract, and isolate the target cells (hematopoietic stem cells or T-cells) from the patient.** A sample of the patient's own target cells is extracted and isolated, typically via apheresis. HSCs are first mobilized, or released, into the bloodstream from the patient's bone marrow (using GCSF) and then collected from the patient's blood. In some cases, HSCs are extracted directly from the patient's bone marrow (bone marrow harvesting). There is also a pre-stimulation step where the isolated HSCs are treated with a mixture of growth factors and additional proprietary processes that help enable an efficient transduction process. These steps are carried out using existing hospital infrastructure and standard protocols already widely in place for stem cell transplant procedures.

3. **The target cell transduction process – creating the gene-modified cells (the "drug product") by inserting a working copy of the dysfunctional gene sequence into the patient's cells *ex vivo*.** The patient's isolated, purified, and pre-treated HSCs are exposed (or infected) *ex vivo* to the lentiviral vectors produced in step 1 containing the appropriate functional gene. This lasts for up to 40 hours to facilitate transduction and insertion of the therapeutic DNA (or the functional gene) into the chromosomes of the target cells (transgene integration), creating the patient's own (autologous) gene-modified cells. The virus enters the cells and releases its "payload" (the transgene RNA) into the cytoplasm, which is then converted into DNA. This is then moved into the nucleus and integrated into the DNA to create "gene modified" HSCs. The cells are then washed to remove any remnants of the viral vector or culture media. This is known as the transduction step (transduction = gene transfer using a viral vector). Once transduction is complete, the gene-modified HSCs are washed and re-suspended into cell culture media to remove any residual impurities. A portion of the harvested cells is removed for quality control release testing, which includes ensuring that transduction was successful and the functional gene delivered by the vector is adequately expressed by the target cells. The remaining cells are appropriately formulated and cryopreserved. The patient's own gene-modified cells are then referred to as the "drug product" that is re-introduced back into the patient (in step 4).

4. **Test and then re-infuse the patient's gene modified cells (HSCs or T-cells).** The final step is to return, or re-introduce, the gene-modified HSCs into the patient. This typically occurs ~1-2 months post the initial extraction of the HSCs. Just prior to dosing, the "drug product" is thawed and sampled for cell number and viability to ensure the dose administered meets a pre-defined minimum. Prior to administering the "drug product," the patient undergoes a standard myeloablation procedure (also used in allogeneic HCST) to remove all endogenous bone marrow cells. The modified HSCs are then re-infused back into the patient (again, this is about ~1-2 months after the initial extraction). They then begin to re-populate a portion of the bone marrow as permanently modified HSCs – this process is known as engraftment. The engrafted genetically altered HSCs then give rise to progenitor cell types with the corrected gene sequences (a percentage of the genetically modified HSCs will differentiate into multiple "genetically normal" cell types) and hopefully produce the desired protein(s) encoded by the therapeutic DNA (therapeutic gene expression), providing an opportunity to treat the disease. Following successful engraftment, it is hoped that the clinical benefits will begin to become evident within 12-24 months of transplant. For example, in CCALD, the idea is

that the stem cells become correctly functioning microglial cells in the brain to "fix" the disease.

Figure 5: bluebird's Four-Step Therapeutic Approach



Source: Company reports

bluebird believes it has developed proprietary, next generation lentiviral vectors with improved potency, efficiency, and safety using a reproducible, scalable manufacturing process. bluebird's lentiviral vectors could be well-suited for treating several different diseases and may have advantages over other viral vectors used in developing gene therapy products. Some potential advantages are highlighted below:

- **The ability to achieve long-term, sustained expression of the modified gene.** Unlike other viral vectors utilizing different viruses, such as adeno-associated viruses, lentiviral vectors have the ability to integrate the functional gene they carry into the DNA of the target cell's chromosome. As a result of this, they can potentially lead to a sustained therapeutic effect in dividing cells, such as HSCs, because the gene sequence introduced becomes part of the cell's natural replicating process that continues with regular cell division (along with the rest of the cell's chromosomal DNA). As such, subsequent dividing cells that result from the initially transduced cell will also carry the inserted gene sequence. In other words, a single insertion of a functional gene into a dividing cell allows for a multiplying effect on downstream cells, leading to sustained expression. While other vector platforms introduce genes into cells, they don't all integrate into a

cell's DNA (non-integrating) and so require many viral events to transform a cell.

- **Reduced risk of insertional oncogenesis.** Oncogenesis is the process whereby the gene is inserted near a gene that is important in cell growth/division, and the insertion causes uncontrolled cell division (i.e., cancer). In past clinical trials involving gene therapy products, earlier generations of integrating viral vectors (based on a mouse gamma-retrovirus) were found to preferentially integrate into particular regulatory regions of genes (such as the promoter regions). In some cases this activated the cell to divide uncontrollably, resulting in cancer through a process called insertional oncogenesis. Such genetic alterations resulted in several well-publicized side effects, including cases of leukemia, and stressed the need to develop new gene therapy vectors with better safety profiles. Next generation lentiviral vectors (unlike gamma retrovirus vectors) have a particular pattern of integrating into regions that provide instructions for making proteins rather than preferentially integrating into regions that can result in cell proliferation. This difference in integration patterns could be critical in improving a vector's safety profile and could distinguish lentiviral vectors from earlier generations of integrating viral vectors. To date, there are no known clinical events of insertional oncogenesis or cancer with a lentiviral vector.

- **Large payload carrying capacity.** Unlike adeno-associated viruses, lentiviruses are capable of carrying large therapeutic gene sequences (up to 8,000 base pairs) into a host cell. As such, lentiviral vectors may offer greater flexibility in terms of the number of potential diseases that can be treated (as some diseases may require a gene sequence that could be too big to fit into an adeno-associated virus construct).

Recent advances in bluebird's platform include vector purity, potency, and scalability, as well as overall transduction efficiency to more efficiently effect gene transfer

In addition, bluebird has developed a proprietary cell-based vector manufacturing process that is reproducible and scalable. This is important, as a key challenge in gene therapy is making the virus in large amounts. Recent advances in bluebird's platform include vector purity, potency, and scalability, as well as overall transduction efficiency to more efficiently effect gene transfer. These advances may allow bluebird to develop first and best-in-class products that deliver high expression levels of missing or dysfunctional proteins and are scalable for commercial production. One physician we consulted with stated that vector manufacturing advances have clearly helped in advancing gene therapy, such as the way bluebird has been able to improve its production method and scale it up with quality material. For example, for beta-thalassemia, a large amount of the gene is required to make the vector at a high enough quantity, and bluebird was able to increase its production methods to do this and is now migrating to a suspension manufacturing process. In other words, bluebird has been able to use its technology to increase the vector copy number (VCN). bluebird's VCN used to be ~0.2-0.5 and now is ~1.0-3.5, representing a ~2-17x improvement.

While gene therapy is still a novel and developing therapeutic field, there are several factors that we believe help de-risk bluebird's approach:

- **bluebird is targeting monogenic diseases.** At least initially, bluebird is pursuing diseases where the genetic abnormality/mutation is known and is found in a single gene (known as monogenic diseases). As such, the company knows

what it is correcting and what gene sequence to insert into a patient's cells. We believe the pursuit of monogenic diseases helps mitigate the uncertainty of disease biology.

- **There is an unmet medical need for the initial indications.** At least initially, bluebird is pursuing indications, such as CCALD and beta-thalassemia that have few or no clinical options. As such, the bar for approval is likely to be lower than for diseases that currently have less of an unmet medical need.

- **The existing practice of transplanting cells from a donor provides proof-of-concept for bluebird's approach.** Clinical proof-of-concept already exists for allogeneic HSCT, as replacing faults in stem cells has been practiced for >40 years in the form of donor hematopoietic stem cell transplants (HSCT). bluebird is focusing on HSCs, and allogeneic HSCT provides proof-of-concept for bluebird's approach, in our view. bluebird is currently pursuing indications for which allogeneic HSCT is a proven therapeutic option. As such, clinical proof-of-concept already exists, although bluebird's approach addresses the significant limitations of HSCT.

- **bluebird's approach involves using a patient's own (gene-modified) cells.** By using the patient's own isolated HSCs, bluebird eliminates several of the challenges associated with allogeneic HSCT, such as the limited availability of optimally matched donors and the risks of transplant rejection which often lead to serious side effects (i.e., GvHD). As such, bluebird's gene therapy approach is likely to side-step much of the risk associated with immune-incompatibility that comes from stem cells supplied by a donor. Even in cases where allogeneic HSCT is deemed a success, several patients need to comply with prolonged immunosuppressive drug regimens that are associated with the risk of opportunistic infections. As bluebird's gene therapy uses the patient's own cells, there is much less risk of immune rejection vs. an allogeneic HSCT. bluebird's approach represents a paradigm shift in the treatment of severe genetic diseases by eliminating the potential complications associated with donor cell transplantation and presenting a one-time potentially transformative therapy using a patient's own stem cells.

- **bluebird modifies the target cells *ex vivo*, which lowers the safety risk.** By inserting the new functional DNA into cells outside the patient's body (*ex vivo*), bluebird reduces the risk of side effects. *Ex vivo* represents a more controlled environment in which to transduce cells and deliver genetic material vs. *in vivo*. In addition, the *ex vivo* insertion eliminates a key complexity, which is getting the "drug" directly to the target cells.

- **Administration of bluebird's drug products uses existing stem cell transplant infrastructure and processes.** The last step of bluebird's gene therapy process, in which patients are myeloablated and then transfused with the finished drug product, is consistent with widely used stem cell transplant clinical practices. In addition, the infrastructure to perform these steps is already widely in use.

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The Regulatory Outlook: Agencies Appear to Be Gaining Comfort with Gene Therapy

An area of uncertainty with gene therapy is the regulatory process given that gene therapy is relatively novel and has a checkered past. Only one gene therapy product has been approved in the Western world (UniQure's Glybera in Europe in November 2012), and thus it's not surprising that significant questions still remain on the evolving regulatory outlook for this immature field.

Questions still remain on the evolving regulatory outlook for gene therapy, as it is an immature field

We believe there is increasing support from the FDA for the development of gene therapies. While the FDA has not yet approved a human gene therapy product, it has at least provided some guidance for their development (including draft guidance on considerations for the design of early-phase clinical trials of gene therapy products in July 2013). For instance, the FDA has established advisory groups with expertise in the field of gene therapy; the Office of Cellular, Tissue and Gene Therapies (OCTGT) within CBER to consolidate the review of gene therapy products, and the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) to advise CBER on its review. In addition, the FDA has issued a growing body of clinical guidelines, and chemical, manufacturing and control (CMC) guidelines intended to aid in the industry's development of gene therapy. The FDA has also published guidance documents related to gene therapy products in general, their preclinical assessment, observing patients involved in gene therapy trials for delayed side effects, potency testing, and CMC information in gene therapy INDs. We view all these as steps in the right direction and signs that the FDA is becoming more comfortable with gene therapy. One gene therapy KOL we spoke with described his own interactions with the FDA on gene therapy as "quite positive," with the agency appearing increasingly supportive in developing this therapeutic modality. He also pointed out that the FDA now has a specific gene therapy unit. However, regulatory requirements governing gene and cell therapy products have changed frequently and may change again in the future.

bluebird has had numerous interactions with regulatory authorities/advisory bodies regarding the clinical development of its products

bluebird has had numerous interactions with the FDA, the EMA, and other regulatory authorities/advisory bodies regarding the clinical development of its products. These interactions regarding the Lenti-D product candidate include Lenti-D being granted orphan drug status by the FDA and EMA for the treatment of CCALD, and bluebird received scientific advice on the design of the planned ALD-102 Study from the French regulatory agency in February 2011, from the EMA in May 2011, and from the UK's Medicines and Healthcare Products Regulatory Agency in May 2012. Moreover, bluebird had a type C pre-IND meeting with the FDA in 2012 on the design of the planned ALD-102 Study, and submitted an IND for the ALD-102 Study in March 2013 with the IND becoming active in April 2013. While risk remains around the ALD-102 Study not being sufficient to act as a pivotal trial to gain approval for Lenti-D, we are encouraged that the trial's design has been discussed with both the FDA and the EMA, that the endpoints for CCALD appear clear and that the talks appear supportive. bluebird has also had, and continues to have, dialogue with the FDA, the EMA and other regulatory authorities and advisory bodies concerning the clinical development of the LentiGlobin product candidate. These interactions include: the LentiGlobin product candidate was granted orphan drug designation by the FDA and the EMA (as well as Fast Track status by the FDA); a type B pre-IND meeting with the FDA was held in 2012 focused on the design of the planned HGB-204 Study and provided guidance on the manufacturing and non-clinical development with a view towards a future IND filing; an IND filing

for the HGB-204 Study was submitted in December 2012 and was effective as of January 2013; a meeting with the French regulatory agency was held in November 2011 regarding the submission of a CTA with a revised clinical protocol to support the use of the LentiGlobin vector in the planned HGB-204 Study; and the CTA was submitted and approved for the HGB-205 Study in 2012.

Other Gene Therapy Development Efforts

Gene therapy is a relatively new therapeutic modality, and we believe bluebird has positioned itself as one of the early leaders in this field. However, other companies and academic institutions are working on gene therapy technologies for gene modification in genetically defined diseases. These include:

We believe bluebird holds scarcity value as really the only pure play public gene therapy company at this time

- **UniQure** has the first marketed gene therapy product, Glybera (alipogene tiparvovec) for lipoprotein lipase deficiency (LPLD). Lipoprotein lipase (LPL) plays a key role in body fat metabolism, in which low levels of LPL result in high levels of fat in the blood stream. Glybera is an adeno-associated virus (AAV) vector packaging a functional LPL gene and helps restore adequate levels of fat in the blood. Glybera was approved in the EU in November 2012. The company is also developing a product to permanently restore Hemophilia B, a disorder that prevents blood clotting caused by the lack of functional Factor IX gene. The gene therapy approach relies on introducing a functional copy of the Factor IX gene into patients' liver cells using an AAV vector. Current standard of care for Hemophilia B is an enzyme replacement therapy involving intravenous infusion of recombinant Factor IX protein to induce blood clotting. Results from a Phase 1 trial showed a sustained reduction in the frequency of prophylactic treatment in patients, and UniQure plans to initiate Phase 1/2 studies in 2013. UniQure is also exploring other indications, including Parkinson's Disease, Sanfilippo B (MPS III), and Acute Intermittent Porphyria (AIP), all of which are currently in Phase 1.

- **Celladon's** lead candidate, MYDICAR, is a genetically targeted enzyme replacement therapy for cardiac diseases. It targets the enzyme SERCA2a found in the sarcoplasmic reticulum (SR) in the heart and regulates the calcium cycle, which is critical for normal heart contraction. Advanced heart failure is associated with declining SERCA2a levels. MYDICAR introduces a copy of the SERCA2a gene into cardiac muscle cells and aims to restore appropriate levels of functional SERCA2a using a recombinant adeno-associated virus (AAV) vector. MYDICAR can be used along with other heart failure treatments (ACE inhibitors, beta-blockers etc.). Initial Phase 2 trials with MYDICAR showed sustained improvement in patient cardiac function and significantly lower adverse events typical with heart failure. Celladon initiated Phase 2b studies of MYDICAR in August 2012.

- **BioMarin** (rated Overweight) has in-licensed a Factor VIII gene therapy program for hemophilia A from University College London Business (UCLB), UCL's technology transfer arm. As part of the agreement, BioMarin can select a drug candidate this year, file an IND by next year, and begin proof-of-concept human studies by the end of 2014.

- **Sangamo Biosciences** is developing novel gene therapies using engineered DNA-binding zinc finger nucleases to modify a cell's DNA. Its proprietary Zinc

Finger Nuclease (ZFN) technology platform (ZFP therapeutics) is being tested for HIV and numerous monogenic diseases. The company's lead candidate, SB-728, uses ZFN to modify a gene encoding the receptor CCR5, which is used by the HIV virus to infect CD4+ T-cells. SB-728 is being evaluated for safety and tolerability in an ongoing Phase 2 study in patients on highly active antiretroviral therapy (HAART), a Phase 1/2 trial evaluating escalating doses of cyclophosphamide (Cytoxan) administered prior to SB-728, and another Phase 1/2 trial in treatment naïve patients/patients not on HAART. Preliminary data from Phase 1/2 trials was presented in May 2013, and a full data readout is expected by YE13. In addition, the company presented positive preliminary data from two Phase 1 trials at the Conference for Retroviral and Opportunistic Infections (CROI) in 1Q12 and at the 51st and 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in 3Q11 and 3Q12, respectively. The company entered into a partnership agreement with Shire in early 2012 to develop ZFP therapeutics for hemophilia and Huntington's disease. These programs are currently in preclinical stages. Sangamo has also out-licensed its ZFP technology to Sigma-Aldrich Corporation (rated Neutral by JPM Life Science Tools & Diagnostics analyst Tycho Peterson) for developing gene editing tools and Dow AgroSciences LLC for developing ZFP-derived plant products.

- **GlaxoSmithKline** (GSK, rated Underweight by JPM European Healthcare analyst James Gordon)), Fondazione Telethon and Fondazione San Raffaele formed a strategic alliance to research and develop novel treatments to address rare genetic disorders, using gene therapy carried out on stem cells taken from the patient's bone marrow (*ex vivo*). The alliance capitalizes on research performed at the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), a joint venture between Fondazione Telethon and Fondazione San Raffaele established since 1995. Under the terms of the agreement, GSK will gain an exclusive license to develop and commercialize an investigational gene therapy, for ADA Severe Combined Immune Deficiency (ADA-SCID) – a rare and life-threatening immune deficiency. Phase 1/2 studies have shown the potential of this treatment option to restore long-term immune function and protect against severe infections in children with ADA deficiency. ADA-SCID is the lead program. In addition, GSK will co-develop six further applications of ex vivo stem cell therapy with Fondazione Telethon and Fondazione San Raffaele using a new gene transfer technology developed by HSR-TIGET scientists, with the potential to treat a range of rare disorders. The first of these will be metachromatic leukodystrophy (MLD) and Wiskott-Aldrich Syndrome (WAS). Others include beta-thalassemia, mucopolysaccharoidosis type I (MPS), globoid leukodystrophy (GLD), and chronic granulomatous disorder (CGD). Clinical trials for WAS and MLD were initiated at HSR-TIGET in spring 2010 and are enrolling patients. All of these disorders have a molecular mechanism that are caused by faults in a single gene, making it possible for this *ex vivo* gene technology to correct the patient's own bone marrow stem cells.

- **HemaQuest Pharmaceuticals** is a private biopharmaceutical company developing short chain fatty acids (small molecules) that induce fetal globin and stimulate blood cell production by targeting genes specific to sickle cell disease and beta-thalassemia. In 2010, the company's lead drug candidate HQK-1001 demonstrated promising proof-of-concept results and is now in Phase 2 for

sickle cell disease and beta-thalassemia. The Phase 2a portion of the study in sickle cell disease completed in March 2012, after which Phase 2b commenced. Two ISTs in beta-thalassemia were initiated in 2012.

- **Intrexon and Ziopharm Oncology** (ZIOP, rated Neutral) announced a worldwide, exclusive channel partnership for synthetic biology DNA-based human oncology therapeutics in January 2011. Ziopharm will develop and commercialize complex transgenes (DNA-based therapeutics) using Intrexon's next-generation UltraVector Technology, which enables tight control over the function and output of living cells by providing external control over in vivo activation and regulation of potent effectors. Ziopharm acquired rights to access Intrexon's entire synthetic biology discovery or human in vivo effector platform, including two Interleukin-12 (IL-12) DNA compounds (DC-RTS-IL-12 and Ad-RTS-IL-12). In June 2013, Ziopharm announced updated results for Ad-RTS-IL-12 from a Phase 1 study in advanced melanoma at the American Society for Clinical Oncology (ASCO) meeting.

- **Novartis SA and the University of Pennsylvania** formed a global research and licensing agreement for the development and commercialization of novel immunotherapies using the chimeric antigen receptor (CAR) technology platform. Development efforts are currently focused on utilizing modified T-cells to treat patients with CLL and will gradually extend to other cancers. Under the alliance, UPenn will grant Novartis (rated Overweight by JPM EMEA Healthcare analyst Richard Vosser) an exclusive worldwide license to CAR technologies in an ongoing trial in CLL, as well as future CAR-based therapies that may be developed. Novartis will invest in setting up a Centre for Advanced Cellular Therapies (CACT) on UPenn's campus. UPenn is entitled to receive milestone and royalty payments as a part of the agreement.

- **Applied Genetic Technologies** (AGTC) is a privately held biotech company developing gene therapy products for inherited genetic disorders like Alpha 1 Antitrypsin deficiency (Alpha 1) and Leber Congenital Amaurosis (LCA). Current treatment for Alpha-1 involves infusion of alpha-1 antitrypsin protein every 1-2 weeks and is expensive (~$100,000 per year). AGTC's gene therapy product for Alpha 1 is currently in a dose-escalation Phase 2 study. LCA is a rare inherited eye disease causing loss of vision early at birth and is implicated by 11 known genes. Preclinical studies under the sponsorship of the National Eye Institute were performed in collaboration with The University of Florida, Cornell University and The University of Pennsylvania. The drug is currently in Phase 1/2 trials. Additionally, AGTC, in collaboration with Genzyme, is developing a product for wet AMD, a medical condition resulting in loss of vision in the elderly population caused by leaking of fluid from blood vessels under the retina. The therapy is designed to provide long-term suppression of vascular endothelial growth factor (VEGF), which promotes leakiness in blood vessels. A Phase 1 study of this product is ongoing.

- **Genzyme** is developing an adeno-associated virus (AAV) vector based therapy for the treatment of Parkinson's disease (PD). Patients with PD lose the ability to send dopamine signals to the striatum, which is compensated by prescribing an approved product L-DOPA (L-3,4-dihydroxyphenylalanine). However, the brain loses its ability to convert L-DOPA to dopamine with age. The AAV vector encodes a human aromatic L-amino acid decarboxylase (hAADC-2) enzyme,

which catalyses the conversion of L-DOPA to dopamine in the brain. Currently, AAV-hAADC-2 is being tested in Phase 1 studies.

- **Chatham Therapeutics** (an affiliate of Asklepios BioPharmaceuticals) **and Baxter International** (covered by Medical Supplies & Devices analyst Michael Weinstein) entered into an exclusive global agreement in June 2012 for the development and commercialization of potential treatments for hemophilia B. The collaboration allows Baxter to use Chatham's recombinant adeno-associated virus-(rAAV) based gene therapy technology, which has shown potential therapeutic benefit in early clinical studies. A small independent study involving six patients using Chatham technology components was the topic of a 2011 article in The New England Journal of Medicine. The agreement between Chatham and Baxter will involve the next generation of this gene therapy technology, which the two companies will investigate through US-based hemophilia B clinical trials.

- **FKD Therapies Oy**, a privately held Finnish company, was granted an exclusive license by Merck (rated Overweight by JPM Pharmaceuticals analyst Chris Schott) to develop and commercialize its gene therapy portfolio in exchange for an equity stake. The lead drug candidate, Instiladrin, is a recombinant adenoviral interferon alfa 2b (rAd-IFN) being developed as a treatment for superficial bladder cancer. Instiladrin uses an adenovirus vector to transport an interferon gene into bladder wall cells. rAd-IFN has completed Phase 1 studies. The license also provides FKD an option to develop a recombinant adenoviral p21 (rAd-p21) for glaucoma surgery failure and conditionally replicating adenoviral technology (CRAV) for solid tumors.

- **Transgene** develops immunotherapeutic products for cancers and infectious diseases leveraging its competency in viral vector development for targeted immunotherapy, with four products currently in Phase 2 studies. Its lead candidate, TG4010, is partnered with Novartis for development in metastatic non small cell lung cancer (NSCLC). TG4010 is a recombinant vaccinia virus vector packaged with MUC1 antigen in combination with human cytokine, Interleukin-2 (IL-2) and is currently in Phase 2b studies, with data expected in 2H13. Other product candidates include JX594/TG6006 in hepatocellular carcinoma (HCC) and metastatic colorectal cancer (mCRC) partnered with Jennerex, and TG4001 in HPV induced head/neck cancers. TG6006 is an altered oncolytic vaccinia virus that has immunostimulatory cytokine GM-SCF, which selectively targets and destroys cancerous cells. Transgene presented data from Phase 2 studies for TG6006 in a variety of cancers including liver, kidney, lung, colon and melanoma in 1H13. TG4001 is based on the MVA virus causing mutation-inactivated HPV 15 E6 and E7 oncoproteins and Interleukin-2. In November 2012, the company collaborated with the European Organization for Research and Treatment of Cancer (EORTC) to develop TG4001 in patients with HPV 16 positive oropharyngeal squamous cell carcinomas (OSCCs). A Phase 2 trial is estimated to start in late 2013.

- **GenVec**'s technology is capable of localizing protein delivery in the body. It does this by using an adenovector platform to locally deliver genes to cells, which then direct production of the desired protein. This approach has the potential to reduce the side effects typically associated with systemic delivery of

proteins. For vaccines, the goal is to induce an immune response against a target protein or antigen. This is achieved using an adenovector to deliver a gene that causes production of an antigen, which then stimulates the desired immune reaction by the body. In collaboration with Novartis, GenVec's hearing loss and balance disorders program is focused on the restoration of hearing and balance function through the regeneration of critical cells of the inner ear. Hearing and balance require specialized cells of the inner ear called sensory hair cells. During embryonic development, an atonal gene (Atoh1) induces the generation of these cells. In multiple animal models, GenVec has demonstrated formation of new inner ear sensory hair cells and the restoration of hearing and balance function using its technology to deliver the Atoh1 gene using GenVec's adenovector technology to the inner ear. In January 2010, GenVec announced its collaboration with Novartis to discover and develop novel treatments for hearing loss and balance disorders so that GenVec now receives funding from Novartis to develop adenovectors for hearing loss.

- In addition, many **universities and private and public research institutes** are active in researching gene therapy. However, many of these are at an earlier stage of development.

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Lenti-D

Lenti-D is bluebird's most advanced gene therapy product candidate, which is being developed initially as a potential one-time treatment to halt the progression of CCALD. The approach with Lenti-D involves the *ex vivo* insertion of a functional copy of the human ABCD1 gene via an HIV-1 based lentiviral vector into the patient's own (autologous) CD34+ hematopoietic stem cells (HSCs) to correct the aberrant expression of ALDP in patients with CCALD. The autologous HSCs that have been modified to carry the functional copy of the ABCD1 gene are referred to as the Lenti-D drug product. Upon successful engraftment of the Lenti-D product, it is expected that some percentage of the genetically corrected macrophages cross the blood-brain barrier (BBB) into the patient's brain. Microglial cells in the brain derived from the transduced HSCs will correct the metabolic abnormalities resulting from excess very long chain fatty acids and stabilize the demyelination and cerebral inflammation characteristic of CCALD.

The approach with Lenti-D involves the *ex vivo* insertion of a functional copy of the human ABCD1 gene via an HIV-1 based lentiviral vector into the patient's own CD34+ hematopoietic stem cells

ALD-101: A Non-Interventional, Retrospective, Natural History Study of CCALD

CCALD is a very rare disease, and, as such, allogeneic HSCT for CCALD has not historically been subject to extensive analysis in controlled clinical studies. Accordingly, the amount of clinical data required to characterize progression of CCALD and the efficacy/safety profile of allogeneic HSCT is limited. Thus, to be able to design future clinical trials for Lenti-D and accurately interpret the results, bluebird carried out (upon recommendation by the FDA, which also had input into the trial design) a non-interventional, retrospective data collection trial to evaluate the natural course of disease in untreated CCALD patients (the untreated group or cohort) vs. the data obtained from patients receiving an allogeneic HSCT (the treated cohort). The goal was to gain a better understanding of the natural course of untreated vs. treated CCALD. Historical clinical records from patients with CCALD were examined to assess the typical course of the disease and the efficacy/safety of the treatment options. bluebird collected neurologic and neuropsychological assessments and neuro-imaging data for both treated and untreated patient cohorts from 5 study centers (4 US sites and one French site) on a total of 137 patients (72 were untreated patients and 65 patients were treated with allogeneic HSCT). This study report was completed in March 2013 and is believed to be the most comprehensive dataset produced to characterize clinical outcomes in untreated vs. allogeneic HSCT-treated CCALD patients.

Findings from this study suggest that, although there are various modalities used to assess CCALD patients, three (the Neurological Function Score (NFS), Loes score, and gadolinium enhancement) are used most widely and consistently.

1. **The Neurological Function Score (NFS).** This is a 25-point neurological function score that measures 15 neurological abnormalities caused by ALD. These neurological abnormalities are:

Figure 6: The 15 Neurological Abnormalities Measured in the NFS

Symptoms	Score
Loss of communication*	3
No voluntary movement*	3
Cortical blindness*	2
Tube feeding*	2
Wheelchair required*	2
Total incontinence*	2
Swalowing/other CNS dysfunctions	2
Spastic gait (needs assistance)	2
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Visual impairments/fields cut	1
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Episodes of incontinency	1
Nonfebrile seizures	1
Total	**25**

* Major Functional Disabilities (MFD)

Source: bluebird bio, Inc.

Among the 15 functional domains, bluebird considers 6 to be of most clinical importance, meaning the patient's ability to function independently is severely compromised. These deficiencies, which bluebird defines as Major Functional Disabilities (MFDs) are 1) loss of communication, 2) complete loss of voluntary movement, 3) cortical blindness, 4) requirement for tube feeding, 5) wheelchair dependence, and 6) total incontinence.

2. **The Loes score.** This is a 34-point scale designed to measure the extent of CNS disease burden (based on brain magnetic resonance imaging studies). The Loes score measures the extent/location of brain abnormalities such as the presence of white matter changes, degree of demyelination, and the presence of focal/global atrophy. A Loes score of $\geq$1 signifies meaningful disease, and patients with a score of $\geq$10 are generally not considered for transplantation based on the perceived advanced stage of disease.

3. **Gadolinium enhancement.** One of the common features of inflammatory disease in ALD is the presence of a compromised blood-brain barrier (BBB) behind demyelinating lesions in the brain. This can be measured using gadolinium, a contrast agent, in brain MRI studies. Evidence of gadolinium enhancement in the brain suggests neuroinflammation and that the BBB has been damaged. Such a gadolinium positive result is known to be a predictive biomarker of disease progression in ALD.

Key findings from the ALD-101 Study. The main findings from the ALD-101 Study are below:

1. **Untreated CCALD patients quickly progress.** In the untreated cohort (n=72), the median overall survival was 92 months (or 7.7 years), and the probability of survival at 5 years was only 55%. However, it is also worth noting that survival was likely influenced by parents' decision to maintain life support in some cases.

2. **Baseline disease severity (measured by NFS and Loes scores) were good predictors of survival.** In the untreated and treated cohorts, meaningfully lower mortality rates were observed in patients with lower baseline NFS and Loes scores vs. patients with higher scores.

Figure 7: Mortality Rates from the ALD-101 Study According to Baseline NFS and Loes Scores

	Mortality Rate*			
	NFS < 1	NFS > 1	Loes ≥ 1 < 9	Loes > 9
Untreated Cohort	42%	85%	46%	76%
Treated Cohort	12%	29%	13%	28%

* Mortality rate determined by the number of deaths that occurred at any time through the observation period post-CCALD diagnosis

Source: bluebird bio, Inc.

Due to this finding, the entry criteria for the potentially pivotal ALD-102 Study exclude patients with evidence of advanced disease on NFS and Loes score. The aim of this is to prevent enrollment of patients whose disease would be expected to progress to a dismal outcome even with treatment.

3. **MFDs occurred in most of the untreated patients who displayed evidence of gadolinium enhancement.** In the 72 patients in the untreated cohort, data were available for the presence of MFDs at 24 months after a diagnosis of CCALD in 56/72 patients. Among these 56 patients, 29 (52%) developed ≥1 MFD throughout the data collection period. Of the 18 cases in the untreated cohort who were gadolinium positive, 13 (72%) had developed ≥1 MFD at 24 months from the time of their first gadolinium positive scan. The observation that a large percentage of the untreated cohort with gadolinium enhancement progress to an MFD at 24 months provides a reference point by which to assess the success of treatment with Lenti-D. These findings support the need that patients enrolled in the potentially pivotal ALD-102 Study show gadolinium enhancement at baseline and support a primary endpoint based on the prevention of MFDs.

4. **Gadolinium enhancement looks to be predictive of the probability of rapid progression in CCALD.** Of the 15 patients in the untreated cohort with scans that were gadolinium-positive that had repeat NFS assessments, 12/15 demonstrated rapid progression of NFS scores (defined as an increase of >5 points), with all 12 patients showing decline within 6-18 months. This finding supports the criteria for patients being enrolled in the pivotal ALD-102 Study to show gadolinium enhancement at baseline, as these patients would be expected to develop progressive disease without treatment.

5. **Allogeneic HSCT was associated with stabilization of disease.** Although there is a risk of morbidity/mortality with allogeneic HSCT, a successful transplant

provided clinically meaningful benefit to CCALD patients, especially for patients with early-stage disease. For most patients in the treated cohort (63%), no MFD showed up at 24 months after a HSCT. In addition, allogeneic HSCT was associated with resolution of gadolinium enhancement. Of those patients who would meet the eligibility criteria for the pivotal ALD-102 study (baseline NFS of 0 or 1, gadolinium-positive at baseline, baseline Loes between 0.5-9, inclusive), 3/20 (15%) patients developed an MFD within 24 months following an allogeneic HSCT.

6. **Allogeneic HSCT was associated with clinically significant morbidity/mortality, especially with unmatched/unrelated donors.**

    a. **Morbidity:** Following an allogeneic HSCT, engraftment failure was observed in 12/65 (18%) patients, and 10/12 (83%) were transplanted with unrelated donor cells. Despite prophylactic treatment, the GvHD rate was 54%, including an acute GvHD rate of 42% and chronic GvHD in 18% of patients. Due to the need for myeloablation before a HSCT, GvHD, and the need for immunosuppressive medication post-transplant, allogeneic HSCT is associated with a meaningful risk of life-threatening infection. Infections were the most frequently observed serious adverse event, with ≥1 serious infection reported in 19/65 (29%) patients following an allogeneic HSCT. The morbidity associated with allogeneic HSCT for CCALD patients supports testing Lenti-D in the pivotal ALD-102 Study as an alternative treatment option that is anticipated to avoid the issues of immune incompatibility that occur with allogeneic HSCT.

    b. **Mortality:** Following an allogeneic HSCT, the 100-day mortality rate was 8% and the one-year mortality rate was 19%. The projected probability of 2- and 5-year survival rates following an allogeneic HSCT were 82% and 74%, respectively. Analysis of survival by donor type (matched sibling donor vs. other) showed that the percentage of deaths following an allogeneic HSCT was lower in matched-sibling donor cases vs. other allogeneic HSCT cases. Most allogeneic HSCTs (46/65 patients; 71%) used an unrelated donor given the limited availability of HLA-matched sibling donors. Based on this analysis, bluebird decided to exclude patients with a sibling-matched donor from the potentially pivotal ALD-102 Study.

The ALD-101 study was able to define clear endpoints for measuring CCALD disease progression

Conclusions and key takeaways from the ALD 101 Study. Firstly, this study was able to define clear endpoints for measuring CCALD disease progression (NFS as a clinical functional score, gadolinium enhancement for MRI brain inflammation status, and Loes score as an MRI-based demyelination score). The ALD-101 Study clearly appears to support the idea that there remains a high unmet medical need for safer therapies, especially for patients lacking the option of a sibling-matched donor. It appears possible that several of the issues that contribute to the mortality/morbidity associated with the current standard of care, allogeneic HSCT, could potentially be avoided using autologous, gene-modified HSCs. bluebird believes the results of this study support its approach of using Lenti-D to treat CCALD, especially with several significant safety concerns commonly associated with allogeneic HSCT. Importantly, the data from the ALD-101 study were used to inform trial design (both patient and endpoint selection) for the upcoming pivotal ALD-102 Study for Lenti-D.

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Compelling Proof-of-Concept for Lenti-D in CCALD

From September 2006 to September 2010, four boys (aged 4-7 years) with CCALD were treated in Paris, France as part of a Phase 1/2 trial utilizing an approach similar to bluebird's Lenti-D with an earlier generation lentiviral vector supplied by a third party that shares many features with the Lenti-D vector. In the TG04.06.01 Study, all four patients had cerebral demyelinating lesions with Loes scores 2-7 prior to treatment. Gadolinium contrast enhancement indicated that the lesions were active and inflammatory in each patient. At the time of enrollment, all four patients had a normal neurologic examination with a NFS score of zero. While the trial is still ongoing, no new patients are expected to be enrolled beyond the initial four boys. The TG04.06.01 Study was sponsored by the French Institute of Health and Medical Research, or Inserm, in Paris.

From September 2006 to September 2010, four boys (aged 4-7 years) with CCALD were treated in Paris, France as part of a Phase 1/2 trial utilizing an approach similar to bluebird's Lenti-D with an earlier generation lentiviral vector

We believe the results in these four boys provide compelling clinical proof-of-concept support for bluebird's Lenti-D and were useful to aid design of the upcoming Phase 2/3 trial. All four boys are alive two years or more after receiving treatment (for context, data from the ALD-101 Study suggests a mortality rate of ~20% in the same two-year window post-allogeneic HSCT) and white matter brain damage has been significantly attenuated relative to what would be expected. The results show prolonged disease stabilization and so contrast with the natural history of CCALD disease in untreated patients, which is characterized by continuous and rapid progression of cerebral demyelination in most cases (especially in patients with gadolinium enhancement on brain MRI). All four patients showed some deterioration of neurologic function within the second year following transplant, which is roughly in line with expectations based on what is also frequently found following an allogeneic HSCT, given the time required for transplant-derived microglial cells to populate the brain. While neurologic deficits have been found in these patients following treatment, neurologic disease progression has been stabilized, or arrested, in all four boys (based on NFS score and Loes score stabilization), and 3/4 patients have shown resolution of gadolinium enhancement on brain MRI (which also indicates disease arrest; patient #3 failed to show this). Overall, these efficacy results appear comparable to outcomes that would be anticipated following a successful allogeneic HSCT. Below is a summary of the efficacy results for each of the four patients in the TG04.06.01 Study:

Patient #1: Loes score stabilized at month 30 and then remained stable through month 75.

Patient #2: Loes score stabilized at month 30 and then remained stable through month 64. Initially, gadolinium enhancement was positive, resolved, reappeared in the parietal area, and then resolved and has remained negative.

Patient #3: Loes score stabilized at month 33, but gadolinium enhancement has persisted. This patient had active, progressive disease following the transplant leading to the development of significant cognitive deficits with loss of ability for new learning consistent with a frontal lobe syndrome (including the loss of spontaneous speech by month 33 and urinary incontinence). At 54 months following transplant, he had no additional decline in NFS or Loes scores since his month 33 evaluation.

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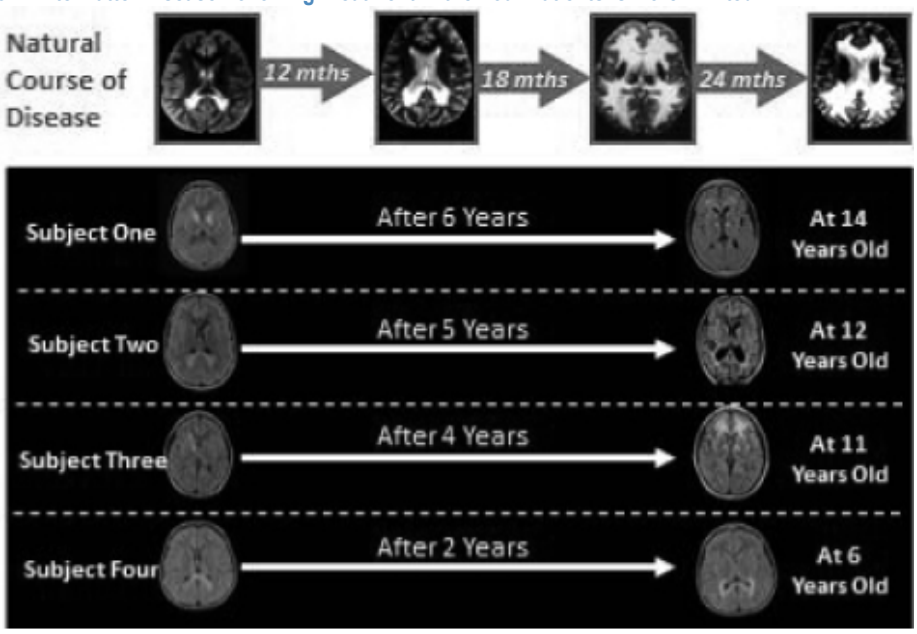
Patient #4: Loes score stabilized at month 16 and then remained stable at 24 months. Gadolinium enhancement disappeared 45 days after transplant and was not detectable at month 12.

As assessed by NFS and brain MRI, patients #1, #2, and #4 showed encouraging evidence of disease stabilization. Additionally, gadolinium enhancement resolved in these same three patients, suggesting a reduction of neuroinflammation. Results for the first two of these patients treated in this study were reported in the November 2009 issue of Science.

Figure 8: Brain MRI Images from the Four Boys Treated in the TG04.06.01 Study; the Progression of White Matter Disease Following Treatment in the Four Patients Is More Limited



Source: Company Reports

Key Opinion Leaders in the field of CCALD were highly encouraged with the proof-of-concept demonstrated by bluebird's gene therapy approach

Very importantly, there have been no incidents of gene therapy-related adverse events so far in the TG04.06.01 Study. The infusion procedure was clinically uneventful for all four patients. All four boys achieved successful engraftment within 15 days following the transplant. In addition, no patient has experienced adverse events due to immune incompatibility issues typically associated with allogeneic HSCT, such as GvHD.

We received encouraging physician feedback on these results. When discussing these findings with ALD Key Opinion Leaders (KOLs), the feedback we gathered was very positive. Each physician agreed that these results show clinically meaningful effects in the progression of the disease, with 3/4 patients showing a very good neurological outcome. In general, the ALD KOLs we spoke with viewed the disease stabilization of CCALD boys in France as clear evidence that Lenti-D could be an effective therapy.

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ALD-102: A Pivotal Phase 2/3 Study to Begin in Late 2013

Based on the promising early clinical proof-of-concept results described above, bluebird plans to initiate a pivotal Phase 2/3 trial, called the ALD-102 Study, in CCALD in the US and Europe (UK and France) in late 2013 to examine Lenti-D in preserving neurological function and stabilizing cerebral demyelination in patients with CCALD. In April 2013, the FDA informed bluebird that the IND filed in March was active. As such, the program is ready to launch, as GMP runs are complete and the company has clinical and regulatory clarity.

If successful, and pending further discussion with the FDA, the results from the ALD-102 Study could potentially form the basis of a BLA submission to the FDA

The ALD-102 Study is likely to be a pivotal trial. If successful, and pending further discussion with the FDA, the results from the ALD-102 Study could potentially form the basis of a BLA submission to the FDA and a MAA to the EMA. One physician we spoke with felt that 15 patients should be sufficient for bluebird to gain approval in CCALD. However, the quality of the clinical data will determine if another study (or data in more patients) is required for approval. bluebird's rationale for moving straight into a potentially pivotal trial is based on the fact that CCALD is a uniformly fatal disease if left untreated, its rarity precludes traditional clinical development, and it has initial clinical proof-of-concept data from the Phase 1/2 TG04.06.01 Study.

ALD-102 Study design. This study will be designed as a single-dose, open-label, non-randomized (single arm), international, multicenter, Phase 2/3 trial to evaluate Lenti-D in preserving neurological function and stabilizing cerebral demyelination in patients with CCALD. The goal is to demonstrate disease stabilization. The patients will be followed for 24 months following transplant. Per the FDA guidance for gene therapy in clinical trials, bluebird will be monitoring patients in a long-term follow-up protocol to evaluate safety for up to 15 years and will monitor efficacy endpoints to show a sustained benefit. Up to 15 patients will be enrolled to obtain at least 12 evaluable patients that have been transplanted with Lenti-D. Patients will be followed over a 24-month period for the onset of major functional disabilities (MFDs) and other key measures of disease progression. The design of the ALD-102 Study is built upon the observations made in the TG04.06.01 Study but will enroll more patients (up to 15 vs. 4) and is a multicenter, international trial with a different primary endpoint (which was determined by analysis of the ALD-101 Study data). The design was consulted with KOLs in the field of gene therapy and has predefined criteria for success.

Key inclusion criteria for the ALD-102 Study. Patients must be age 15 years or younger with a confirmed diagnosis of active CCALD, including elevated levels of plasma very long chain fatty acids (VLCFA), a brain MRI Loes score of 0.5-9 (inclusive), evidence of gadolinium enhancement, and an NFS of 0 or 1. Essentially bluebird is trying to enroll children that are gadolinium positive but have not yet progressed in their disease. Based on the ALD-101 natural history trial, bluebird believes these children may benefit most from Lenti-D.

Exclusion criteria for the ALD-102 Study. Importantly, patients with a willing matched sibling HSCT donor will be excluded from the study. In addition, patients with NFS >1 will be excluded to avoid boys that have already seen rapid progression.

The primary endpoint in the ALD-102 Study will be the proportion of patients who have no major functional disabilities (MFDs) at 24 months (+/- 2 months)

post-transplant. Six MFDs have been identified as being key, including 1) loss of communication, 2) cortical blindness, 3) tube feeding, 4) total incontinence, 5) wheelchair dependence, and 6) complete loss of voluntary movement. If any MFDs develop, then the patient has deemed to have failed. This is effectively a composite primary endpoint and was based on results from bluebird's retrospective ALD-101 Study and consultation with KOLs in the field of ALD. Secondary endpoints (in each case measured at 24 months, +/-2 months post-transplant) capture the key measures of CCALD disease status, including the change from baseline in NFS and Loes score, resolution of gadolinium enhancement on MRI, and determination of MFD-free survival and overall survival. The number of patients for this study was not determined by formal statistical methods, but bluebird believes 12 patients may be sufficient to show a robust effect on the binary response endpoint, where a responder is defined as a patient with no MFD at 24 months (+/-2 months) following transplant. Safety evaluations will be performed during the trial and will include assessment of the success and kinetics of HSC engraftment, the incidence of transplant-related mortality through 100 and 180 days post-transplant, detection of vector-derived replication of the HIV-1 virus, and characterization and quantification of events related to the location of insertion of the functional gene in target cells. Patients will be followed for up to 15 years for safety.

The Phase 2/3 ALD-102 Study is the first trial that will use bluebird's current Lenti-D viral vector and product candidate

The Phase 2/3 ALD-102 Study is the first trial that will use bluebird's current Lenti-D viral vector and product candidate. While this could be viewed as a risk associated with the ALD-102 Study, this product is believed to be more potent than the product used in the Phase 1/2 TG04.06.01 Study due to use of an improved vector. With improvements in the vector manufacturing and transduction processes, bluebird expects to obtain a higher frequency of gene-modified HSCs in the patients treated in the ALD-102 Study vs. what was achieved in the TG04.06.01 Study. This could translate into improved clinical benefit due to the increased expression of normally-functioning ALDP.

bluebird was granted orphan drug designation for Lenti-D by both the FDA and the EMA in June 2012. Orphan drug designation, which is intended to aid drug development for rare diseases, provides benefits, including the potential for funding for certain clinical trials, study-design assistance, and multiple years of market exclusivity upon regulatory approval.

Preclinical data. bluebird has completed a single-dose toxicology study for Lenti-D in immunodeficient mice following a single IV administration. This study evaluated the engraftment of normal human HSCs transduced with Lenti-D vector and the reversibility of any toxicity after a 28- and 91-day post-treatment recovery period. Toxicity was assessed based on mortality, clinical observations, body and organ weights, and anatomic pathology. In addition, engraftment of the HSCs was analyzed in the bone marrow of all the animals by fluorescence-activated cell sorting and by polymerase chain reaction procedures. Encouragingly, results found no Lenti-D-related effects in body and organ weight, hematology, or clinical chemistry parameters. In addition, histopathological assessment did not show any Lenti-D-related microscopic findings. There were no significant differences (aside from slight individual animal variation) in cellularity of the bone marrow in treated control and test animals. Overall, Lenti-D appeared to be well tolerated after a single IV injection.

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Additional potential indications for Lenti-D. The ACALD and AMN subsets of ALD represent potential additional indications for Lenti-D. Allogeneic HSCT has shown some early success in ACALD patients, suggesting autologous gene therapy with Lenti-D may also be useful in these patients. Although AMN represents a heterogeneous population of patients, ~40% present with cerebral symptoms. However, no allogeneic HSCT studies have been carried out in the AMN population to provide evidence for a gene therapy based approach to treat the disease. The safety risks associated with allogeneic HSCT have restricted its use in treating ACALD and AMN, which may provide an opportunity to expand the use of Lenti-D in these populations.

What Does the Competitive Landscape Look Like for CCALD?

As far as we are aware, there are no competing products in clinical development for CCALD

For CCALD, the current standard of care is allogeneic stem cell transplant, if a matched donor can be found and the patient is healthy enough to undergo transplant. However, HSCT is sub-optimal due to the risk of treatment-related side effects and toxicity (or GvHD). Somehow reducing the risk of GvHD with allogeneic HSCT would represent a competing technology and various academic centers around the world are seeking to develop improvements to this procedure. As far as we are aware, there are no competing products in clinical development for CCALD. Some physicians recommend glyceryl trierucate (also known as Lorenzo's Oil) to patients with ALD or AMN even though this treatment has not been clinically proven to address the cerebral symptoms of ALD and has not been approved by any major regulatory agency. However, there are efforts underway to gain FDA approval for Lorenzo's Oil. In addition, there are also some early-stage, preclinical efforts in academic centers to test anti-oxidants for AMN patients.

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LentiGlobin

bluebird's next most advanced product candidate is LentiGlobin, which it is developing as a potential one-time treatment for both beta-thalassemia and sickle cell disease (SCD). bluebird's approach involves the *ex vivo* insertion of a single codon variant of the fully functional human ß-globin gene via an HIV-1 based lentiviral vector into a patient's own HSCs with the aim of restoring expression of the ß-globin protein required for hemoglobin production. The goal is to produce correctly functioning hemoglobin A and normal RBCs in patients with beta-thalassemia and SCD. The codon variant, referred to as T87Q, also serves as a distinct biomarker used to quantify expression levels of the functional ß-globin protein derived from the vector (bb305) in patients. The gene-modified HSCs are referred to as the LentiGlobin drug product. bluebird is currently conducting a Phase 1/2 trial in France to investigate an earlier generation of its LentiGlobin vector for the treatment of beta-thalassemia major and SCD. Initial proof-of-concept data from this study were published in Nature (2010). bluebird recently began an extension of this study under a revised protocol for LentiGlobin, the HGB-205 Study. In addition, the company is planning to begin a second Phase 1/2 study in the US for LentiGlobin, the HGB-204 Study, for beta-thalassemia major in mid-2013. The approach of using autologous gene-modified HSCs to treat these diseases would avoid the adverse effects of immune incompatibility that are responsible for the mortality/morbidity associated with allogeneic HSCT. While successful allogeneic HSCT may achieve transfusion independence, the risk of death with allogeneic HSCT in adults with beta-thalassemia major is >20%, and for this reason it is not standard practice for adult patients.

bluebird's approach with LentiGlobin involves the *ex vivo* insertion of a single codon variant of the fully functional human ß-globin gene via an HIV-1 based lentiviral vector into a patient's own HSCs

Clinical Data with LentiGlobin for Beta-Thalassemia Major

From September 2006 through November 2011, three patients with beta-thalassemia major were treated in France as part of a Phase 1/2 trial, the LG001 Study, with autologous HSCs transduced *ex vivo* with an earlier generation of bluebird's LentiGlobin vector, called HPV569 (the "HPV569 drug product"). No additional patients will be treated with the HPV569 vector.

Results from the LG001 Study. Four patients were enrolled in the LG001 Study, although only three patients were treated and successfully transplanted with the HPV569 drug product as one patient was ineligible due to pre-transplant complications. Only two of the three patients that were successfully transplanted achieved successful engraftment. All the patients required significant transfusion support prior to treatment. Below are the outcomes for each patient:

- **Patient #1 (non-evaluable):** Patient withdrew prior to treatment, as the patient was ineligible for transplant due to pre-transplant complications.

- **Patient #2 (a 29-year old female):** The patient received a low dose of HPV569 drug product (pre-bluebird) with cell counts far below the current standards in transplant practice. As such, the patient was not deemed to be dosed correctly and failed to engraft. This patient would not have been eligible for the upcoming Phase 1/2 trials.

- **Patient #3 (an 18-year old male, when transplanted):** This patient had been transfusion dependent since the age of two and was administered the HPV569 vector in 2007, aged 18. The patient's revised stem cells repopulated his bone marrow, and the revised versions now make up ~10-15%. For the first year following transplant, this patient experienced a decline in both the volume and frequency of transfusion requirements and eventually became transfusion-independent ~1 year after treatment. Encouragingly, the patient has remained transfusion-independent since 2008 (is in remission), even with frequent blood withdrawals to eliminate iron accumulation, and so is classified as a "responder." He is producing over one-third of his hemoglobin from the gene therapy treatment and his levels of hemoglobin are roughly two-thirds the normal level, so while the patient is still mildly anemic, his condition is no longer life-threatening. The patient had some functional hemoglobin production already; not enough to survive without blood transfusions, but enough that the additional activity of the inserted gene brought him up to manageable levels. The patient has experienced no serious adverse events. Side effects deemed to be treatment-related were attributed to study procedures or myeloablative conditioning, not the HPV569 drug product itself. One notable finding in this patient was the detection of partial clonal dominance of a common myeloid progenitor bearing an integrated vector in the third intron of the HMGA2 gene, which led to a relatively large proportion of the gene therapy modified cells being derived from a single clone in which the lentiviral vector had inserted into the HMGA2 gene (i.e. a disproportionate number of cells had the same insertion site). This persisted for 2-3 years, and while there was some initial concern that the observed clonal dominance might represent a pre-leukemic event, there have been no adverse clinical consequences, or any signs of cancer, in >5 years since the finding. Encouragingly, the presence of the HMGA2 clone has steadily declined over time so that it is not the most common clone any more. Data from Patient #3 were first reported in Nature (2010).

The achievement of transfusion independence in Patient #3 (1 of 3 patients who were successfully transplanted) appears to be a direct benefit of that patient being treated with the HPV569 drug product

- **Patient #4 (female):** Following transplant, this patient showed a delayed recovery of platelets and needed platelet transfusion 3x/week until day 100, with the final transfusion on day 122. Therapeutic hemoglobin in reticulocytes was detectable 1 month after the transplant. At 2 and 6 months following the transplant, therapeutic hemoglobin was expressed in 4.0% and 3.1% of reticulocytes, respectively. This patient is clinically stable, has fully engrafted, and feels well, although has not "responded" yet as importantly, transfusion requirements remain unaltered at ~1x/month with T87Q corrected globin stably expressed at levels well under those shown by Patient #3 at comparable time points. This patient has not mimicked the pharmacodynamics of Patient #3 and is transducing at a lower level than hoped for. Additional follow-up is needed to establish the complete trajectory of T87Q globin production and vector copy number. Side effects deemed to be treatment-related were all attributed to study procedures or myeloablative conditioning, not the HPV569 drug product.

The results of the Phase 1/2 LG001 Study provide human proof-of-concept for the use of LentiGlobin in beta-thalassemia major. The achievement of transfusion independence in Patient #3 (1 of 3 patients who were successfully transplanted) appears to be a direct benefit of that patient being treated with the HPV569 drug product, as there do not appear to be any reported cases of spontaneous transfusion independence in patients with beta-thalassemia major in the literature. Data from this

patient have provided initial evidence of transfusion independence following treatment with gene modified HSCs. We believe this finding provides clinical proof-of-concept as the lentiviral vector used in this study shares many features with bluebird's current LentiGlobin vector. While Patient #4 is stable, she is still transfusion dependent, with bluebird indicating that the patient is transducing at a lower level than it would have hoped for. However, the company believes this could be overcome by using its next-generation vector. With the improvements introduced into the vector manufacturing and transduction processes, bluebird expects to obtain a higher frequency of gene-therapy modified HSCs in the patients treated in the HGB-205 and HGB-204 clinical trials vs. what was achieved in the LG001 Study. In turn, this could translate into greater clinical efficacy and an improved clinical benefit by virtue of a higher level of production of normally functioning hemoglobin. Overall, the results of the LG001 Study were helpful for informing the design of the HGB-205 and HGB-204 clinical trials.

Going forward, bluebird plans to use its new LentiGlobin vector based on higher transduction efficiency and expression of ß-globin protein in target cells vs. the HPV569 vector. At the request of the French regulatory agency, in 2012 bluebird submitted a CTA with a revised clinical protocol for the LG001 Study as a result of the company's decision to use its newer LentiGlobin BB305 vector for clinical studies going forward. Preclinical work on the LentiGlobin BB305 vector showed that its transduction efficiency was higher vs. the HPV569 vector used in the LG001 Study, resulting in higher expression of the therapeutic ß-globin protein in transduced cells, despite unchanged expression levels per vector copy. With the next-generation BB305 vector estimated to be ~3-4 times more potent than the HPV569 vector, this provides some comfort going forward. However, it is also worth noting that the new vector appears to have also caused increased production of a protein associated with benign tumors. One physician we consulted with on this topic stated the need to wait for actual human data with the new LentiGlobin vector before getting too enthusiastic but that, based on the in vitro studies (animal models and lab work) of cell transduction, the next-generation vector looks impressive. The CTA was accepted in 2012, resulting in an active study, now called the HGB-205 study (which bluebird recently launched in France).

On giving his impressions of the data from the LG001 Study, one physician described them as a "mixed bag" but that some proof-of-concept was certainly apparent

On giving his impressions of the data from the LG001 Study, one physician described them as a "mixed bag" but that some proof-of-concept was certainly apparent. The "mixed bag" quote alluded to success in some patients (especially Patient #3), but not in others (as yet), such as Patient #4. However, he believes proof-of-concept is certainly apparent in Patient #3 with ~3 g/dL improvement in the level of hemoglobin. While the lack of success in Patient #2 may just be a technical issue, he also stated that the findings from Patient #4 put pressure on the new LentiGlobin vector in upcoming trials. Lastly, he also stated that the question on whether there is a time limit for how long the LentiGlobin drug candidate would function effectively for remains unanswered.

HGB-205 Study: Phase 1/2 Trial in France for Beta-Thalassemia Major and Sickle Cell Disease

The HGB-205 Study is a Phase 1/2 continuation study investigating the LentiGlobin drug candidate in up to 7 additional patients (three have been treated already with the old HPV569 vector) with beta-thalassemia major or SCD from a single site in France (open label). The study will evaluate blood transfusion requirements following

transplant, as well as the number of hospitalization days post-transplant discharge. In SCD patients only, efficacy will also be measured based on the number of vaso-occlusive crises or acute chest syndrome events.

Inclusion criteria. Patients must be between 5-35 years of age with a diagnosis of beta-thalassemia major or SCD. Patients with beta-thalassemia must have received >100 mL/kg/year of pRBCs per year for the previous two years, and patients with SCD must have failed to achieve clinical benefit from hydroxyurea and have an additional poor prognostic risk factor (e.g., recurrent veno-occlusive crises or acute chest syndromes). In addition, patients must be eligible for allogeneic HSCT, but without a matched related donor.

Exclusion criteria. Patients with a matched sibling allogeneic HSCT donor will be excluded from the HGB-205 study.

Efficacy and safety measures. For all patients, efficacy will be measured by RBC transfusion requirements per month and per year, post-transplant and the number of total in-patient hospitalization days (post-transplant discharge) at 6, 12 and 24 months. For SCD patients only, efficacy will be measured by the number of vaso-occlusive crises or acute chest syndrome events at 6, 12 and 24 months. Safety evaluations to be performed during the study include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient, and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.

HGB-204 Study: A US-Based Phase 1/2 Trial for Beta-Thalassemia Major

Preliminary data from the HGB-204 Study is expected in late 2014

In December 2012, bluebird submitted an IND with the FDA for a Phase 1/2 trial, the HGB-204 Study, for the LentiGlobin product candidate. The trial is a single-dose, open-label, non-randomized, multi-center Phase 1/2 trial in the US to investigate the new LentiGlobin product candidate (with improved potency and transduction vs. the old HPV569 vector, according to bluebird) in increasing hemoglobin production and eliminating/reducing transfusion dependence. bluebird was cleared to begin the study in January 2013. This trial is also expected to begin in mid-2013 and up to 15 adults will be enrolled from four US sites. The study will also be a 24-month trial, just like the HGB-205 French trial and all patients will go into the 13-year long-term follow-up. This trial is ready to launch, as GMP runs are complete, and the IND (US) is active (for beta-thalassemia). Preliminary data from the HGB-204 Study is expected in late 2014.

Inclusion criteria. Patients must be 18-35 years of age with a diagnosis of beta-thalassemia major and who receive >100 mL/kg/year of pRBCs or >8 transfusions of pRBCs/year in each of the two years prior to enrollment. Patients also must be eligible for allogeneic HSCT. One difference from the French HGB-205 Study, which is enrolling patients 5-35 years old, is that the US HGB-204 Study will enroll adults only.

Efficacy measures. Efficacy will be assessed mainly by the production of ³2.0 g/dL of hemoglobin A containing ßA-T87Q-globin for the 6-month period between 18-24 months following the transplant (the primary endpoint). In order to allow for

endogenous hemoglobin production following the transplant, patients will be transfused with RBCs only when total hemoglobin falls <7.0 g/dL. The rationale for the primary endpoint is that production of ³2.0 g/dL of hemoglobin A containing ßA-T87Q -globin represents a clinically meaningful increase in endogenous hemoglobin production that would be expected to diminish transfusion requirements and could result in transfusion independence. Exploratory efficacy endpoints include RBC transfusion requirements per month and per year, following the transplant. The ultimate goal of this therapy is to reduce the number of required blood transfusions. Safety evaluations include success and kinetics of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived replication-competent lentivirus in any patient and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia. Each patient will remain on study for ~26 months from time of consent and then will be enrolled in a long-term follow-up protocol that will assess the patient beyond the initial 24 months.

One beta-thalassemia treating physician we spoke with believes that if LentiGlobin can lower the frequency of blood transfusions by ~50% then that would be clinically meaningful, with the ultimate goal being transfusion independence

The ultimate goal is to achieve transfusion independence. Following successful engraftment, it is hoped that the clinical benefits for LentiGlobin in beta-thalassemia and SCD, indicated by reduction/elimination of blood transfusion requirements, and number of in-patient hospitalization days (post-transplant discharge) in beta-thalassemia patients and, for SCD, several additional endpoints, will begin to become evident within 12-24 months after the transplant. Both the HGB-205 and the HGB-204 trials are open label studies. As such, based on the outcomes, bluebird will make a decision about when the appropriate time to move into a pivotal program is. We anticipate a decision on this could potentially be made ~late 2014. If the LentiGlobin product candidate is unable to raise hemoglobin levels high enough, then this program could just be viewed as a great science experiment without any clinical application. One beta-thalassemia treating physician we spoke with believes that if LentiGlobin can lower the frequency of blood transfusions by ~50% then that would be clinically meaningful, with the ultimate goal being transfusion independence. For example, raising a patient's hemoglobin level from 6 g/dL to 8 g/dL could potentially remove the need for transfusions (15 g/dL is the normal hemoglobin level). However, raising the level from 2 g/dL to 5 g/dL would not remove the patient's need for transfusions. Physicians we consulted with generally saw the range of transfusion independence as 7-9 g/dL hemoglobin (with 10 g/dL representing a "good" level), although this level might not be high enough for all forms of beta-thalassemia. As such, we view clinical success in beta-thalassemia as a higher clinical hurdle vs. the CCALD indication.

Preclinical data review. Various preclinical studies have been carried out using the LentiGlobin BB305 vector in human HSCs isolated from patients with SCD and in *in vivo* mouse transplant models. Results showed that transduction efficiency was higher with the LentiGlobin BB305 vector vs. the HPV569 vector, based on higher expression levels of the therapeutic ß-globin protein in cells transduced with this vector despite unchanged protein expression levels per vector copy. *In vivo* pharmacology and safety studies conducted in a mouse model for beta-thalassemia also provided no evidence that bluebird's lentiviral vectors resulted in any side effects or alteration of bone marrow homeostasis in animals treated with cells transduced with either the HPV569 or the BB305 vector. In two independent *in vitro* immortalization assays, the LentiGlobin BB305 vector demonstrated a reduced risk of IVIM and genotoxicity in murine HSCs vs. positive control vectors known to have oncogenic potential. Results of integration site analyses in mice treated with

syngeneic bone marrow cells transduced with either LentiGlobin BB305 or HPV569 vectors showed no signs for clonal outgrowth. The integration site profile of the two vectors was similar and typical for HIV-1 based lentiviral vectors. Both vectors showed a large overlap of integration sites in identical common integration site regions. Although integration near oncogenes was increased in the analyzed vector samples vs. the theoretical random integration site data, there was no increase of integration sites near oncogenes in the post-transplant samples isolated from the bone marrow at necropsy vs. pre-transplant samples of transduced bone marrow.

In 2001, a preclinical study corrected SCD in mice using gene therapy. Mice were bioengineered to contain a human gene that produced defective hemoglobin, resulting in SCD. HSCs containing the defective gene were removed from the bioengineered mice and gene-modified through the addition of an anti-sickling gene via a lentiviral vector. The modified gene (T87Q) produced ß-globin that resulted in a modified normal hemoglobin molecule that prevented the sickling process. This gene construct is the same construct bluebird uses in its LentiGlobin drug candidate. After inserting the anti-sickling gene, the corrected marrow was transplanted into other mice with SCD whose bone marrow had been removed by radiation. Ten months later, blood samples from the transplanted mice showed a high level of expression of the anti-sickling ß-hemoglobin gene. Data from this preclinical study were published in Science (2001).

Manufacturing scale up is ongoing

bluebird is currently in the process of adapting its LentiGlobin vector production technology to a larger, suspension-based bioreactor process. This could potentially scale up production from 100 to >1,000 liters in a single production run. To date, bluebird has successfully produced LentiGlobin vectors on a small scale and is transferring the new process to a contract manufacturer in compliance with Good Manufacturing Practices to accommodate future demand for its product candidates.

What Does the Competitive Landscape Look Like for Beta-Thalassemia?

For beta-thalassemia, patients must undergo chronic blood transfusions (to address the anemia) and long-term iron chelation regimens (to remove excess iron in their blood). In addition, some patients with beta-thalassemia receive HCST treatment, especially if a sufficiently well-matched source of donor cells is identified. However, HSCT is sub-optimal due to the risk of treatment-related side effects and toxicity (i.e., GvHD; again improving the HSCT procedure would be competitive). Various approaches are being tested to improve the current treatment options, including iron modulating agents and fetal hemoglobin regulators. There are also several different groups developing gene therapy approaches for beta-thalassemia. Some use a similar *ex vivo* autologous approach to bluebird but with different vectors and different cell processing techniques. These include Memorial Sloan Kettering (received approval for its IND in 2012, and is recruiting for a Phase 1/2 gene therapy study), GlaxoSmithKline (which has entered into an agreement with the San Raffaele Telethon Institute for Gene Therapy to advance several gene therapy programs, including one for beta-thalassemia), and Sangamo (which has announced plans to test zinc finger nuclease-mediated gene-correction techniques in hemoglobinopathies including beta-thalassemia). In addition, sotatercept (ACE-536), an investigational protein therapeutic that increases RBC levels by targeting molecules in the TGF-β superfamily, is being developed for beta-thalassemia by Acceleron as part of a global

collaboration with Celgene. However, the drug has a very different mechanism of action vs. LentiGlobin. It is in Phase 2 testing but is not seen as a competitor product to bluebird's, as it is more for symptomatic relief (to treat the anemia) and so could potentially be used in combination with LentiGlobin.

What Does the Competitive Landscape Look Like for SCD?

The current standard of care for SCD in the developed world is chronic blood transfusions or hydroxyurea. In addition, such patients regularly receive iron chelation therapy to help manage the iron overload associated with chronic blood transfusions. There are ongoing studies that are testing hydroxyurea in various populations, and data from these studies could influence its future use. In addition, some patients with SCD receive allogeneic HSCT, especially if a sufficiently well-matched source of donor cells is available. Various academic centers around the world are seeking to develop improvements to allogeneic HSCT. In addition, there is interest from academic centers and biopharmaceutical companies in developing new treatments for SCD. A number of different approaches are being developed, targeting various aspects of SCD pathophysiology, including fetal hemoglobin regulators (i.e., HQK-1001 in Phase 2 trials supported by HemaQuest Pharmaceuticals, and vorinostat in Phase 2 trials supported by Merck), and pan-selectin inhibitors (including GMI-1070 in Phase 2 trials supported by GlycoMimetics/Pfizer for vaso-occlusive crisis (VOC) of sickle cell disease). There are also several different groups developing gene therapy approaches for SCD. Some of these groups use a similar *ex vivo* autologous approach to bluebird, but use different vectors and different cell processing techniques. These include UCLA (which may pursue a Phase 1/2 gene therapy study for SCD) and Sangamo BioSciences (which has plans to investigate the use of zinc finger nuclease-mediated gene-correction techniques in hemoglobinopathies including SCD).

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Safety: So Far, So Good…

Importantly, no adverse safety events have emerged to date in either the Lenti-D CCALD or the LentiGlobin beta-thalassemia programs over the past ~six years. This is important, as in some previous clinical studies involving viral vectors for gene therapy, some patients have experienced serious adverse events, including the development of leukemia due to vector-related insertional oncogenesis. In addition, no evidence has emerged to date of transplant rejection commonly associated with allogeneic stem cell transplant.

No adverse safety events have emerged to date in either the Lenti-D CCALD or the LentiGlobin beta-thalassemia programs

However, the risk of insertional oncogenesis remains a concern for gene therapy. A risk in any gene therapy product based on viral vectors is that the vector will insert near cancer-causing oncogenes resulting in uncontrolled clonal proliferation of mature cancer cells in the patient. Gene therapy experts we consulted with cited the potential development of leukemias as possibly the biggest risk factor regarding safety to be on the look out for. Having said this, previous gene therapy clinical trials that experienced leukemic events often employed murine retrovirus vectors rather than lentiviral vectors (like the HIV-1 virus), which are a subtype of retrovirus used today by bluebird and others in this field. The integration of site selectivity of lentiviral vectors is fundamentally different vs. murine retrovirus vectors (which have significant enhancer elements), and bluebird now has a growing number of patients (from multiple trials in four countries) treated with lentiviral vectors in which no safety signals have emerged. One gene therapy KOL we consulted with was “fairly confident” that there will not suddenly be a change with regards to safety results with the use of lentiviral vectors. In addition, there are also better preclinical models (genotoxicity models) for testing gene therapies nowadays.

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Revenue Builds

We estimate ~$250 million in worldwide peak sales for Lenti-D in CCALD. bluebird, along with KOLs with whom we spoke, estimates an annual incidence of CCALD in the developed world at ~200 patients. We assume slight year-over-year growth in this number. This, however, could be overly conservative, as several US states, for example, are currently considering universal newborn screening for ALD. Physicians expect that newborn screening will be widely adopted in the US within the next five years, and potentially elsewhere, providing for the opportunity to identify more boys and allowing intervention at the first sign of disease onset. We assume 20% of CCALD patients are able to find a sibling match and so are not considered candidates to receive Lenti-D. bluebird decided to exclude patients with a sibling-matched donor from the pivotal ALD-102 Study, so we do not assume use in these patients in our model, although, over time, treatment with Lenti-D could be shown to be as good as a sibling match. In the remaining patient pool, we then assume peak penetration of 85% five years post launch. Regarding price, we assume a base case price of $1.5 million per patient, which translates into peak sales of ~$250 million. With a more conservative pricing assumption of $1 million per patient, we achieve peak sales of ~$160 million, and with a more aggressive pricing assumption of $2 million per patient, we achieve peak sales of ~$360 million. We assume a launch in 2018, but this timeline depends on the ALD-102 Study enrollment rate.

Figure 10: Our Lenti-D Revenue Build for CCALD

CCALD	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
WW annual incidence	200	202	204	206	208	213	219	224	230	235	241	247	254
% of pts unable to find a sibling match	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
No. of pts unable to find a sibling match	160	162	163	165	166	171	175	179	184	188	193	198	203
Penetration rate	0%	0%	0%	0%	0%	10%	30%	55%	75%	85%	85%	85%	85%
No. of pts treated	0	0	0	0	0	17	52	99	138	160	164	168	172
Pricing assumptions:													
Low assumption						$1,000,000	$1,000,000	$1,000,000	$1,000,000	$1,000,000	$1,000,000	$1,000,000	$1,000,000
Base assumption						$1,500,000	$1,522,500	$1,545,338	$1,568,518	$1,592,045	$1,615,926	$1,640,165	$1,664,767
High assumption						$2,000,000	$2,060,000	$2,121,800	$2,185,454	$2,251,018	$2,318,548	$2,388,105	$2,459,748
Sales ($,M):													
Low pricing assumption						$17.1	$52.5	$98.6	$137.8	$160.1	$164.1	$168.2	$172.4
Base pricing assumption						**$25.6**	**$79.9**	**$152.4**	**$216.2**	**$254.9**	**$265.2**	**$275.9**	**$287.1**
High pricing assumption						$34.1	$108.1	$209.2	$301.2	$360.4	$380.5	$401.7	$424.1

Source: J.P. Morgan estimates

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We estimate ~$1.175 billion in worldwide peak sales for LentiGlobin in beta-thalassemia. bluebird estimates that the worldwide annual prevalence of beta-thalassemia is 10,000-15,000 patients, with ~60-80% of these patients considered to be severe (or major) based on being transfusion dependent. We estimate a peak penetration of LentiGlobin of 15% into this prevalence pool (before declining). In addition, bluebird estimates that the worldwide annual incidence of beta-thalassemia is 1,000-1,500 patients with 60-80% of these patients transfusion dependent. Patients who are regularly transfused are the target market, in our view. Approximately 20% of these patients are assumed to be able to find a sibling match, and with the remaining 80% of patients, we assume peak penetration of 55%. Regarding price, we assume a base case price of $750,000 per patient, which translates into peak sales of ~$1.175 billion. With a more conservative pricing assumption of $500,000 per patient, we achieve peak sales of ~$725 million, and with a more aggressive pricing assumption of $1 million per patient, we achieve peak sales of ~$1.685 billion. As beta-thalassemia is a more prevalent disease vs. CCALD, we assume a lower price for the indication. We assume a launch in 2019, but this timeline depends on the timing of pivotal studies, the enrollment rate of patients, and the necessary duration of follow-up.

Figure 11: Our LentiGlobin Revenue Build for Beta-Thalassemia

Beta-Thalassemia	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Prevalence pool													
WW annual prevalence	12500	12563	12625	12688	12752	12816	12880	12493	11856	11086	10171	9154	8367
% considered severe based on transfusion dependence	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
No. of pts considered severe based on transfusion dependence	8750	8794	8838	8882	8926	8971	9016	8745	8299	7760	7120	6408	5857
Penetration rate	0%	0%	0%	0%	0%	0%	5%	8%	10%	13%	15%	13%	10%
No. of pts treated from prevalence pool	0	0	0	0	0	0	451	700	830	970	1,068	833	586
Incidence pool													
WW annual incidence	1250	1263	1275	1288	1301	1314	1327	1340	1354	1367	1381	1395	1409
% considered severe based on transfusion dependence	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
No. of pts considered severe based on transfusion dependence	875	884	893	902	911	920	929	938	947	957	967	976	986
% of pts unable to find a sibling match	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
No. of pts unable to find a sibling match	700	707	714	721	728	736	743	750	758	766	773	781	789
Penetration rate	0%	0%	0%	0%	0%	0%	5%	15%	30%	45%	50%	55%	55%
No. of pts treated from incidence pool	0	0	0	0	0	0	37	113	227	345	387	430	434
No. of pts treated from incidence+prevalence pool	0	0	0	0	0	0	488	812	1,057	1,314	1,455	1,263	1,019
Pricing assumptions:													
Low assumption						$500,000	$500,000	$500,000	$500,000	$500,000	$500,000	$500,000	$500,000
Base assumption						$750,000	$761,250	$772,669	$784,259	$796,023	$807,963	$820,082	$832,384
High assumption						$1,000,000	$1,030,000	$1,060,900	$1,092,727	$1,125,509	$1,159,274	$1,194,052	$1,229,874
Sales ($,M):													
Low pricing assumption					$0.0	$0.0	$244.0	$406.1	$528.7	$657.2	$727.3	$631.3	$509.7
Base pricing assumption					**$0.0**	**$0.0**	**$371.4**	**$627.6**	**$829.2**	**$1,046.4**	**$1,175.2**	**$1,035.4**	**$848.6**
High pricing assumption					$0.0	$0.0	$502.6	$861.7	$1,155.4	$1,479.5	$1,686.2	$1,507.5	$1,253.8

Source: J.P. Morgan estimates

Despite a steep up-front cost, gene therapy in the long run may be cost-effective by eliminating expensive ongoing care, intervention and complications

The pricing of bluebird's products is highly variable and a somewhat controversial aspect of these revenue builds. How do you price a one-time potentially curative therapy? bluebird's products potentially allow for these diseases to be arrested, corrected or treated with a single therapeutic administration, as many of the corrected cells will live in the patient's body in perpetuity and have the potential to deliver long-term (possibly life-long) effects. Since gene therapy represents a unique opportunity to change the way patients with severe genetic and orphan diseases are treated by addressing the underlying cause of disease, rather than offering solutions that focus only on their symptoms, we believe bluebird's products will command a high price. The value proposition offered by the products for patients, families, providers and payors would be significant given that existing treatments do not fully address the medical need and often involve significant hospitalization, risk of side effects, and toxicity. Despite a steep up-front cost, gene therapy in the long run may be cost-effective by eliminating expensive ongoing care, intervention and complications, although we acknowledge that there could be initial "sticker shock" with the price. While we currently model a high one-time payment for bluebird's products, a risk-sharing pricing model is also possible (i.e., collect a series of installments over a period of years). Physicians we spoke with had no issues on the potential value effective gene therapies bring as potential cures. We also assume our pricing estimates are not unreasonable given that Glybera is targeting a cost of ~$1.6 million, albeit spread out over five years. Also, for context, an allogeneic transplant costs ~$100-200K per treatment, and if the patient develops GvHD, then this increases to ~$1-2 million. Additionally, one can consider the pricing model for other successful orphan drugs administered on a chronic basis. These therapies can cost as much as $300,000-$500,000 per year, every year.

Royalties owed by bluebird. bluebird owes royalties to multiple organizations on sales of its products (Inserm, Institut, Stanford, MIT, and Research Development Foundation). However, in total these only add up to a single-digit percentage of sales.

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Potential Follow-On Indications

Why choose CCALD and beta-thalassemia as the initial indications? bluebird believes its initial indications (CCALD and beta-thalassemia) are well-suited to be treated by gene therapy because they are known to result from a genetic defect in a single gene. As such, the company knows what it is correcting and what gene sequence to insert into a patient's cells. We believe the pursuit of monogenic diseases like CCALD and beta-thalassemia will help mitigate the uncertainty of disease biology. Beyond this, such diseases, called monogenic diseases, also have a high degree of unmet medical need, with few (or no) long-term curative treatment options currently available. As such, the bar for approval is likely to be somewhat lower than for diseases that currently have less of an unmet medical need.

bluebird's gene therapy platform technology provides for broad therapeutic potential

Although the initial focus is on CCALD and beta-thalassemia, bluebird's gene therapy platform technology provides for broad therapeutic potential. bluebird is confident that its lentiviral vectors can be used to introduce virtually any gene insert and have the potential to be manufactured on a commercial scale reproducibly and reliably, as each new vector is produced using primarily the same process. The majority of the viral production system can remain the same, so the company can potentially only change the therapeutic gene "cassette" depending on the disease. In other words, the vector "backbone" remains the same, with only the therapeutic gene and related sequences being altered. bluebird appears relatively confident that it could move forward in pursuit of additional indications using its lentiviral vector backbone and associated assays simply by switching the therapeutic gene insert and associated control elements. bluebird can also take advantage of the lentivirus' ability to transduce HSCs more efficiently vs. other vectors (such as those derived from an adeno-associated virus), which gives the company the potential to address diseases in a variety of cell lineages that are derived from HSCs, such as microglia (useful for CCALD), red blood cells (useful for beta-thalassemia and SCD), T cells (useful for cancer and immunology), as well as others.

bluebird is looking to pursue additional applications of its technology for other monogenic diseases in cells derived from HSCs. To start with, sickle cell disease (SCD) is a sister disease to beta-thalassemia, and the company is looking to finalize its SCD development plans in the near future and expects to file an IND for this indication in 2014. In addition, other monogenic diseases include hemophilia A, cystic fibrosis, Tay sachs disease, Fragile X syndrome, and Huntington's disease. Other opportunities also include lysosomal storage disorders, other neurological diseases, and autoimmune diseases. Overall, bluebird's strategy is likely to be to pursue indications with a high unmet medical need and a high probability of clinical, regulatory, and commercial success.

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Childhood Cerebral Adrenoleukodystrophy (CCALD) Background

What is Adrenoleukodystrophy (ALD)? ALD is a rare (ultra-orphan), X-linked, monogenic, inherited, neurological disorder affecting young boys that is often fatal. ALD is also sometimes referred to as Lorenzo's Oil disease.

What is the cause of ALD? ALD is caused by mutations in the ABCD1 gene, which encodes for a transporter protein called the ALD protein (ALDP). Essentially there is a single problem in a single gene in the brain cells of patients. The ALD protein has a key function in the breakdown and metabolism of very long-chain fatty acids (VLCFA), and without functional ALDP, VLCFA accumulate in cells, including neural cells, eventually leading to a toxic build-up ("white clouds"), as the microglial cells in the brain can no longer clear the VLCFAs. In its most severe form, this leads to cerebral inflammation and causes demyelination, which is progressive destruction of the myelin sheath (a protective, insulating layer of membranes that surround or incase nerve cells) in the brain, leading to severe loss of neurological function and eventual death.

ALD is caused by mutations in the ABCD1 gene, which encodes for a transporter protein called the ALD protein (ALDP)

What are the different types of ALD? ALD is a heterogeneous disease that can be divided into sub-categories. There are three main phenotypes that impact brain function:

- **Adrenomyeloneuropathy (AMN).** AMN is the most common neurological form of ALD, accounting for ~40-45% of all ALD patients. AMN generally develops in adults 21 years old and up, and patients present with more slowly progressive symptoms caused by (non-inflammatory) disruption of the axons (which allow nerve signals to be transmitted) in the spinal cord. Approximately 40% of AMN patients have or will develop cerebral disease similar to CCALD, with different degrees of associated inflammation.

- **CCALD.** This is the most severe and devastating form of ALD and accounts for ~30-40% of ALD patients. CCALD presents in young boys and is characterized by progressive destruction of myelin, leading to severe loss of neurological function, and eventually death. Learning and behavioral problems, as well as other symptoms, usually appear in mid-childhood between 3-15 years old (the median age of onset is 7). Head trauma can sometimes set the development of symptoms off. In the absence of any kind of treatment, CCALD patients usually experience rapid degeneration into a vegetative state, and ultimately die within a decade of being diagnosed.

- **Adult Cerebral ALD (ACALD).** This generally develops in males 15 years old and up. It is also very severe, with progression of neurologic symptoms that resembles the disease course of CCALD. All ALD patients will develop spinal cord disease at some point, but not all will develop cerebral ALD. ACALD accounts for only ~5% of ALD patients.

How is CCALD diagnosed? MRI is the main tool, along with performance IQ. However, the most common diagnosis is through another family member who is symptomatic (family screening). Once diagnosed, patients are normally referred to a

center with experience in treating this disease. ALD patients are often diagnosed too late to treat, and, as such, an early diagnosis is key. bluebird estimates that 20-50% of CCALD patients may have disease so advanced at the time of diagnosis that a beneficial treatment outcome is unlikely. This is attributed to rapid disease progression and difficulty with early diagnosis, as the initial presentation of the signs and symptoms of CCALD are frequently misdiagnosed, for example as attention deficit hyperactivity deficit disorder. Newborn screening through a simple and inexpensive blood test is being developed, however, to enable earlier diagnosis, but is not yet widely available. Several US states are considering universal newborn screening for ALD (it is currently available in NY and CT), and so newborn screening could be widely adopted in the US within the next ~5 years, and potentially elsewhere. This would reduce the need for diagnosis and provide for the opportunity to identify more boys for proactive monitoring of disease symptoms and early disease intervention. Once newborn screening is in place, physicians will watch patients and treat them as soon as the MRI changes.

Several US states are considering universal newborn screening for ALD

What are the symptoms of CCALD? Damage to the myelin sheath in the brain can result in:

- decreased motor coordination and function,
- visual and hearing disturbances,
- loss of cognitive function,
- dementia,
- seizures, and
- adrenal dysfunction.

Boys afflicted with this form of ALD develop normally until the onset of symptoms. Symptoms often progress rapidly and, in just months or years, can result in a vegetative state and, ultimately, death.

Untreated cerebral ALD leads to dismal outcomes (vegetation and death). CCALD is often fatal, with children typically dead by the age of 5-10 years old. CCALD patients see rapid disease progression with only a 55% survival rate at 5 years post diagnosis.

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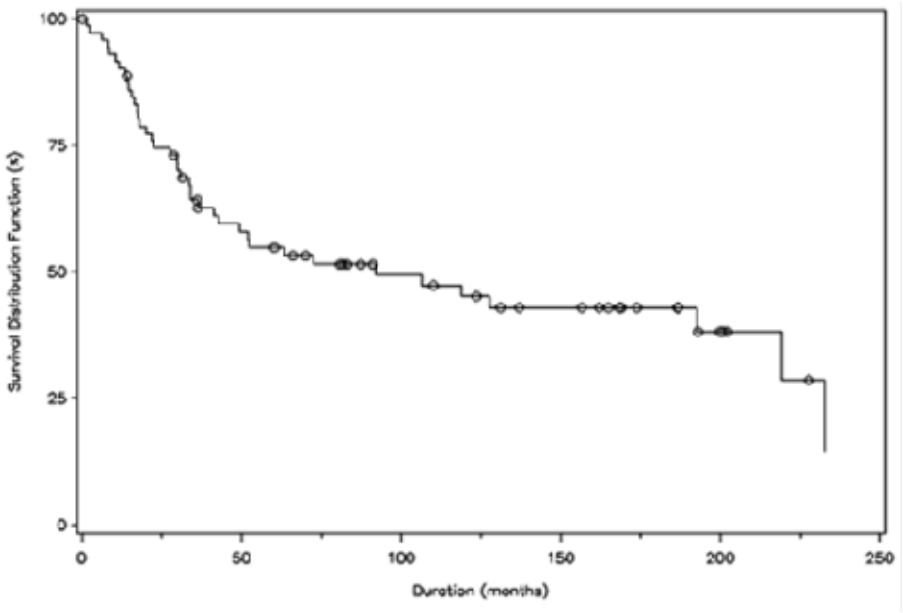
Figure 9: Survival Data from the Untreated Cohort of CCALD Patients from the ALD-101 Study



Source: bluebird bio, Inc.

What is the epidemiology? The incidence rate for ALD is ~1 in every 20,000 newborn males, and the US National Institute of Health estimates a prevalence of 1 in 20,000. The annual incidence of CCALD in developed countries is estimated to be ~200 patients. CCALD has not been linked to any ethnic pre-disposition.

Currently, the only effective treatment option for CCALD is allogeneic hematopoietic stem cell transplant, but this is only an option when there is an appropriate donor

What are the current treatment options? Currently, the only effective treatment option for CCALD is allogeneic hematopoietic stem cell transplant (HSCT), but this is only an option when there is an appropriate donor. The idea is that the patient is treated with HSCs containing the correctly functioning copy of the gene (which is contributed by a donor). HSCT is typically performed early in the course of the disease, ideally using an unaffected, matched sibling HSC donor, although non-sibling matched donor cells and cord blood cells are also sometimes used. Sibling matched donors are only available for <30% of patients, and the difficulty of finding a suitable sibling-matched donor is one of the primary drawbacks of this approach. As such, the majority of allogeneic HSCT procedures for CCALD are carried out with non-sibling matched donor cells, partially matched related or unrelated donor cells and umbilical cord blood cells because a matched sibling donor is not available in most cases. The goal of HSCT is to stabilize disease progression. Almost every patient is transplanted, even if mismatched, as there are no other options, and otherwise the patient will die. Patients are typically treated at a select few transplant centers. If diagnosed early on, physicians look to treat patients when they first see changes on the brain MRI. At this point, the transplant team gets involved so that the patient can be treated before symptoms appear.

What are the drawbacks of HSCT? Allogeneic HSCT is associated with significant morbidity and mortality (related to myeloablation, which decreases or eliminates the cells in the bone marrow and blood, serious infection, graft failure, and graft-versus-host-disease), especially in patients who undergo non-sibling matched allogeneic HSCT (which is the case for >70% of transplants). Complications of allogeneic HSCT include a 10-30% risk of engraftment failure in unrelated Human-

Leukocyte-Antigen (HLA) matched patients, a 12-16% incidence of life-threatening infection, and a ~30% risk of grade 2-4 graft-versus-host-disease (GvHD), a frequent complication where donor immune cells (white blood cells in the graft) recognize the cells of the recipient (the host) as "foreign" and attack them. As such, allogeneic HSCT in patients whose donor is not a matched sibling result in significant mortality rates. There is a ~22% on- year mortality in allogeneic HSCT patients whose donor is not a matched sibling. Acute GvHD is treated with immune suppression, but ~10% of patients still develop chronic GvHD. In addition, because of the requirement for long-term immunosuppressive medications following allogeneic HSCT, there is a prolonged risk of opportunistic infections and other serious side effects associated with immunosuppressive drugs. As such, transplant sites prefer to reserve transplants until patients' NFS score is <1.

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Beta-Thalassemia Background

What is Beta-thalassemia? It is a rare, inherited (monogenic) blood disorder caused by a genetic abnormality of the ß-globin gene resulting in defective red blood cells (RBCs).

In beta-thalassemia, genetic mutations cause the absence (or reduced production) of the beta chains of hemoglobin thereby preventing correct formation of hemoglobin

What is the cause? Nearly 200 different mutations have been described in beta-thalassemia patients. These genetic mutations cause the absence (or reduced production) of the beta chains of hemoglobin, or ß-globin, thereby preventing correct formation of hemoglobin A, which normally accounts for >95% of the hemoglobin in adult blood. Hemoglobin A consists of four chains (two chains of a-globin and two chains of ß-globin, normally existing at a ~1:1 ratio). Genetic mutations that prevent (or reduce) the production of ß-globin can result in a relative excess of a-globin, which causes the premature death of RBCs. The clinical implications of the a-globin/ß-globin imbalance are that patients lack sufficient RBCs and hemoglobin to effectively transport oxygen throughout the body and so can become severely anemic. In addition, the shortened life span and ineffective production of RBCs can result in complications such as splenomegaly, marrow expansion, bone deformities, and iron overload in major organs. The clinical course of beta-thalassemia correlates with the degree of globin chain imbalance.

Mutations responsible for beta-thalassemia can be categorized as those which result in little or no functional ß-globin production (ß0) and those which result in decreased functional ß-globin production (ß+). Beta-thalassemia major refers to any mutation pairing that leads to the need for chronic blood transfusions due to severe anemia, and is the clinical finding in patients with ß0ß0 genotype as well as many with the ß0ß+ genotype. Affected patients produce as little as 1-7 g/dL of hemoglobin (for context, a normal adult produces 12-18 g/dL of hemoglobin). Beta-thalassemia major is the most severe form of beta-thalassemia.

What are the symptoms? Symptoms of beta-thalassemia can include:

- severe anemia,
- splenomegaly,
- marrow expansion,
- bone deformities, and
- iron overload in major organs.

However, the clinical presentation of these symptoms varies widely, dependent primarily on the number and type of inherited mutation.

Epidemiology of beta-thalassemia. Beta-thalassemia is one of the most common single-gene inherited conditions known globally. This disease is concentrated in populations of Mediterranean, South and Southeast Asian and Middle Eastern descent. The total annual incidence of symptomatic patients is estimated at 1 in 100,000 globally, and 1 in 10,000 individuals in the EU. The global incidence of beta-thalassemia (which is symptomatic) is estimated at ~60,000, and the global

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beta-thalassemia major prevalence (patients who are treated) is estimated at ~288,000. Beta-thalassemia is rare in the US, and, as such, published research on its prevalence in the US is limited. However, the prevalence of beta-thalassemia major (treated patients) in the US and Europe is estimated at ~15,000. Due to changing immigration patterns, it is estimated that 1.8 in 100,000 births in California are affected by beta-thalassemia.

Patients with beta-thalassemia major receive chronic blood transfusion regimens with the aim of maintaining a steady state of hemoglobin of ~9-10 g/dL to treat the severe anemia

What are the treatment options? Essentially, beta-thalassemia patients need hemoglobin from somebody else or they will die. As such, in geographies where the treatment is available, patients with beta-thalassemia major receive chronic blood transfusion regimens with the aim of maintaining a steady state of hemoglobin of ~9-10 g/dL to treat the severe anemia. These consist of infusions every 3-5 weeks, the timing of which is based primarily on monitoring hemoglobin levels. Chronic blood transfusions are required for patients just to survive, and these can be effective at preventing the symptoms of childhood beta thalassemia major, but are not curative. With regular transfusions patients can survive to ~30-40 years of age, but with a low quality of life (average age of death is seven years without transfusions). Allogeneic transplants are used when a sibling match is available, and these transplants currently offer the only hope of a cure.

What are the drawbacks of chronic blood transfusions? Chronic transfusions often lead to a large iron overload, which over the course of time leads to death via iron-associated heart and liver toxicity (organ failure as accumulation of iron is very toxic for the heart and liver). Patients can die by the age of 15-20 years due to accumulation of iron through the absence of chelation with cardiac fibrosis from iron overload being a typical cause of death. In order to prevent iron overload-associated risks, patients must adhere to daily iron chelation treatment regimens. However, poor patient compliance with chelation regimens remains an important challenge to overcome. Despite the use of transfusion and iron chelation therapies, overall survival is significantly reduced. Some patients are successfully transfused and chelated as well, and live fairly regular lives. It is estimated that with typical compliance, the overall life expectancy for a patient with transfusion-dependent beta-thalassemia is only 28 years. However, even patients who are compliant with transfusion and iron chelation regimens experience a reduced quality of life as a result of the burden of therapy and the fluctuating month-to-month levels of hemoglobin. Overall, beta-thalassemia major remains a devastating disease and unmet medical need. In developing countries where beta-thalassemia is more prevalent, such as Thailand, the lack of readily available chronic blood transfusions and optimal iron chelation regimens represents a significant challenge. In these countries especially, children with beta-thalassemia major have a poor prognosis and experience growth retardation, hepatosplenomegaly (enlargement of the spleen), and skeletal deformities resulting from extra-medullary hematopoiesis. Most die in childhood.

The only potentially curative therapy for beta-thalassemia is allogeneic HSCT. However, due to the risk of transplant-related morbidity/mortality (i.e., graft-versus-host disease), transplants are primarily only offered to pediatric patients with matched sibling donors (a match only occurs in <25% of cases, however).

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Sickle Cell Disease (SCD) Background

What is sickle cell disease? Sickle cell disease, or SCD, is a hereditary (monogenic) blood disorder resulting from a mutation in the ß-globin gene that causes polymerization of hemoglobin proteins and abnormal red blood cell (RBC) function. SCD is a sister disease to beta-thalassemia (with the main difference being that in SCD, enough protein is made but it is mutated).

What causes SCD? The disease results from a mutation in the ß-globin gene that causes polymerization of hemoglobin proteins and abnormal RBC function, and chronic anemia. Under low-oxygen conditions, which are exacerbated by the RBC abnormalities, the mutant hemoglobin aggregates causing the RBCs to become deformed and take on a sickle shape, which results in them aggregating and obstructing small blood vessels, thereby restricting blood flow to organs. This leads to pain, cell death and organ damage. If oxygen levels are restored, the hemoglobin can disaggregate and the RBCs will return to their normal shape. However, over time, the sickling damages the cell membrane and the RBCs do not return to the normal shape even in high-oxygen conditions. Moreover, the sickle-shaped RBCs have a tendency to rupture more easily, frequently leading to damage to the blood vessels and iron overload that can ultimately lead to organ failure and death.

What are the symptoms? SCD is characterized by:

- anemia,
- vaso-occlusive pain crisis (a common complication of SCD in which there is severe pain due to obstructed blood flow in the bones, joints, lungs, liver, spleen, kidney, eye, or CNS),
- infections,
- stroke,
- splenomegaly,
- poor quality of life, and
- early death in a large subset of patients.

Where adequate medical care is available, patients with severe sickle cell disease generally receive chronic blood transfusion regimens or hydroxyurea

Epidemiology of SCD. SCD is concentrated in populations of African, Middle Eastern and South Asian descent. The worldwide incidence of SCD is estimated to be 250,000-300,000 births annually, and the worldwide prevalence of the disease is estimated to be ~20-25 million. In the US, SCD is a standard part of mandatory newborn screening, and the incidence is >1,600 births/year with an estimated prevalence of ~100,000 individuals.

What are the treatment options? Where adequate medical care is available, patients with severe SCD generally receive chronic blood transfusion regimens or hydroxyurea. However, both are non-curative. In controlled clinical trials, hydroxyurea has been found to significantly reduce the burden of vaso-occlusive crisis and related complications, but it does not eliminate them altogether. In

addition, many SCD patients find it difficult to comply with hydroxyurea, partly because they cannot tolerate the higher doses required to achieve optimal outcomes. The only potentially curative therapy for SCD is allogeneic HSCT. However, because of the significant risks associated with this, transplants are only offered primarily to patients with available sibling matched donors, but a match is uncommon and the treatment is associated with high morbidity/mortality due to GvHD. Notably, it is even more difficult to find suitable donors for SCD patients of African descent, and it is estimated that only ~10% of eligible patients are able to find such donors.

As is the case with beta-thalassemia, chronic transfusions pose a compliance burden and introduces the risk of iron overload, which over time leads to death through iron-associated heart and liver toxicity

Limitations of current treatment options. As is the case with beta-thalassemia, chronic transfusions pose a compliance burden and introduce the risk of iron overload, which over time leads to death through iron-associated heart and liver toxicity. As such, patients must comply with daily iron chelation regimens. In addition, a significant number of patients with SCD find it difficult to adhere to hydroxyurea treatment regimens due in part to drug-related toxicities. The only potentially curative therapy currently available for SCD is allogeneic HSCT; however, because of the significant risk of transplant-related morbidity and mortality, this option is usually offered primarily to pediatric patients with available sibling-matched donors. It is particularly difficult to find suitable donors for individuals of African descent, and it is estimated that approximately 10% of eligible patients do so. In light of these factors, we believe SCD is a devastating disease with a significant unmet medical need.

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Chimeric Antigen Receptor (CAR) T-Cells

What is CAR T-cell therapy? This is the genetic manipulation of autologous T-cells. Blood is withdrawn from a patient, and then the T cells are extracted, isolated, and genetically modified *ex vivo* with the intention of programming the T cells to recognize and attack cancer cells. This gives them a targeted function. The modified T cells, which are called chimeric antigen receptor (CAR) cells, are then re-introduced into the patient's blood to selectively bind to and kill the target cancer cells. These modified T cells have been shown to have beneficial effects in human clinical trials for B cell lymphoma patients.

bluebird's recent partnership with Celgene helps validate CAR T cells as a therapeutic approach. In March 2013, bluebird announced the formation of a broad, worldwide, strategic, multi-year, R&D collaboration with Celgene to discover, develop, and commercialize novel disease-altering gene therapies in oncology using a patient's own genetically modified T cells (CAR T-cells) to selectively target and destroy cancer cells. This is a three-year collaboration with an option to extend it for an additional three years. Celgene has an option to license any products resulting from the collaboration after the completion of a Phase 1 trial for each product. bluebird will be responsible for R&D activity through Phase 1. The two companies are collaborating to evaluate CAR T cell therapies for a range of hematologic malignancies and solid tumors. Separately, Celgene and bluebird are also collaborating with the Center for Cell and Gene Therapy at Baylor College of Medicine, Texas Children's Hospital and The Methodist Hospital, Houston, to advance new and existing CAR T-cell programs. There are a few Phase 1 trials sponsored by Baylor College that have been ongoing since 2009.

bluebird's partnership with Celgene helps validate CAR T cells as a therapeutic approach

Financial terms of the bluebird/Celgene collaboration. These include an upfront payment of $75 million to bluebird and up to $225 million per product in potential option fees and clinical/regulatory milestones. bluebird also has the right to participate in the development and commercialization of any licensed products resulting from the collaboration through a 50:50 co-development and profit share in the US (in exchange for a reduction of milestones). Royalties on sales would also be paid to bluebird in regions where there is no profit share, including the US if bluebird declines to exercise its co-development and profit-sharing rights there.

Celgene has a change in control call option and a right to acquire a target antigen license. During the initial three-year term of the collaboration and, if extended, during the first extension term (which is two years), if bluebird were to engage in a change of control transaction, including a merger/consolidation or the sale of all assets, then Celgene has the right to terminate the collaboration agreement and obtain non-terminable, worldwide, exclusive licenses to all of bluebird's product candidates previously identified under the collaboration agreement. Under this call option, the product candidates to which Celgene would have the right to acquire licenses include any product candidate previously licensed out of the collaboration during the term of the collaboration, any product candidate for which bluebird has exercised its right to co-develop and co-promote the product candidate within the US, any product candidate for which Celgene previously declined its option to obtain a license, and any product candidate for which at least *in vivo* efficacy studies have been initiated or authorized by the joint steering committee for the collaboration.

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Intellectual Property

bluebird's intellectual property estate consists of both patented and non-patented intellectual property. The company owns or has license to several patents around certain genes, including 176 exclusively owned/licensed patents and applications and 58 patents non-exclusively owned/licensed related to lentiviral vectors and vector systems; 18 patents owned/licensed and 7 non-exclusively in-licensed patents related to vector manufacturing or production. bluebird also has exclusive rights to patents related to therapeutic cellular products. A summary of the key patent portfolios owned or licensed by bluebird is provided below. Additionally, the company also relies on trade secrets, and purposefully chooses not to file some patents so as not to disclose know how.

Outside of the patents, we expect bluebird will receive 12-year biologic drug exclusivity and 7 years of orphan drug exclusivity (running concurrently). While we believe bluebird's IP protection is extensive (summarized below), we do not believe it is likely that generic companies would attempt a gene therapy product in the foreseeable future.

Figure 12: bluebird's Patent Portfolio

Childhood Cerebral Adrenoleukodystrophy (CCALD) - 3 Patent Portfolios			
Portfolio	**Subject of Protection**	**Summary**	**Expiration (excluding potential term extensions)**
Pasteur Institute	• FLAP/cPPT elements • lentiviral vectors used to produce Lenti-D product	Exclusive license to: - 4 issued US patents - 4 pending US applications Corresponding Ex-US patents/applications in Australia, Canada, China, Europe, Hong Kong, Israel, and Japan	Issued COM Patents- US: 2019-2023; ROW: 2019-2020 Pending COM patents- 2019-2020 Other Patents/applications- 2019-2020
Research Development Foundation (RDF)	• lentiviral vectors used to produce Lenti-D product	Exclusive license to: - 3 issued US patents - 1 pending US applications Corresponding Ex-US patents/applications in Canada, Europe, and Israel.	Issued COM Patents- 2022-2023 Pending COM patents- 2021-2022 Other Patents/applications- 2021-2022
bluebird bio	• compositions of matter for CCALD gene therapy vectors • compositions and methods of using the vectors • compositions in cell-based gene therapy of adrenoleukodystrophy or adrenomyeloneuropathy	Own: - 1 pending US application - 1 pending Patent Cooperation Treaty (PCT) due for national stage entry in December 2013	Pending COM patents- WW: 2032 Other Patents/applications- 2032
ß-thalassemia/SCD - 3 Patent Portfolios			
Portfolio	**Subject of Protection**	**Summary**	**Expiration (excluding potential term extensions)**
Pasteur Institute	• lentiviral vectors used to produce LentiGlobin product for ß-		As described above
Research Development	• lentiviral vectors used to produce LentiGlobin product for ß-		As described above
MIT/bluebird bio	• specific compositions of matter for lentiviral ß-globin expression vectors	Co-own: - 1 issued US patent - 2 pending US patent applications Corresponding Ex-US patents/applications in Europe and Hong Kong	Issued COM Patents- 2023 Pending COM patents- 2023 Other Patents/applications- 2023
Lentiviral platform (e.g., vectors, manufacturing, and cell therapy products) potentially relevant to CCALD, ß-thalassemia, SCD, other potential programs			
Portfolio	**Subject of Protection**	**Summary**	**Expiration (excluding potential term extensions)**
Pasteur Institute	• lentiviral vectors used to produce LentiGlobin product for ß-		As described above
Research Development	• lentiviral vectors used to produce LentiGlobin product for ß-		As described above
bluebird bio	• certain specific compositions of matter • improved methods for selecting and delivering transduced cells	Own: - 1 pending Patent Cooperation Treaty (PCT) due for national stage entry in July 2013	Pending COM patents- 2031 Other Patents/applications- 2031
	• compositions of matter for improved packaging cells and cell lines • improved methods for transfection and transduction of therapeutic cells	Own: - 2 provisional US applications - 2 pending PCT applications due for national stage entry in December 2013 and March 2014	Pending COM patents- 2032

Source: Company reports

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Financial Outlook

bluebird is a developmental-stage biotechnology company with key upcoming trial initiations in 2013 (the potentially pivotal Phase 2/3 ALD-102 trial for Lenti-D in CCALD and the Phase 1/2 HGB-204 trial for LentiGlobin in beta-thalassemia). The company does not expect to be profitable for the foreseeable future, and we do not anticipate a consistent revenue contribution until Lenti-D (or LentiGlobin) is approved.

bluebird ended 1Q13 with ~$132 million in cash

The company's cash, cash equivalents, and marketable securities totaled ~$132 million as of March 31, 2013. However, this does not include ~$108 million of net proceeds from a public offering of common stock in June 2013. Including this capital, we estimate bluebird will end 2013 with ~$226 million in cash. While R&D expenses may creep up slightly over time, it should not increase too much going forward, as the trials are going to be relatively small. As for SG&A, we expect this to only really ramp up as the company gets closer to commercialization. However, the cost of building a commercial infrastructure is not expected to be large, as CCALD treatment is highly concentrated with very well established treatment centers around the world.

Share count

We estimate bluebird currently has ~28.5 million fully diluted shares outstanding (including ~22.8 million common shares, 3.7 million stock options, 0.4 million warrants, and 1.6 million restricted stock at this time).

Figure 13: BLUE Key Financial Metrics

Key Financial Metrics	2011A	2012A	2013E	2014E	2015E	2016E	2017E
In $ M							
December financial year-end							
Cash	25.6	67.0	239.7	227.5	210.6	297.7	217.7
Debt	-	-	-	-	-	-	-
CFOp + CapEx (burn)	(12.2)	(21.0)	64.7	(12.2)	(16.9)	(62.9)	(80.0)
Expected financing	-	-	108.0	-	-	150.0	-
Revenue	-	0.3	19.9	25.0	25.0	5.3	-
EPS	$0.00		($0.82)	($1.07)	($1.20)	($2.58)	($3.06)
Average shares outstanding	-	-	23.1	24.1	25.1	29.4	30.4
Fully diluted shares outstanding	-	2.8	28.8	29.8	30.8	35.1	36.1

Source: Company reports and J.P. Morgan estimates

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Valuation

We are initiating coverage of BLUE with an Overweight rating and a December 2014 price target of $44. Our target is based on a blended average of our proprietary probability-adjusted scenario analysis (33%), a risk-adjusted NPV model (33%), and a DCF analysis (33%).

Figure 14: BLUE Valuation Summary

BlueBird Bio : Valuation Summary

Discount rate	15%		
Main value driver	**Prob of approval**	**Peak sales est (avg. scenario)**	**Avg peak yr**
CCALD	50%	$ 255	2022
B-Thalassemia	25%	$ 1,175	2023
Sickle Cell Disease	0%	$ -	-
Valuation methodology	Value	Weighting	Adj. value/ share
P/E 2015	$ -	0%	$ -
Real options scenario analysis	$ 43.18	33%	14.4
Risk adjusted NPV analysis	$ 34.14	33%	11.4
DCF analysis	$ 54.15	33%	18.1
Total			$ 43.82
Catalyst/liquidity discount			0%
YE14 Valuation			**$ 44**

Source: J.P. Morgan estimates

Risk-adjusted NPV analysis (33% weighting)

In our risk-adjusted NPV analysis, we estimate the revenues and associated expenses (including taxes) over the expected patent life of a product. We complete this exercise for conservative, moderate, and aggressive sales scenarios and then assign a range of probabilities to each of these outcomes as well as to the possibility that the product is ineffective and generates zero value. For Lenti-D, we assume patent protection until 2030. We apply a discount rate of 15% and believe this is appropriate given the applied probability adjustments.

Proprietary real options scenario analysis (33% weighting)

Using this model, we estimate the value of the company's development programs by assigning a range of probabilities to six different commercial scenarios (ranging from an ineffective product that generates zero value to a breakthrough treatment option) and analyze them over several possible peak sales years. We also evaluate a range of price-to-peak sales multiples for an asset (including from 4-6x for a wholly owned gene therapy drug product). Additionally, we again apply a discount rate of 15%.

Value contribution of Lenti-D (for CCALD) and LentiGlobin (for β-Thal)

Below, we demonstrate our analysis for Lenti-D for CCALD and LentiGlobin for beta-thalassemia. We assume a 50% and 25% probability that Lenti-D and LentiGlobin reach the market, and assume that sales peak in 2022 and 2023, respectively. Below is our calculated value contribution from Lenti-D and LentiGlobin for a range of multiples if the drugs generates peak sales of ~$255 million and ~$1.2 billion, respectively.

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Figure 15: Lenti-D and LentiGlobin Scenario Analysis

Product:	Lenti-D	Peak year	2021			2022			2023			Average
Indication:	CCALD	Discount period	7.0			8.0			9.0			prob-adj
Assumption:	WW Market											value
		Price/sales mult.	4	5	6	4	5	6	4	5	6	
		Peak sales	Share of peak sales									
	Prob.	(millions)	Value/Share									
Ineffective	50%	$ -	$ -	$0	$0	$0	$0	$0	$0	$0	$0	$0	$ -
Disappointment	3%	127	127	$6	$8	$10	$6	$7	$8	$5	$6	$7	0.18
Below average	10%	191	191	$10	$12	$14	$8	$10	$13	$7	$9	$11	1.06
Average	25%	255	255	$13	$16	$19	$11	$14	$17	$10	$12	$15	3.52
Above average	10%	382	382	$19	$24	$29	$17	$21	$25	$15	$18	$22	2.11
Breakthrough	3%	510	510	$26	$32	$39	$22	$28	$34	$19	$24	$29	0.70
Total	**100%**												**$ 7.57**

Product:	LentiGlobin	Peak year	2022			2023			2024			Average
Indication:	B-Thalassemia	Discount period	8.0			9.0			10.0			prob-adj
Assumption:	WW Market											value
		Price/sales mult.	4	5	6	4	5	6	4	5	6	
		Peak sales	Share of peak sales									
	Prob.	(millions)	Value/Share									
Ineffective	75%	$ -	$ -	$0	$0	$0	$0	$0	$0	$0	$0	$0	$ -
Disappointment	3%	588	588	$26	$32	$39	$22	$28	$34	$20	$24	$29	0.71
Below average	5%	881	881	$39	$48	$58	$34	$42	$50	$29	$37	$44	2.12
Average	10%	1,175	1,175	$52	$64	$77	$45	$56	$67	$39	$49	$59	5.64
Above average	5%	1,763	1,763	$77	$97	$116	$67	$84	$101	$59	$73	$88	4.23
Breakthrough	3%	2,350	2,350	$103	$129	$155	$90	$112	$135	$78	$98	$117	2.82
Total	**100%**												**$ 15.52**

Source: J.P. Morgan estimates

For both our proprietary probability-adjusted scenario analysis and risk-adjusted NPV model, we have also assigned $400 million of value to bluebird's technology platform. While this value is difficult to calculate, our estimate includes the technology platform itself, additional indications that bluebird may choose to pursue (most notable sickle cell disease), and the value of the company's collaboration with Celgene for the development of CAR T-cell products in oncology.

Discounted cash flow analysis (33% weighting)

We also utilize a DCF for BLUE. In fact, we believe this may prove to be more appropriate longer term than our NPV analysis for BLUE given that it assigns some terminal value, as we see it as unlikely that this technology becomes susceptible to generic competition. Rather, we suspect that it's eventually at greater risk of some other potentially superior technology/approach coming along. Using this model, we project cash flows out to 2030 at which point we assign a terminal rate of 1.25%. Our DCF utilizes a discount rate of 15%.

Management

bluebird's team consists of a number of leading gene therapy authorities with extensive scientific and technical expertise in the development and manufacturing of viral vectors for gene therapy. Given the complicated nature of this process, we believe bluebird's experienced team in this field counts for a lot.

Nick Leschly – CEO

Nick Leschly has served as the president and CEO of bluebird bio since September 2010. Previously, he served as the interim chief executive officer from March 2010 - September 2010. Formerly a partner of Third Rock Ventures since 2007, Mr. Leschly played a key role in the formation, development and business strategy of several of Third Rock's portfolio companies, including Agios Pharmaceuticals and Edimer Pharmaceuticals. Prior to joining Third Rock, he worked at Millennium Pharmaceuticals, leading several early-stage drug development programs and he served as the product and alliance leader for Velcade. Mr. Leschly also founded and served as CEO of MedXtend Corporation. He received his B.S. in molecular biology from Princeton University and his M.B.A. from Wharton Business School.

Mitchell Finer, Ph.D. – CSO

Mitchell Finer, Ph.D., has served as the CSO of bluebird bio since March 2010. Prior to joining bluebird, Dr. Finer served as senior VP of development and operations for Novocell (now ViaCyte), a stem cell engineering company researching treatments for diabetes and other chronic diseases from November 2008 - March 2010. From July 2005 - November 2008, Dr. Finer served as CEO of Intracel Holdings. From June 2003 - June 2005, he held the position of president and CEO of Genteric. Previously, he had served as Genteric's CSO from November 2002 - June 2003 and as VP of R&D for the Gencell division of Aventis Pharma (now Sanofi) from April 2002 - November 2002. He was also a founder and VP of research for Cell Genesys, and a founder of Abgenix and Avalanche Biotechnologies. Dr. Finer received his B.A. in biochemistry and bacteriology from the University of California at Berkeley and his Ph.D. in biochemistry and molecular biology from Harvard University. He completed a postdoctoral fellowship at the Whitehead Institute for Biomedical Research.

David Davidson, M.D. – CMO

David Davidson, M.D., has served as bluebird's CMO since February 2012. Prior to joining bluebird, Dr. Davidson served as a senior medical director at Genzyme, where he led clinical research for programs in Phases 1 through 4 across a wide range of therapeutic areas for more than 10 years. Most recently, Dr. Davidson was the medical leader for Genzyme's gene therapy and Pompe disease enzyme replacement therapy programs. In addition to Dr. Davidson's translational medicine experience, he has also worked on commercial products, including Fabrazyme and Myozyme/Lumizyme, and helped craft the NDA that resulted in approval of Welchol. Prior to Genzyme, Dr. Davidson was a medical director at GelTex Pharmaceuticals. Previously, he completed clinical and research fellowships in infectious diseases at the Harvard Longwood Combined Infectious Diseases Program. Dr. Davidson received his B.A. from Columbia University and his M.D. from New York University School of Medicine. In addition, he completed an internal

medicine internship, residency training and an endocrinology research fellowship at the University of Chicago Hospitals.

Jeffrey Walsh – COO

Jeffrey Walsh has served as the COO for bluebird since May 2011 and as the secretary since March 2013. Mr. Walsh has 25 years of experience in executive leadership positions with responsibility for finance, business development, commercial and business operations, strategic planning and legal functions with established and emerging public and private life sciences companies. From November 2008 - February 2011, Mr. Walsh served as chief business officer of Taligen Therapeutics where he played a key role in the growth of the company and the sale of Taligen Therapeutics to Alexion Pharmaceuticals in January 2011. Mr. Walsh started his career at SmithKline Beecham Corporation in finance and worldwide business development roles. He subsequently held senior business development, finance and operations roles at PathoGenesis, Allscripts Healthcare Solutions, EXACT Sciences Corporation, and Inotek Pharmaceuticals. Mr. Walsh received his B.A. in sociology and economics from Yale University and his M.B.A. from the Kellogg Graduate School of Management at Northwestern University.

Linda Bain, CPA – VP, Finance & Business Operations

Linda Bain, CPA, has served as bluebird's VP of finance and business operations since October 2011 and as the treasurer since March 2013. Previously, she served as VP of corporate finance at Genzyme from September 2008 - September 2011, at Fidelity Investments from September 2007 - September 2008 and a number of positions at AstraZeneca from May 2000 - September 2007. She received her B.S. from the University of the Orange Free State in South Africa.

Richard Smith, Ph.D. – VP, Investor Relations

Richard Smith, Ph.D., has served as bluebird's VP of investor relations since March 2013. From March 2012 - March 2013, Dr. Smith served as a consultant for a number of biotech companies. Previously, Dr. Smith served as VP of investor relations and corporate communications at Pharmasset from October 2008 - January 2012, when Pharmasset was acquired by Gilead Sciences. From May 2004 - August 2008, Dr. Smith was an equity research analyst at J.P. Morgan covering biotech companies. Dr. Smith received his B.Sc. in Applied Zoology from the University of Leeds, his M.Sc. in Toxicology from the University of Surrey and his Ph.D. in Clinical Virology from the University of Oxford.

Cyrus Mozayeni, M.D. – Senior Director, Business Development

Cyrus Mozayeni, M.D., has served as bluebird's senior director of business development since June 2010. Previously, he served as director of strategic/business development at PPD Dermatology (Magen Biosciences until April 2009) from April 2007 - May 2010. Dr. Mozayeni received his B.S. in neuroscience from Brown University, his M.D. from the University of Virginia School of Medicine and his M.B.A. from the Kellogg Graduate School of Management at Northwestern University.

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Models

Figure 16: BLUE Income Statement

Fiscal Year Ends Dec 31	2011A	2012A	1Q13A	2Q13E	3Q13E	4Q13E	2013E	2014E	2015E	2016E	2017E
Lenti-D - CCALD ($,M)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
LentiGlobin - B-Thal ($,M)	-	-	-	-	-	-	-	-	-	-	-
Collaboration revenue ($M)	-	-	1.0	6.3	6.3	6.3	19.8	25.0	25.0	5.3	-
Research and Licensing Fees ($M)	0.6	0.3	0.1	-	-	-	0.1	-	-	-	-
Grant Revenue ($M)	0.2	-	-	-	-	-	-	-	-	-	-
Total Revenue	**$ 0.9**	**$ 0.3**	**$ 1.1**	**$ 6.3**	**$ 6.3**	**$ 6.3**	**$ 19.9**	**$ 25.0**	**$ 25.0**	**$ 5.3**	**$ -**
COGS		-	-	-	-	-	-	-	-	-	-
Gross Profit		0.1	1.1	6.3	6.3	6.3	**19.9**	**25.0**	**25.0**	**5.3**	**-**
R&D	11.4	17.2	5.3	6.0	8.7	10.1	30.0	42.0	46.0	51.5	57.5
Sales and Marketing		-	-	-	-	-	-	-	-	21.0	26.3
General and Administrative	4.6	6.8	2.3	2.4	2.5	2.6	9.8	10.8	11.9	12.5	13.1
Total Operating Expenses	**$ 16.0**	**$ 24.1**	**$ 7.6**	**$ 8.35**	**$ 11.2**	**$ 12.7**	**$ 39.9**	**$ 52.8**	**$ 57.9**	**$ 85.0**	**$ 96.9**
Operating income	(15.1)	(23.7)	(6.5)	(2.1)	(5.0)	(6.5)	(20.0)	(27.8)	(32.9)	(79.7)	(96.9)
Other income, net	(0.5)	0.0	(0.06)	0.40	0.40	0.4	1.1	2.1	2.7	4.0	3.7
Pretax Income	(15.6)	(23.7)	(6.5)	(1.7)	(4.5)	(6.0)	(18.8)	(25.7)	(30.2)	(75.7)	(93.1)
Income Tax (benefit)	-	-	-	-	-	-	-	-	-	-	-
Net Income	**$ (15.6)**	**$ (23.7)**	**$ (6.5)**	**$ (1.7)**	**$ (4.5)**	**$ (6.0)**	**$ (18.8)**	**$ (25.7)**	**$ (30.2)**	**$ (75.7)**	**$ (93.1)**
Net Loss applicable to common stockholders	**(20.6)**	**(3.613)**	**$ (6.5)**	**$ (1.7)**	**$ (4.5)**	**$ (6.0)**	**(18.8)**	**(25.7)**	**(30.2)**	**(75.7)**	**(93.1)**
Average shares Outstanding				22.8	23.1	23.3	23.1	24.1	25.1	29.4	30.4
EPS, Basic and Diluted				**(0.07)**	**(0.20)**	**(0.26)**	**(0.82)**	**(1.07)**	**(1.20)**	**(2.58)**	**(3.06)**
Margin Analysis:											
Gross margin		*NM*	*NM*	*NM*	*NM*	*NM*	*100%*	*100%*	*100%*	*100%*	*NM*
Operating margin		*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Net margin		*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Cost Analysis:											
COGS as % of tot. prod. sales		*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
R&D as % of tot. revenue		*5061.76%*	*468.86%*	*95.20%*	*139.20%*	*161.60%*	*151.10%*	*168.00%*	*184.00%*	*980.95%*	*NM*
S&M as % of tot. revenue		*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*400.00%*	*NM*
G&A as % of tot. revenue		*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Year-over-year growth:											
Total revenue			*1225.88%*	*NM*	*NM*	*NM*	*5746.18%*	*25.77%*	*0.00%*	*-79.00%*	*NM*
R&D Expense			*36.96%*	*NM*	*NM*	*NM*	*74.51%*	*39.84%*	*9.52%*	*11.96%*	*11.65%*
S&M Expense			*70.51%*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*25.00%*
G&A Expense							*43.50%*	*10.00%*	*10.00%*	*5.00%*	*5.00%*
Total operating expenses			*45.72%*	*NM*	*NM*	*NM*	*65.69%*	*32.49%*	*9.62%*	*46.81%*	*13.97%*
Operating income			*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Net income			*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
EPS			*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Tax Rate			*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*

Source: Company reports and J.P. Morgan estimates

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Figure 17: BLUE Balance Sheet

Bluebird Balance Sheet ($ millions)	2011A	2012A	2013E	2014E	2015E	2016E	2017E
Assets							
Cash and cash equivalents	$ 25.6	$ 67.0	$ 239.7	$ 227.5	$ 210.6	$ 297.7	$ 217.7
Marketable Securities	$ 3.5	$ -					
Accounts Receivable, Net							
Prepaid Expenses	$ 0.9	$ 0.8					
Total Current Assets	**30.0**	**67.8**	**239.7**	**227.5**	**210.6**	**297.7**	**217.7**
PPE, Net	0.7	1.3					
Restricted Cash	0.2	0.3					
Other				25.0	62.4	101.0	162.6
Total Assets	**30.92**	**69.32**	**239.73**	**252.53**	**272.97**	**398.64**	**380.27**
Liabilities & Equity							
Accounts Payable	1.8	2.2					
Accrued Expenses and other current liabilities	0.8	2.1					
Deferred revenue, current portion	0.3	0.3					
Total Current Liabilities	**2.9**	**4.6**	**-**	**-**	**-**	**-**	**-**
Warrant Liability	0.6	0.2					
Deferred rent, net of current portion	0.0	0.0					
Deferred revenue, net of current portion	0.7	0.3	69.4	61.9	54.4	46.9	39.4
Long-Term Debt			-	-	-	-	-
Others			7.9	-	-	-	-
Total Liabilities	**4.22**	**5.23**	**77.28**	**61.88**	**54.38**	**46.88**	**39.38**
Series A-1 convertible pref. stock ($0.01)	9.2	-					
Series A-2 convertible pref. stock ($0.01)	15.8	7.1					
Series B convertible pref. stock ($0.01)	41.5	40.3					
Series C convertible pref. stock ($0.01)	15.9	12.4					
Series D convertible pref. stock ($0.01)	-	60.0					
Series A-1 convertible pref. stock ($0.01) no liquidation preference	-	2.3					
Common Stock	0.0	0.1					
Additional Paid in capital	7.7	15.2					
Accumulated Comprehensive Income	0.0	-					
Accumulated Deficit	(63.4)	(73.4)	54.5	82.7	110.6	201.8	190.9
IPO proceeds			108.0	108.0	108.0	150.0	150.0
Total Shareholders' Equity	**(55.7)**	**(55.7)**	**162.5**	**190.7**	**218.6**	**351.8**	**340.9**
Total Liabilities & Equity	**30.918**	**69.32**	**239.73**	**252.53**	**272.97**	**398.64**	**380.27**

Source: Company reports and J.P. Morgan estimates

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Figure 18: BLUE Cash Flow Statement

Bluebird Cash Flow Statement ($ millions)

	2011A	2012A	2013E	2014E	2015E	2016E	2017E
Cash Flow from Operations							
Net Income	$ (15.6)	$ (23.7)	$ (18.8)	$ (25.7)	$ (30.2)	$ (75.7)	$ (93.1)
Adjustments to reconcile net loss to net operating cash							
Depreciation & Amortization	0.2	0.3	5.6	7.5	7.5	7.5	7.5
Stock-based compensation	0.8	0.8	2.8				
Issuance of common stock warrants for consulting services	0.1	-					
Issuance of restricted stock warrants for consulting services	0.0	-					
Re-measurement of warrants	0.4	(0.0)					
Amortization of premium on marketable securities	0.0	-					
Loss on disposal of equipment	-	0.0					
Changes in operating assets and liabilities							
Changes in Prepaid expenses and other current assets	(0.34)	0.1					
Changes in Accounts Payable	0.9	0.4					
Changes in Accrued expenses and other liabilities	0.4	1.4					
Changes in deferred revenue	1.0	(0.3)	69.4				
Others		-	5.8	5.9	5.8	5.3	5.6
Cash Flow from Operations	**$ (12.2)**	**$ (21.0)**	**$ 64.7**	**$ (12.2)**	**$ (16.9)**	**$ (62.9)**	**$ (80.0)**
Restricted Cash	(0.04)	(0.04)					
Purchase of PPE	(0.4)	(0.9)					
Purchase of maerketable securities	(5.3)	-					
Proceeds from sale of maturities of marketable securities	1.8	3.5					
Cash Flow from Investing	**$ (4.0)**	**$ 2.6**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**
IPO planned Issuance costs	-	-					
Proceeds from sale of convertible pref. stock, net	32.4	59.8					
Proceeds from sale of restricted stock, net	0.0	-					
Proceeds from issuance of common stock	0.0	0.0	108.0			150.0	
Additional Paid-In Capital	-	-					
Cash Flow from Financing	**$ 32.4**	**$ 59.9**	**$ 108.0**	**$ -**	**$ -**	**$ 150.0**	**$ -**
Total Change in Cash	16.3	41.4	172.7	(12.2)	(16.9)	87.1	(80.0)
Beginning Cash Balance	9.4	25.6	67.0	239.7	227.5	210.6	297.7
Ending Balance: Cash and Investments	**$ 25.6**	**$ 67.0**	**$ 239.7**	**$ 227.5**	**$ 210.6**	**$ 297.7**	**$ 217.7**

Source: Company reports and J.P. Morgan estimates

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bluebird bio: Summary of Financials

Income Statement - Annual	FY12A	FY13E	FY14E	FY15E
Revenues	0	20	25	25
Cost of products sold	0	0	0	0
Gross profit	-	-	-	-
SG&A	(7)	(10)	(11)	(12)
R&D	(17)	(30)	(42)	(46)
Operating income	(24)	(20)	(28)	(33)
EBITDA	(24)	(20)	(28)	(33)
Net interest (income) / expense	0	1	2	3
Other income / (expense)	0	(0)	0	0
Income taxes	0	0	0	0
Net income - GAAP	(1)	(19)	(26)	(30)
Net income - recurring	(4)	(19)	(26)	(30)
Diluted shares outstanding	0	23	24	25
EPS - excluding non-recurring	-	(0.82)	(1.07)	(1.20)
EPS - recurring	-	(0.82)	(1.07)	(1.20)

Balance Sheet and Cash Flow Data	FY12A	FY13E	FY14E	FY15E
Cash and cash equivalents	67	240	227	211
Accounts receivable	0	0	0	0
Inventories	-	-	-	-
Other current assets	1	0	0	0
Current assets	68	240	227	211
PP&E	1	0	0	0
Total assets	69	240	253	273
Total debt	0	0	0	0
Total liabilities	5	77	62	54
Shareholders' equity	64	162	191	219
Net income (including charges)	(24)	(19)	(26)	(30)
D&A	0	6	8	8
Change in working capital	2	69	0	0
Other	1	3	0	0
Cash flow from operations	(21)	65	(12)	(17)
Capex	(1)	0	0	0
Free cash flow	(22)	65	(12)	(17)
Cash flow from investing activities	3	0	0	0
Cash flow from financing activities	60	108	0	0
Dividends	-	-	-	-
Dividend yield	-	-	-	-

Income Statement - Quarterly	1Q13A	2Q13E	3Q13E	4Q13E
Revenues	1A	6	6	6
Cost of products sold	0A	0	0	0
Gross profit	-	-	-	-
SG&A	(2)A	(2)	(3)	(3)
R&D	(5)A	(6)	(9)	(10)
Operating income	(6)A	(2)	(5)	(6)
EBITDA	(6)A	(2)	(5)	(6)
Net interest (income) / expense	0A	0	0	0
Other income / (expense)	(0)A	0	0	0
Income taxes	0A	0	0	0
Net income - GAAP	(7)A	(2)	(5)	(6)
Net income - recurring	(7)A	(2)	(5)	(6)
Diluted shares outstanding	0A	23	23	23
EPS - excluding non-recurring	-	(0.07)	(0.20)	(0.26)
EPS - recurring	-	(0.07)	(0.20)	(0.26)

Ratio Analysis	FY12A	FY13E	FY14E	FY15E
Sales growth	(61.5%)	5746.2%	25.8%	0.0%
EBIT growth	56.6%	(15.7%)	39.2%	18.3%
EPS growth - recurring	-	-	30.7%	12.7%
Gross margin	-	-	-	-
EBIT margin	(6975.3%)	(100.5%)	(111.2%)	(131.5%)
EBITDA margin	(6975.3%)	(100.5%)	(111.2%)	(131.5%)
Tax rate	0.0%	0.0%	0.0%	0.0%
Net margin	(1062.6%)	(94.8%)	(102.7%)	(120.6%)
Net Debt / EBITDA	282.6%	1199.8%	818.1%	640.3%
Net Debt / Capital (book)	2296.5%	310.2%	617.7%	(2629.7%)
Return on assets (ROA)	(7.2%)	(12.2%)	(10.4%)	(11.5%)
Return on equity (ROE)	(8.0%)	(16.6%)	(14.5%)	(14.7%)
Enterprise value / sales	-	-	-	-
Enterprise value / EBITDA	-	-	-	-
Free cash flow yield	-	9.3%	(1.7%)	(2.2%)

Source: Company reports and J.P. Morgan estimates.
Note: $ in millions (except per-share data).Fiscal year ends Dec

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Important Disclosures

- **Market Maker:** JPMS makes a market in the stock of bluebird bio.
- **Lead or Co-manager:** J.P. Morgan acted as lead or co-manager in a public offering of equity and/or debt securities for bluebird bio within the past 12 months.
- **Client:** J.P. Morgan currently has, or had within the past 12 months, the following company(ies) as clients: bluebird bio.
- **Client/Investment Banking:** J.P. Morgan currently has, or had within the past 12 months, the following company(ies) as investment banking clients: bluebird bio.
- **Investment Banking (past 12 months):** J.P. Morgan received in the past 12 months compensation from investment banking bluebird bio.
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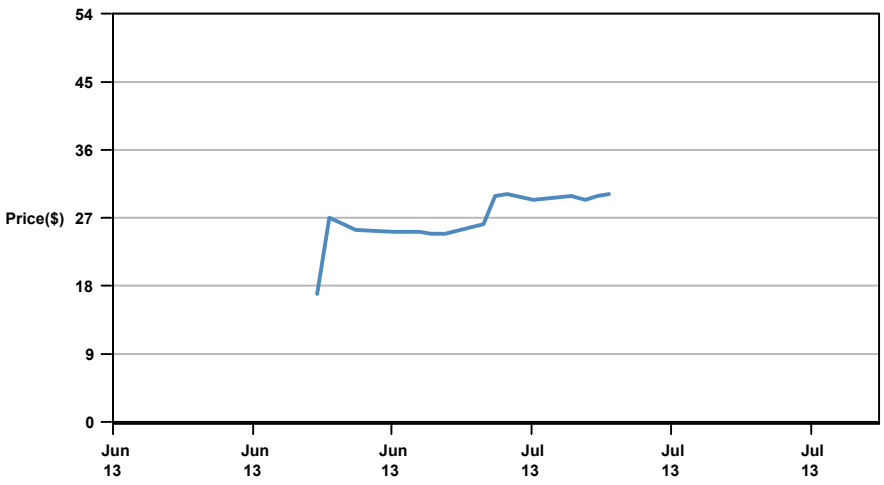
bluebird bio (BLUE, BLUE US) Price Chart



Source: Bloomberg and J.P. Morgan; price data adjusted for stock splits and dividends.

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