bluebird bio (BLUE)

Initiating Coverage at OUTPERFORM with a $40 Price Target: BLUE: Gene Therapy Is Back and BLUE

- **Bluebird's gene therapy platform could provide lifelong cures of genetic diseases with a single procedure, and is potentially applicable to a broad range of inherited diseases**.
- **The platform introduces functional genes into the hematopoietic stem cells of patients via bluebird's proprietary lentiviral vectors, with the manipulated cells delivered to the patient via autologous stem cell transplantation.**
- **Bluebird could begin a pivotal Phase II/III trial for its lead product candidate, LENTI-D, in H2:13 in patients with childhood cerebral adrenoleukodystrophy (CCALD).** We believe positive results from this two-year trial should support BLA and MAA submissions.
- **CCALD is the most rapidly progressing, and earliest onset form of adrenoleukodystrophy (ALD), and, absent treatment, rapidly causes severe neurological decline and death in the affected child**. Treatment with a previous generation vector successfully halted disease progression in four boys.
- **Bluebird's second product candidate, LENTIGLOBIN, could enter Phase I/II studies in mid:13 for *β*-thalassemia and sickle cell disease (SCD), inherited hemoglobin mutations.** Initial treatment with an earlier version of LENTIGLOBIN has eliminated one β-thalassemia patient's transfusion requirements.
- **Bluebird is also partnering with Celgene to discover and develop gene therapies in oncology.** The collaboration will focus on developing products comprised of chimeric antigen receptor (CAR) cells, or modified T cells that attack the patient's own cancer.
- **We view bluebird as a leader in gene therapy, with potential broad applicability of its transformative technology in rare diseases and oncology.**
- **Initiating coverage with an OUTPERFORM rating and $40 price target.** Our price target of $40 is derived from applying an 8X multiple to estimated 2020 revenues of $1.36B for LENTI-D and LENTIGLOBIN products, discounted 35% annually. We do not include CAR-T in our valuation.

FYE Dec	2012A	2013E			2014E		
REV	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	$2.4A	$1.1A		N/A	$0.6E		N/A
Q2 Jun	2.2A	0.7E		N/A	0.5E		N/A
Q3 Sep	5.4A	0.6E		N/A	0.4E		N/A
Q4 Dec	4.9A	0.4E		N/A	0.4E		N/A
Year*	**$0.3A**	**$2.8E**		**N/A**	**$1.8E**		**N/A**
Change	-61%	717%			-33%		
	2012A	2013E			2014E		
EPS	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	($0.21)A	($0.39)A		N/A	($0.43)E		N/A
Q2 Jun	(0.48)A	(0.34)E		N/A	(0.43)E		N/A
Q3 Sep	(0.43)A	(0.41)E		N/A	(0.44)E		N/A
Q4 Dec	(0.62)A	(0.47)E		N/A	(0.45)E		N/A
Year*	**($1.81)A**	**($1.62)E**		**N/A**	**($1.75)E**		**N/A**
P/E	--	--			--		
Change	99%	10%			-8%		

Consensus estimates are from Thomson First Call.
** Numbers may not add up due to rounding.*

July 15, 2013

Price
$32.35

Rating
OUTPERFORM

12-Month Price Target
$40

David M. Nierengarten, Ph.D.
(415) 274-6862
david.nierengarten@wedbush.com

Gregory R. Wade, Ph.D.
(415) 274-6863
greg.wade@wedbush.com

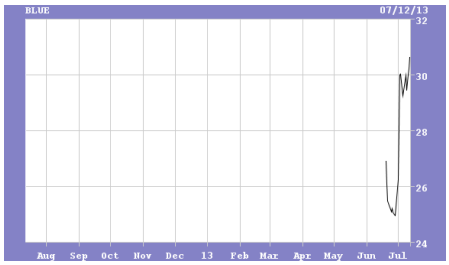
Christopher N. Marai, Ph.D.
(415) 274-6861
christopher.marai@wedbush.com

Company Information

Shares Outst (M)	23.5
Market Cap (M)	$760.2
52-Wk Range	$24.00 - $31.14
Book Value/sh	$-177.00
Cash/sh	$9.51
Enterprise Value (M)	$497.8
LT Debt/Cap %	0.0
Cash Burn (M)	$32.9

Company Description

Bluebird bio is developing LENTI-D, a gene therapy in a Phase II/III trial for treating CCALD, and LENTIGLOBIN, a gene therapy in Phase I/II trials for treating beta-thalassemia and sickle cell disease. With Celgene, it is also developing CAR-T in oncology.



Source: Thomson Reuters

Investment thesis

Bluebird bio is a gene therapy company focused on the treatment of rare genetic diseases, with two product candidates currently in development. Recent technical advances in gene therapy have revived strong interest in its curative potential and bluebird bio has made significant strides in the clinic. LENTI-D, its lead clinical product, will be entering a pivotal Phase II/III trial in H2:13 in patients with childhood adrenoleukodystrophy (ALD). Its other product in clinical development, LENTIGLOBIN, could enter two Phase I/II trials in patients with the inherited hemoglobin disorders, β-thalassemia and sickle cell disease. Bluebird is also collaborating with Celgene to discover, develop and commercialize genetically modified T-cells, also called chimeric antigen receptor (CAR) cells, for the targeted destruction of cancer cells.

Valuation

Our price target of $40 is derived from applying an 8x multiple to estimated 2020 revenues of $1.36B. Our valuation does not take into account the company's compounds in preclinical development with Celgene, and we believe that program could represent upside to our target.

Risks

Risks to the achievement of our price target include failure to gain approval for products in development, failure to achieve sales estimates for any marketed product and failure to achieve earnings estimates.

Key points

- Bluebird bio is developing gene therapy based on the introduction of functional genes via an engineered viral vector to a patient's own hematopoietic stem cells (HSCs), delivered via autologous stem cell transplantation.
- These therapies could provide lifelong disease cure with a single procedure, and are potentially broadly applicable to diseases caused by single-gene defects.
- The company's lead product, LENTI-D, could become the first gene therapy product approved in the U.S., potentially by 2017.
- Due to potential patient benefit (life-saving and curative), if LENTI-D is approved we expect reimbursement to be $1.5M per patient. Our current estimates assume the revenue per patient to be paid upfront, but if insurers/government agencies use other reimbursement strategies (installment plans, "pay for success" etc), we expect a similar net economic value per treatment.
- Demonstrating the wider applicability of bluebird's platform, we expect bluebird to enter Phase I/II trials for LENTIGLOBIN in *β*-thalassemia and sickle cell disease (SCD) in mid:13.
- Building out bluebird's platform, the company has a broad collaboration with Celgene to create chimeric antigen receptor (CAR) T-cells for immunotherapeutic oncology indications.
- We view bluebird as a leader in gene therapy with multiple potential indications in rare diseases and oncology.
- Applying a 8x multiple (in line with other rare-disease-focused biotechnology companies) to an estimated $1.36B in revenues in 2020, discounted by 35% annually, we arrive at our price target of $40.

Bluebird bio, Inc. Overview

Bluebird bio is based in Cambridge, Massachusetts and focuses on developing gene therapies (via autologous hematopoietic stem cell transplants) for genetic disorders. The company's lead product candidate, LENTI-D, is entering a potentially pivotal Phase II/III clinical trial in late 2013 for CCALD. LENTI-D is also in the preclinical stage for adult cerebral adrenoleukodystrophy (ACALD). The company's next most advanced product candidate, LENTIGLOBIN, could enter Phase I/II clinical trials in patients with *β*-thalassemia major and SCD. The company also has CAR T-cells in preclinical testing for solid tumors and hematologic malignancies.

Upcoming milestones

Mid:13	Initiate Phase I/II trial, "Study 204," of LENTIGLOBIN in β-thalassemia in the US
Mid:13	Initiate Phase I/II trial "Study 205" of LENTIGLOBIN in France in β-thalassemia and sickle cell disease indications
H2:13	Initiate Phase II/III pivotal trial, "ALD-102," of LENTI-D in CCALD
H2:14	Fully enroll ALD-102
H2:14	Fully enroll Study 204 & 205
H2:16	File NDA for LENTI-D
H2:16	Top-line data for Studies 204 and 205

Exhibit 1: Product Development Table

Product	Indication/Field	Stage of Development	Partner
LENTI-D	CCALD	Phase II/III	none
LENTI-D	ACALD	Preclinical	none
LENTIGLOBIN	*β*-thalassemia	Phase I/II	none
LENTIGLOBIN	SCD	Phase I/II	none
CAR T-cells	Solid and hematologic tumors	Preclinical	Celgene

Source: Company reports

We believe that the Phase II/III ALD-102 trial evaluating LENTI-D for CCALD is sufficient to support a BLA submission. Although the FDA normally requires more than a single clinical study to approve a drug or biologic product, the agency makes exceptions if the product demonstrates a clinically meaningful effect on mortality or prevents a serious disease and a confirmatory study would be impossible for ethical or practical reasons. We believe this exception would apply to LENTI-D, due to the limited number of CCALD patients and the severity of the disease. If so, LENTI-D could be approved and launched in 2017.

Gene Therapy

Long on promises, short on results

Gene therapy involves transferring a functional copy of a defective gene into a patient's own cells. The appeal of gene therapy is that it can offer a curative benefit for genetic diseases, whereas pharmacological methods can only offer chronic, often only symptomatic treatment of genetic disorders. As a result, gene therapy has garnered strong interest from researchers and patients, since a single procedure could provide a lifelong benefit to people suffering from genetic disorders and negate the need for chronic therapeutic intervention.

The basic steps involved in gene therapy are the isolation of the specific corrective gene, the delivery of this gene to a target cell by a vector, and the integration of the gene into the cell (with subsequent production of the corrective gene product). All gene therapies use this basic framework, although there can be differences in the types of vectors used and whether the gene transfer takes place inside (*in vivo*) or outside (*ex vivo*) the patient's body. The gene transfer process, which is most commonly accomplished through a non-replicating viral vector, is referred to as transduction. Types of viruses that have been used for transduction include retroviruses and adenoviruses. Lentiviruses are a subclass of retroviruses, distinguished by their ability to integrate into the genome of non-dividing cells, whereas other retroviruses can only infect dividing cells.

As of yet, no gene therapy product has been approved by the FDA. The first gene therapy procedure occurred in 1990 on a four-year old child suffering from severe combined immunodeficiency disease (SCID) due to a mutated adenosine deaminase (ADA) gene that failed to produce the ADA enzyme. Scientists at the NIH's Clinical Center in Bethesda, Maryland, took white blood cells from the child, inserted ADA producing genes into them *ex vivo*, and then transfused the cells back in. Although the child's condition improved, there was skepticism in the medical community whether this was due to the gene therapy procedure or due to the concurrent treatment that the patient was receiving with synthetic ADA injections. In addition, of the 19 children that were treated with gene therapy in the early 90s, five developed leukemia from the treatment.

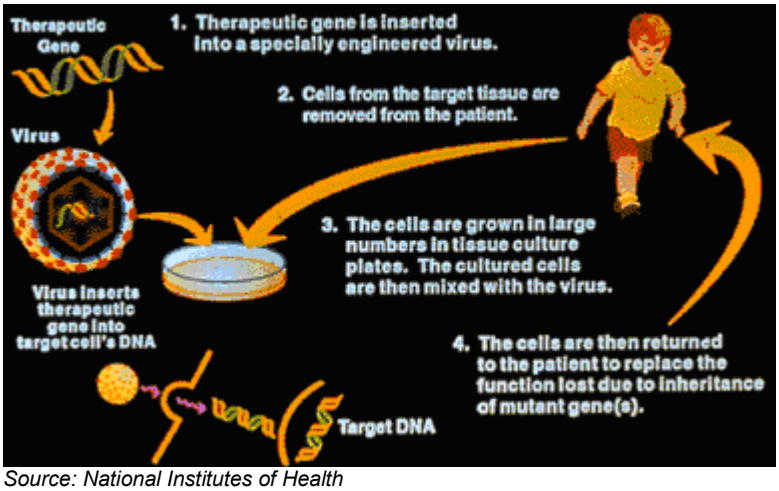
Gene therapy development also suffered a major setback in 1999, when an 18-year old patient with ornithine transcarbamylase deficiency died during a University of Pennsylvania-conducted trial after having suffered a massive immune response triggered by the adenoviral vector. Other notable setbacks include a temporary 2003 FDA ban on the use of retroviral vectors in blood stem cells in gene therapy trials, following reports that two children in a European gene therapy trial using retroviral vectors had developed leukemia. Recent clinical setbacks include the 2009 failure of Genzyme's gene therapy product to achieve a statistically significant benefit in patients with peripheral artery disease and limited mobility.

Why Bluebird's approach is different

Bluebird's gene therapy platform and approach has several advantages compared to prior gene therapy attempts, including:

- **Use of lentiviral vectors**: compared to other viral vectors, lentivirals are safer and more efficient at transducing HSCs, with no known gene therapy-related adverse events having been observed.
- **Use of autologous HSCs**: the use of autologous HSCs from the patient removes the likelihood of the body rejecting the modified-cells.
- **Transduction done *ex vivo***: Bluebird modifies the patient's stem cells outside the body and then transplants them back into the patient, which reduces the risk of adverse events and removes the complexity of getting the drug directly to the target cells during *in vivo* transduction. *In vivo* transduction has been a common method used in prior gene therapy efforts, and while it may have a role in local diseases or organ repair, for systemic diseases a systemic approach is likely required.

Exhibit 2: *ex vivo* Gene Therapy



Source: National Institutes of Health

An approved gene therapy, and others in development

The only gene therapy treatment approved in the Western world is UniQure's Glybera (alipogene tiparvovec), which the European Commission approved in 2012 for treating familial hyperchylomicronemia with recurring acute pancreatitis. Familial hyperchylomicronemia is a rare, inherited metabolic disease where the patient has errors in their lipoprotein lipase (LPL) gene that codes for the LPL protein, resulting in the patient's being unable to metabolize fat particles carried in the blood. Glybera is comprised of the LPL gene with variant S447X in a vector derived from adeno-associated virus serotype 1 (AAV1). Treatment with Glybera involves a one-time series of intramuscular injections, with muscle cell transduction occurring *in vivo*.

Another gene therapy treatment in development is a product candidate for Wiskott Aldrich Syndrome, a rare and severe immune deficiency disease. The product uses an HIV-derived lentiviral vector to transfer genes *ex vivo* into autologous CD34+ HSCs. The product candidate and associated vector is being developed by Genethon, a French non-profit firm funded by the French Muscular Dystrophy Association. In 2010, bluebird and Genethon entered into a research collaboration focusing on the development and scale-up efforts for manufacturing lentiviral vectors.

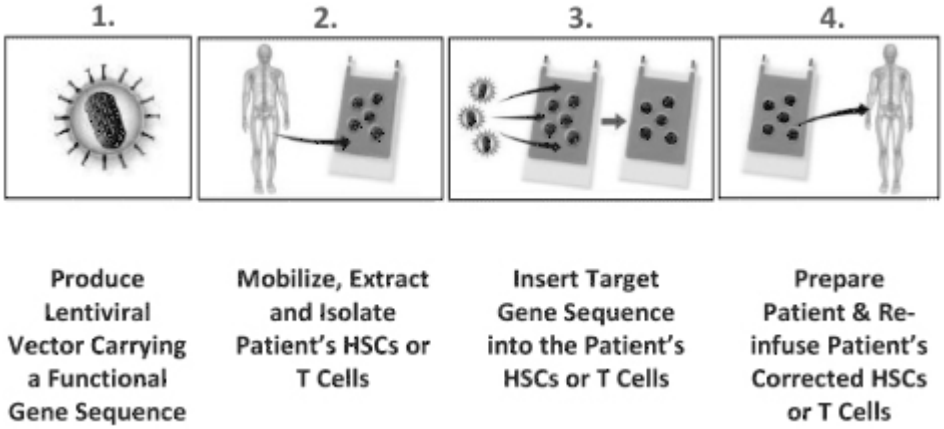
Bluebird's Gene Therapy Platform: the Lentiviral Advantage

Bluebird's gene therapy platform is based on its lentiviral vectors, a modified, non-replicating form of the HIV-1 virus. The lentiviral vectors are used to introduce a functional copy of a gene to CD34+ HSCs, derived from the patient's own body. Since HSCs are replicating cells that differentiate into a wide range of cell types, the procedure should allow for sustained expression of the modified gene in a variety of tissues.

Lentivirals can also transduce HSCs more efficiently than other viral vectors, such as those derived from the adeno-associated virus (AAV), which gives potential to address disease in a variety of cell lineages derived from HSCs. Unlike AAVs, lentiviruses are capable of sustained expression since they integrate the functional gene they carry into the DNA of the target cell's chromosome. This results in daughter cells also carrying the newly inserted gene sequence. AAVs introduce genes into cells, but do not integrate into a cell's DNA, which means that its daughter cells generally do not produce the desired protein. In addition, unlike AAVs, lentiviral vectors can carry large gene sequences of up to 8,000 base pairs into a host cell. This means lentiviral vectors offer more flexibility than AAVs to treat certain diseases that would require a too-large sequence for an AAV construct.

Lentivirals are also likely to be safer than the earlier generation of integrating viral vectors which were based on a gamma-retrovirus, since they have a distinct pattern of integrating into regions that provide instructions for making proteins. Gamma retrovirus-based viral vectors were shown to integrate into certain promoter regions of genes and in some instances, activate the cell to divide uncontrollably, leading to insertional oncogenesis.

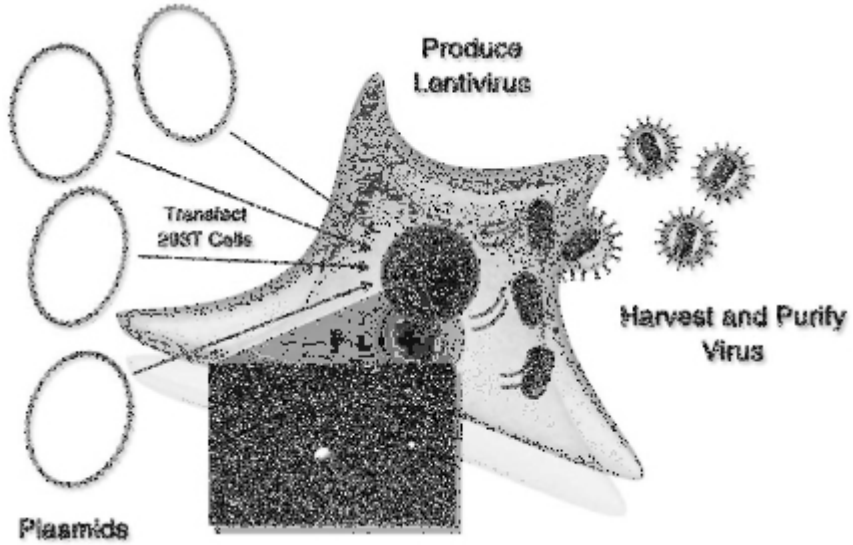
Exhibit 3: Bluebird's Lentiviral Manufacturing Process



Source: Bluebird bio S-1

Bluebird has a cell-based vector manufacturing process for its lentiviral vectors that has the potential to be manufactured on a commercial scale reliably. The lentiviral vectors are assembled using a human cell line called HEK293T grown in culture trays, although the company is in the process of adapting the production technology to a larger suspension-based bioreactor.

Exhibit 4: Bluebird's Lentiviral Manufacturing Process



Source: Company reports

In addition to lentiviral vector production, an essential component of bluebird's gene therapy platform is its target cell transduction process. This process consists of five steps:

1. **Selection**: HSCs are extracted from peripheral blood mononuclear cells (PBMCs) obtained from the patient's blood by apheresis or bone marrow harvest following mobilization via a colony stimulating factor
2. **Pre-Stimulation**: The isolated HSCs are prepared for transduction with a mixture of growth factors and proprietary processes
3. **Transduction**: The HSCs are exposed to bluebird's lentiviral vector of choice, depending on the disease to be treated. During this process, the virus integrates into the cells' chromosomes.
4. **Final harvest**: When transduction is complete, the now gene-modified HSCs are purified and checked for successful transduction and gene product expression before release and use in the patient.
5. **Formulation and freeze**: The remaining cells are appropriately formulated and stored for eventual use in the patient (after conditioning for stem cell transplantation).

The patient undergoes myeloablation to prepare for the transplant, and the transduced cells delivered. As the cells engraft, they should produce the gene product that was introduced, halting disease progression (in the case of CCALD) or curing the disease (β-thalassemia, sickle cell disease, and potentially others).

Adrenoleukodystrophy—A Rare, Inherited Nervous System Disease

Adrenoleukodystrophy (ALD) is a rare, inherited neurological disorder caused by mutations in the ABCD1 gene, which encodes for the ALD protein. ALD plays a role in the metabolism of very long-chain fatty acids (VLCFA), and the lack of functional ALD results in the accumulation of VLCFA in cells. For neural cells, VLCFA causes damage to the myelin sheath, resulting in a host of problems including decreased motor coordination and function, visual and hearing disturbances, loss of cognitive function, dementia, seizures, adrenal dysfunction and other complications, including death. The disorder is X-linked, and affects about one in 20,000 newborn males.

ALD is divided into three sub-types:

- Childhood cerebral adrenoleukodystrophy (CCALD): accounting for 30-40% of ALD patients, CCALD is the most severe form of ALD. It is characterized by progressive destruction of myelin, leading to severe loss of neurological function and eventual death. CCALD presents itself in young boys, with learning and behavioral problems often observed between the ages of 3 and 15 (median age 7). Without treatment, these boys typically suffer significant neurological decline over several years with death usually occurring within a decade of diagnosis.
- Adrenomyeloneuropathy (AMN): accounting for 40-45% of ALD patients, AMN is the most common form of ALD. It is characterized by the non-inflammatory axon disruption in the spinal cord, with slower symptom progression compared to CCALD. About 40% of AMN patients develop cerebral disease similar to CCALD. AMN typically presents itself in adults over 21 years old.
- Adult cerebral adrenoleukodystrophy (ACALD): accounting for about 5% of all ALD patients, ACALD mirrors the severe progression of neurologic symptoms seen in CCALD. ACALD typically develops in males aged 15 years and older.

Current ALD Treatment

The only effective treatment option available currently for boys with CCALD is allogeneic hematopoietic stem cell transfer (HSCT). In this procedure, donor HSC's containing the properly functioning copy of the gene are intravenously infused into the patient. In addition to the significant mortality/morbidity risks involved with ablation of the patient's bone marrow to allow for the engraftment of the foreign donor cells, another major drawback to this method is finding a suitable donor match to minimize complications. As the best match is an unaffected sibling, these matches are understandably rare. In the majority of CCALD cases the procedures use unmatched donors, resulting in significant mortality/morbidity rates. Allogeneic HSCT also requires long-term immunosuppression afterwards, resulting in a prolonged risk of opportunistic infections and other serious side effects.

An alternative treatment some physicians recommend is glyceryl trierucate, also known as Lorenzo's Oil (popularized in a 1992 movie of the same name). A 4:1 mixture of erucic acid and oleic acid, the oil in conjunction with a diet low in VLCFA is thought to be able to normalize the accumulation of VLCFA in the brain. Glyceryl trierucate has not been approved by any major regulatory agency as a prescription drug.

ALD Clinical Data

The ALD-101 retrospective study

Bluebird conducted a retrospective study (ALD-101) of CCALD patients in order to guide future clinical studies of LENTI-D. ALD-101 examined the natural progression of CCALD in an untreated cohort compared to a treated cohort of patients who received allogeneic HSCT. Data was collected from 137 patients, including 72 in the untreated and 65 in the treated cohort, from four US sites and one French site.

The study used three functional and radiographic measurements to assess the patient groups: Neurological Function Score (NFS), Loes score and gadolinium enhancement.

- NFS is a 25-point neurological function score that assesses 15 neurological abnormalities typically caused by ALD. Of the 15 abnormalities, six are defined by bluebird as Major Functional Disabilities (MFD).

- Loes score is a radiographic, magnetic resonance imaging (MRI)-based assessment of changes in the brain using a 34-point scale. MRI scans determine the extent and location of brain abnormalities such as white matter changes, degree of demyelination and the presence of focal or global atrophy. A Loes score >=1 indicates significant disease, with patients scoring a Loes score >=10 generally considered too advanced for treatment.

- A gadolinium positive result, or evidence of gadolinium enhancement in the brain in a MRI study, is considered to be a marker of disease progression. Gadolinium is a contrast agent that indicates the presence of a compromised blood-brain barrier behind the leading edge of demyelinating lesions in the brain.

Exhibit 5: Neurological Function Score (NFS)

Symptom	Score	Major Functional Disability (MFD)
Loss of communication	3	Yes
No voluntary movement	3	Yes
Cortical blindness	2	Yes
Tube feeding	2	Yes
Total incontinence	2	Yes
Wheelchair required	2	Yes
Swallowing/other CNS dysfunctions	2	
Spastic gait (needs assistance)	2	
Hearing/auditory processing problems	1	
Aphasia/apraxia	1	
Visual impairment/fields cut	1	
Running difficulties/hyperreflexia	1	
Episodes of incontinency	1	
Nonfebrile seizures	1	
Walking difficulties/spasticity/spastic gait (no assistance)	1	

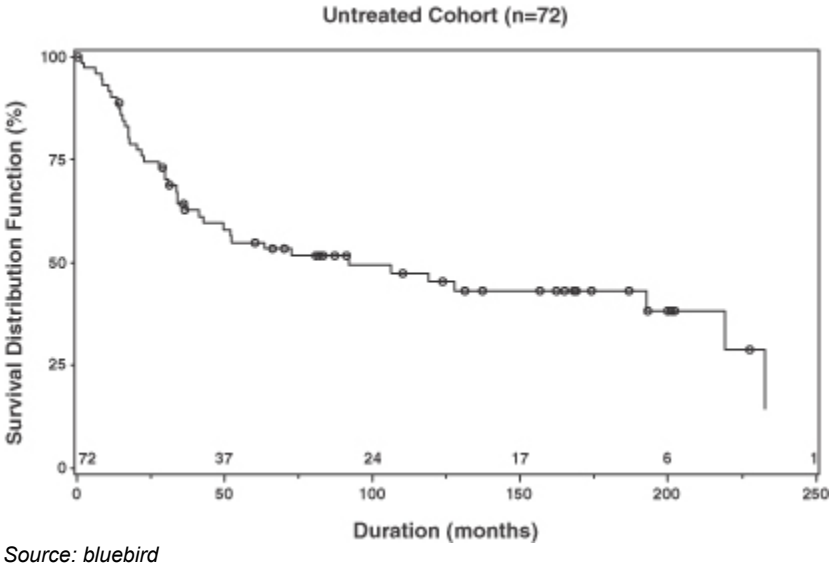
Source: bluebird

Results and Analysis

The study established that NFS, Loes and gadolinium enhancement were valid measurements of disease state, survival and disease progression. Gadolinium enhancement, in particular, appeared to predict disease progression.

This analysis confirmed the dismal nature of CCALD, finding a median overall survival of just 92 months and the estimated probability of survival at five years was 55% in untreated patients. We note that overall survival includes patients in a vegetative state prior to death. Generally, significantly lower mortality rates were seen in patients with lower baseline NFS and Loes scores than those with higher scores. Gadolinium enhancement was also shown to be a predictive measure of the likelihood of rapid disease progression.

Exhibit 6: Survival in Untreated CCALD Patients



Source: bluebird

For the treated cohort, allogeneic HSCT was associated with disease stabilization in patients with CCALD. However, it was also associated with clinically significant morbidity and mortality rates, particularly with unmatched and unrelated donors.

Exhibit 7: Historical CCALD-Associated Mortality Rates

Cohort	NFS<=1	NFS>1	1<=Loes<=9	Loes>9
Untreated	42%	85%	46%	76%
Treated	12%	29%	13%	28%

Source: bluebird

Clearly allogeneic HSCT can stabilize the disease, providing proof-of-concept that HSCTs with a normal ABCD1 gene can produce clinically relevant levels of the protein, relative to untreated patients. However, allogeneic HSCT transplants carry a significant mortality/morbidity risk, with overall 1-year mortality of 19%, and a GVHD incidence of 54% (42% acute and 18% chronic GVHD), along with 29% of allogeneic transplant patients experiencing a serious infection. Autologous HSCTs are associated with much lower mortality/morbidity risks, and with that background, *ex vivo* modification of autologous HSCs should carry the best risk/benefit profile.

The TG04.06.01 study

TG04.06.01 was a four-year French Phase I/II study in four boys with CCALD treated with autologous HSCs transduced *ex vivo* with a lentiviral vector carrying a functional ABCD1 gene (the lentiviral vector was supplied by a third party company not affiliated with bluebird). Baseline disease was established with the four boys having a NFS=0 and Loes scores between two and seven, with gadolinium enhancement in all four patients.

Results and Analysis

- Patient One: Loes score stabilized at month 30 and remained stable through month 75.
- Patient Two: Loes score stabilized at month 30 and remained stable through month 64. Gadolinium enhancement was initially positive, resolved, reappeared, resolved again and then remained negative.
- Patient Three: Loes score stabilized at month 33, but gadolinium enhancement persisted. Patient had active, progressive disease post-transplant resulting in the development of significant cognitive deficits. No further decline in NFS or Loes scores were seen at 54 months since the 33-month evaluation.
- Patient Four: Loes score stabilized at month 16 and remained stable at 24 months. Gadolinium enhancement disappeared 45 days post-transplant and was still not detectable at month 12.

Subjects One, Two and Four showed evidence of disease stabilization and a reduction of neuroinflammation as assessed by MRI and NFS. There is a lag time from treatment to stabilization, during which patients experienced some decline in function. The delay to stabilization is due to the time required for transplant-derived microglial cells to populate the brain, and delays are also observed in patients receiving allogeneic stem cell transplants. There were no reported safety issues related to the therapy, and all patients achieved successful engraftment within 15 days after transplant. In contrast with the historical study, none of the patients experienced adverse events due to immune incompatibility issues, such as graft rejection or GVHD. Results were published in *Science* (2009).

The clinical data compiled provided proof-of-concept and support for bluebird's pivotal Phase II/III clinical study (the ALD-102 trial).

LENTI-D

LENTI-D is bluebird's most advanced product candidate, which the company is developing as a one-time treatment to halt the progression of CCALD. LENTI-D refers to autologous HSCs that have been modified to carry a functional copy of the ABCD1 gene. The functional ABCD1 gene is inserted into the autologous HSCs *ex vivo* via an HIV-1 based lentiviral vector, and the final product is transplanted back into the patient. It is believed that the brain microglia derived from the transduced HSCs will correct the abnormalities resulting from excess VLCFA and stabilize the cerebral inflammation characteristic of CCALD.

ALD-102 (H2:13 start)

ALD-102 is a single-dose, open-label, non-randomized, international, multi-center Phase II/III study to test the safety and efficacy of LENTI-D in preserving neurological function and stabilizing cerebral demyelination in subjects with CCALD. Up to 15 patients will be followed for 24 months post-transplant, with the assumption that number will be sufficient to have 12 evaluable patients. Inclusion criteria include: active CCALD, elevated levels of plasma VLCFA, a brain MRI Loes score of 0.5 to nine (inclusive), gadolinium enhancement and an NFS <= 1. Subjects with a willing matched sibling HSCT donor will be excluded from the study. ALD-102 is expected to start in late 2013.

The primary endpoint in the ALD-102 study is the proportion of subjects who have no MFDs, as measured by NFS, at 24 months (±two months) post-transplant. Secondary endpoints, in each case measured at 24 months (±two months) post-transplant, include the change from baseline in NFS and Loes score, resolution of gadolinium enhancement on MRI and determination of MFD-free survival and overall survival.

Given the positive results from the TG04.06.01 trial and that allogeneic HSCT stopped disease progression in ALD-101, we expect LENTI-D to show significant clinical benefit in the ALD-102 trial, as measured by reductions in NFS and Loes score and resolution of gadolinium enhancement. We also believe results will be meaningful enough to support a regulatory filing.

ALD Market

Around the world, the incidence rate for ALD is about one in 20,000 newborn males. This comes to approximately 200 boys with ALD born annually in the U.S. and EU combined. Since the CCALD form comprises about 40% of those afflicted, this results in a total of 80 boys born with CCALD each year in the U.S. and EU combined. Currently an estimated 20% to 50% of CCALD afflicted individuals are diagnosed at such an advanced stage of disease that a beneficial treatment outcome is unlikely. However, the screening of newborns for ALD through a simple, inexpensive blood test could be widely adopted in the U.S. within the next five years, providing the opportunity to identify more boys for early disease intervention, particularly should LENTI-D prove a safe and efficacious treatment. We believe that the expansion of newborn screening should reduce the percent of CCALD afflicted individuals unsuitable for treatment to the lower end of the range. As a result, we believe that the annual market opportunity for CCALD is about 65 new patients in the U.S. and EU regions combined.

Additional potential expansion opportunities for LENTI-D would be the treatment of patients with AMN or ACALD, the other forms of ALD. Allogeneic HSCT has shown some early success in ACALD patients, but it has not yet been tested in AMN patients. The number of males born with ACALD in the U.S. and Europe amount to 10 individuals each year, with symptoms not developing until adulthood. The AMN market is larger, with approximately 90 males born in the U.S. and EU region each year, but only about 35 of them will develop the CCALD-like cerebral symptoms that would justify HSC transplantation.

For a life-saving, curative treatment, we estimate pricing of the LENTI-D product would be $1.5M for a one-time treatment. By comparison, Glybera, a gene therapy approved in the EU for lipoprotein lipase deficiency is priced at EUR 1.25M. Because of the high upfront cost, alternative means of reimbursement could be employed—a series of payments, or several payments based on "successful" treatment over time. Whatever the means of revenue collection, we would expect similar economics to this upfront price. We estimate approval by 2017, with rapid adoption leading to $116M in estimated revenues. Due to the rarity of the disease, we also estimate a plateau of LENTI-D revenues at about that level.

Competition

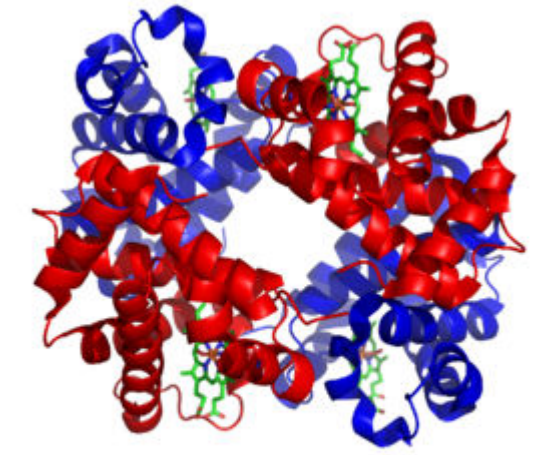
There are no other autologous HSC therapies in development for the treatment of ALD to our knowledge.

There are pharmacological studies being conducted aimed at reducing the accumulation of VLCFA in patients with ALD. The aforementioned glyceryl trierucate (Lorenzo's Oil) is currently being evaluated in a Phase II/III trial conducted by the Kennedy Krieger Institute. Another drug being evaluated in a Phase I trial in ALD patients is sobetirome, a selective thyroid hormone receptor β agonist previously in development for treating elevated LDL cholesterol. This follows the failure of another drug approved for hyperlipidemia called bezafibrate, which in a 2011 trial, failed to reduce VLCFA levels in the plasma and lymphocytes of AMN patients.

Hemoglobin Disorders

Hemoglobin is the protein in red blood cells (RBCs) responsible for carrying oxygen to the body's tissues and organs. The hemoglobin molecule is composed of 4 polypeptide chains: 2 α- and 2 β-globin chains, with each chain containing 1 iron heme group that binds to an oxygen molecule. Hemoglobinopathies like SCD and β-thalassemia arise from genetic defects that result in an abnormal hemoglobin structure.

Exhibit 8: Structure of Hemoglobin



Structure of human hemoglobin. The proteins' α and β subunits are in red and blue, and the iron-containing heme groups in green.

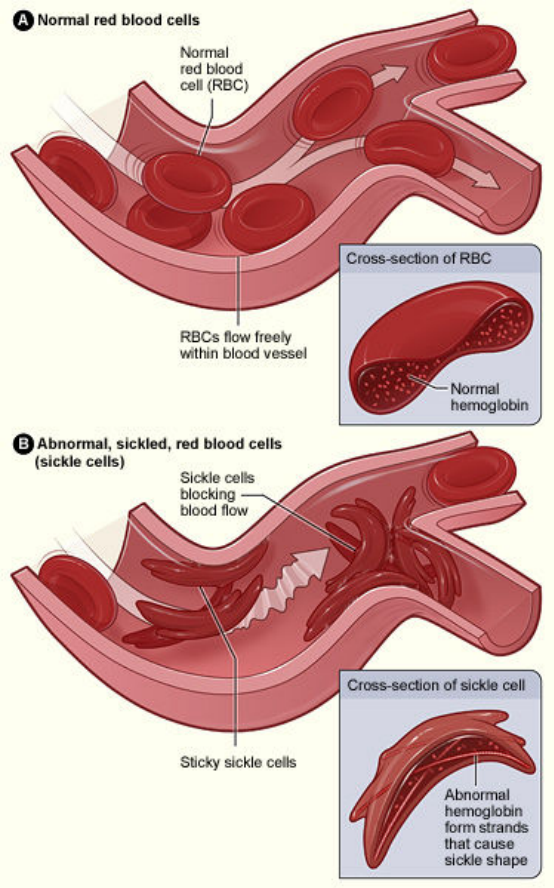
Source: Proteopedia

β-thalassemia
β-thalassemia major (also known as Cooley's anemia) is a rare hereditary blood disorder caused by a mutation in the Hemoglobin B gene on chromosome 11, resulting in an excess of α-chains and defective RBCs. The lack of sufficient RBCs and hemoglobin to effectively transport oxygen throughout the body means the patient can become severely anemic, requiring transfusion, and the shortened life span and ineffective production of RBCs can lead to other complications such as splenomegaly, marrow expansion, bone deformities, and iron overload in major organs.

β-thalassemia minor is where the patient is heterozygous for the disease. Individuals with thalassemia minor may have mild anemia, but will have a normal blood iron level and no medical treatment is necessary. α-thalassemia is where there are defects in the α-globin genes, resulting in an excess of β-globin chains. Fetuses that are homozygous for α-thalassemia are usually stillborn or die shortly after birth.

Sickle Cell Disease
SCD is a hereditary blood disorder caused by a mutation in the β-globin gene, which results in defective RBCs that take on a sickle shape. This shape causes them to aggregate and obstruct small blood vessels, restricting blood flow to organs, resulting in pain, cell death, and organ damage due to blood vessel occlusion. Sickle-shaped RBCs also rupture more easily, resulting in damage to blood vessels and iron overload that can lead to organ failure and death.

Exhibit 9: Sickled Cells



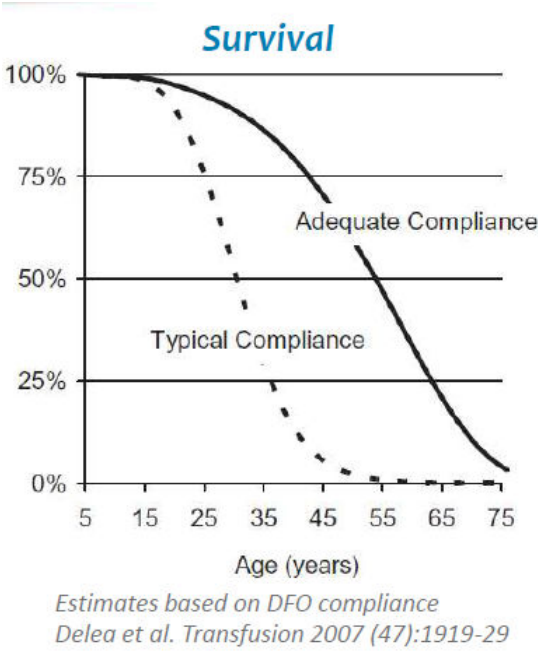
Source: NIH

Current Treatment

β-thalassemia

Patients with β-thalassemia major receive chronic blood transfusion regimens aimed at maintaining steady-state hemoglobin levels. These regimens consist of infusions with units of packed RBC every three to five weeks, the timing of which is based predominantly on monitoring hemoglobin levels. Although effective at treating symptoms, the chronic blood transfusions can lead to a large iron overload, which, over time, leads to iron-associated heart and liver toxicity, causing early death. To reduce iron overload-associated risks, patients must adhere to therapeutic iron chelation regimens to reduce iron levels. Poor compliance with chelation regimens is a problem, with overall life expectancy under typical compliance for a patient being only 28 years, although patients with good compliance can live into their mid-50's. In many developing countries where such treatment methods are unavailable, children have a poor prognosis and most die in childhood.

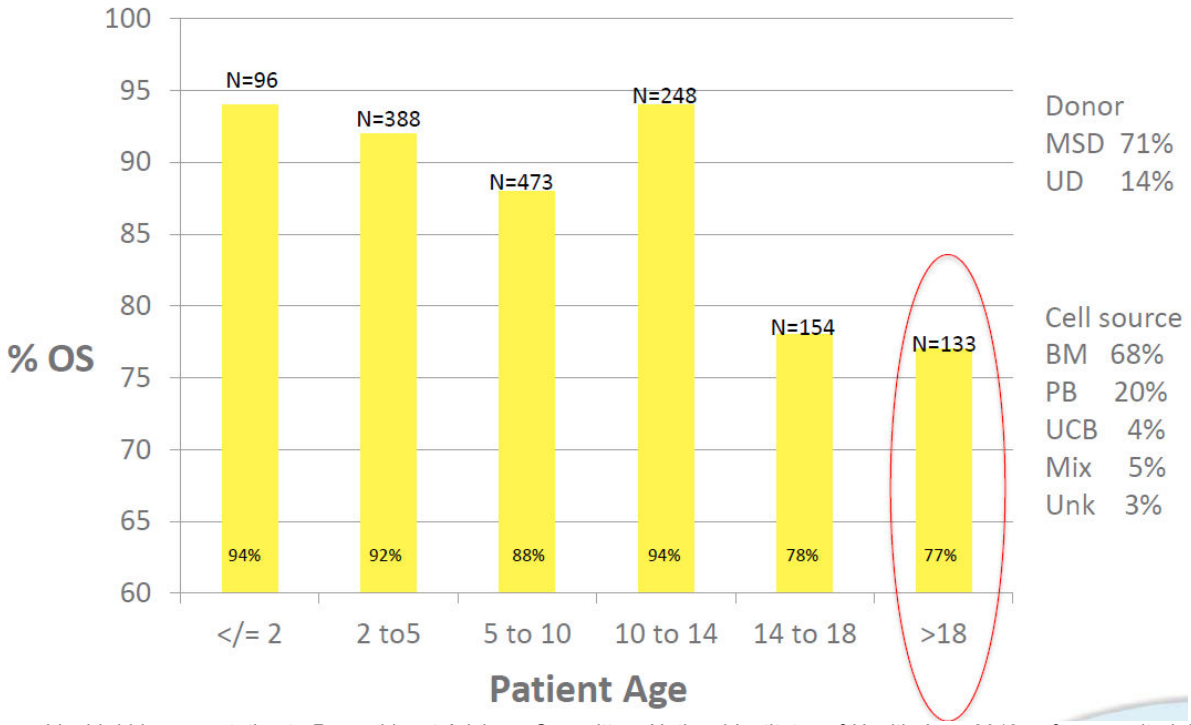
Exhibit 10: B-Thalassemia Associated Mortality



Source: bluebird bio presentation to Recombinant Advisory Committee, National Institutes of Health June 2012, reference cited in figure

The only potentially curative therapy for β-thalassemia major is allogeneic HSCT, but transplants are typically offered only to pediatric patients with a matched sibling donor (which occurs in less than 25% of all cases) due to the significant risk of allogeneic transplant-related morbidity and mortality.

Exhibit 11: Overall Survival after Allogeneic HSCT in β-thalassemia Patients Performed in Europe Since 2000



Source: bluebird bio presentation to Recombinant Advisory Committee, National Institutes of Health June 2012, reference cited: Baronciani, ASH 2011, Abstract #905

When attempted, though, HSCT has been successful, again provided proof of concept that the introduction of HSCTs containing a normal Hb gene can cure the disease.

Sickle Cell Disease (SCD)
Patients with SCD often require blood transfusions and are sometimes treated with hydroxyurea, which can reduce the frequency of painful episodes and blood transfusions by making RBCs more flexible. As with β-thalassemia, patients must deal with the risks associated with chronic blood transfusions and adhere to daily iron chelation regimens. Patients often require narcotic pain relief during acute episodes.

The only potentially curative therapy currently available is allogeneic HSCT, but due to the significant transplant-related risks, this option is usually offered only to pediatric patients with sibling-matched donors (which occurs in only about 10% of cases, due to the particular difficulty in finding suitable donors for patients of African descent).

LENTIGLOBIN BB305

LENTIGLOBIN refers to autologous HSCs that have been modified to enable expression of normally functioning hemoglobin and formation of normal RBCs in patients with β-thalassemia major and SCD. A single codon variant (referred to as T87Q) of a normal β-globin protein is inserted into the autologous HSCs *ex vivo* via the BB305 vector, and the final product is engrafted back into the patient. BB305 is bluebird's next-generation HIV-1-based lentiviral vector, replacing the older generation HPV569 vector.

Preclinical studies
In a 2001 preclinical proof-of-concept study conducted at Harvard Medical School and MIT, mice that were bioengineered to contain a human gene that induced SCD had HSCs containing the defective gene removed and replaced with the T87Q variant of the *β*-globin gene via a lentiviral vector. The corrected marrow was then transplanted into other mice with SCD whose bone marrow had been removed by radiation. At ten months post-transplant, blood samples from the transplanted mice showed a high level of expression of the T87Q-corrected globin.

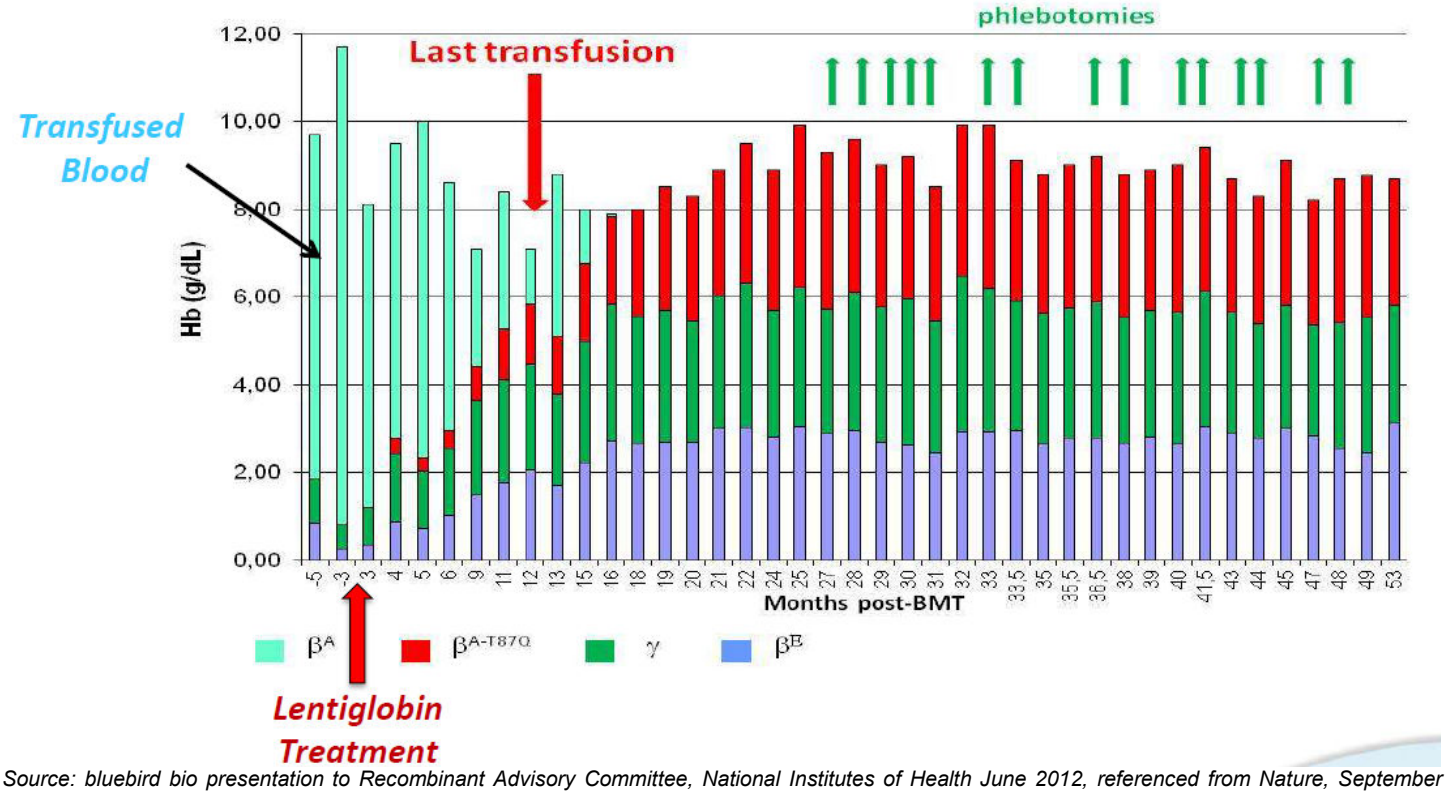
LG001 study

Design
LG001 was a five-year French Phase I/II study in three subjects with β-thalassemia major treated with autologous HSCs transduced *ex vivo* with the earlier generation LENTIGLOBIN HPV569 vector. Four patients were enrolled, although only three were treated since Subject One was ineligible due to pre-transplant complications. All subjects enrolled required significant transfusion support prior to treatment.

Results and Analysis
Subject two received a dose of the HPV569 product with cell counts below current standards in transplant practice and failed to engraft. The results for the subjects with successful engraftment are as follows:

- Subject Three: This subject experienced a decline in both volume and frequency of transfusions and eventually became transfusion-independent about one year post-treatment. Subject Three has remained transfusion-independent during the subsequent 4 years post-transplant. A partial clonal dominance in the HMGA2 gene (a gene associated embryonic cells and stem cells, and potentially oncogenic) was observed, but there have been no adverse clinical consequences or any signs of cancer in the over five years. Indeed, the presence of the HMGA2 clone has declined in this patient over time to the point that it is no longer the most common clone observed.

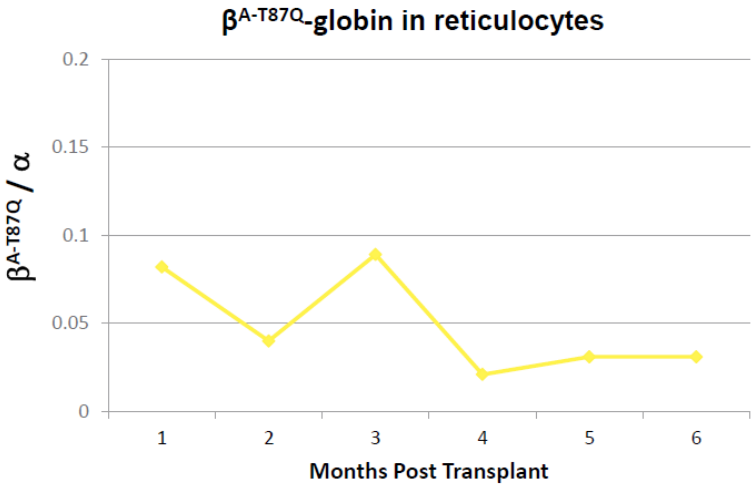
Exhibit 12: Hemoglobin Concentrations in the Blood of Subject 3



Source: bluebird bio presentation to Recombinant Advisory Committee, National Institutes of Health June 2012, referenced from Nature, September 2010

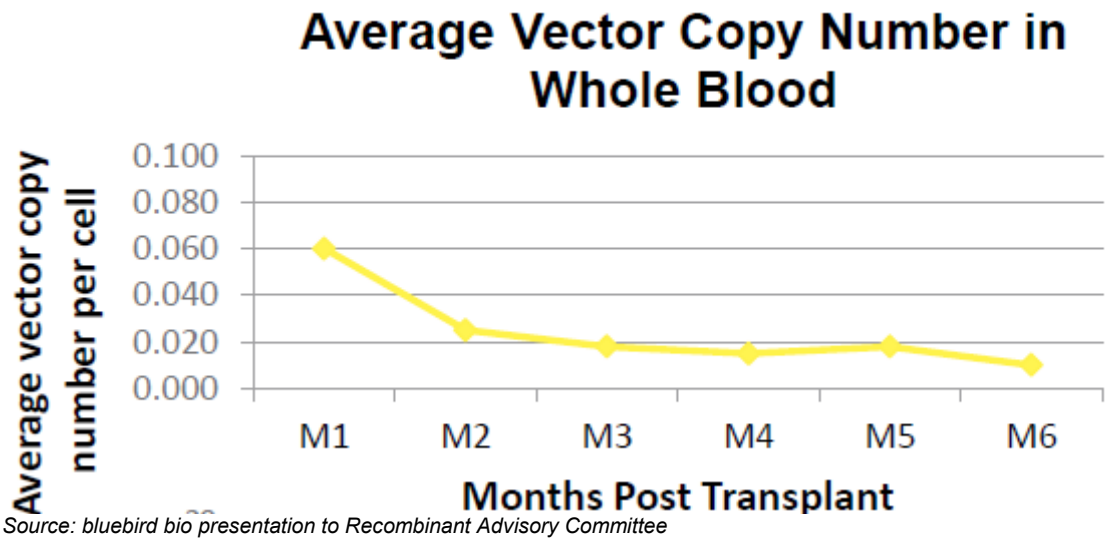
- Subject Four: After transplant, Subject Four experienced delayed platelet recovery and required platelet transfusion, with the last transfusion on day 122. Therapeutic hemoglobin in reticulocytes was detectable by one month post-transplant, with therapeutic hemoglobin expressed in 4.0% and 3.1% of reticulocytes at two and six months post-transplant, respectively. Subject Four is stable and has fully engrafted, however, transfusion requirements remain unchanged with T87Q-corrected globin expressed at levels below those demonstrated by Subject Three at similar time points. There were no adverse events related to the HPV569 product.

Exhibit 13: Subject Four Corrected Globin Expression Levels in Reticulocytes



Source: bluebird bio presentation to Recombinant Advisory Committee

Exhibit 14: Subject Four's Average Vector Copy Number in Whole Blood



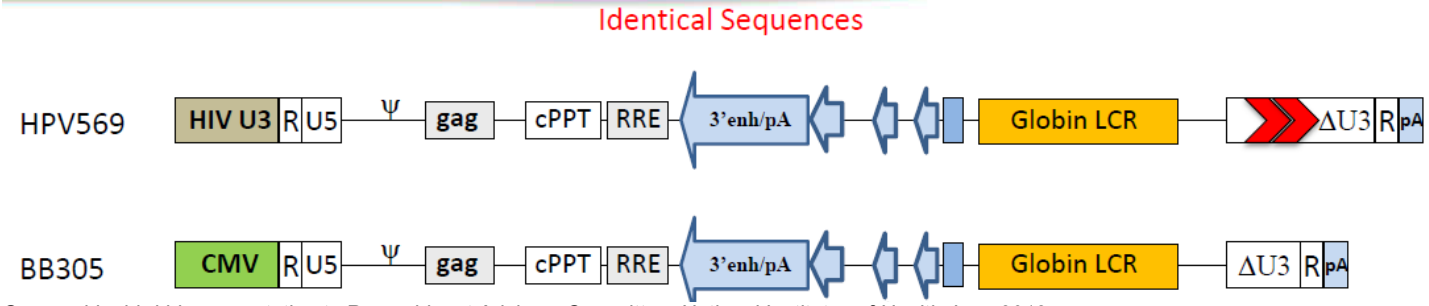
Source: bluebird bio presentation to Recombinant Advisory Committee

There have been no reported developments of spontaneous transfusion independence in patients with β-thalassemia major, leading to the conclusion that Subject Three gained independence as a direct result of treatment. Since the lentiviral vector HPV569 shares many features with the current LENTIGLOBIN BB305 vector, the LG001 study provides a clinical proof-of-concept and design basis for the HGB-204 and -205 studies. With the improvements to the vector contained in BB305 described below (particularly higher transduction efficiency, a more consistent clinical outcome could be achieved in future studies, ultimately leading to approval of BB305 in β-thalassemia and sickle cell disease.

LENTIGLOBIN BB305 Compared to HPV569

Bluebird bio is using an improved vector, BB305 in its Phase I/II trials of LENTIGLOBIN in patients. The new vector has an improved titer, higher transduction efficiency and equivalent globin expression per vector. The major sequence changes incorporate the CMV promoter, removal of the *tat* (trans-activator of transcription, a HIV-1 protein) sequence and the removal of "insulator" sequences.

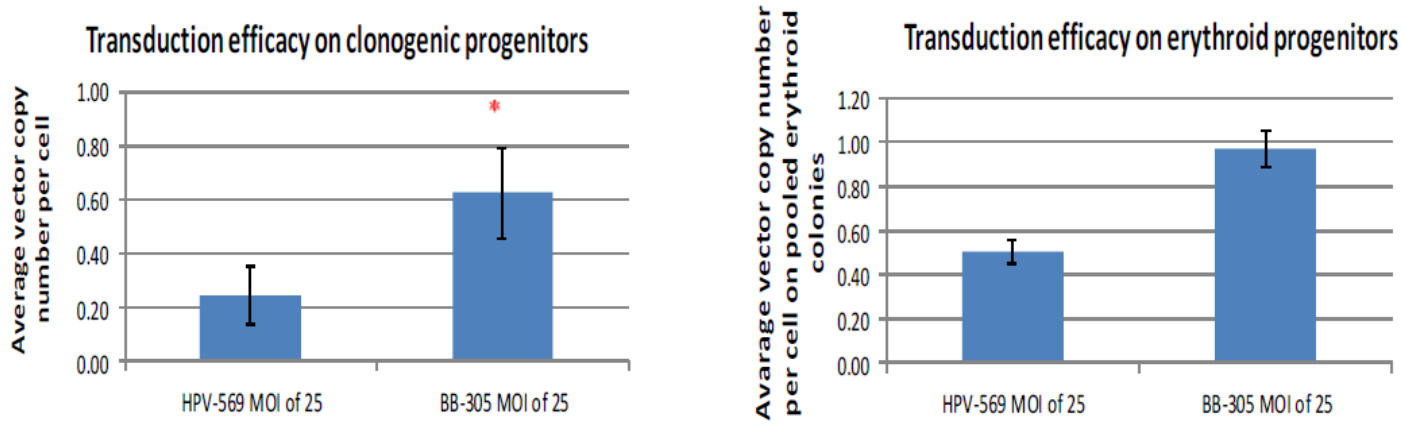
Exhibit 15: Differences in HPV569 and BB305 Vectors



Source: bluebird bio presentation to Recombinant Advisory Committee, National Institutes of Health June 2012

In preclinical studies, the BB305 vector construct shows higher transduction efficiency, as seen below.

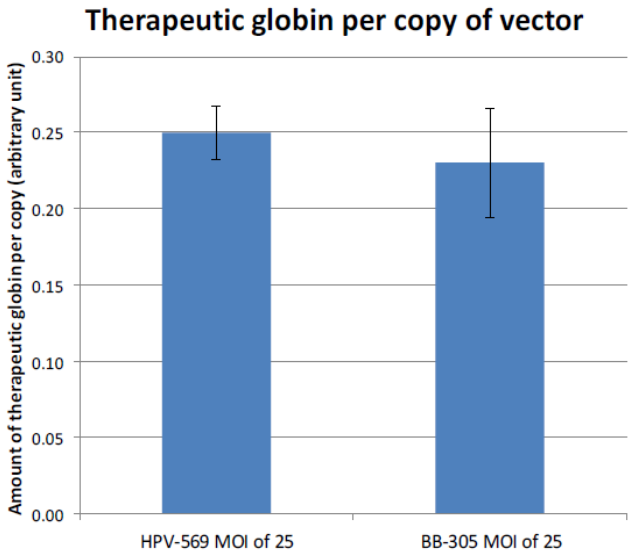
Exhibit 16: BB305 Transduction Efficiency Compared to HPV569



Source: bluebird bio presentation to Recombinant Advisory Committee, National Institutes of Health June 2012

The amount of globin produced per vector (productivity) is about the same between HPV569 and BB305, and so with the increased transduction efficiency, should lead to a consistently higher production of the protein.

Exhibit 17: Therapeutic Globin per Vector Copy Comparing HPV569 to BB305



Source: bluebird bio presentation to Recombinant Advisory Committee, National Institutes of Health June 2012

HGB-204 Study (mid-2013 start)

HGB-204 is a single-dose, open-label, non-randomized, multi-site U.S. Phase I/II study in up to 15 adults with β-thalassemia, evaluating safety and efficacy of LENTIGLOBIN BB305 in increasing hemoglobin production and eliminating or reducing transfusion dependence following treatment. The primary endpoint is production of at least 2 grams/dL of hemoglobin containing the codon variant T87Q for the six-month period between 18 and 24 months post-transplant. Secondary endpoints include RBC transfusion requirements and safety monitoring (survival etc). Each subject will remain on study for approximately 26 months from time of consent and then will be enrolled in a long-term follow-up protocol that will assess safety and efficacy beyond 24 months.

HGB-205 Study (mid-2013 start)

HGB-205 is a Phase I/II continuation study of the French LG001 study, evaluating the use of the current LENTIGLOBIN BB305 vector instead of the last-generation HPV569 vector. Up to seven additional subjects with a diagnosis of β-thalassemia or SCD will be enrolled in the trial. For all subjects, efficacy will be measured by transfusion requirements post-transplant, along with the number of hospitalization days at 6, 12 and 24 months post-transplant. For SCD patients, efficacy will be measured by the number of vaso-occlusive crises or acute chest syndrome events at 6, 12 and 24 months.

Market

The geographic distribution of β-thalassemia and SCD is similar to that of malaria-prone regions, since both disorders offer a protective benefit to the mosquito-borne illness.

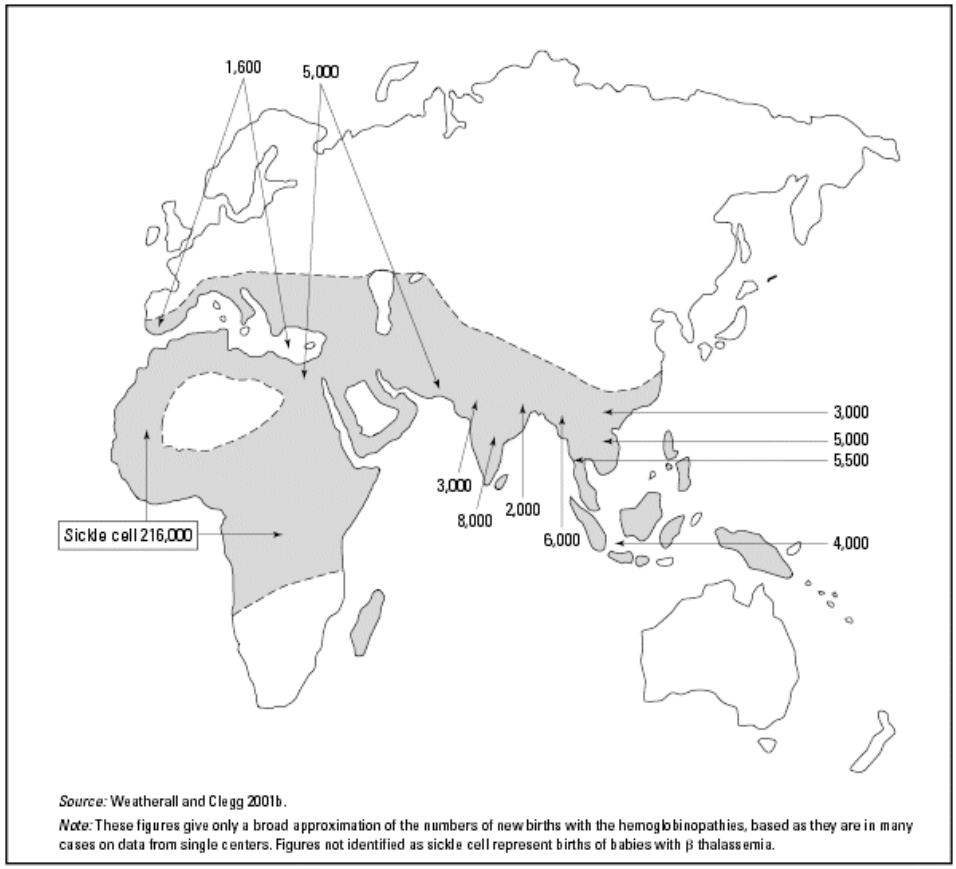
β-thalassemia

β-thalassemia is concentrated in populations of Mediterranean, South and Southeast Asian and Middle Eastern descent. The total annual incidence of symptomatic individuals is estimated at one in 100,000 throughout the world and one in 10,000 people in the European Union, with the highest concentrations in Greece and Italy. Although still rare in the U.S., changing immigration patterns are increasing the rate of individuals affected by β-thalassemia, with about 1.8 in 100,000 newborns in California being affected by the disease.

Sickle Cell Disease

SCD is concentrated in populations of African, Middle Eastern and South Asian descent. The global incidence of SCD is estimated to be 250,000-300,000 births annually, and the global prevalence of the disease is estimated to be about 20-25 million. In the U.S., where SCD is a standard part of mandatory newborn screening, the incidence is more than 1,600 births annually with an estimated prevalence of 100,000 individuals.

Exhibit 18: New Births with β-thalassemia or Sickle Cell Disease



Source: Disease Control Priorities Project (World Bank Group)

We estimate LENTIGLOBIN commercialization beginning 2019, with pricing of $450,000 per treatment in the U.S. and EU, and $150,000 in Asia (specifically Thailand, where we anticipate the bulk of the revenue-generating ROW market to be). Our cost of treatment is based on the estimated lifetime cost of care for a β-thalassemia or sickle cell disease patient. In the U.S., lifetime costs of sickle cell disease is estimated at $460,000 (American Journal of Hematology. 2009 June: 84 (6): 323-7), and in Thailand, the lifetime (30-year) cost of treating a severe β-thalassemia patient is estimated to be $150,000 (BMC Res. Notes, 2010: 3:29). While our revenue estimates assume, for simplicity, an initial, upfront payment of the entire amount for treatment, alternative payment methods could be employed (annual payments, an upfront payment, followed by reimbursement for "success," i.e., transfusion independence, and such). In the end, however, we would expect similar economics to accrue whatever method of reimbursement is negotiated with payors.

Our revenue estimates attempt to incorporate both prevalence and incidence of the diseases, as there is a relatively large prevalent population despite the rarity of the disease. We estimate that among the prevalent population, the treatment would be used in relatively young patients that have not developed significant disease-related morbidities that cannot be cured by LENTIGLOBIN. At the same time, we would expect greater market penetration into "newly incident" patients—those birth cohorts approaching the age where LENTIGLOBIN could be used (we expect childhood to adolescence). Taking these dynamics into account, we estimate an available prevalent population of 25% of the total (i.e., a 10-year age cohort centered around late adolescence), and an available incident population of 75% in the U.S./EU markets, and 45% in the Asian (Thai) markets. Similarly, we estimate that the procedure is likely to be used more frequently in "newly incident" cases that have not experienced significant disease burden, and use in the prevalent population will be more restricted to those who have not (10-20% of the population). Taking these assumptions into account leads us to estimate revenues beginning in 2019, rising to $1.24B in 2020, our valuation year. Again, we would note that alternative reimbursement methods noted above could alter the slope of the top-line revenue growth significantly, but we expect net-net that the economics of treatment to remain similar.

Competition

Memorial Sloan-Kettering Cancer Center and Chicago-based Errant Gene Therapeutics are developing Thalagen, which refers to autologous HSCs transduced *ex-vivo* with a normal β-globin gene via Errant Gene's TNS 9.55.3 lentiviral vector. Thalagen's safety and tolerability is currently being evaluated in up to 10 patients with β-thalassemia in a Phase I trial. Sloan-Kettering is responsible for clinical development and of arranging drug-development partnerships for Thalagen for the treatment of β-thalassemia and SCD.

Other methods to raise total hemoglobin levels and achieve transfusion-independence in patients are currently being investigated. These methods include the use of fetal hemoglobin (HbF) inducers such as 5-azacytidine, decitabine, and hydroxyurea, which has shown success in reducing the frequency of transfusions in SCD patients. However not all patients respond to HbF inducers, and serious side effects like neutropenia and thrombocytopenia can occur with their use. Short-chain fatty acid derivatives like 2,2-dimethylbutyrate are also being investigated as they are thought to be inhibitors of histone deacetylases (HDACs), which play a role in silencing HbF gene expression in adult RBCs. Hemoglobin levels can also be increased through the use of erythropoietic-stimulating agents like Epo and darbepoetin alfa.

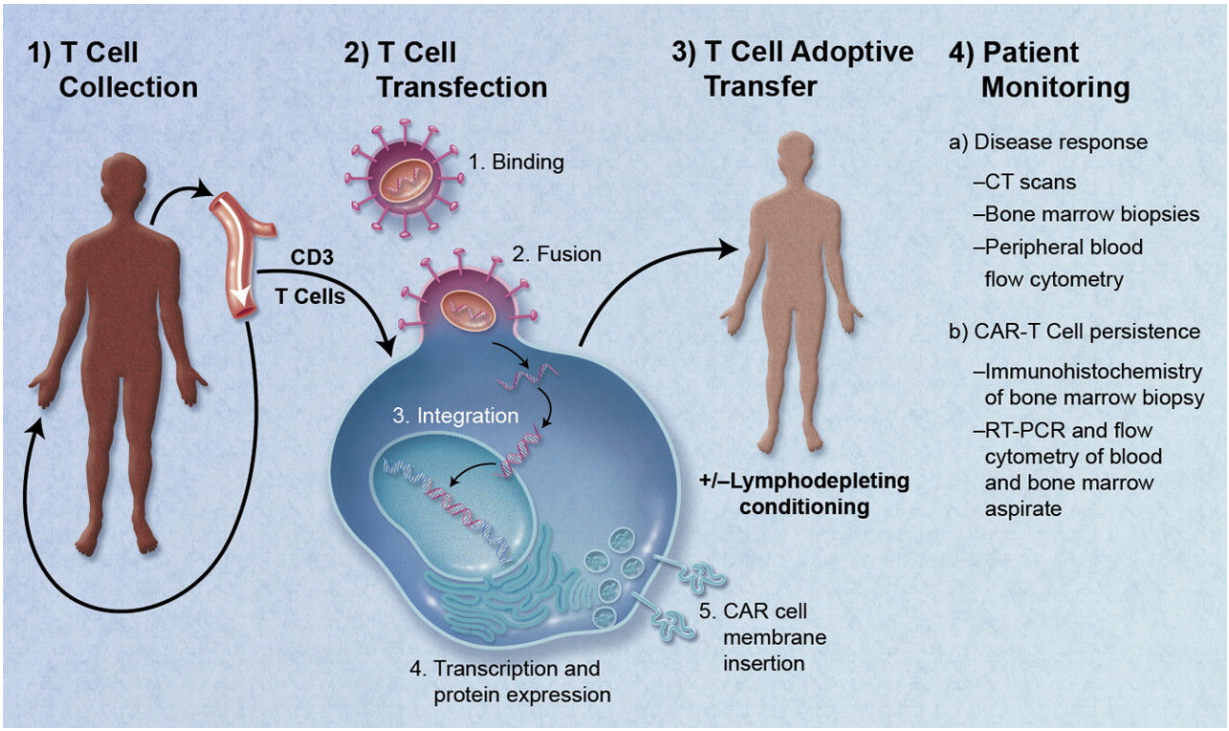
Celgene Alliance

In March 2013, bluebird entered into a three-year research and development collaboration with Celgene to discover, develop and commercialize gene therapies in oncology, with a focus on chimeric antigen receptor (CAR) T cells for the targeted destruction of cancer cells. Bluebird received $75 million upfront as part of the collaboration, and Celgene has the option to extend the term length by paying additional undisclosed fees.

Bluebird will develop (through Phase I) any product candidate selected by the companies' joint steering committee. Celgene has the option to obtain an exclusive worldwide license to develop and commercialize the product candidate, and in exchange bluebird would be eligible for up to $225 million in fees and milestones and an estimated 5-15% royalty. Bluebird retains the option to split U.S. rights, in which case the fee payment would be reduced and royalty would only apply to ex-U.S. sales. In the case that bluebird is acquired, Celgene has the right to terminate the agreement and obtain a worldwide, exclusive fully paid license to any product candidate identified under the collaboration.

The collaboration will focus on applying gene therapy technology to genetically modify a patient's own T-cells to target and destroy cancer cells. The process involves collecting T-cells from a patient and transfecting them with a lentivirus to express a receptor that binds to a surface antigen expressed on the patient's own tumor cells. After infusion back into the patient, the T-cells home to the disease sites and persist over time.

Exhibit 19: Treatment with CAR T-cells



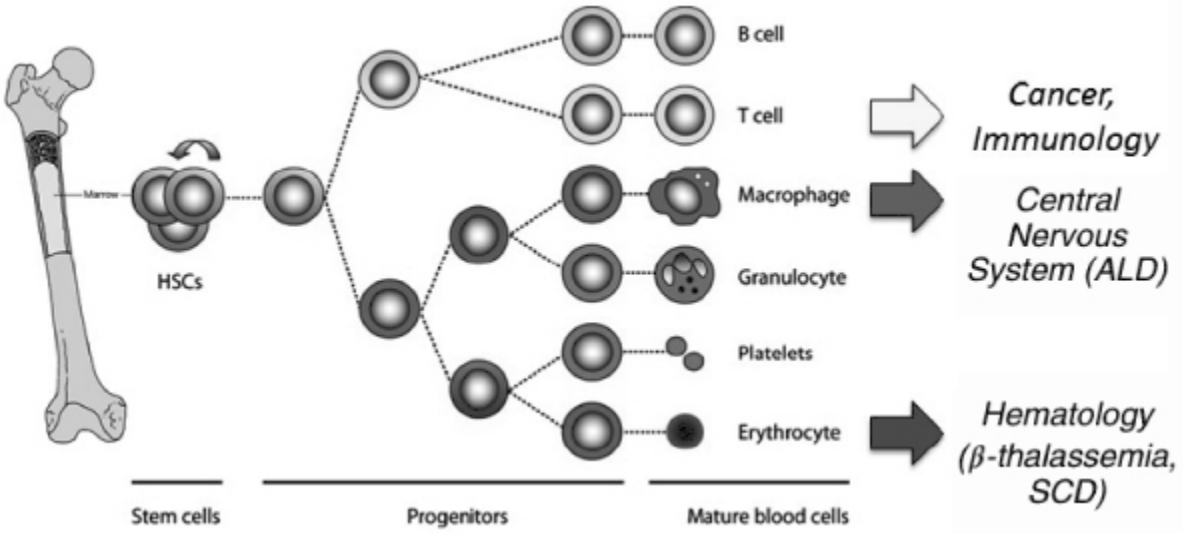
Source: Jacobson, C.A. & Ritz, J. (2011). Time to put the CAR-T before the horse. Blood, 118 (18), Page 4761.

CAR T cells have been shown to have beneficial effects in human clinical trials for patients with cancer. In studies conducted by the Memorial Sloan-Kettering Cancer Center in patients with refractory chronic lymphocytic leukemia (CLL) or relapsed B-cell acute lymphoblastic leukemia (ALL), 3 of 4 evaluable patients with bulky CLL exhibited either a significant reduction or a mixed response in lymphadenopathy without concomitant development of B-cell aplasia. The CAR T cells showed rapid trafficking to the tumor and were well tolerated. CAR T cells that were retrieved 8 days after infusion retained *ex vivo* cytotoxic potential. Our view is that CAR T treatment has significant potential in hematological malignancies, but we do not include it our valuation at this time.

Platform Potential

Since much of bluebird's viral production system stays the same regardless of disease, with only the therapeutic gene insert and related sequences changing, we believe bluebird's lentiviral vectors have broad applicability for other monogenic hereditary diseases. Since the viral vectors will remain largely unchanged, the development time for any new product candidates should be shortened. There are numerous diseases associated with genetic abnormalities in cell types derived from HSCs that bluebird can target using their gene therapy platform.

Exhibit 20: Cell Types Derived from HSCs



Source: bluebird

Monogenic Hereditary Disorders
In addition to ALD and thalassemia, other disorders that are due to a single-gene defect that bluebird's gene therapy platform could potentially target in the future include:

- Hemophilia: a bleeding disorder in which there is a partial or total lack of an essential clotting factor. In hemophilia A, the most common form, the disorder is due to defects in the F8 gene that encodes the blood-clotting protein Factor VIII. Since hemophilia is an X-linked recessive trait, it occurs primarily in males, with an incidence of 1 in 5,000 male births. An estimated 20,000 hemophiliacs live in the U.S.. The standard of care is infusion of the clotting factor, either prophylactically on a regular basis or on-demand when bleeding episodes arise.

- Lysosomal storage disorders (LSDs). Typically these disorders are caused by a single-gene defect in an enzyme, and while potentially treatable by enzyme replacement therapy, not every replacement has been or can be manufactured. Treatment is also expense, at $250,000+ per year for a lifetime. A one-time curative treatment, even priced at $1M+ could have pharmacoeconomic benefit.

- Fragile X syndrome: a neural disorder that results in mental and physical disabilities that is caused by a mutation on the FMR1 gene on the X chromosome. The disease affects about 1 in 4,000 males and 1 in 5,000 females, Treatments are based around minimizing the secondary characteristics of the disease.

Bluebird could also leverage its expertise with lentiviral and AAV vectors to expand into the *in vivo* transduction setting. Although this introduces additional complexity associated with finding the target cell *in vivo*, this method could be more suitable for certain indications that affect localized disease sites, such as ocular or muscular diseases caused by gene defects.

Exhibit 21: Management

Position	Background
Nick Leschly, CEO, President	Nick Leschly has served as president and CEO since September 2010. Previously, he served as interim CEO from March 2010 to September 2010. Formerly a partner of Third Rock Ventures, prior to joining Third Rock, he worked at Millennium Pharmaceuticals, leading several early-stage drug development programs and 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.
Jeffrey T. Walsh, COO	Jeffrey T. Walsh has served as COO since May 2011 and as secretary since March 2013. From November 2008 to February 2011, Mr. Walsh served as CBO of Taligen Therapeutics (acquired by Alexion). 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 (acquired by Chiron), 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.
Mitchell H. Finer, PhD, CSO	Mitchell H. Finer, Ph.D. has served as CSO since March 2010. Prior to joining, Dr. Finer served as SVP of development and operations for Novocell (now ViaCyte) from November 2008 to March 2010. From July 2005 through November 2008, Dr. Finer served as CEO of Intracel Holdings. From June 2003 to June 2005, he held the position of president and CEO of Genteric. Previously, he had served as Genteric's CSO from November 2002 to June 2003 and as VP of research and development for the Gencell division of Aventis Pharma (now Sanofi) from April 2002 to 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, MD, CMO	David Davidson, M.D. has served as CMO since February 2012. Prior to joining, Dr. Davidson served as a senior medical director at Genzyme. 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.
Linda C. Bain, CPA, VP of Finance and Business Operations	Linda C. Bain, CPA has served as vice president of finance and business operations since October 2011 and as treasurer since March 2013. Previously, she served as VP of corporate finance at Genzyme from September 2008 to September 2011, at Fidelity Investments from September 2007 to September 2008 and a number of positions at AstraZeneca from May 2000 to September 2007. She received her B.S. from the University of the Orange Free State in South Africa.

Exhibit 22: Financial Model

WEDBUSH
PACGROW LIFE SCIENCES

David M. Nierengarten, Ph.D.

7/14/2013

Bluebird Bio, Inc.

Annual Financial Results & Projections
($ in thousands except per share data)
Ticker: BLUE (Nasdaq)

	FY:12A	Q1	Q2	Q3	Q4	FY:13E	FY:14E	FY:15E	FY:16E	FY:17E	FY:18E	FY:19E	FY:20E
Revenue:													
Sales	0	0	0	0	0	0	0	0	0	116,154	115,864	692,511	1,355,330
Collaboration revenue	0	1,042	700	550	400	2,692	650	150	0	0	0	0	0
Grant, license fees and other revenue	340	85	0	0	0	85	1,200	1,200	1,200	1,200	1,200	1,200	1,200
Total Revenues	**$340**	**$1,127**	**$700**	**$550**	**$400**	**$2,777**	**$1,850**	**$1,350**	**$1,200**	**$117,354**	**$117,064**	**$693,711**	**$1,356,530**
Cost and Expenses:													
Costs of goods sold	0	0	0	0	0	0	0	0	0	29,038	28,966	173,128	338,833
Research and Development	17,210	5,284	6,341	7,609	8,750	27,984	35,441	38,466	43,294	51,176	62,204	75,610	91,904
Sales, General and Administrative	6,846	2,324	2,556	2,812	2,925	10,617	11,845	13,397	20,807	36,988	36,933	146,496	272,431
Other operating expenses	0	0	0	0	0	0	0	0	0	0	0	0	8,000
Total Costs and Expenses	**$24,056**	**$7,608**	**$8,897**	**$10,421**	**$11,675**	**$38,601**	**$47,286**	**$51,863**	**$64,101**	**$117,202**	**$128,103**	**$395,233**	**$711,168**
Operating Income (loss)	(23,716)	(6,481)	(8,197)	(9,871)	(11,275)	(35,824)	(45,436)	(50,513)	(62,901)	152	(11,040)	298,477	645,362
Net Interest Income (Expense)	5	3	132	224	209	568	674	639	539	729	696	868	6,373
Other income / (Expense)	41	(66)	0	0	0	(66)	0	0	0	0	0	0	0
Income Before Income Taxes	(23,670)	(6,544)	(8,065)	(9,647)	(11,066)	(35,322)	(44,762)	(49,874)	(62,362)	881	(10,344)	299,345	651,735
Net Income	**($23,671)**	**($6,544)**	**($8,065)**	**($9,647)**	**($11,066)**	**($35,322)**	**($44,762)**	**($49,874)**	**($62,362)**	**$689**	**($10,344)**	**$284,378**	**$423,628**
GAAP Basic EPS with sFAS123	**(1.81)**	**(0.39)**	**(0.34)**	**(0.41)**	**(0.47)**	**(1.62)**	**(1.75)**	**(1.78)**	**(2.11)**	**0.02**	**(0.32)**	**8.86**	**13.15**
GAAP Diluted EPS with sFAS123	**(1.81)**	**(0.39)**	**(0.33)**	**(0.40)**	**(0.46)**	**(1.58)**	**(1.70)**	**(1.74)**	**(2.06)**	**0.02**	**(0.32)**	**8.64**	**12.83**
Weighted shares outstanding	13,112	16,717	23,549	23,574	23,599	21,860	25,618	27,962	29,562	31,912	32,012	32,112	32,212
Fully diluted shares outstanding	13,112	16,717	24,138	24,163	24,189	22,302	26,258	28,661	30,301	32,709	32,812	32,914	33,017
Cash Burn	(22,849)	(5,883)	(7,477)	(9,058)	(10,476)	(32,893)	(42,200)	(47,078)	(59,406)	3,880	(7,142)	287,589	426,849
Cash Balance	67,011	131,836	224,000	208,900	192,661	192,661	128,600	166,771	193,836	176,884	165,580	400,108	791,372

Analyst Biography

David is an Analyst covering stocks in the Biotechnology/Biopharmaceuticals/BioDefense sector. His prior sell-side research experience at Robert W. Baird & Co. covered biotechnology companies of all market capitalizations, with a focus on oncology and rare diseases.

David received his B.S. (Biochemistry) from the University of Wisconsin-Madison and Ph.D. (Molecular and Cell Biology) from the University of California-Berkeley.

David's Edge: David's early stage venture capital investing experience gives him a balanced perspective on developmental-stage biotechnology companies and their ultimate risk/reward potential. His experience on the other side of that equation in a clinical-stage, venture backed biotechnology company provides him with insights into corporate operations. The combination of experiences creates a focus on value creation in this event-driven space.

Analyst Certification
I, David M. Nierengarten, Ph.D., Gregory R. Wade, Ph.D., Christopher N. Marai, Ph.D., certify that the views expressed in this report accurately reflect my personal opinion and that I have not and will not, directly or indirectly, receive compensation or other payments in connection with my specific recommendations or views contained in this report.

Disclosure information regarding historical ratings and price targets is available at http://www.wedbush.com/ResearchDisclosure/DisclosureQ213.pdf

Investment Rating System:
Outperform: Expect the total return of the stock to outperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
Neutral: Expect the total return of the stock to perform in-line with the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
Underperform: Expect the total return of the stock to underperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.

The Investment Ratings are based on the expected performance of a stock (based on anticipated total return to price target) relative to the other stocks in the analyst's coverage universe (or the analyst's team coverage).*

Rating Distribution (as of June 30, 2013)	**Investment Banking Relationships (as of June 30, 2013)**
Outperform:54% Neutral: 41% Underperform: 5%	Outperform:15% Neutral: 1% Underperform: 0%

The Distribution of Ratings is required by FINRA rules; however, WS' stock ratings of Outperform, Neutral, and Underperform most closely conform to Buy, Hold, and Sell, respectively. Please note, however, the definitions are not the same as WS' stock ratings are on a relative basis.

The analysts responsible for preparing research reports do not receive compensation based on specific investment banking activity. The analysts receive compensation that is based upon various factors including WS' total revenues, a portion of which are generated by WS' investment banking activities.

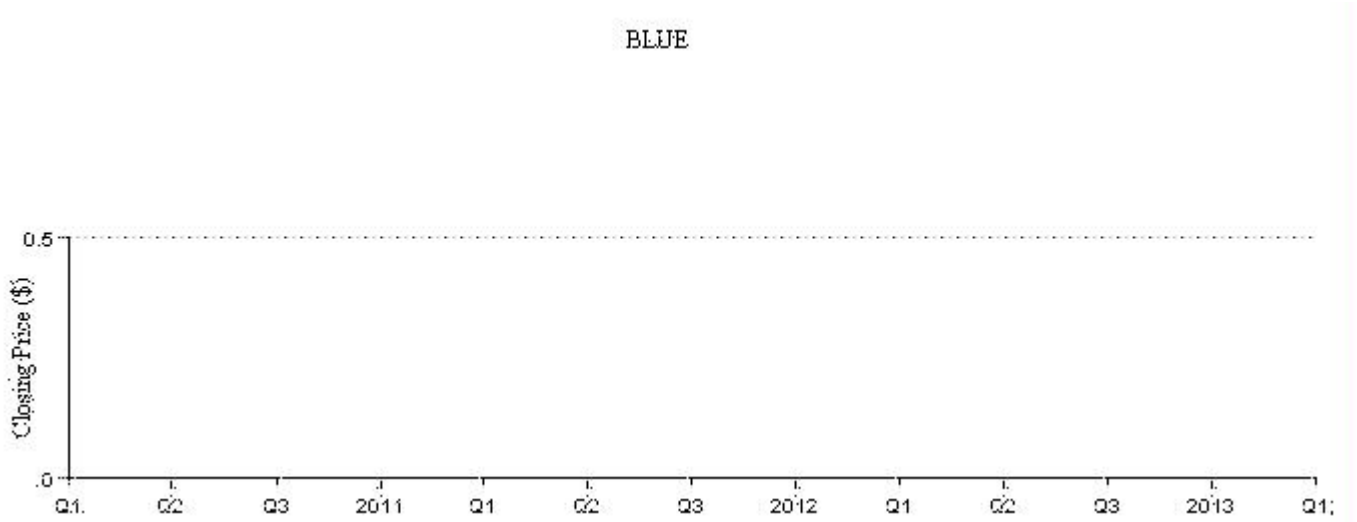
Wedbush Equity Research Disclosures as of July 15, 2013

Company	Disclosure
bluebird bio	1,3,5,7

Research Disclosure Legend
1. WS makes a market in the securities of the subject company.
2. WS managed a public offering of securities within the last 12 months.
3. WS co-managed a public offering of securities within the last 12 months.
4. WS has received compensation for investment banking services within the last 12 months.
5. WS provided investment banking services within the last 12 months.
6. WS is acting as financial advisor.
7. WS expects to receive compensation for investment banking services within the next 3 months.
8. WS provided non-investment banking securities-related services within the past 12 months.
9. WS has received compensation for products and services other than investment banking services within the past 12 months.
10. The research analyst, a member of the research analyst's household, any associate of the research analyst, or any individual directly involved in the preparation of this report has a long position in the common stocks.

11. WS or one of its affiliates beneficially own 1% or more of the common equity securities.
12. The analyst maintains Contingent Value Rights that enables him/her to receive payments of cash upon the company's meeting certain clinical and regulatory milestones.

Price Charts
Wedbush disclosure price charts are updated within the first fifteen days of each new calendar quarter per FINRA regulations. Price charts for companies initiated upon in the current quarter, and rating and target price changes occurring in the current quarter, will not be displayed until the following quarter. Additional information on recommended securities is available on request.



* WS changed its rating system from (Strong Buy/Buy/Hold/Sell) to (Outperform/ Neutral/Underperform) on July 14, 2009.
Please access the attached hyperlink for WS' Coverage Universe: http://www.wedbush.com/services/cmg/equities-division/research/equity-research Applicable disclosure information is also available upon request by contacting Ellen Kang in the Research Department at (213) 688-4529, by email to ellen.kang@wedbush.com, or the Business Conduct Department at (213) 688-8090. You may also submit a written request to the following: Business Conduct Department, 1000 Wilshire Blvd., Los Angeles, CA 90017.

OTHER DISCLOSURES

RESEARCH DEPT. * (213) 688-4505 * www.wedbush.com
EQUITY TRADING Los Angeles (213) 688-4470 / (800) 421-0178 * EQUITY SALES Los Angeles (800) 444-8076
CORPORATE HEADQUARTERS (213) 688-8000

WEDBUSH

EQUITY RESEARCH DEPARTMENT

(213) 688-4529

DIRECTOR OF RESEARCH
Mark D. Benson (213) 688-4435

MANAGER, RESEARCH OPERATIONS
Ellen Kang (213) 688-4529

RETAIL AND CONSUMER

Consumer Products
Rommel T. Dionisio (212) 938-9934
Kurt M. Frederick, CFA CPA (415) 274-6822

Footwear, Apparel and Accessories
Corinna Freedman (212) 668-9876
Alicia Reese (212) 938-9927

Healthy Lifestyles
Kurt M. Frederick, CFA CPA (415) 274-6822

Restaurants
Nick Setyan (213) 688-4519
Colin Radke (213) 688-6624

Specialty Retail: Hardlines
Joan L. Storms, CFA (213) 688-4537
John Garrett, CFA (213) 688-4523

Specialty Retail: Softlines
Betty Chen (415) 273-7328
Alex Pham (415) 273-7315

RETAIL/CONSUMER MARKET RESEARCH

Gabriella Santaniello (213) 688-4557

INDUSTRIAL GROWTH TECHNOLOGY

Clean Technology
Craig Irwin (212) 938-9926
Min Xu (212) 938-9925

Environmental Services / Building Products
Al Kaschalk (213) 688-4539

Industrial Biotechnology
Liana Moussatos, Ph.D. (415) 263-6626
Christopher N. Marai, Ph.D. (415) 274-6861

Water and Renewable Energy Solutions
David Rose, CFA (213) 688-4319

TECHNOLOGY, INTERNET, MEDIA & SOCIAL MEDIA

Communications and Application Software
Shyam Patil, CFA (213) 688-8062

Communications Equipment
Rohit Chopra (212) 668-9871
Sanjit Singh (212) 938-9922
Ryan Flanagan (212) 938-9942

Computer Services: Financial Technology
Gil B. Luria (213) 688-4501
Aaron Turner (213) 688-4429

Enterprise Software
Steve Koenig (415) 274-6801

Entertainment: Retail
Michael Pachter (213) 688-4474
Nick McKay (213) 688-4343
Nick Citrin (213) 688-4495

Entertainment: Software
Michael Pachter (213) 688-4474
Nick McKay (213) 688-4343
Nick Citrin (213) 688-4495

Internet and E-Commerce
Michael Pachter (213) 688-4474
Nick McKay (213) 688-4343
Nick Citrin (213) 688-4495

Media
James Dix, CFA (213) 688-4315

Movies and Entertainment
Michael Pachter (213) 688-4474
Nick McKay (213) 688-4343
Nick Citrin (213) 688-4495

Semiconductors
Betsy Van Hees (415) 274-6869
Ryan Jue, CFA (415) 263-6669

LIFE SCIENCES

Biotechnology/Biopharmaceuticals/BioDefense
Gregory R. Wade, Ph.D. (415) 274-6863
David M. Nierengarten, Ph.D. (415) 274-6862
Christopher N. Marai, Ph.D. (415) 274-6861

Emerging Pharmaceuticals
Liana Moussatos, Ph.D. (415) 263-6626
Richard Lau (415) 274-6851
Christopher N. Marai, Ph.D. (415) 274-6861

Healthcare Services - Managed Care
Sarah James (213) 688-4503
Daniel Patt (212) 938-9937

Medical Devices
Tao Levy (212) 938-9948

Medical Diagnostics and Life Sciences Tools
Zarak Khurshid (415) 274-6823

EQUITY SALES		EQUITY TRADING	
Los Angeles	(213) 688-4470 / (800) 444-8076	Los Angeles	(213) 688-4470 / (800) 421-0178
San Francisco	(415) 274-6800	San Francisco	(415) 274-6811
New York	(212) 938-9931	New York	(212) 344-2382
Boston	(617) 832-3700	Boston	(617) 832-3700

CORPORATE HEADQUARTERS
1000 Wilshire Blvd., Los Angeles, CA 90017-2465
Tel: (213) 688-8000 www.wedbush.com