INITIATING COVERAGE
Biotechnology
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Eric Schmidt, Ph.D.
eric.schmidt@cowen.com 1 (646) 562-1345
Nicholas Bishop, Ph.D.
nicholas.bishop@cowen.com 1 (646) 562-1378

BLUEBIRD BIO INC (NASDAQ:BLUE)

Initiation: Gene Therapy Has Come Of Age

We are initiating coverage of bluebird bio with an Outperform rating. bluebird's gene therapies have produced proof-of-concept data in two orphan disorders. We view shares as 40-45% undervalued.

Recommendation

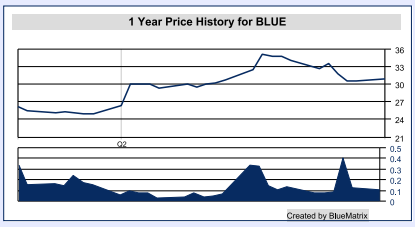
Rating:	Outperform
Price Target (in $):	$44.00
Expected Return:	42.6%
Dividend:	NA
Enterprise Value (MM):	$694.1

Stock Statistics as of 07/29/2013 (in $)

Price:	$30.85
52W Range:	$36.25-$17.00
Shares Out (MM):	16.0
Market Cap (MM):	$703.7
Net Debt (MM):	$0.0

Fundamentals

Earnings Per Share ('12A)	*$(1.83)*
Earnings Per Share ('13E)	*$(1.17)*
Earnings Per Share ('14E)	*$(1.20)*
Revenue (MM) ('12A)	0.3
Revenue (MM) ('13E)	10.1
Revenue (MM) ('14E)	12.0



Gene Therapy Made Possible

bluebird's ex vivo lentiviral-based gene therapies represent one-time treatments that can have a transformative impact on patients. The company has spent years optimizing and industrializing its platform to enable potent, durable, and safe gene expression. bluebird is targeting only single-gene orphan disorders where the risks to success are lowest.

Lenti-D To Enter A Potentially Pivotal Trial By Year End

Lead candidate Lenti-D looks to replace the genetic defect in boys with childhood cerebral adrenoleukodystrophy (CCALD), a rapidly progressive and severe neurodegenerative disorder. Proof-of-concept data comes from a four-patient study in France using a related lentiviral gene therapy vector. In that study, patients experienced favorable outcomes that have lasted for six years running. A 15-patient Phase II/III trial that could support worldwide approvals will start by year end. We view CCALD as a low risk $100-200MM commercial opportunity.

LentiGlobin Has Activity In Thalassemia, And Maybe Also Sickle Cell Disease

Patients with beta thalassemia have mutations in the beta globin gene that impair hemoglobin production and red blood cell survival. LentiGlobin is designed to correct this defect via a transgene that expresses a variant of the wild-type gene. An earlier generation of LentiGlobin successfully enabled transfusion independence for 4+ years in one of three treated patients. Phase I/II trials with a higher potency vector are ongoing. bluebird has selected the variant of beta globin within LentiGlobin for its anti-sickling properties and has also begun Phase I/II trials in patients with sickle cell disease. We view beta thalassemia and sickle cell disease as $500MM+ market opportunities that could support regulatory filings in 2019-2020.

Please see addendum of this report for important disclosures.

Investment Summary

bluebird bio seeks to provide transformative one-time gene therapy-based treatments to patients with severe orphan diseases. The company has assembled a leading gene therapy platform (novel vectors, transduction protocols, manufacturing processes) that has been industrialized to the point where it is capable of delivering consistent, high-quality gene therapies at scale. bluebird bio is directing its gene therapies toward indications of high unmet need where the likelihood of clinical, regulatory and commercial success in greatest. The company has generated proof-of-concept data in two genetic conditions: childhood cerebral adrenoleukodystrophy (CCALD), an X-linked disorder of progressive neurodegenerative decline, and β-Thalassemia, an autosomal recessive disease of red blood cell dysfunction characterized by severe anemia. bluebird retains full ownership to these programs. A separate, early-stage collaboration with Celgene based upon chimeric antigen receptor (CAR) T cells is aimed at cancer. Following a $100MM+ IPO completed in June, bluebird has over $200MM in cash, enough to fund operations for 5+ years assuming no new business development activity. We expect multiple value creating milestones to drive stock outperformance.

Gene Therapy Par Excellence

Gene therapy has long been a holy grail of drug discovery as the promise of replacing defective genetic material with healthy DNA is intuitive and potentially applicable to multiple disease states. However, reducing the concept of gene therapy to practice has been a frustratingly slow process. First generation gene therapy companies encountered a wave of setbacks relating to both efficacy (a failure to deliver, express, and sustain the desired protein in a target cell) and safety (mostly related to the immunogenicity and potential off-target effects of viral vectors). The field was dealt a major setback in 1999 with the death of Jesse Gelsinger, an 18-year old patient treated at the University of Pennsylvania for ornithine transcarbamylase deficiency. The FDA subsequently suspended several clinical trials, and re-evaluated ethical and procedural practices relating to gene therapy. Following the Gelsinger tragedy corporate funding became scarce and, academic groups were forced to take the lead advancing gene therapy technologies. Multiple successful human trials have since been completed, and Europe approved the first gene therapy (UniQure's Glybera) in November 2012.

A Brief History of Gene Therapy

Event	Date
Freidmann and Roblin propose the concept of gene therapy in *Science*	1972
First U.S. trial of gene therapy in a patient with SCID was performed at the NIH	1990
Italian physicians begin trials in SCID patients that were reported to be successful, but later suspended due to leukemia-like side effects	1992
Jesse Gelsinger dies from a massive immune response to therapy four days after receiving treatment with a AV vector	1999
Two independent groups report success in treating Leber's congenital amaurosis (a rare form of blindness) with a AAV vector	2008
French researchers publish data in *Science* on the positive effects of lentiviral gene therapy in patients with CCALD	2009
French scientists publish data in *Nature* on the successful treatment of β-Thalassemia with a lentiviral vector	2010
U. Penn researchers report success with CAR T Cells for treating CLL in *NEJM*	2011
The EMA approves Glybera (an AAV vector delivered via intramuscular injection) for lipoprotein lipase deficiency	2012

Source: Cowen and Company

Despite some notable successes, including the recent EMA approval of Glybera, it has been challenging to develop a gene therapy that is effective and safe. Gene therapy strategies are generally classified by whether their delivery approach is either viral (lentiviruses, andenoviruses, or adeno-associated viruses) or non-viral (plasmids, liposomes, zinc fingers) and further segregated by whether the gene transfer is performed outside the patient's body (ex-vivo) or via direct injection (in vivo). bluebird believes that historically most strategies have failed simply because they did not provide the potent and durable expression of the transgene that is necessary to demonstrate efficacy. The company views its ***viral-based*** (lentivirus), ***ex vivo*** approach as optimal for inducing high levels of gene expression.

Pros and Cons of bluebird's Lentiviral, Ex-Vivo Gene Therapy Platform

Potential Positives	Potential Negatives
Lentivirus vector enables delivery of large genes	Process is individualized to the patient, must be repeated in full for each treatment
Lentivirus integrates into the genome, enabling sustained gene expression	Viral integration still poses some safety risks despite a distinct lentiviral integration patterns
Transduced cells can divide yielding more cells capable of gene expression	Myeloablation and stem cell transplantation are aggressive, costly procedures
An autologous approach associated with low potential for immunogenicity	Requires regional transduction facilities in order to serve global markets
Lentivirus can transduce dividing and non-dividing cells, improving efficiency	
Ex vivo therapy enables delivery of vector directly to target cells	
Leverages known practices of stem cell transplants	

Source: Cowen and Company

While ex vivo, lentivirus-based gene therapy may be associated with several innate competitive advantages, it is also critical to create an efficient, industrial scale production process for ensuring the consistency and quality of any gene therapy. bluebird has spent years optimizing its lentiviral vectors, associated manufacturing techniques, and scale up processes. These efforts have resulted in vectors with greatly improved potency and purity that can be manufactured in a reproducible manner. These accomplishments not only position bluebird as the leader in gene therapy, but also provide a significant competitive barrier to other entrants.

Lenti-D Takes On CCALD

Historically many gene therapy companies have neglected to target their efforts at the lowest hanging fruits. bluebird is avoiding this pitfall by pursuing only monogenic, rare, severe diseases. The company's first target is adrenoleukodystrophy (ALD), a disorder in which long chain fatty acids accumulate throughout the body. The disease is caused by mutations on the ABCD1 gene, which resides on the X chromosome. Approximately one-third of ALD patients present with the severe childhood cerebral form of this disease (CCALD). Affected males develop normally in early childhood, but rapidly progress to a neurodegenerative state followed by death within a decade of diagnosis. Each year there are approximately 40 cases of childhood cerebral ALD diagnosed in the U.S.

The only effective treatment for CCALD is allogeneic stem cell transplantation (SCT). Boys treated with allogeneic SCT receive a wild-type copy of the ABCD1 gene from a sibling or otherwise matched donor. When performed early in the course of disease, allogeneic stem cell

transplantation can be effective, but the associated complications (including engraftment failure, infections, graft versus host disease, and death) can be severe.

Lenti-D represents a potential improvement over allogeneic SCT. The product candidate is derived from the insertion of a functional copy of the ABCD1 gene into a patient's own stem cells via lentiviral based gene delivery. The CCALD patient then undergoes an ***autologous*** stem cell transplantation procedure which is known to be associated with fewer complications than an allogeneic procedure, but hopefully as much or more corrective benefit. Proof-of-concept for bluebird bio's approach comes from a four-patient CCALD trial conducted in France using a related lentiviral gene therapy vector. In this study, 3 of 4 patients witnessed a good response to therapy that has been shown to be durable for 6+ years. Bluebird will initiate a U.S. Phase II/III trial (n=15) on Lenti-D in late 2013 that could serve as the basis for FDA and EMA approval. We project a BLA filing in the 2019 timeframe, and view Lenti-D as having revenue potential of $100-200MM.

LentiGlobin Directed At Thalassemia And Sickle Cell Disease

β-thalassemia is a rare genetic blood disorder caused by mutations in the β-globin gene, one of two proteins that make up hemoglobin. Patients with β-thalassemia have an excess of α-globin, the other protein within hemoglobin, and such an imbalance can cause premature death of red blood cells, leading to anemia, splenomegaly, and bone marrow expansion. There are nearly 200 different known mutations in the β-globin gene that cause β-thalassemia, and the degree of globin chain imbalance correlates with the degree of symptomology. In more severe forms of the disease (β-thalassemia major), patients require chronic transfusions to sustain life.

β-thalassemia is more common in Mediterranean, South and Southeast Asian, and Middle Eastern populations. It is estimated that ~280K patients worldwide receive treatment for β-thalassemia major, of which 15,000 reside in the U.S. and Europe. Many patients receive transfusions every 3-5 weeks to maintain hemoglobin levels in the 9-10g/dL range, but such transfusions are often complicated by iron overload, which can cause heart and liver toxicity. Allogeneic stem cell transplantation offers the potential for curative therapy, but because of the risk of transplant-related morbidity and mortality, it tends to be reserved for pediatric patients with matched sibling donors (<25% of all cases).

bluebird's approach to β-thalassemia is similar to its approach to CCALD. LentiGlobin consists of a patient's own stem cells that have been modified with a near-normal copy of the β-globin gene inserted via a lentiviral vector. As in the case of Lenti-D, LentiGlobin is delivered via an autologous stem cell transplantation procedure that is expected to be associated with greatly reduced morbidity and mortality. The inserted β-globin gene within LentiGlobin contains a single codon variant (T87Q). This variant is capable of producing fully functional β-globin, with a biomarker that can serve to measure production of the transgene. In addition, the T87Q mutation was selected for its anti-sickling properties, a potential benefit for sickle cell anemia patients who harbor β-globin gene mutations that can lead to polymerization of hemoglobin proteins with potentially severe side effects. Because of the known anti-sickling properties of

T87Q, a study of LentiGlobin is enrolling patients with sickle cells disease. Proof-of-concept for LentiGlobin in β-thalassemia major comes from a small trial conducted in France using an earlier generation version of LentiGlobin. As reported in *Nature* (2010) one of the three treated patients has performed particularly well, maintaining transfusion-independence for 4+ years. bluebird is now conducting two Phase I/II trials of LentiGlobin. A French trial, initiated in mid 2013 is enrolling seven patients with β-thalassemia major or refractory sickle cell disease. A U.S. trial will soon begin enrolling up to 15 patients with β-thalassemia major. Initial data from both studies could be available in late 2014. We assume regulators will require an additional trial prior to approval, and that regulatory filings could occur in the 2019-2020 timeframe.

Celgene Collaboration Rounds Out The Pipeline

bluebird intends to maintain full rights to Lenti-D and LentiGlobin and to commercialize these and potentially other therapies for rare, severe genetic diseases on its own. However, the company's gene therapy platform can be applied more broadly, and bluebird's management team intends to forge partnerships with a limited number of parties to advance lentiviral gene therapy candidates in other indications as well as offset the costs associated with bringing Lenti-D and LentiGlobin forward.

bluebird's first such collaboration is with Celgene, focused on oncology. The partners will apply gene therapy to genetically modify a patient's own T cells to recognize and destroy cancer cells. The approach, known as chimeric antigen receptor (CAR) T cells has shown much promise in academic settings for treating B-cell lymphomas, but has proven costly and difficult to commercialize. Under the March 2013 collaboration with Celgene, bluebird received an upfront payment of $75MM, and is responsible for all research activities and development through Phase I trials. Celgene has the option to acquire any candidates after Phase I trials in return for additional milestones (up to $225MM per candidate) and royalties (mid-single digits to mid-teens). We believe the Celgene collaboration provides outside validation of bluebird's leading capabilities in gene therapy.

bluebird R&D Pipeline

Therapeutic Class/Product	Indication	P-C	I	II	III	FILING	MKT	Comments
Orphan Disorders								
Lenti-D	Childhood cerebral ALD			•	⇒			Phase II/III trial to begin in late 2013
Lenti-D	Adult CALD	•						2-5% of all ALD cases
LentiGlobin	β -Thalassemia / sickle cell disease			•				Phase I/II trial ongoing in France
LentiGlobin	β -Thalassemia			•				Phase I/II trial starting shortly in the U.S.
Oncology								
CAR T Cell therapy	Hematologic malignancies	•						In collaboration with Celgene
CAR T Cell therapy	Solid Tumors	•						In collaboration with Celgene
Total Drugs In Development		**3**	**0**	**3**	**0**	**0**	**0**	
Cambridge, MA	**Investor Relations Contact: Richard Smith (617) 491-5601**							

Source: Company reports

So What Are BLUE Shares Worth?

bluebird bio completed a $116MM IPO in June, and has estimated cash on hand of approximately $230-240MM as of the end of Q2. With a burn rate of between $30-40MM, the company is well financed for the foreseeable future. BLUE shares have been well received in the public markets, and as of July 29, the company's enterprise value was approximately $475MM.

We view bluebird as having many if not all of the characteristics that we look for when investing in a biotechnology company. These include a proprietary and differentiated technology platform, an orphan drug focus, proof-of-concept data, biologic capabilities, a renewable pipeline, and a strong management team. We are particularly encouraged by the fact that bluebird has established the efficacy of Lenti-D and LentiGlobin in two areas of high unmet need, and view the risks to success in these indications as fairly modest. Our sum-of-the-parts analysis suggests shares may be 40-45% undervalued. This outlook could be deemed conservative in that it includes no value for LentiGlobin in sickle cell disease, the CELG collaboration, or future pipeline programs.

BLUE Sum-Of-The-Parts Valuation

Asset	Value	Value/share
NPV of Lenti-D for CCALD	$135MM	$5.75
NPV of LentiGlobin for Thalassemia (only)	$460MM	$19.73
Gene Therapy platform	$200MM	$8.58
Net cash	$230MM	$9.87
Other (CELG collaboration, sickle cell disease, etc.)	$0MM	$0.00
Total	**$1.02B**	**$43.93**

Source: Cowen and Company

On the other hand, the company is unlikely to derive revenue from commercial products until around 2020. bluebird's stock has benefitted from a glass-half-full view toward biotech IPOs and shares could trade at the market's whim for much of the next 12-18 months. The next major milestone is likely to be interim Phase II data on LentiGlobin in β-thalassemia and sickle cell patients toward the end of 2014. Hence, investors may need to exercise some patience in order to reap the rewards from bluebird's fundamental progress.

Upcoming bluebird bio Milestones

Event	Timing
Begin enrollment in U.S. LentiGlobin Study 404 in β-thalassemia patients	Mid 2013
Begin enrollment in Phase II/III Lenti-D study in CCALD	Late 2013
Initiate U.S. trial of LentiGlobin in sickle cell patients	2014
Initial data from E.U. LentiGlobin Study 405 in seven β-thalassemia / sickle cell patients	Late 2014
Initial data from U.S. LentiGlobin Study 404 in up to 15 β-thalassemia patients	Late 2014
Possible initiation of Lenti-D trials in adult CALD patients	2015
Possible initiation of a pivotal trial on LentiGlobin	2015

Source: Cowen and Company

NPV Analysis of Lenti-D and LentiGlobin

Financial Year End	12/31/2012
Valuation Date	7/29/2013
Discount Rate	**13.0%**
Perpetual Growth Rate	**0.0%**

bluebird bio NPV Valuation

Valuation Date: Monday, July 29, 2013

$MM	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
Lenti-D Sales	0	0	0	0	0	0	0	0	20	55	80	100	115	135	155	165
Growth (%)										*175%*	*45%*	*25%*	*15%*	*17%*	*15%*	*0%*
LentiGlobin Sales	0	0	0	0	0	0	0	0	0	10	75	200	300	425	500	550
Growth (%)											*650%*	*167%*	*50%*	*42%*	*18%*	*10%*
Total Revenue	0	0	0	0	0	0	0	0	20	65	155	300	415	560	655	715
										225%	*138%*	*94%*	*38%*	*35%*	*17%*	*9%*
COGS	0	0	0	0	0	0	0	0	3	10	23	45	62	84	98	107
COGS as a % of total sales									*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
R&D	17	23	28	30	32	35	37	38	30	16	16	15	12	11	7	7
R&D as a % of Revenues									*150%*	*25%*	*10%*	*5%*	*3%*	*2%*	*1%*	*1%*
SG&A	7	11	12	14	16	18	20	22	40	65	70	75	83	106	118	122
SG&A as a % of Revenues									*200%*	*100%*	*45%*	*25%*	*20%*	*19%*	*18%*	*17%*
Operating Income	-24	-33	-40	-44	-48	-53	-57	-60	-53	-26	47	165	257	358	432	479
Operating Margin										*-40%*	*30%*	*55%*	*62%*	*64%*	*66%*	*67%*
Tax	0	0	0	0	0	0	0	0	0	0	0	0	0	18	112	127
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*26%*	*27%*
Approx Free Cash Flow	(24)	(33)	(40)	(44)	(48)	(53)	(57)	(60)	(53)	(26)	47	165	257	340	320	352
Years	-0.58	0.42	1.42	2.42	3.42	4.42	5.42	6.42	7.42	8.42	9.42	10.42	11.42	12.42	13.42	14.42
Discount Factor	1.07	0.95	0.84	0.74	0.66	0.58	0.52	0.46	0.40	0.36	0.32	0.28	0.25	0.22	0.19	0.17
NPV of Cash flows	(26)	(32)	(34)	(33)	(32)	(31)	(29)	(27)	(21)	(9)	15	46	64	75	62	60

Terminal Value Calculation

Final year FCF	382
Perpetual Growth Rate	0.0%
Terminal Value	**2,936**
Discount Factor	0.15
Present Value of Terminal Value	**446**
Present Value of Cash Flows	**148**
Enterprise Value	**594**
Market Value	**594**
Fully Diluted Shares Outstanding	23.3
Value per Fully Diluted Share	**$25.48**

Source: Cowen and Company.

The Gene Therapy Field Has Matured, Both In Technique…

Ever since the dawn of molecular biology, the dream of curing genetic diseases by correcting or replacing the defective gene(s) has captivated researchers. Unfortunately, early attempts at gene therapy served to highlight that the technology had not matured enough to make the dream a reality. One notable example was an attempt to treat patients with X-linked severe combined immunodeficiency (SCID) by inserting a normal copy of the defective gene using a murine gamma-retroviral vector, in a trial conducted from 2000 – 2002. This transgene corrected the disease, showing the promise of the approach in principle, but unfortunately the vector also caused leukemia in 5 of 20 patients. This was due to the propensity of this vector to insert near the promoter region of genes driving cellular growth, promoting the development of cancer (a process termed insertional oncogenesis). In another highly publicized case, Jesse Gelsinger, a patient with a genetic liver disease, died in 1999 after suffering a massive immune reaction to a adenoviral gene transfer vector. Thus, safety is a major concern with any gene therapy approach.

A technical turning point in gene therapy came in the mid-2000's with the first reports of lentiviral vectors being used to carry the transgenes used in gene therapy trials. Lentiviral vectors are based on a "gutted" HIV genome, in which the genes required for replication are removed and replaced with a human transgene of interest. Thus the pathogenic elements are eliminated, yet the vector retains HIV's ability to permanently insert into the genome and drive sustainable expression of any chosen gene. Importantly, lentiviral vectors preferentially integrate within genes, rather than in regions controlling gene expression, so the theoretical risk of insertional mutagenesis is low. One of the earliest reports of the use of lentiviral vectors in human trials was a 2009 report in *Nature* describing the successful treatment of childhood cerebral adrenoleukodystrpohy (CCALD), a lethal neurodegenerative disease, with good safety. These data form the theoretical basis of bluebird's Lenti-D product candidate, and are discussed in more detail below. In 2010, researchers reported success in treating β-thalassemia using a lentiviral gene therapy approach, again with good safety; these data formed the proof of concept for bluebird's LentiGlobin product candidate, discussed in more detail below. Two 2013 *Science* reports detail three patients each with Wiskott-Aldrich syndrome and metachromatic leukodystrophy who were treated with lentiviral vectors, again with good safety. While follow-up continues on all these patients, thus far it appears that lentiviral delivery does not carry the same risk of oncogenesis or catastrophic immune reactions that have troubled earlier delivery approaches.

…And Regulatory Environment

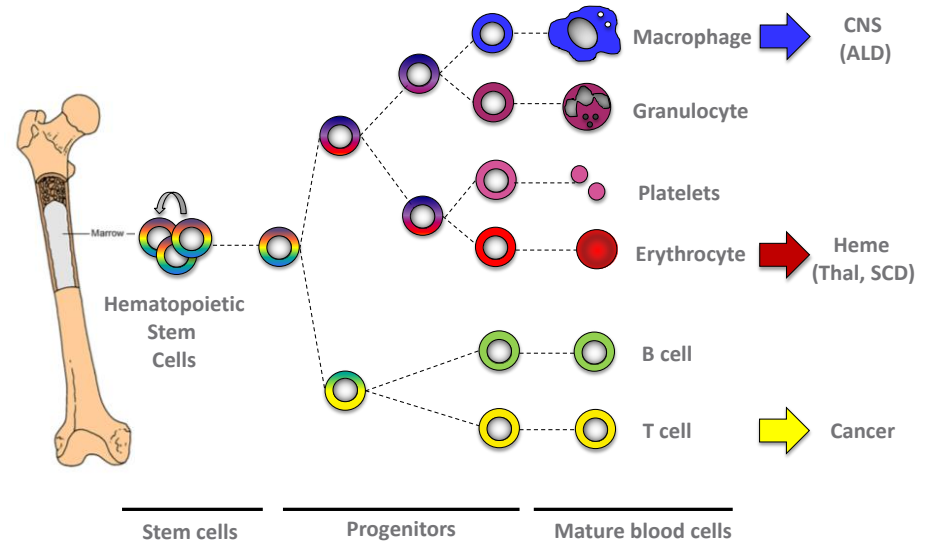
The regulatory environment surrounding approval of gene therapies has also matured. In the EU, for example, the first gene therapy ever to win EMA approval, uniQure's Glybera for treating the orphan disease LPL deficiency, received marketing authorization in 2012. The FDA, meanwhile, has begun to provide clear guidance on the regulatory path for gene therapy. The FDA has formed an Office of Cellular, Tissue, and Gene Therapies (OCTGT) within CBER, and has issued a number of Guidances to Industry to help facilitate commercial

development of gene therapies. Thus, the regulatory environment appears ripe for bringing gene therapy to market.

bluebird Has Created An Optimized Gene Therapy Platform

bluebird is using lentiviral transduction technology to address serious genetic disease and cancer. The general approach involves *ex vivo* transduction of hematopoietic stem cells (HSCs) isolated from patients with defined monogenic diseases, inserting a normal copy of the gene that is defective in these patients. The patient's native hematopoietic system is then ablated and the transduced HSCs are engrafted. Use of the patient's own cells (an autologous transplant) is important to note, as this should avoid some of the serious immune complications associated with allogeneic transplants such as graft-versus host disease (GVHD), which require management with harsh immunosuppressive therapies and can be fatal. HSCs are a self-renewing cell type that reconstitutes the patient's hematopoietic system, thus providing permanent, life-long expression of the normal gene from this one-time treatment. Because HSCs differentiate to form a variety of terminal cell types, this general approach is potentially applicable to a variety of genetic diseases and cancer in a modular, repeatable fashion, providing to bluebird a true gene therapy platform. Initially, bluebird is focusing on indications that can already be treated successfully through allogeneic HSC transplants, minimizing clinical risk.

Targeting HSCs Enables Diverse Downstream Opportunities

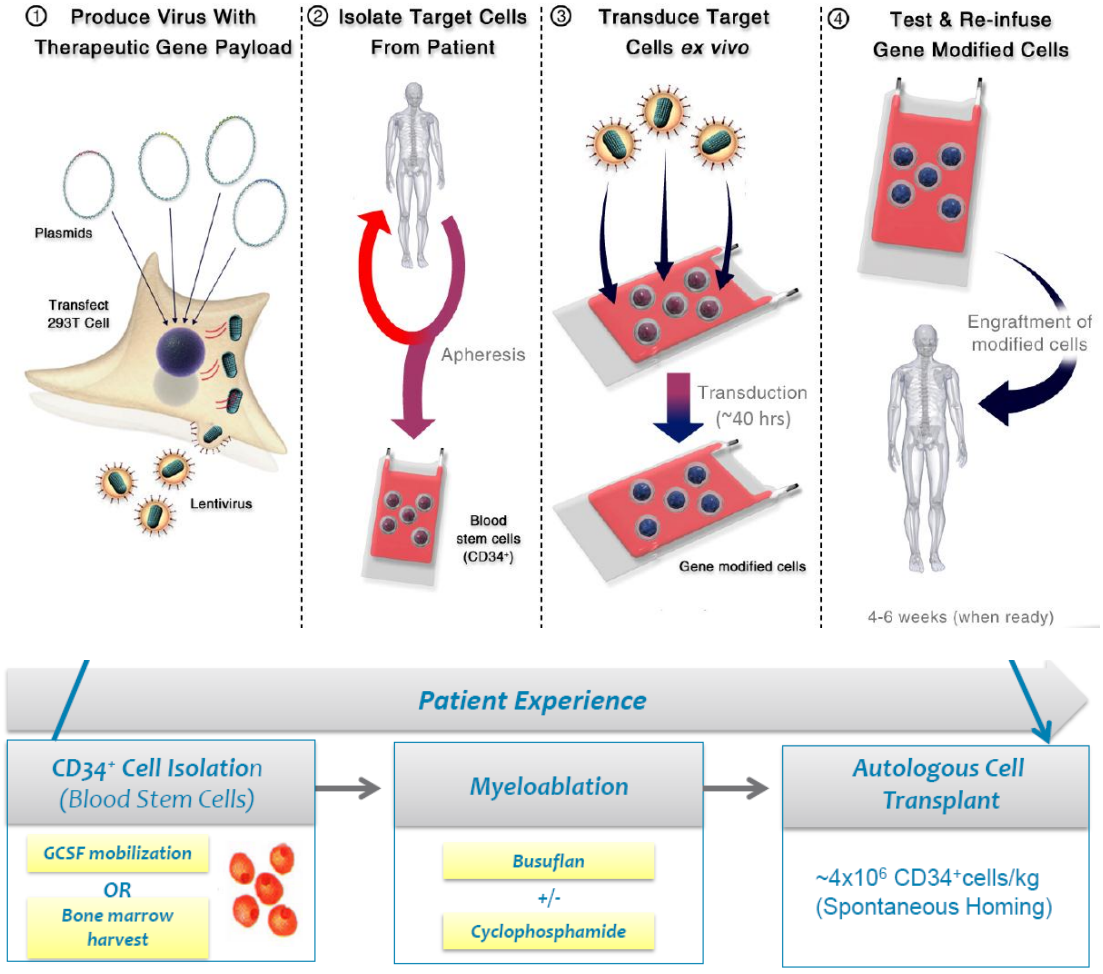


Source: bluebird bio

The lentiviral vector bluebird uses is based on the HIV virus. The vector takes advantage of the virus' natural ability to integrate into the host genome in both dividing and non-dividing cells in order to efficiently deliver the chosen genetic payload. However the vector has been modified in a number of ways to render it nonpathogenic. Virtually all the viral genes have been removed to make room for the transgene and eliminate the virus' ability to replicate. The

infectious viral particles are generated by co-transfecting producer cells with separate plasmids containing the "gutted" viral backbone and transgene, the viral capsid proteins and viral polymerase to make viral RNA from the DNA plasmid, reverse transcriptase to make DNA from the virus' RNA, and VSV – a pantropic envelope protein that allows infection of a variety of human cell types (not just CD4+ T cells). This results in the production of infectious viral particles carrying the viral RNA, reverse transcriptase protein, and viral integrase protein. When the virus infects target cells, it is thus able to undergo the process of reverse transcription and integration into the genome, but because the natural viral genes are not present, it can only undergo this single cycle of transduction and cannot replicate or infect other cells. To make doubly sure of this, the terminal ends of the viral genome are also modified to be "self-inactivating," so that they would no longer be recognized for excision even if the necessary viral proteins were present. Thus, the transgene is stably, safely inserted into the host genome.

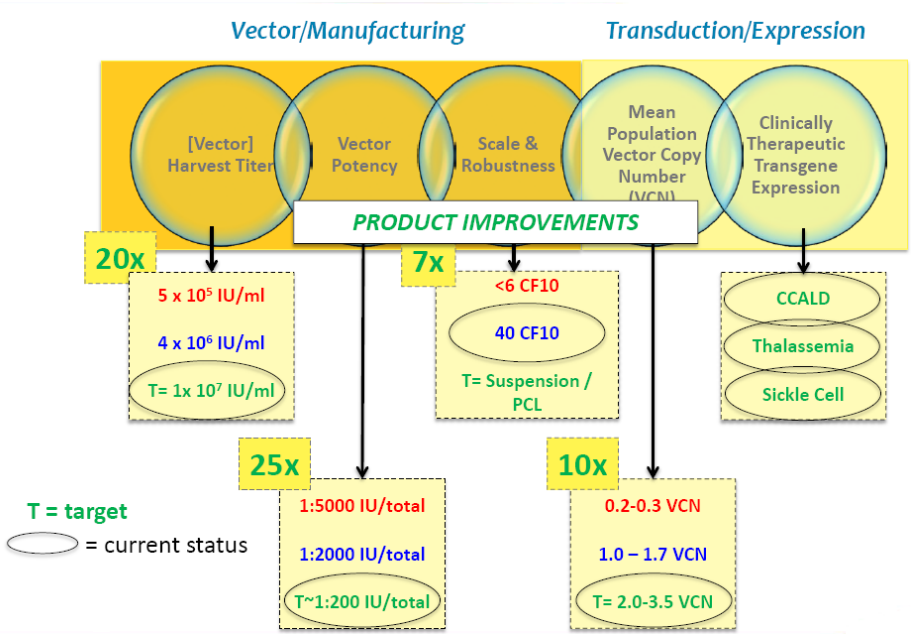
Targeting HSCs Enables Diverse Downstream Opportunities



Source: bluebird bio

While lentiviral transduction is a standard technique in modern academic molecular biology labs, bluebird has put considerable effort into "industrializing" its lentiviral production platform, making generally applicable process enhancements to allow modular, reproducible production of lentiviral particles at commercial scale. bluebird's many process enhancements have led to increases in viral particle yield, potency, scale, and average vector copy number in transduced cells. In fact, with multiple copies of the transgene integrating into the average cell, essentially 100% of target cells are transduced, and bluebird has no need of a selection process *ex vivo*. bluebird currently produces its viral particles using cells cultivated as adherent monolayers in 40 ten tray cell factories (TTCF), though the company is working on scaling up to 100-1,000L suspension bioreactors in the future. This process should be generalizable to any future product candidates; since the vector backbone is expected to remain the same, bluebird anticipates that future indications could be addressed by simply swapping out the transgene and applying the same optimized process. In addition to the orphan drug exclusivities and patents that protect bluebird's product candidates, these proprietary trade secrets and know-how provide another layer of protection and a barrier to entry for any would-be competitors.

bluebird's "Industrialized" Viral Production And Process Improvements



Source: bluebird bio

CCALD Is A Devastating Neurodegenerative Disease

Adrenoleukodystrophy (ALD) is an X-linked, heritable disorder caused by a mutation in the ABCD1 gene, occurring in about 1 in 20,000 male births. The mutation results in defective peroxisomal fatty acid metabolism, and consequent buildup of very long-chain fatty acids (VLCFAs) in various cell types. The excess VLCFAs cause particular damage to the myelin sheaths of neurons in the brain and CNS.

ALD is clinically heterogeneous in severity. The most severe form, childhood cerebral ALD (CCALD), accounts for about 30-40% of cases. Disease symptoms begin to present in mid-childhood (age 3 to 15), and include progressive cerebral inflammation and demyelination, and loss of motor and cognitive function, eventually progressing to a vegetative state and death within a few years of diagnosis if left untreated. Other forms of ALD include AMN (adrenomyeloneuropathy), accounting for 40-45% of cases, which typically occurs with adult onset and is more slowly progressive, causing gradual demyelination of spinal nerve axons and motor dysfunction, including walking defects and bladder/bowel problems. About 40% of AMN cases will progress to cerebral manifestations similar to CCALD. About 5% of ALD cases have the adult cerebral form (ACALD), which is characterized by cerebral symptoms similar to CCALD, though with onset later in life (after age 15) and without a preceding AMN phenotype.

The only current treatment for CCALD consists of allogeneic HSC transplant. Patients' hematopoietic cells are ablated and the HSCs of a healthy individual are transplanted. Eventually, these cells reconstitute the patient's blood cells, including microglia that reside in the brain. These cells are able to scavenge the excess LCFAs and halt progression of the disease. While effective, allogeneic HSC transplant has significant drawbacks. One of the most important is tissue type mismatch between the donor and recipient, which can cause potentially fatal GVHD and limit engraftment success. Therefore, the ideal donor is an HLA-matched normal sibling, though in most cases a matched sibling is not available, so partially matched donor cells, or umbilical cord cells, are typically used. According to consultants, 80% of CCALD transplants do not use cells from a matched sibling. Treatment by HSCT entails significant risk of near-term morbidity and mortality, especially with donors who are not matched siblings. Consultants indicate that about 5-10% of patients will die within 100 days due to complications inherent to the HSCT transplant procedure (harsh myeloablative chemotherapy, acute infections). Another 10-20% will die over the first two years due to complications of GVHD arising from the unmatched tissue donor. In addition, unmatched recipients face a 10-30% chance of engraftment failure and a 30% overall chance of developing GVHD. The chronic immunosuppression required to control risk of GVHD places patients at long-term risk of opportunistic infections.

Lenti-D Is bluebird's Gene Therapy Candidate For CCALD

bluebird is developing Lenti-D as a potential treatment for CCALD. The Lenti-D product candidate consists of a CCALD patent's own HSC cells, which have been transduced *ex vivo* using a lentiviral vector that delivers the normal ABCD1 gene. This approach is expected to provide comparable therapeutic efficacy to a normal HSCT, while reducing the complications associated with non-sibling-matched transplants, including failure to engraft, GVHD, and infection risk stemming from chronic immunosuppression. Proof-of-concept for this approach comes from an academic study in which four boys were treated with promising results. bluebird has conducted a retrospective natural history study to characterize CCALD with or without treatment, providing great confidence that the (uncontrolled) academic study has demonstrated real benefit, and also informing the design of Lenti-D's pivotal ALD1 trial, set to begin in late 2013. Lenti-D has received Orphan Drug designation from both the FDA and EMA.

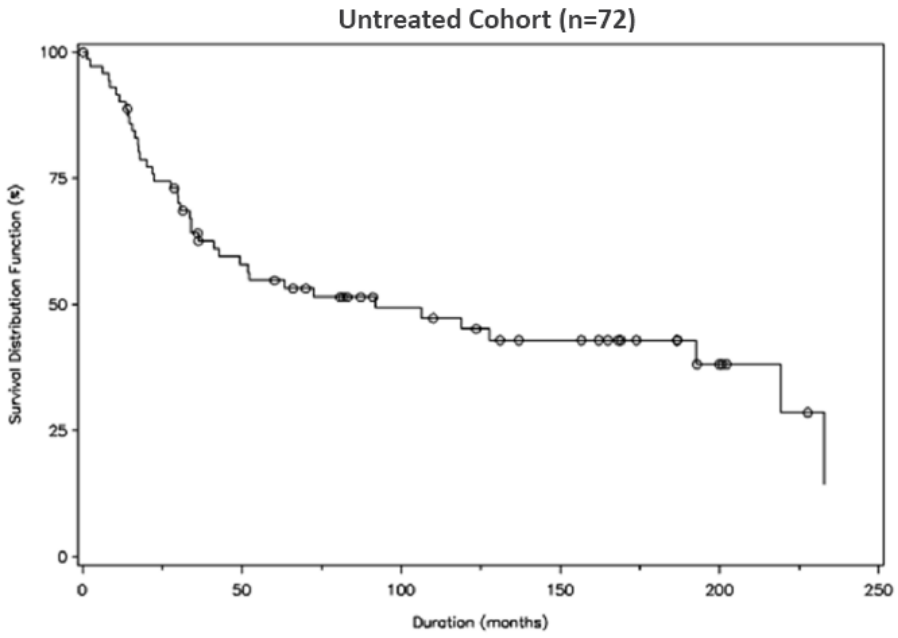
Retrospective Natural History Study Defines CCALD Disease Course

bluebird has conducted a retrospective natural history study (ALD-101) to characterize the disease course and inform pivotal trial design. The study consisted of chart reviews for CCALD patients who were either left untreated, or treated with allogeneic HSCT, seeking to gather neurologic and neuropsychological assessments, as well as neuroimaging data and mortality data, as available. The study included 137 patients (72 untreated and 65 treated with HSCT) from 4 U.S. sites and 1 French site.

The ALD-101 study revealed that three clinical scores are most commonly used to monitor clinical progression in CCALD patients: the neurological function score (NFS), the Loes score, and gadolinium enhancement. The NFS is a 25-point scale assessing 15 abnormalities that can be caused by ALD. bluebird considers 6 of these (termed Major Functional Disabilities or MFDs) to be most critical, as they lead to significant loss of patient functionality and independence: loss of communication, complete loss of voluntary movement, cortical blindness, requirement for tube feeding, wheelchair dependence, and total incontinence. The Loes score is a 34-point scale intended to allow objective measurement of CNS disease based on MRI readings. A score of 1 indicates the presence of CNS abnormality and serious disease; a score of 10 or higher would indicate such advanced disease that a patient would not normally be considered suitable for transplant therapy. Gadolinium is a contrast enhancement agent that is indicative of neuroinflammation, as it is able to enter the brain and be detected by MRI only if such inflammation is present and the blood-brain barrier is compromised.

ALD-101 showed that left untreated, outcomes for CCALD patients are terrible, with a median post-diagnosis survival of 7.7 years and a 5-year survival of 55% (note, however, that these results may include patients kept alive artificially after progressing to a vegetative state). In addition, the study showed that higher NFS and Loes scores (indicating more advanced disease) were predictive of worse outcomes in both treated and untreated patients; therefore bluebird's pivotal trial will exclude patients with NFS and/or Loes scores that would be predictive of a poor outcome regardless of treatment.

CCALD Natural History – ALD-101 Study



	Mortality Rate*			
			Loes	
	NFS£ 1	NFS > 1	³ 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

In addition, the ALD-101 study found that gadolinium enhancement appeared to be predictive of MFD occurrence. 13 of 18 (73%) gadolinium-positive patients experienced NFS-MFDs within two years (vs. 29 of 52 evaluable patients (52%) overall). Therefore, bluebird's pivotal study requires that patients be gadolinium-positive at study entry, and has a primary endpoint based on MFD occurrence. Moreover, 12 of 15 (80%) evaluable gadolinium-positive patients showed a rapid increase in NFS score (meaning a 5-point or greater increase) within 6 to 18 months.

ALD-101 also characterized the effects of treatment with allogeneic HSCT. HSCT stabilized the disease in many patients, with 63% experiencing no NFS-MFD within 24 months, and many resolved gadolinium enhancement. For patients who would meet the enrollment criteria for the ALD-102 pivotal study (NFS at baseline of 0 or 1, gadolinium-positive, baseline Loes between 0.5 and 9), just 15% (3 of 20) experienced and MFD through 24 months.

ALD-101 also showed that, as expected, HSCT was associated with significant morbidity and mortality. 12 of 65 (18%) patients experienced engraftment failure, the majority of whom (83%) received unrelated donor cells. GVHD occurred in 54% of patients, including acute GVHD in 42% of patients and chronic GVHD in 18%. 29% of patients experienced a serious infection.

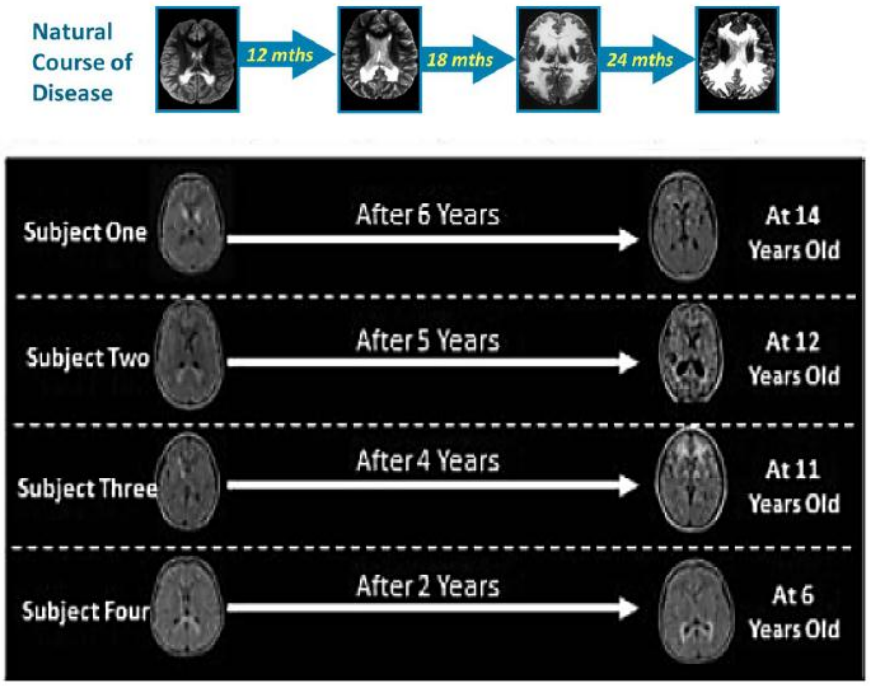
The 100-day mortality rate was 8% and the one-year mortality rate was 19%. 5-year survival was 74%. However, the majority of deaths occurred in patients not receiving matched sibling donor cells; therefore, bluebird's pivotal trial will exclude patients with a matched-sibling donor available.

Academic Study Provides Proof Of Concept

Between 2006 – 2010, the Phase I/II TG04.06.01 study, conducted at Inserm in France, treated four boys with CCALD using *ex vivo* transduction of their HSCs with a lentiviral vector containing a normal copy of the ABCD1 gene. Results were published in *Science* in 2009, and follow-up continues.

Results were remarkably positive. At baseline, patients had Loes scores ranging from 2 to 7, all were gadolinium positive, and NFS scores were all zero. With follow-up now ranging from 2 to 6 years, all patients' Loes scores have stabilized and three of four patients' gadolinium enhancement has stabilized. These results appear consistent with the efficacy expected from allogeneic HSCT. In contrast to the expected outcomes from the natural history study, patients have not inexorably progressed, but rather have seen their neurologic disease stabilize. All patients did experience some functional decline within the first 2 years post-transplant, as it took about 10-15 months for the disease to stabilize, though this also occurs with allogeneic HSCT due to the time taken for normal microglia migrate throughout the brain. The third patient fared a bit worse than the others, though the trial investigators attribute this to his poorer engraftment (4% of peripheral blood cells transduced vs. 10-14% in the first 2 patients).

CCALD Natural History – ALD-101 Study



Source: bluebird bio

Just as important as the efficacy, there have been no reported gene-therapy related safety issues in this study. Moreover, the patients have not exhibited the morbidity issues that would normally have been expected from allogeneic transplant: engraftment was efficient in all four subjects, and none has experienced GVHD. We believe these data provide compelling proof-of-concept for bluebird's approach, as the Lenti-D lentiviral vector is broadly similar to that used in this study (apart from potency and scale enhancements that should, if anything, improve results).

Pivotal Trial Ready To Get Underway

Based on the insights from the ALD-101 natural history study, and in consultation with U.S. and E.U. regulators, bluebird has designed the pivotal Phase II/III ALD-102 study, aimed at registration of Lenti-D. The IND was accepted in April 2013, and the trial is set to begin in late 2013.

The ALD-102 trial will enroll up to 15 CCALD patients at 4 sites (2 in the U.S., two in the E.U.) in order to obtain at least 12 evaluable patients. Patients will be required to have early disease at baseline (defined as gadolinium-positive, NFS or 0 or 1, and Loes of 0.5 to 9, inclusive). Patients with a matched-sibling donor available will be excluded. Patients will be treated with a single dose of Lenti-D and followed for 2 years post-transplant for efficacy. The primary endpoint will be the proportion of patients who have no MFS at 24 months post-transplant. Key

secondary endpoints include change from baseline NFS and Loes score, resolution of gadolinium enhancement, MFS-free survival and overall survival. We expect that the FDA will compare the proportion of patients who are MFS-free at 2 years in ALD-102 to that in bluebird's untreated natural history study as part of the efficacy assessment. Safety assessments will include efficiency of engraftment, 100 day and 180 day mortality, incidence of GVHD, and measurements of potential replication and insertion pattern of the vector.

As bluebird's natural history study showed that 73% of untreated gadolinium-positive patients experienced an MFS within two years, while only 15% of HSCT-treated patients meeting the ALD-102 enrollment criteria did, success in this trial looks quite likely. Moreover, consultants suggest that up to 30% of patients receiving unmatched HSCT die, in part due to complications of GVHD and/or immunosuppression; 5-year survival is more like 90% with matched siblings. Therefore, we believe the autologous Lenti-D approach may lead to a noticeable mortality benefit at two years, as well, assuming it behaves like sibling matched HSCT.

Consultants Expect Success

Our expert consultants concur that the French trial results would not be expected to occur spontaneously given the natural history of the disease, and therefore the data constitute clear proof-of-concept for this approach. They expect the results to be replicated in bluebird's pivotal trial, especially given the greater efficiency of transgene delivery in the company's optimized process. The consultants think that the efficacy in the French trial appears comparable to a sibling-matched donor HSCT transplant, and speculate that efficient overexpression of the ABCD1 gene in Lenti-D could even improve efficacy over natural HSCT. On safety, the consultants are watching for signs of insertional oncogenesis, but are not concerned about it. They wonder if there might be a time limit to how long the HSCT transfer will remain effective, but are also not particularly worried about this, as the French follow-up is now as long as 6 years, and the longest follow-up of HSCT is about 20-25 years, with no sign of diminishing efficacy.

Lenti-D's Market Opportunity

bluebird estimates that there are about 80 new diagnoses of CCALD in the U.S. and E.U. combined annually, and 300-400 worldwide. Our consultants estimate that only about 25 CCALD boys are currently transplanted in the U.S. annually, however, because many are too advanced at presentation to benefit. Newborn screening would increase the number of transplant eligible patients, and efforts are underway to introduce this in the U.S.

bluebird's discussions with payors have suggested that at least $1MM per patient would be acceptable for a one-time curative treatment, given the lifetime of medical care it would avoid. UniQure's pricing of Glybera at 1.2MM euros ($1.5MM) would appear to support this expectation, and should help set the stage for bluebird to introduce Lenti-D at a high one-time price. Given that chronically administered ERTs can cost millions of dollars every few years for the lifetime of a patient, we would expect payors to appreciate the value of a one-time

transformative therapy. Nevertheless, it will be interesting to observe the market and payor reception of Glybera.

One challenge to the international expansion of Lenti-D will be the need to establish regional cell transduction centers to manufacture the Lenti-D from individual patients' cells, as well as the expectation that sufficiently advanced medical facilities to do the transplant and follow up care will be available in all parts of the world. bluebird believes the necessary infrastructure for global expansion can be built.

Unfortunately, because of the lag time from transplant to repopulation of the brain with normal microglia, difficulty in diagnosing CCALD in the early stages, and delays in identifying appropriate donors, an estimated 20-50% of patients have disease too advanced to justify the HSCT, as a positive outcome would be unlikely. Newborn screening tests are being developed, and bluebird is hopeful that ALD will become part of the standard universal screen in the coming years. This would expand the addressable market by increasing the percentage of children whose disease is detected early enough to intervene. Consultants indicate that newborn screening is likely to be added to the state panels as more effective therapeutic options become available.

ACALD represents a potential additional expansion opportunity, as HSCT has shown some benefit in these patients; however, survival outcomes tend to be relatively poor in these older patients, even with HLA-matched donors (perhaps 80% survival at the most experienced centers). AMN could be another expansion opportunity, particularly in the 40% of patients with cerebral manifestations, though no HSCT treatment attempts have been made in these patients, to our knowledge. Partially this is because of the mortality risk due to unmatched donor cells, GVHD, and immunosuppression. Consultants think that conceivably these concerns could be alleviated through bluebird's autologous approach, and open these other subsets of ALD to therapy. However, at present the HSCT procedure itself would still carry a 10% mortality risk that could be dissuading unless the procedure is improved. If early mortality risk were minimized sufficiently, there might be a valid argument for treating even presymptomatic patients with ALD.

Our revenue model assumes that Lenti-D's initial addressable market is CCALD boys who (1) are diagnosed early enough in their disease to benefit from treatment; and (2) do not have a matched sibling donor. We assume a 1:20,000 male birth incidence of ALD, and that 35% of ALD cases are CCALD. Over time, our model assumes that newborn screening increases the percentage of CCALD children who are diagnosed early enough to be treated. We also assume that over time, Lenti-D will begin to replace even sib-matched transplantation in CCALD, as we would expect perfectly matched autologous transplants to exhibit better safety and engraftment vs. even sib-matched transplants. We assume initial pricing of $1.5MM per patient worldwide, in line with Glybera's pricing. We assume annual increases in price in the U.S., though not the E.U. Our model assumes approximately 40% of global sales ultimately come from rest-of-world patients, consistent with the percentage of sales from R.O.W. that other orphan drug companies have achieved (e.g. Alexion, BioMarin). Our model suggests peak global revenue for Lenti-D of about $175MM. We do not assume any use in ACALD or

AMN with cerebral involvement, though these patient segments together could approximately double the market opportunity.

Lenti-D Revenue Model

Global Lenti-D Revenue Model

U.S.	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**
# Incident male ALD patients (all types)	100	100	100	100	100	100	100	100	100
% AMN type	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*	*45%*
# AMN type	45	45	45	45	45	45	45	45	45
% ACALD type	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
# ACALD type	5	5	5	5	5	5	5	5	5
% CCALD type	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
# CCALD type	35	35	35	35	35	35	35	35	35
% CCALD diagnosed in time to treat	*70%*	*70%*	*70%*	*74%*	*80%*	*86%*	*92%*	*92%*	*92%*
# CCALD diagnosed in time to treat	25	25	25	26	28	30	32	32	32
% CCALD not getting transplant from matched sibling	*80%*	*80%*	*80%*	*80%*	*84%*	*88%*	*92%*	*93%*	*94%*
# CCALD without matched sibling	20	20	20	21	24	26	30	30	30
% treated with Lenti-D	*68%*	*81%*	*83%*	*89%*	*89%*	*89%*	*89%*	*90%*	*89%*
# CCALD treated with LentiD	**13**	**16**	**16**	**18**	**21**	**24**	**26**	**27**	**27**
Price per patient per year ($000)	$1,500	$1,575	$1,654	$1,736	$1,823	$1,914	$2,010	$2,111	$2,216
U.S. Lenti-D Revenue ($MM)	**$20.0**	**$25.0**	**$27.0**	**$32.0**	**$38.0**	**$45.0**	**$53.0**	**$57.0**	**$60.0**
E.U.									
# Incident male ALD patients (all types)	125	125	125	125	125	125	125	125	125
% CCALD type	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
# CCALD type	44	44	44	44	44	44	44	44	44
% CCALD diagnosed in time to treat	*70%*	*70%*	*70%*	*70%*	*72%*	*74%*	*76%*	*78%*	*80%*
# CCALD diagnosed in time to treat	31	31	31	31	32	32	33	34	35
% CCALD not getting transplant from matched sibling	*80%*	*80%*	*80%*	*80%*	*84%*	*88%*	*92%*	*93%*	*94%*
# CCALD without matched sibling	25	25	25	25	26	28	31	32	33
% treated with Lenti-D	*0%*	*41%*	*68%*	*79%*	*81%*	*82%*	*83%*	*84%*	*85%*
# CCALD treated with LentiD	**0**	**10**	**17**	**19**	**21**	**23**	**25**	**27**	**28**
Price per patient per year ($000)	$1,500	$1,500	$1,500	$1,500	$1,500	$1,500	$1,500	$1,500	$1,500
E.U. Lenti-D Revenue ($MM)	**$0.0**	**$15.0**	**$25.0**	**$29.0**	**$32.0**	**$35.0**	**$38.0**	**$40.0**	**$42.0**
R.O.W.									
R.O.W. Lenti-D Revenue ($MM)	**$0.0**	**$15.0**	**$28.0**	**$39.0**	**$45.0**	**$55.0**	**$64.0**	**$68.0**	**$73.0**
As a % of U.S. Sales	*0%*	*60%*	*104%*	*122%*	*118%*	*122%*	*121%*	*119%*	*122%*
As a % of Global Sales	0%	27%	35%	39%	39%	41%	41%	41%	42%
Total WW Lenti-D Revenue ($MM)	**$20.0**	**$55.0**	**$80.0**	**$100.0**	**$115.0**	**$135.0**	**$155.0**	**$165.0**	**$175.0**
% growth Y/Y		*175%*	*45%*	*25%*	*15%*	*17%*	*15%*	*6%*	*6%*

Source: Cowen and Company

LentiGlobin Is Targeting β-Thalassemia And Sickle Cell Disease

bluebird is developing its next product candidate, LentiGlobin, as a potential treatment for two disorders: β-thalassemia and sickle cell disease. This lentiviral candidate delivers a normal copy of β-globin, the gene that is mutated in both diseases. In addition, the LentiGlobin

transgene includes an engineered point mutation (T87Q) which: (1) has anti-sickling properties that should be beneficial in sickle cell disease, and (2) provides a means of tracking expression of the gene in patients.

Background On β-Thalassemia

β-thalassemia is a rare genetic disorder caused by mutations in the β-globin gene, resulting in defective production of hemoglobin A. Hemoglobin functions as the oxygen-carrying molecule in red blood cells. Inadequate hemoglobin leads to insufficient oxygen transport, as well as red blood cell death, leaving patients severely anemic and dependent on blood transfusions. The severity of clinical disease depends on which of the over 200 identified mutations in β-globin a patient carries. "β-thalassemia major" refers to a severe presentation in which patients are chronically dependent on transfusions to survive, due to carrying mutations severely curtailing hemoglobin levels ("β-null" mutations) in one or both copies of the β globin gene. Such patients may produce only 1-7 g/dL of hemoglobin (normal range 12-18 g/dL).

Current treatment for β-thalassemia major includes blood transfusions every 3-5 weeks. Chronic blood transfusions would lead to iron overload if patients were not also taking oral iron chelators. (Iron overload can lead to potentially fatal heart and liver toxicities). Compliance is an issue with these chelators, and it is believed that despite best current therapy, patients with β-thalassemia major are likely to live a shortened lifespan, and certainly suffer reduced quality of life. Consultants also note that about 5-10% of patients develop antibodies that make transfusion problematic. HSCT is the only potentially curative treatment, but is offered only to a minority of patients (e.g., pediatric patients with matched sibling donors, perhaps 25% of such patients), as the risks of GVHD, failure to engraft, etc., increase to unacceptable levels with unmatched donors and at more advanced ages. Indeed, adult HSCT may cause 20% mortality due to GVHD. In the developing world, where most β-thalassemia patients live, chronic blood transfusion and iron chelation may not be available, leading to poor prognosis, including splenomegaly, skeletal deformities, and shortened lifespan. bluebird is hopeful that a safe, one-time treatment such as LentiGlobin could be transformative for these patients.

Background on Sickle-Cell Disease

Another genetic disorder caused by mutation in the β-globin gene is sickle cell disease (SCD). In this disease, a mutation in the β-globin gene causes aggregation of hemoglobin and alters the shape of red blood cells into a "sickle-like" form. Patients suffer anemia, as well as painful "crises" caused by occlusion of blood vessels by the abnormally shaped cells, cutting off the blood supply to affected organs and potentially causing damage. Patients may also suffer from infections, stroke, and early death.

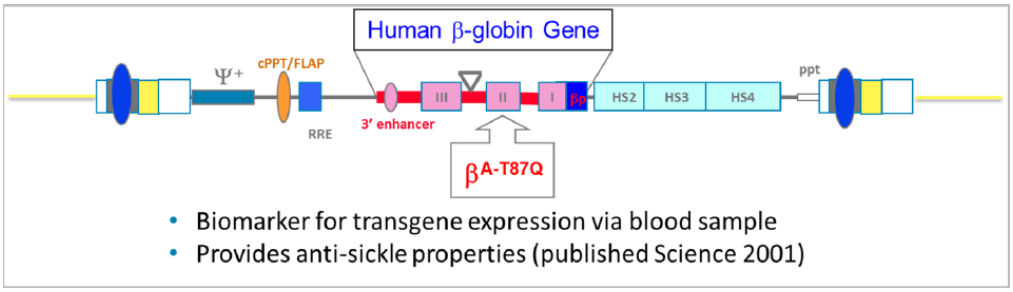
Sickle cell disease is quite common among persons of African, Middle Eastern, and South Asian descent (likely because the heterozygous mutation confers resistance to malaria, endemic to these regions). Global birth incidence is approximately 250,000 – 300,000, with global prevalence of 20-25 million. In the U.S., SCD is subject to mandatory newborn screening. U.S. incidence is over 1,600 annually and prevalence is about 100,000.

Current treatment for SCD consists primarily of hydroxyurea and blood transfusions. The blood transfusions carry the same risks and need for iron chelation as discussed for β-thalassemia. Also as with β-thalassemia, the only potentially curative treatment is HSCT, but this is offered only to a minority of pediatric patients, due to the difficulty in identifying matched donors.

Academic Trial Provides Proof Of Concept For Treatment Of β-Thalassemia

An academic study conducted in France provided proof of concept for the treatment of β-thalassemia via *ex vivo* transduction of HSCs with a lentiviral vector carrying a normal β-globin gene. The vector used included the native, erythrocyte-specific promoter and the locus-control elements from the β-globin gene, as well as the anti-sickling T87Q mutation. (It also included a chromosomal insulator at each end of the vector; bluebird subsequently found these to be unnecessary and detrimental to transduction efficiency, so has removed them from its final LentiGlobin vector.)

Structure Of Academic Study Lentiviral Vector



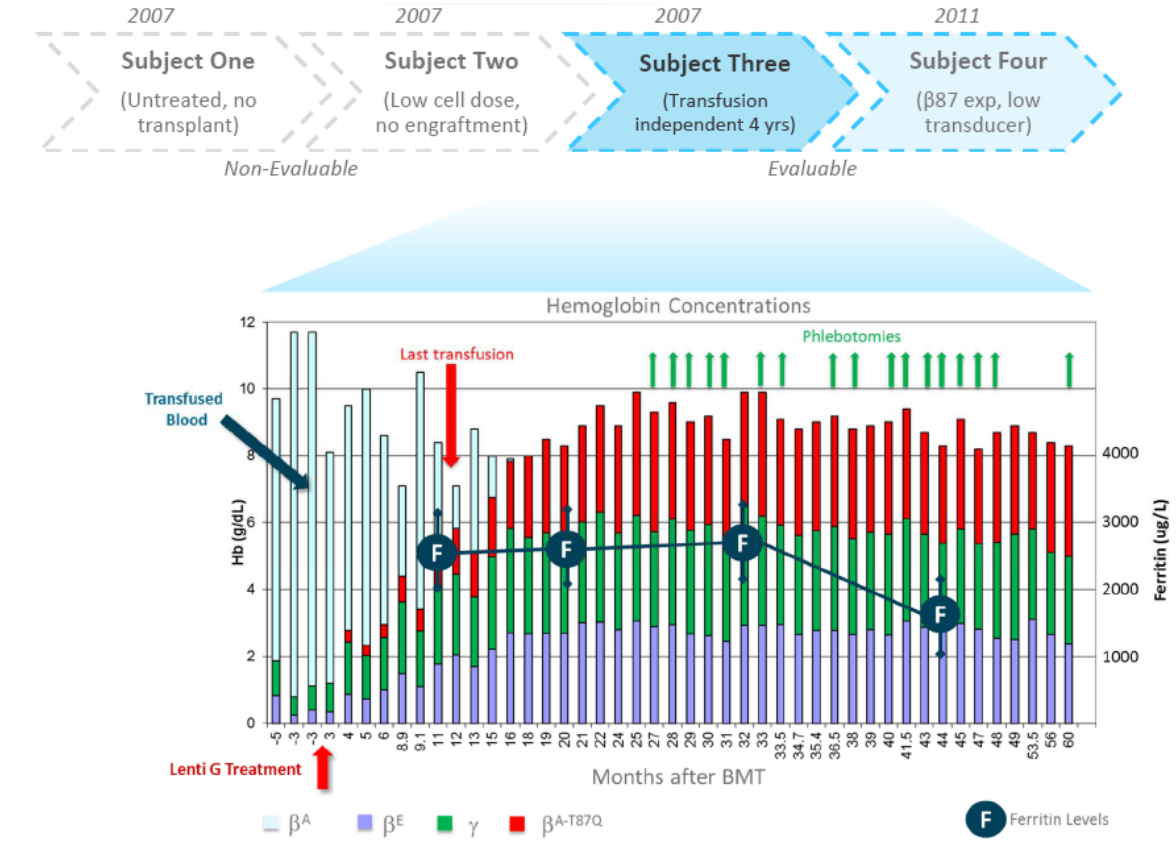
Source: bluebird bio

The trial was conducted in France. Between 2006 and 2011, four patients were enrolled. The first was never actually treated, and the second was given a very low dose of transduced cells that never engrafted. However, patient 3 provided dramatic proof of concept for this approach, in results published in *Science* in 2010. This patient had been transfusion dependent since age 2. He was treated with transduced HSCs at age 18, in 2007. Within one year, he became transfusion independent and has remained transfusion independent for the 4+ years of follow-up – this has never happened spontaneously in β-thalassemia, and represents striking proof of concept. The 4th patient had relatively inefficient gene transfer during transduction, and stabilized post-transplant with only about 3% of reticulocytes expressing the normal β-globin transgene. Her transfusion requirements remain unchanged. While it remains to be seen what clinical benefit she will ultimately derive, if any, it is notable that bluebird's enhancements to vector potency and yield should allow the company to achieve more robust and reliable transduction than has been observed in the French trial to date (in fact bluebird has reported a ~3x increase in vector copy number in transduced cells vs. the academic trial).

There were no gene-therapy related AEs in the trial. Initially there had been some concern regarding the partial clonal dominance of a single clone with an insertion of the transgene in the HMG2A gene, as this could perhaps have indicated a pre-leukemic event, as had been

observed with mouse gamma retrovirus studies a decade earlier in treatment of X-linked SCID. However, there have been no concerning sequelae in the 5 years of follow-up, and in fact the frequency of the HMG2A clone has declined so that it is no longer the most common.

β-Thalassemia Academic Trial Efficacy Summary



Source: bluebird bio

LentiGlobin Moving Forward In Two Clinical Trials

LentiGlobin is currently progressing in a clinical trial for β-thalassemia and SCD in France (the HGB-205 trial), and a US study for β-thalassemia is set to begin in mid-2013 (the HGB-204 trial). bluebird hopes to have initial interim data from one or both studies by late 2014. A U.S. IND filing for SCD is also planned in 2014.

The HGB-205 trial is actually a continuation of the French academic study, but with the slightly modified and more efficient LentiGlobin vector. This continuation stage began in mid-2013, and will enroll up to seven additional patients with β-thalassemia or SCD. β-thalassemia patients must have received at least 100 mL/kg in red blood cell transfusions per year for the prior two years; SCD patients must have failed hydroxyurea therapy and have another poor prognostic risk factor, such as recurrent crises. Patients with a matched sibling HSCT donor will be excluded. Measurements of efficacy for all patients will include number of transfusions required

per month and per year, as well as days of hospitalization by 6, 12, and 24 months. For SCD patients, efficacy will additionally be gauged by measuring the frequency of crises or other exacerbations by 6, 12, and 24 months.

The IND for the planned U.S. trial, HGB-204, is active and the study is set to begin in mid-2013. The trial will enroll up 15 adults with β-thalassemia and a transfusion requirement of at least 100 mg/dL RBCs per year for the prior two years, or at least 8 transfusions per year. The primary efficacy endpoint is the production of at least 2.0 mg/dL of T87Q-marked transgenic hemoglobin during the period from 18-24 months post-transplant. The reasoning for this threshold is that 2.0 mg/dL is considered clinically meaningful and likely to reduce transfusion frequency; the third French patient achieved a 3.0mg/dL increase, so this bar should be achievable with bluebird's more efficient transduction. Efficacy in terms of transfusion requirements per month and year will also be assessed.

Our consultants believe it will take about 6 – 12 months to see evidence of repopulation of the hematopoietic system with the corrected cells. They believe patients will need to achieve a hemoglobin level of at least 8-9 mg/dL to achieve transfusion independence; untreated, severe patients can have Hb levels as low as 2 mg/dL, so complete transfusion independence in the most severe patients may be a challenge, though achievable in a more moderately affected group. Nevertheless, even a 50% reduction in transfusion frequency would be very clinically meaningful, according to our physicians. The consultants caution that predicting success in SCD is trickier, because the issue is not so much the level of hemoglobin, as the ratio of normal to mutant hemoglobin. One consultant estimated that one would need 60% normal hemoglobin to override the sickling propensity of the mutant form, though he allowed that the anti-sickling mutation in the LentiGlobin vector could reduce that percentage.

Safety evaluations for each study will include engraftment success, transplant-related mortality, overall survival, and any sign of replication competent lentivirus or signs of clonal dominance or leukemia.

LentiGlobin Clinical Development Plan

	HGB-204	HGB-205
Trial Location	US	France
Phase	I/II	I/II
N	15	7
Indication	β-thalassemia	β-thalassemia & sickle cell disease
Sites	Multi-center	1
Status	IND active Initiate in mid 2013	CTA active Trial initiated

Source: bluebird bio

Ideally, of course, bluebird would like to substantially reduce or eliminate transfusions. Consultants highlight the risk that the transgene expression might not be sufficient to replace hemoglobin to a level high enough to achieve this in β-thalassemia major, as indeed was the case in at least one of the four patients treated in the French trial. However, the company believes its transgene's expression level is sufficient to achieve such meaningful reduction of transfusions, due to a higher percentage of cells transduced (essentially 100%) and a higher average vector copy number per cell than seen in the French trial.

LentiGlobin's Market Opportunity

β-thalassemia exhibits geographical variation in prevalence, and is particularly common in the Mediterranean and South/Southeast Asia. The World Health Organization (WHO) estimates that about 40,000 β-thalassemia patients are born annually, mostly in the developing world. Of these, about 25,000 require regular blood transfusions to survive, but sadly, due to misdiagnosis and poor medical care availability in the endemic regions, only about 12% of patients requiring transfusions are able to get them, with the rest generally dying at a young age. Nevertheless, the WHO estimates that there are about 100,000 transfusion-dependent β-thalassemia patients currently living worldwide. Based on registry data, the Thalassemia International Foundation estimates that there could be 288,000 treated β-thalassemia major patients worldwide, including 15,000 residing in the U.S. or Europe, though some consultants view this source skeptically.

Global Incidence And Prevalence Of β-Thalassemia Major

	Estimated annual births β thalassemias		Transfusion			
WHO region	Total	Transfusion-dependent	Annual no. starting transfusion	% of transfusion-dependent patients transfused	Annual deaths because not transfused	No. of known patients
African	1,386	1,278	35	2.7	1,243	–
American	341	255	134	52.4	121	2,750
Eastern Mediterranean	9,914	9,053	1 610	17.8	7,443	39,700
European	1,019	920	140	15.5	780	16,230
South-east Asian	20,420	9,983	962	9.6	9,021	35,500
WesternPacific	7,538	4,022	108	2.7	3,914	3,450
World	**40,618**	**25,511**	**2,989**	**11.7**	**22,522**	**97,630**

Source: WHO, Cowen and Company

β-thalassemia is overwhelmingly present ex-U.S., and largely ex-E.U. One of our U.S.-based consultants estimated that there might be only about 1,000 treated hemophilia patients in the U.S. and Canada altogether, with roughly 600 of those being classified as "major." These patients tend to be treated at major medical centers of expertise; this consultant had 50 such

patients at his hospital in Philadelphia. The disease is somewhat more prevalent in Europe, with perhaps 15,000 patients, but the vast bulk of patients are found in Eastern Mediterranean countries such as Turkey, and particularly in South and Southeast Asia.

bluebird has suggested that the β-thalassemia treatment could be priced around $400-500K per patient. Consultants indicate that the cost of chronic treatment for β-thalassemia is $40-80K/year, so this seems reasonable for a one-time curative therapy. The consultants say an HSCT costs about $120-140K, with no pushback from payors. Consultants note that even in parts of the developing world (for example, Thailand), HSCT is paid for in β-thalassemia major when an HLA-matched donor is available because it is cheaper than a lifetime of therapy. We note that bluebird will still need to increase its manufacturing capacity to the bioreactor scale in prior to commercializing LentiGlobin.

Our revenue model assumes that LentiGlobin launches into a U.S. β-thalassemia major market of about 600 patients with an annual birth incidence of 50. We assume that the drug is priced at $500K/patient initially, increasing by 5% annually. We assume that 15% of prevalent patients are treated annually at peak in the U.S., generating about $50MM in peak revenue. In Europe, we model 15,000 prevalent patients, 150 incident patients per year, and a $400K price (no increases). We assume only 4% annual treatment rate at peak, given the austerity in Europe, and the fact that many of the more highly affected European nations (Greece, Italy, Spain) are also some of the most austere. Nevertheless, we model over $200MM in peak revenue in Europe. The R.O.W. nations include a number that will pay for expensive orphan drugs, notably Turkey for example, though many of these nations likely will not pay for such drugs. We assume a discounted, $250K price per patient for ROW, and only 2% of patients treated annually at peak. Still, with our modeled 85,000 prevalent patients, ROW is by far the largest revenue segment in our β-thalassemia model, generating nearly $400MM+ in annual revenue at peak. Worldwide, we model LentiGlobin as a $650MM drug in β-thalassemia alone.

Global β-Thalassemia Major Revenue Model

U.S.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Beta-thalassemia birth incidence		50	50	50	50	50	50	50	50
LentiGlobin-naïve Beta-thalassemia major prevalence	600	630	651	636	591	552	519	491	468
% treated with LentiGlobin	*3%*	*5%*	*10%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
# treated with LentiGlobin	20	29	65	95	89	83	78	74	70
Price per patient per year ($000)	$500	$525	$551	$579	$608	$638	$670	$704	$739
U.S. Beta-Thalassemia Revenue ($MM)	**$10**	**$15**	**$36**	**$55**	**$54**	**$53**	**$52**	**$52**	**$52**
E.U.									
Beta-thalassemia birth incidence			150	150	150	150	150	150	150
LentiGlobin-naïve Beta-thalassemia major prevalence		15,000	15,000	14,850	14,555	14,122	13,707	13,309	12,927
% treated with LentiGlobin		*1%*	*2%*	*3%*	*4%*	*4%*	*4%*	*4%*	*4%*
# treated with LentiGlobin		150	300	446	582	565	548	532	517
Price per patient per year ($000)		$400	$400	$400	$400	$400	$400	$400	$400
E.U. Beta-Thalassemia Revenue ($MM)		**$60**	**$120**	**$178**	**$233**	**$226**	**$219**	**$213**	**$207**
R.O.W.									
Beta-thalassemia birth incidence (survivors)			2,500	2,500	2,500	2,500	2,500	2,500	2,500
LentiGlobin-naïve Beta-thalassemia major prevalence		85,000	87,500	89,824	92,057	94,004	95,620	97,006	98,165
% treated with LentiGlobin		*0%*	*0%*	*0%*	*1%*	*1%*	*1%*	*1%*	*2%*
# treated with LentiGlobin		0	176	266	553	885	1,114	1,341	1,565
Net price per patient per year ($000)		$250	$250	$250	$250	$250	$250	$250	$250
R.O.W. Beta-Thalassemia Revenue ($MM)		**$0**	**$44**	**$67**	**$138**	**$221**	**$278**	**$335**	**$391**
Total WW Beta-Thal Revenue ($MM)	**$10**	**$75**	**$200**	**$300**	**$425**	**$500**	**$550**	**$600**	**$650**
% growth Y/Y			*167%*	*50%*	*42%*	*18%*	*10%*	*9%*	*8%*

Source: WHO, Cowen and Company

β-Thalassemia And Sickle Cell Disease More Competitive Than CCALD

β-thalassemia and sickle cell disease are fairly popular targets for drug development, and there are a number of competitive risks to consider. The first is that, unlike CCALD, there are non-transplant standard-of-care treatments for these diseases, which although imperfect, are reasonably effective and will increase the barrier to undergo a transplant based therapy. HSCT is not routinely performed in adult β-thalassemia patients today because the potential for cure is outweighed by the risk of mortality resulting from the procedure or subsequent complications. While the autologous nature of the LentiGlobin product will reduce the mortality risk substantially, it will likely not eliminate it. We are unsure whether patients who have made it to adulthood on standard therapy will be willing to risk, say, a 5-10% chance of death for the opportunity of a cure.

Apart from existing treatments, the β-thalassemia and SCD pipelines are rich with diverse approaches to the disease. There are other groups developing gene therapy approaches to β-thalassemia. MSKCC, for example, is actively recruiting now in a Phase I/II trial using *ex vivo* transduction of autologous HSCs, similar to bluebird, albeit with a different vector and cell processing technique. GSK has an academic partnership with an Italian Institute pursuing gene

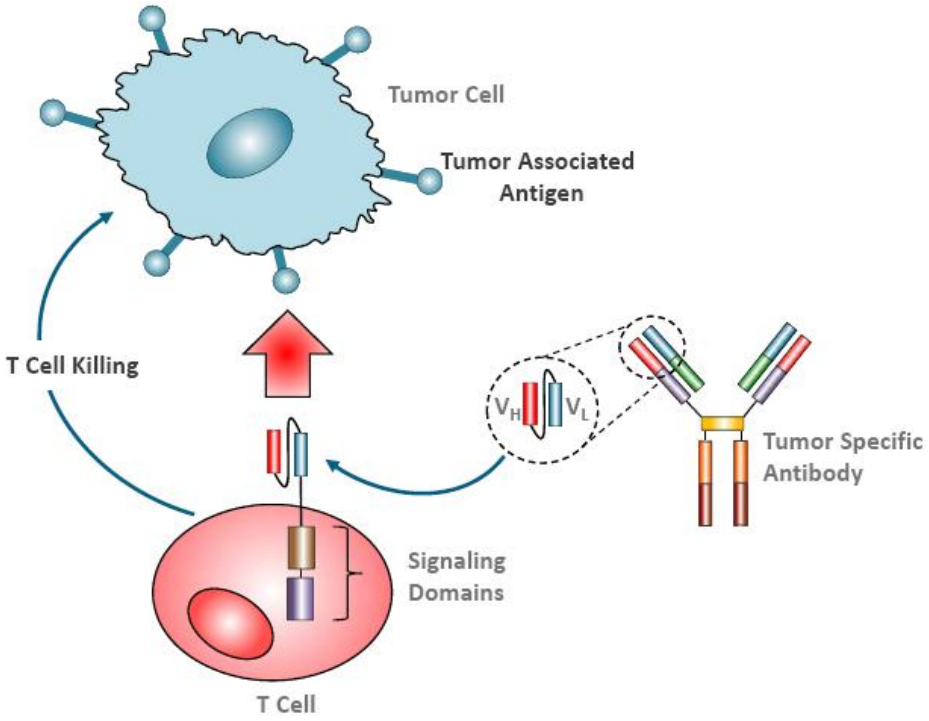
therapy, including a planned β-thalassemia trial, though this study has not begun. Sangamo Biosciences has also announced plans to target β-thalassemia and SCD through its zinc finger nuclease approach, though this initiative also has not begun any clinical trials. UCLA plans to initiate an *ex vivo* lentiviral transduction trial for SCD, but has not yet done so. Celgene and Acceleron have ACE-536 in Phase II for β-thalassemia, though unlike bluebird this trial is focused on non-transfusion dependent patients. A number of novel drug approaches are in development for SCD: these include fetal hemoglobin regulators (HemaQuest's HQK-1000 and Merck's vorinostat, each in Phase II) and GlycoMimetics'/Pfizer's pan-selectin inhibitor, GMI-1070, also in Phase II.

Developing CAR-T Cells For Cancer In Collaboration With Celgene

In March 2013, bluebird entered a research collaboration with Celgene surrounding chimeric antigen receptor T cells (CAR-T cells). In CAR-T technology, a patient's own T-cells are genetically modified to express a recognition domain derived from an antibody against a tumor-specific antigen. The recognition domain is also coupled to a T-cell activating domain, forming the CAR. As a result, the T cell is able to self-activate upon binding the target antigen, obviating the need of a second helper T cell, and thus mounting an aggressive anti-tumor cell – killing response. Moreover, the cells have been shown to expand in humans to 10-1000x their initial engraftment level upon activation, driving a persistent anti-tumor response. Several groups have reported striking activity in small pilot trials using this technology. One example is a 2013 report in *Science Translational Medicine* in which 5 relapsed ALL patients were treated with CD19-specific CAR-T cells; all 5 achieved CRs. At ASH 2012, another group extended its initial *NEJM* study of CD19-specific CAR-T cells in one CLL patient to a total of 9. Of the 9 relapsed, refractory CLL patients treated, all over 65 years of age, 7 responded (3 CRs).

bluebird's expertise in lentiviral transgenesis should allow rapid extension of these pioneering discoveries. The partners are currently deciding on indications, and plan to attack both liquid and solid tumors.

CAR-T Cells



Source: bluebird bio

Under the terms of the Celgene deal, bluebird will be responsible for funding and developing candidates through the end of Phase I. Celgene then has the option, on a per-candidate basis, to license the product. Celgene would owe an option fee, though bluebird retains the right to opt in to a 50/50 U.S. co-development, co-promotion and profit share, in which case Celgene's option payment would be reduced. The option fee plus future milestones total up to $225MM per program, and bluebird is also entitled to mid-single digit to mid-teen digit royalties on sales. bluebird received a $75MM upfront in connections with the deal, for an initial three year term (until March 2016). Celgene has the right to extend the term twice, for an initial further two years, and then for one additional year, in each case for an additional payment.

Intellectual property

bluebird's development programs are protected by a robust portfolio of intellectual property, as well as proprietary process know-how and, in the case of Lenti-D, orphan drug exclusivity. The portfolio includes over 175 exclusive patents or applications relating to lentiviral vectors and vector systems; over 50 non-exclusive patents or applications licensed from third parties related to lentiviral vectors; nearly 20 patents or applications owned or co-owned with MIT relating to manufacturing processes; about 7 non-exclusive patents in licensed from third parties relating to vector manufacture; and 12 exclusive patents or applications related to therapeutic cellular products.

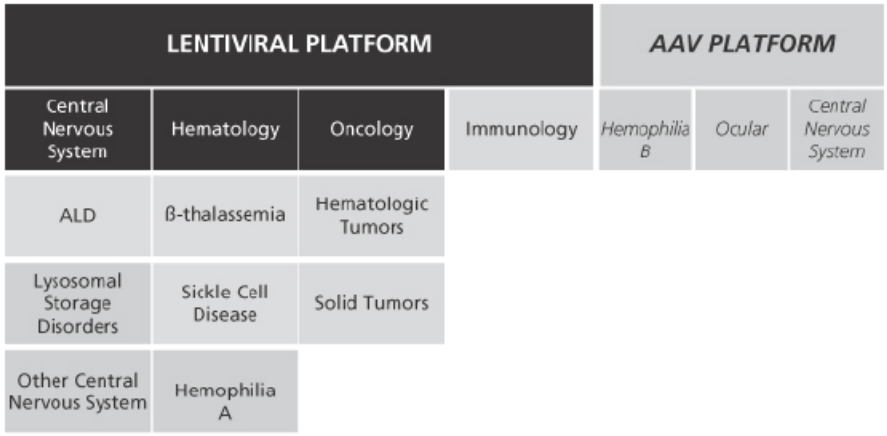
Specific key patents include exclusive license to composition of matter on elements of the Lenti-D vector and LentiGlobin vector, lasting through 2019-2023 in the U.S. and 2019-2020 ROW. bluebird also has exclusive license to patents protecting composition of matter on the platform used to produce Lenti-D and LentiGlobin through 2022-2023 in the U.S. (2021-2022 ROW). bluebird has also applied for additional composition patents on the Lenti-D vector and cell therapy product, which if issued, would last through 2032. bluebird co-owns (with MIT) composition patents on the LentiGlobin expression vector, lasting through 2023 worldwide.

bluebird also has pending applications on its manufacturing process enhancements (lasting through 2031-32 if issued). The company believes its proprietary manufacturing know-how also present a formidable barrier to competition.

Possible Future Directions

bluebird has assembled considerable in-house talent and knowhow that should enable it to develop numerous additional gene therapy treatments for a variety of diseases. The company's current lentiviral platform based on *ex vivo* HSC transduction has the potential to treat a number of other possible monogenic genetic diseases, such as lysosomal storage diseases (proof of concept published in *Science* in 2013, with lentivirus used to treat three patients with the LSD metachromatic leukodystrophy), other neurological diseases, autoimmune diseases, immunodeficiencies (proof of concept published in *Science* in 2013, with lentivirus used to treat three patients with the immune deficiency Wiskott-Aldrich syndrome), and hemophilia A. The company also envisions potentially using lentiviral transduction *in vivo*, to deliver transgenes directly to target tissue, with potential applications for diseases affecting, for example, the brain or eye. The bluebird team also has extensive experience with another gene therapy delivery approach, the adeno-associated virus (AAV). There is support in the literature for clinical benefit derived from treatment of patients with this system, and bluebird believes the AAV system might be better suited for systemically delivered gene therapy. Clearly, the future potential of gene therapy appears huge in bluebird's capable hands.

bluebird's Broad Expertise And Possible Future Directions



Source: bluebird bio

bluebird bio Quarterly P&L Model ($MM)

	2012A	Q1:13A	Q2:13E	Q3:13E	Q4:13E	2013E
Lenti-D Revenue						
LentiGlobin Revenue						
Collaborative and Grant Revenue	0.3	1.1	3.0	3.0	3.0	10.1
Total Revenue	**0.3**	**1.1**	**3.0**	**3.0**	**3.0**	**10.1**
Y/Y growth						*NM*
COGS	0.0	0.0	0.0	0.0	0.0	0.0
R&D	17.2	5.3	5.5	6.0	6.0	22.8
SG&A	6.8	2.3	2.5	2.8	3.0	10.6
Total Expenses	**24.1**	**7.6**	**8.0**	**8.8**	**9.0**	**33.4**
Operating Income/ Loss	**(23.7)**	**(6.5)**	**(5.0)**	**(5.8)**	**(6.0)**	**(23.3)**
Non-Operating Income	0.0	(0.1)	(0.1)	(0.1)	(0.1)	(0.4)
Pre-tax Income/ Loss	**(23.7)**	**(6.5)**	**(5.1)**	**(5.9)**	**(6.1)**	**(23.6)**
Tax rate (%)	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Provision for income taxes	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Loss) From Operations	**(23.7)**	**(6.5)**	**(5.1)**	**(5.9)**	**(6.1)**	**(23.6)**
GAAP EPS	**($1.83)**	**($0.41)**	**($0.28)**	**($0.25)**	**($0.26)**	**($1.17)**
Diluted Shares	12.9	16.0	18.0	23.3	23.4	20.2

Source: Cowen and Company

bluebird bio Annual P&L Model ($MM)

	2012A	2013E	2014E	2015E	2016E	2017E
Lenti-D Revenue	0.0	0.0	0.0	0.0	0.0	0.0
LentiGlobin Revenue	0.0	0.0	0.0	0.0	0.0	0.0
Collaborative and Grant Revenue	0.3	10.1	12.0	14.0	15.0	16.0
Total Revenue	**0.3**	**10.1**	**12.0**	**14.0**	**15.0**	**16.0**
Y/Y growth			*18%*	*17%*	*7%*	*7%*
COGS	0.0	0.0	0.0	0.0	0.0	0.0
R&D	17.2	22.8	28.0	30.0	32.0	34.5
SG&A	6.8	10.6	12.0	14.0	16.0	18.0
Total Expenses	**24.1**	**33.4**	**40.0**	**44.0**	**48.0**	**52.5**
Operating Income/ Loss	**(23.7)**	**(23.3)**	**(28.0)**	**(30.0)**	**(33.0)**	**(36.5)**
Non-Operating Income	0.0	(0.4)	(0.8)	(1.0)	(1.0)	(1.0)
Pre-tax Income/ Loss	**(23.7)**	**(23.6)**	**(28.8)**	**(31.0)**	**(34.0)**	**(37.5)**
Tax rate (%)	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Provision for income taxes	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Loss) From Operations	**(23.7)**	**(23.6)**	**(28.8)**	**(31.0)**	**(34.0)**	**(37.5)**
GAAP EPS	**($1.83)**	**($1.17)**	**($1.20)**	**($1.15)**	**($1.10)**	**($1.10)**
Diluted Shares	12.9	20.2	24.0	27.0	31.0	34.0
Y/Y growth				*-4%*	*-4%*	*1%*

Source: Cowen and Company

Valuation Methodology & Investment Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Company Specific Risks

bluebird bio has no approved products and limited revenue. The company may need to raise additional capital from the public markets prior to turning profitable. bluebird's two lead candidates (Lenti-D and LentiGlobin) are gene therapies with little clinical trial experience. Each faces a number of clinical, regulatory, and commercial hurdles prior to becoming successful.

Addendum

STOCKS MENTIONED IN IMPORTANT DISCLOSURES

Ticker	Company Name
BLUE	bluebird bio Inc

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Cowen and Company Rating System effective May 25, 2013

Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

Buy – The fundamentals/valuations of the subject company are improving and the investment return is expected to be 5 to 15 percentage points higher than the general market return

Sell – The fundamentals/valuations of the subject company are deteriorating and the investment return is expected to be 5 to 15 percentage points lower than the general market return

Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

COWEN AND COMPANY RATING ALLOCATION

Distribution of Ratings/Investment Banking Services (IB) as of 06/30/13

Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	380	58.37%	48	12.63%
Hold (b)	247	37.94%	2	0.81%
Sell (c)	24	3.68%	1	4.17%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

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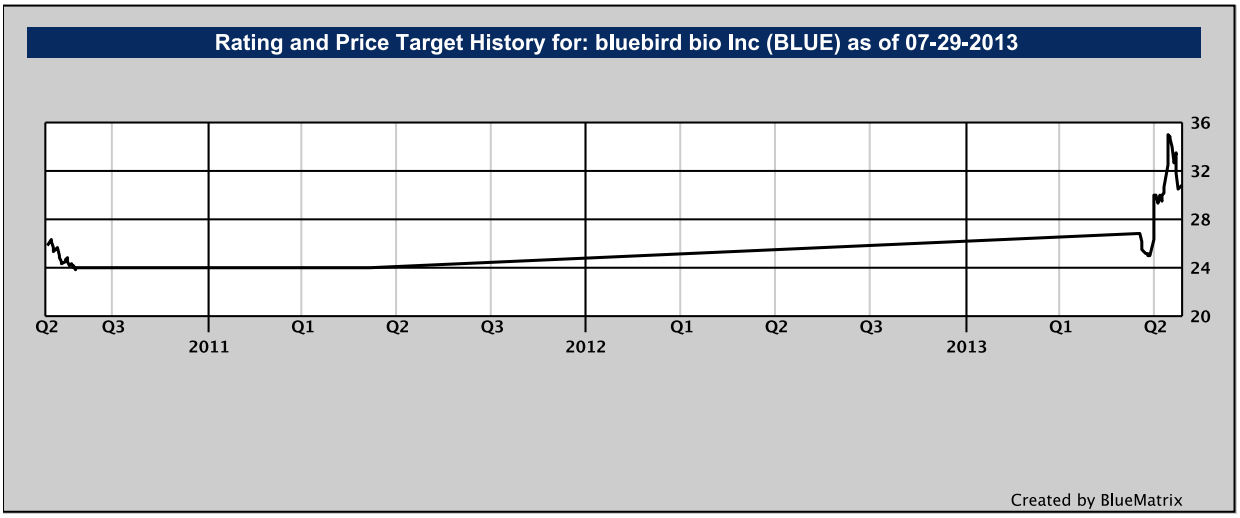

Legend for Price Chart:

I = Initation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | T = Terminated Coverage | $xx = Price Target | NA = Not Available