bluebird bio

BLUE : NASDAQ : US$30.65

BUY

Target: $45.00

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COMPANY STATISTICS:

52-week Range:	24.00 - 31.14
Market Cap (M):	US$670
Avg. Daily Vol. (000s):	422
Shares Out (M):	21. 9

EARNINGS SUMMARY:

FYE Dec		2012A	2013E	2014E
EPS:		(13.79)	(1.42)	(0.63)
Revenue (M):	Q1	-	1.1A	-
	Q2	-	6.2	-
	Q3	-	6.8	-
	Q4	-	6.8	-
Total		0.3	21.0	27.3
EPS:	Q1	-	(19.94)A	-
	Q2	-	(0.92)	-
	Q3	-	(0.14)	-
	Q4	-	(0.23)	-
Total		(13.79)	(1.42)	(0.63)

SHARE PRICE PERFORMANCE:

Source: Interactive Data Corporation

COMPANY DESCRIPTION:

bluebird bio is a clinical-stage biotechnology company focused on gene therapy approaches to severe genetic and orphan disorders. The lead product is Lenti-D for CCALD. The second product is LentiGlobin for beta-thalassemia and sickle cell disease, and bluebird is also developing CAR T-based cancer therapies thorough a partnership with Celgene. bluebird is based in Cambridge, MA.

All amounts in US$ unless otherwise noted.

Life Sciences -- Biotechnology

THE FOREFRONT OF A GENE THERAPY REVOLUTION; INITIATING WITH BUY, $45 PT

bluebird is defined by its gene therapy platform – a novel approach that uses a vector (modified virus) to add functioning genes to a patient's own stem cells, which are then reinfused back into the body. Gene therapy has the potential to be highly disruptive given the promise to cure any disease caused by disruption of a single gene, with one treatment. The lead product is Lenti-D for childhood cerebral adrenoleukodystrophy (CCALD), an orphan, genetic CNS disorder, to enter a pivotal P2/3 trial by YE13. We are optimistic on this trial given physician diligence and a P1/2 trial where three of four boys treated with an earlier version of the vector (~3x less potent) demonstrated disease stabilization and no neurological defects. The second product, LentiGlobin for treatment of beta-thalassemia and sickle cell disease (SCD), rare genetic blood disorders, has potential to treat a larger population, but is less proven in the clinic (one of three patients achieved transfusion independence): one P1/2 trial recently initiated (E.U.) and the U.S. study is on tap for mid-2013 (newer vector likely to provide improved outcomes). We view bluebird as a leader in gene therapy given its clinical progress and expertise (signed a recent partnership with CELG to target oncology), and model for peak revenue recognized by bluebird of $1.23B in 2026 from Lenti-D for CCALD ($207M; 75% chance of success) and LentiGlobin for β-thalassemia ($1.04B, 30% chance of success). The next key data catalysts will be interim data from one or both P1/2 LentiGlobin trials in late-2014.

- **Physicians are optimistic on Lenti-D, look for more data on LentiGlobin:** They expect similar results from the Lenti-D pivotal trial vs. P1/2 (~75% of patients will not demonstrate a major functional disability; minimal safety risk from leukemia) and widespread uptake on approval given no effective treatments. For LentiGlobin, they look for replication/improvement on the best results in a prior P1/2 trial (one of three patients achieved transfusion independence with ~3g/dL increase in Hb) in the current P1/2 trials, and are cautiously optimistic given improvements in vector design.
- **Platform is upside:** While we only model for Lenti-D in CCALD and LentiGlobin in β-thalassemia, the lentiviral-based gene therapy platform has potential in multiple indications. Notably, LentiGlobin in SCD represents a sizable opportunity, and bluebird/Celgene have a collaboration to target cancer based on genetically-modified chimeric antigen receptor T (CAR T) cells. bluebird also has a second vector platform, the adeno-associated virus (AAV), which has potential for *in vivo* approaches.

INVESTMENT THESIS

Gene therapy's curative ability per a single dose gives it the potential to be highly disruptive: Gene therapy uses DNA to treat disease – by turning a patient's own cells into therapeutic factories, it holds the promise to permanently cure disease with a single treatment. While the field is still developing, gene therapy has the potential to cure any disease caused by disruption of a single gene. In bluebird's system, a patient's own stem cells are removed, vectors (type of modified virus) add working copies of genes to these cells outside of the body (ex vivo), and the modified stem cells are reinfused back into the patient. We will be watching the 2013 launch of uniQure's Glybera for lipoprotein lipase deficiency (approved as the first gene therapy for an orphan disease in the E.U. in November 2012) for details on the economic model, response and uptake by the medical community and long-term safety from a gene therapy. We note that the FDA recently published a draft guidance on July 2 acknowledging "increasing interest and activity" in gene therapies, emphasizing the need for a risk/benefit analysis, noting that some toxicities "may be expected and acceptable," healthy volunteer trials are likely not acceptable, blinded early-stage trials may not be desirable and addressing patient-specific products (like bluebird's ex-vivo approach; mostly with respect to the time frame of product manufacturing) – a positive for gene therapies in general and bluebird in particular given the comments are in line with the company's approach. We see gene therapy as having the potential to upend current therapeutic paradigms, given the potential for a one-time curative treatment that can be applied to many diseases. Given bluebird's intellectual property and expertise in this field, the company is at the forefront of a potential revolution in disease treatment.

bluebird's lead program is Lenti-D for childhood cerebral adrenoleukodystrophy (CCALD): Lenti-D is a vector (modified virus) used to add working copies of the *ABCD1* gene to a patient's hematopoietic stem cells. It will enter a U.S./E.U. pivotal Phase 2/3 trial for CCALD (a severe, genetic orphan neurological disorder in young boys caused by mutations in *ABCD1* that typically leads to death) in late 2013. Given data from four CCALD patients in a Phase 1/2 trial treated with a previous version of Lenti-D that demonstrated long-term disease stabilization (in four patients) and no loss of cognitive ability (in three patients) without signs of clonal expansion (a precursor to leukemia, a key safety concern), the key question is whether the Phase 1/2 results can be replicated in the 12-15 patients in the Phase 2/3 trial – however with a ~3x more potent vector. Although we acknowledge the following concerns with Lenti-D – clinical (small number of patients treated to date; newer vector version being used; leukemia still a possibility), regulatory (the FDA has yet to approve a commercial gene therapy product) and commercial (Lenti-D would be bluebird's first product; finding patients will be difficult given the ultra-rare nature of CCALD) – we are optimistic on success on these fronts given the monogenic (one gene) nature of the disease, bluebird's expertise in gene therapy, the lack of good treatment options for CCALD patients (particularly those without a matched sibling stem cell donor) and recent FDA draft guidance. We expect 50-75% of patients in the Phase 2/3 trial (i.e. 6 to 9 of 12) will demonstrate disease stabilization with no major functional disabilities (MFDs) at 24 months after treatment. With ≥50% disease stabilization and a clean safety profile, we believe bluebird can achieve approval given an attractive risk/reward profile and comparison to a natural history trial (7.7 year median overall survival after symptom onset in untreated patients) and unmatched hematopoietic stem cell transplant (~55% overall

survival at five years). We note patients with a matched donor may not initially be candidates for Lenti-D, given 74% - 95% 10-year survival in this group (we do not model for this group).

Physicians are eager for a treatment and like Lenti-D's chances of success: They understand the mechanism of action behind Lenti-D and like the data from the four patients in the Phase 1/2 trial, noting that untreated CCALD does not spontaneously stabilize. They look to the upcoming Phase 2/3 trial to answer several key questions: 1) will the vector prove to be efficacious in a larger population?; 2) will a newer version of the Lenti-D vector prove to be more efficacious?; 3) will any pre-leukemic or other safety signal arise?; and 4) is bluebird's scoring scale (six major functional disabilities) a good measure of patient outcomes? They are eager for a therapy for CCALD patients, particularly those without a matched sibling donor (80% - 90% of CCALD patients) – but see potential expansion into patients with a matched donor (allogeneic stem cell transplant poses a risk in this population given ~35% will develop graft-versus-host disease, versus ~60% in unmatched transplants) or later-stage ALD to prevent neural degeneration. On approval, they expect to offer this therapy to all CCALD patients without a matched donor, and look to gradual rollout of newborn CCALD screening to identify more patients.

bluebird's second lead product - LentiGlobin for beta-thalassemia and sickle cell disease - is behind Lenti-D in the clinic but has much larger potential market: LentiGlobin is a lentiviral-based gene therapy system for treatment of beta-thalassemia and sickle cell disease (SCD), rare genetic blood disorders, – currently in one Phase 1/2 trial in France for both indications and to enter a second Phase 1/2 trial in the U.S. for beta-thalassemia only in mid-13 (SCD trial in the U.S. expected in 2014). While similar to Lenti-D, the drug contains a modified version of the beta-globin gene with anti-sickling properties (prevents the characteristic abnormal shape of the red blood cells in SCD). Although the LentiGlobin data to date is not as strong vs. Lenti-D (one of three treated beta-thalassemia patients achieved transfusion-independence, one achieved engraftment but did not achieve transfusion independence, and one failed to engraft), we look to the ongoing Phase 1/2 trials to see if improvements in the LentiGlobin vector will improve the success rate. Physicians like the idea of using gene therapy to treat these diseases, noting that current therapies have substantial drawbacks (stem cell transplant carries safety risks – particularly for patients with non-matched donors; the standard-of-care blood transfusions causes iron buildup that can be detrimental to health, even with chelation therapy). They also note that stem cell transplant for beta-thalassemia can make economic sense given the cost of lifetime transfusion – with the same logic possible for gene therapy. In the Phase 1/2 trials, physicians want to see an improvement on the 33% success rate from the previous trial, with an average hemoglobin increase of ≥2 g/dL, with levels >7 g/dL sufficient for transfusion independence in most patients. For SCD, they are less sure on the risk/benefit for LentiGlobin given the life expectancy (~50s for SCD vs. ~30s for beta-thalassemia) and the lack of data, but look to the ongoing clinical trials for color on the path forward in this indication. We model for peak revenue to bluebird from LentiGlobin for β-thalassemia of $1.04B in 2026 and 30% chance of success.

We model for peak revenue recognized by bluebird of $1.23B in 2026: In ALD, we estimate 59 boys progress to the severe CCALD form in the U.S. and 85 in the E.U. in 2018 (~35% of the 1/20K male births), ~80% of which will be eligible for treatment (no matched sibling donor for hematopoietic stem cell transplant). We assume Lenti-D launches for CCALD patients without a matched sibling donor in mid-2018 in the U.S. and early-2019 in the

E.U. Based on pricing of $1.75M (in-line with gene therapy Glybera's current expected pricing of ~$1.6M), assuming a 3% annual price increase in the U.S., payors reimbursing over the course of three years and peak penetration into the eligible population of 82% (U.S.) and 76% (E.U.), we arrive at peak worldwide sales of $212M – with $207M recognized by bluebird in 2028, and assign a 75% chance of success.

For beta-thalassemia, we estimate ~1K patients with beta-thalassemia major and ~100 births/year in the U.S. and ~16K and ~1.5K, respectively in the E.U. (larger population due to different genetic makeup), with 75% eligibility in newly-diagnosed patients (~25% have sibling match) and 25% eligibility in existing patients (we only assume penetration into patients older than 20 years of age who are not well-controlled with existing therapies). Given launches in mid-2020 (U.S.) and early-2021 (E.U.), $1.5M pricing (discount to Lenti-D due to larger patient population and less severe disease), peak penetrations into newly-diagnosed patients of 57% (U.S.) and 46% (E.U.) in 2028 and peak penetrations into existing patients of 9.1% (U.S.; 2022) and 7.2% (E.U.; 2023), we arrive at peak worldwide sales of $1.06B in 2024 and peak revenue recognized by bluebird of $1.04B in 2025 and assign a 30% chance of success.

Partnership with Celgene to address oncology: bluebird has an ongoing collaboration with Celgene to discover therapies for the treatment of cancer based on chimeric antigen receptor T (CAR T) cells – a type of white blood cell modified via gene therapy to target and destroy cancer. For this collaboration, bluebird received a $75M upfront payment and Celgene can license any product that arises from this venture post Phase 1 in return for milestones (up to $225M) and royalties (mid-single-digits to mid-teens) on net sales. Although we are intrigued by CAR T-based approaches for the treatment of cancer, we do not model for product sales given the early nature of this collaboration.

Other Lenti-D and -Globin indications, Celgene collaboration, ex-U.S./E.U. geographies and AAV platform represent upside: Lenti-D has potential in less severe forms of ALD: adult cerebral ALD (ACALD) and adrenomyeloneuropathy (AMN) – however, bluebird has not announced clinical plans in these indications. LentiGlobin also has the potential to treat SCD (a Phase 1/2 trial ongoing in France; U.S. trial to initiate in 2014), but given the LentiGlobin clinical data to date is in beta-thalassemia, we only model for penetration into this indication. In addition, we do not model for revenue from the Celgene oncology partnership other than recognition of the $75M upfront over three years given the pre-clinical nature of this research. Given the Lenti-D and LentiGlobin trials are being conducted in the U.S. and E.U., we do not model for sales outside these territories; however, we note that bluebird owns worldwide patents to its technology, and has cited Asian countries (e.g., Thailand) as a potentially large source of beta-thalassemia patients (>90% of worldwide beta-thalassemia patients are ex-U.S./E.U.). We also do not model for other applications of bluebird's gene therapy platform (e.g. lysosomal storage diseases; hemophilia; immunology) and look for clinical development in these indications for greater clarity on the path forward. We view sales in any of these indications or territories ex-U.S./E.U. as upside to our estimates. bluebird is also developing an adeno-associated virus (AAV)-based gene therapy system – although development is early, they intend to use this platform for *in vivo* applications.

bluebird's has ~$235M in cash following the IPO: At end-Q1, bluebird had $131.8M in cash and equivalents, not including net proceeds from the IPO of ~$103.5M (6.8M shares @ $17/share). We believe this position will be sufficient to fund operations into early 2017

and model for an equity offering of $200M in mid-2016, although we note the Celgene partnership has the potential to provide an infusion of cash (peak potential milestones of $225M).

VALUATION

We arrive at our 12-month price target of $45 via averaging two valuation methods: 1) a sum-of-the-parts discounted cash flow analysis equating to $46 a share which ascribes $15/share from Lenti-D, $24/share for LentiGlobin and $8/share in cash, with the following assumptions: we assign Lenti-D a 75% chance of success and LentiGlobin a 30% chance of success and we assign a WACC of 10% and a 1% terminal growth rate; and 2) a discounted EPS equating to $44/share, applying a 35x multiple to our FY22 fully diluted GAAP EPS estimate of $9.57, discounted back to mid-2014 at 27%.

INVESTMENT RISKS

The primary risks for bluebird include the following:

1. Lenti-D clinical development risk: efficacy - will the Phase 2/3 trial demonstrate efficacy that compares favorably against the natural history trial (we note that the primary endpoint of no major functional disabilities is stringent and the new vector used in this trial has not been evaluated in the clinic; and safety – will a safety signal emerge (particularly leukemia or pre-leukemic clonal expansion)?
2. LentiGlobin clinical development risk: efficacy – will the two Phase 1/2 trials demonstrate efficacy in beta-thalassemia patients (particularly sufficient hemoglobin for patients to become transfusion independent) and safety?
3. Commercial risk, including the possibility that Lenti-D and LentiGlobin do not achieve the peak commercial revenue estimates in our model (due to patient identification, market size, penetration rates, and/or pricing/reimbursement – particularly given the anticipated price of $1.5M+).
4. Regulatory risk: including failure to secure U.S. and E.U. approval for both Lenti-D and LentiGlobin.
5. Product competition, for Lenti-D, advances in hematopoietic stem cell transplant using non-related donors or other techniques to prevent demyelination or development of competing gene therapy techniques; for LentiGlobin, other gene therapy approaches or advances in the ability to upregulate the fetal gamma globin gene.
6. Financing risk – we model for one equity offering ($200M; 5M shares @ $40/share) in mid-2016.

PIPELINE SUMMARY

bluebird bio is a clinical-stage biotechnology company focused on using gene therapy to address severe and rare genetic diseases. Its lead product, Lenti-D, is slated to enter a pivotal Phase 2/3 trial for patients with childhood cerebral adrenoleukodystrophy (CCALD) in late 2013. The second product, LentiGlobin, is being evaluated in an ongoing Phase 1/2 trial for patients with β-thalassemia and sickle cell disease (SCD) in the E.U. and is to enter a Phase 1/2 trial in the U.S. for β-thalassemia in mid-2013. bluebird also has a partnership with Celgene to develop gene therapies using chimeric antigen receptor (CAR) T cells for the treatment of cancer.

Figure 1: bluebird pipeline

Product	Indication	Partner	Status
Lenti-D	Childhood cerebral adrenoleukodystrophy (CCALD)		Pivotal Phase 2/3 (initiating late-13)
LentiGlobin	ß-thalassemia; sickle cell disease (SCD)		Phase 1/2
CAR T Cells	Cancer	Celgene	Pre-clinical

Source: Company reports, Canaccord Genuity estimates

Figure 2: Upcoming milestones expected

Product	Indication	Timing	Milestone
LentiGlobin	β-thalassemia	mid-13	Phase 1/2 U.S. trial (HGB-204) initation
Lenti-D	CCALD	4Q13	Pivotal Phase 2/3 U.S./E.U. pivotal trial (ALD-102) initation
LentiGlobin	SCD	2014	IND submission; U.S. Phase 1/2 trial initation
LentiGlobin	β-thalassemia / SCD	4Q14	Interim Phase 1/2 data
Lenti-D	CCALD	2H15	Interim Phase 2/3 data

Source: Company reports, Canaccord Genuity estimates

BLUEBIRD'S GENE THERAPY PLATFORM HAS A CLEAR CLINICAL PATH FORWARD IN TWO+ INDICATIONS

bluebird is defined by its gene therapy platform – a revolutionary, disruptive approach – with the ability to cure disease with a single dose. In bluebird's system, a patient's own stem cells are removed, vectors (type of modified virus; see page 27) add working copies of genes to these cells outside of the body (*ex vivo)*, and the modified stem cells are reinfused back into the patient. In trials that are ongoing or are to initiate shortly, bluebird will be using improved versions of prior vectors with ~3x greater potency (ability to add new copies of the working genes). Due to the random insertion into the genome, there is a risk of activating an oncogene (may lead to leukemia) – however, bluebird's vectors have been designed to prevent this kind of activation, and the increased potency is still likely below the threshold where leukemia is a concern.

The lead product is Lenti-D, which is slated to enter a pivotal Phase 2/3 trial (U.S./E.U.) in late 2013 for childhood cerebral adrenoleukodystrophy (CCALD; the most severe form of adrenoleukodystrophy), a rare and serious disease that can cause death in young boys. bluebird's treatment of CCALD involves removing a patient's own hematopoietic stem cells (HSCs; can grow into any blood cell type), using Lenti-D to add working copies of the *ABCD1* gene (encodes a protein that transports molecules across membranes), performing myeloablation (destroying endogenous bone marrow with radiation and/or chemotherapy) and infusing the modified HSCs back into the patient where they can engraft (repopulate the bone marrow and grow). Our physician feedback is positive on Lenti-D, citing preliminary data from patients treated with earlier versions of the Lenti-D vector – particularly four patients with CCALD who demonstrated disease stabilization following treatment. They expect success in the Phase 2/3 CCALD trial, with ~3/4 of treated patients demonstrating no major functional disabilities (in line with Phase 1/2 data and given window for disease progression) and widespread uptake in CCALD patients without a matched sibling donor (untreated, these patients have median survival of 7.7 to 8.6 years) following approval. Although they note safety concerns with any gene therapy treatment, they see the headline risk of leukemia as very minimal and view the risk/reward profile as attractive. They see the greatest risk to clinical success as an inability of the transformed hematopoietic stem cells to engraft. Engraftment ability of these cells has been increased from improvements across multiple stages in the Lenti-D production process (e.g., stimulation, transduction, harvesting), that has increased the average number of integrations per cell from ~0.6 in the Phase 1/2 trial to ~1.7 now.

The second lead product is LentiGlobin, a similar gene therapy treatment for ß-thalassemia and sickle cell disease (SCD). ß-thalassemia and SCD are caused by mutations in the hemoglobin gene, which prevents red blood cells (RBCs) from carrying oxygen and leads to their destruction. Patients with these diseases require blood transfusions to replace RBCs and have shortened life-spans (30s to 50s, depending on the disease and severity). Although LentiGlobin represents a larger opportunity given greater population sizes, it is further behind in the clinic, with one Phase 1/2 trial (E.U.) ongoing and another Phase 1/2 trial (U.S.) to initiate in mid-2013. Physicians are also optimistic for LentiGlobin, although they note the data is less mature than Lenti-D. They see the one patient (of three) who achieved independence from transfusion as indicative that LentiGlobin is successfully treating the root cause of the disease, and expect a greater success rate with higher levels of hemoglobin produced with newer versions of

the vector. They expect 2-3 g/dL hemoglobin improvement in most patients in the Phase 1/2 trials (in line with best success rate of patients in the Phase 1/2 trial), which should be sufficient for transfusion independence for patients with baseline Hb levels of 4-5 g/dL. (levels above ~7 g/dL are generally required for transfusion independence).

bluebird also has a partnership with Celgene to discover cancer therapeutics, based on gene therapy-based modification of chimeric antigen receptor (CAR) T cells. A CAR T cell is a type of patient-specific white blood cell that has been modified to express a protein to identify and destroy cancer cells. Celgene paid bluebird $75M upfront and has the right to license any product after Phase 1 in return for royalties on net sales and development and regulatory milestones.

bluebird also sees potential for use of its platform in the treatment of other diseases, such as lysosomal storage disorders (currently addressed by enzyme replacement therapies) or other central nervous system or hematologic diseases.

We expect full data from the Phase 2/3 CCALD trial in mid-2017, with Lenti-D regulatory filings at YE17 and launches in mid-2018 (U.S.) and early 2019 (E.U.). For LentiGlobin for ß-thalassemia, we expect preliminary Phase 1/2 data in H2/14, pivotal trial initiation in early 2016, data in mid-2019, filings in YE19 and launches in mid-2020 (U.S.) and early 2021 (E.U.). We view other pipeline indications (e.g. Lenti-D in adult ALD; LentiGlobin in SCD; CAR T cancer products from the Celgene partnership) as potential upside to our estimates and model for peak revenue to bluebird of $1.23B in 2026 with a 75% chance of success for Lenti-D in CCALD (peak revenue to bluebird of $207M in 2028) and 30% chance of success for LentiGlobin in ß-thalassemia (peak revenue of $1.04B in 2026).

Lenti-D will enter a pivotal trial based on strong preliminary data

bluebird's lead product Lenti-D is a modified virus that carries the *ABCD1* gene. The strongest proof-of-concept data for Lenti-D comes from a Phase 1/2 trial (TG04.06.01) that used an earlier (less potent) version of Lenti-D to treat four boys with CCALD (data from two of these patients was reported in *Science* in 2009). Specifically, all four patients demonstrated initial disease stabilization via MRI scores (at months 16, 30, 30 and 33 post-treatment) and remained stable as of months 24, 64, 75 and 54, respectively – although these patients continue to be followed. While gadolinium enhancement (measure of lesions in the blood-brain barrier) resolved in three patients, one did not and demonstrated cognitive defects, though he remains stable since. None of the patients developed gene therapy-related safety concerns.

bluebird plans to initiate a pivotal Phase 2/3 trial (ALD-102) in 12-15 patients in late 2013 – boys with an *ABCD1* mutation and without a matched sibling donor will be monitored until evidence of disease progression, at which point they will be treated with Lenti-D. The trial will be single-arm, with the primary endpoint of the number of patients with no major functional disabilities (see page 14) at 24 months following treatment.

Physicians we spoke to were very bullish on Lenti-D, particularly the risk/reward profile given the severe nature of the disease (median 7.7-8.6 years from symptom onset to death if untreated) and the risks associated with the standard of care – hematopoietic stem cell transplant requires destroying a patient's bone marrow, which greatly increases the risk of infection; unmatched transplants also carry the risk of graft-versus-host disease (a patient's immune system mounts a response against the transplanted

stem cells). Although they note a risk from leukemia, they see this risk as minimal given modifications to bluebird's vectors (specifically, the vectors cannot activate nearby genes when they insert into the genome) and the risk/reward profile favors the latter given the disease severity. They expect success in the upcoming Phase 2/3 pivotal Lenti-D trial, and on approval would offer Lenti-D to all their patients without a matched sibling donor. They expect quick and deep uptake given severe need for therapy and concentrated patients in a few centers (particularly University of Minnesota and Duke). On the competitive front, apart from hematopoietic stem cells transplant, other therapies (e.g., Lorenzo's Oil; antioxidants) have not demonstrated clinical benefit.

Given the preliminary data and physician feedback, we anticipate ≥50% of the patients in the Phase 2/3 CCALD trial will demonstrate disease stabilization with no major functional disabilities (MFDs), which should be sufficient for approval given comparison to bluebird's natural history trial and published data indicating median overall survival of 7.7 years and 8.6 years, respectively, in untreated patients. We note that patients with early-stage disease (neurological deficit score of 0 or 1; MRI severity score < 9) who have been transplanted from a matched donor demonstrate 95% survival at 10 years (though we note only 10-20% of patients have a matched donor).

We model for full Phase 2/3 Lenti-D data in mid-2017, regulatory filings by YE17 and approval/launch in mid-2018 (U.S.) and early 2019 (E.U.). From pricing at launch of $1.75M (premium to the gene therapy Glybera – approved in the E.U. for lipoprotein lipase deficiency, or LPLD, with expected pricing of ~£1M, or ~$1.6M), peak penetration into new CCALD cases of 82% in the U.S. and 76% in the E.U. in 2028 and revenue recognized over a three-year period, we arrive at peak revenue from Lenti-D recognized by bluebird of $212M in 2028, and assign a 75% chance of success.

LentiGlobin lags Lenti-D in development but represents a larger opportunity

The second lead product, LentiGlobin for ß-thalassemia and sickle cell disease (SCD), is similar to Lenti-D, but it contains a modified version of the ß-globin gene with anti-sickling properties (prevents the characteristic abnormal shape of the red blood cells in SCD). Three ß-thalassemia patients were treated in a Phase 1/2 trial in France (LG001) that utilized an earlier form of the LentiGlobin vector. Of the three patients, one was treated with low concentrations of vector and did not express the modified gene, one had a successful engraftment but still requires transfusions, and the last achieved transfusion independence starting at one year post-treatment.

bluebird is evaluating a newer version of the LentiGlobin vectors in two Phase 1/2 trials: a French Phase 1/2 trial (HGB-205) initiated in Q2 for patients with ß-thalassemia or SCD, and a Phase 1/2 trial in the U.S. (HGB-204) to start in mid-2013 for patients with ß-thalassemia (IND submission for a U.S. trial of patients with SCD is expected in 2014).

In our diligence, physicians like LentiGlobin for ß-thalassemia and SCD, although they note the data is less robust (particularly that only one of three treated patients achieved transfusion independence) and the risk/reward is less obvious in this disease (ß-thalassemia patients treated with transfusions and iron chelation can live into their 30s; SCD patients can live into their 50s). They see the key question in these trials as the amount of increased hemoglobin that treated patients will produce, with increases to levels above ~7 g/dL required for a clinically meaningful difference (i.e., transfusion independence) in most patients. They also want to see more patients demonstrate

successful engraftment (two of three patients engrafted in the previous trial), and look to the two Phase 1/2 trials for clarity on how well the newer version of the LentiGlobin vector will perform. Beyond blood transfusions, stem cell transplant can be curative: reported event-free survival and overall survival rates reach a plateau one year after matched transplant at 82% and 75%, respectively. We note that transfusions are standard of care – of ~16K ß-thalassemia patients in the E.U., only ~130-200 undergo stem cell transplant annually.

For ß-thalassemia, we expect patients in the Phase 1/2 trials will demonstrate average hemoglobin increases of 2-3 g/dL, which should be sufficient for transfusion reduction or independence in most patients.

We expect preliminary data (engraftment levels) from one or both of these trials by YE14, pivotal trial initiation for β-thalassemia patients in early 2016, full data in mid-2019, regulatory filings in YE19, and approval/launch in mid-2020 (U.S.) and early 2021 (E.U.). From pricing at launch of $1.5M (discount to Lenti-D given larger population sizes) and 3% annual price increases in the U.S., peak penetration into new β-thalassemia cases of 57% (U.S.) and 46% (E.U.) in 2028, peak penetration into the bolus of existing β-thalassemia patients of 9% (U.S.; 2021) and 7% (E.U.; 2023) and revenue recognized over a 3-year period, we arrive at peak revenue from LentiGlobin recognized by bluebird of $1.04B in 2026, and assign a 30% chance of success. We do not model into sickle cell disease given the lack of clinical data and view this indication as upside.

PHYSICIANS LIKE THE MECHANISM AND RISK/REWARD OF BLUEBIRD'S GENE THERAPY – PARTICULARLY FOR CCALD

Physicians like the odds of Lenti-D Phase 2/3 success…

Physicians we spoke to are optimistic on clinical and regulatory success for Lenti-D – citing the four-patient French trial as having very strong data (particularly observing disease stabilization in gadolinium-enhanced patients) and expect that these results "are clearly going to be replicated" in the Phase 2/3 trial – with ~75% achieving the primary endpoint of no MFDs as measured via a neurological function score. They see the primary risk in this trial as emergence of leukemia and bluebird's ability to produce enough cells with sufficient *ABCD1* expression levels. On approval, physicians expect to offer the treatment to all CCALD patients without a matched sibling donor, with the patient pool potentially expanding to patients with a sibling donor and later-onset patients (~2/3 of ALD). They expect newborn screening for ALD to be adopted state-by-state in the U.S. in the next few years (accelerated process once a therapeutic is available), which should increase the known population size. They also see no other therapeutic option other than stem cell transplant on the horizon.

…but want to see more data for LentiGlobin

On LentiGlobin, they like the best efficacy results in the Phase 1/2 trial (~3 g/dL improvement in hemoglobin [Hb] in one of three treated patients), but note only one of three treated patients achieved this result, and look to the next-generation vector for improvement. They see a key risk to success as the required expression levels (RBC cells need to produce large amounts of ß-globin to have a clinically meaningful difference). As a result, they believe patients with a higher baseline Hb level would likely be better candidates for LentiGlobin therapy (i.e., 3 g/dL improvement would be clinically

meaningful for a patient with a baseline level of 5 g/dL, but not for a patient at 2 g/dL) – although patients with similar Hb levels can have different clinical outcomes. They are looking for ≥2 g/dL average increase in Hb in the Phase 1/2 trials to move to a pivotal trial, with a 3-4 g/dL increase in a pivotal trial (sufficient to eliminate transfusions for ~50% of ß-thalassemia patients) and a clean safety profile required for widespread uptake. However, even if transfusions cannot be eliminated, reducing their frequency by ≥50% would be clinically meaningful and allow for successful chelation (removing excess iron from patients' blood) of virtually all patients. Although better chelators are on the horizon, they do not see them as game-changers, and note that no other ß-thalassemia gene therapy treatments are ready for clinical use. Physicians see potential for LentiGlobin in sickle cell disease, but do not have conviction on the success in this disease given the absence of clinical data. For SCD patients in the Phase 1/2 trial, they will look to the balance of normal:mutated Hb as a measure of success (≥40% normal Hb required to prevent disease-related complications). They see the initial target population for LentiGlobin as older ß-thalassemia patients (more likely to have issues with iron chelation), those without a sibling match, or those unable to control their disease with transfusions and chelation.

Safety is not a key concern, especially for CCALD

On safety, physicians see the key risks for both Lenti-D and LentiGlobin as leukemia caused by genomic integration and note that prior cases of leukemia were a result of earlier vector design. Although they note the risk of cancer cannot be eliminated, they are confident that no signal will be observed in the Phase 2/3 CCALD trial (one sees the risk as "nearly zero" given the new vector design), but would want to have the minor risk on safety balanced by high levels of certainty on efficacy. Although they see a trade-off between vector efficiency and safety (more integration into the genome means more risk of leukemia), efficiency rates would have to be >10x higher than they are at present to present a significant concern. They also note that a risk of leukemia has to be weighed against CCALD/ß-thalassemia and graft-versus-host disease from HSCT. Other risks cited include immune system attacking the novel proteins on the vector, although "rebooting" the immune system on reinfusion would be expected to ameliorate this issue; and high-dose chemotherapy/radiation to destroy the bone marrow (~5% mortality rate at one year). They would be comfortable with the overall risk profile with 2-5 years of follow-up. They also like the bluebird vector, with one physician noting that the company has the best technology in the gene therapy field. Although there was some interest in site-specific genomic editing (e.g. zinc-finger nucleases), some see these techniques as much further from the market (several years from clinic), while other questioned whether sufficient efficacy can be achieved for this to be a viable technique given the difficulty in targeting the proper genetic sequence. They see the main competitor to bluebird in CCALD as hematopoietic stem cell transplants, noting that transplant techniques are improving.

Physicians see high levels of usage on approval

On Lenti-D approval, physicians anticipate widespread uptake in patients with demonstrated disease progression without a matched sibling donor. Although they acknowledge finding patients may be challenging given the ultra-low incidence rate, they look to newborn screening programs (via genotyping; to start in New York in 2014; bills pending in the New Jersey and Connecticut legislatures). They anticipate expansion to

later-onset ALD patients, or CCALD patients with matched donors, given greater physician experience. For LentiGlobin, they look to clinical data to make the determination on which patients would receive the therapy. They anticipate that they would offer LentiGlobin initially to patients who cannot control their disease with transfusions and chelation alone, without a matched sibling donor (~50% of patients >20 years old). Although treatments exist for ß-thalassemia and SCD, physicians are not satisfied with existing options, given issues with compliance, lifetime costs and efficacy.

WHAT ARE THE KEY RISKS FOR BLUEBIRD?

- **Emergence of a safety signal:** The key safety risk in the ongoing trials is the emergence of leukemia as a result of a genomic insertion that activates an oncogene. We see this risk as minimal, given: 1) bluebird has designed the vector to self-inactivate when it inserts into the genome; 2) no clonal expansion (precursor to leukemia) was observed in the CCALD trials, and a potential clonal expansion in the ß-thalassemia trial resolved; and 3) compared to CCALD or ß-thalassemia, leukemia is manageable. However, we expect that >1 case of clonal expansion (with WBC count abnormalities) or leukemia in a patient enrolled in the clinical trials may be sufficient to halt development of the vector (though we note risk/reward favors reward in light of severity of disease).
- **Questions on efficacy:** Based on Phase 1/2 data and physician feedback, we have a high level of confidence in the ability of Lenti-D to prevent CCALD disease progression, and look to Phase 1/2 data for confidence on LentiGlobin. However, we note only five patients have been successfully treated with either vector, and we look to the ongoing trials to reproduce these results. Additionally, there is a window between disease diagnosis and the treatment becoming efficacious (stem cells removed and transfected; patient myeloablated; stem cells have to engraft) in which either disease (particularly CCALD) could progress. Given the relatively high bar in the Phase 2/3 CCALD trial (development of no MFDs), some patients may miss the primary endpoint (particularly those with more severe disease). Lastly, although the vectors being used in the new trials have demonstrated increased (~3x) transfection ability in cell lines and patient cells, we look to see this data and look to see if improved transfection can be sustained and if this will translate into clinically meaningful outcomes.
- **Are the patients out there, and can they be found?** CCALD in particular is an ultra-rare disease, and finding patients may be difficult. Newborn screening programs have not been implemented across the entire U.S., and although efforts are underway to implement them, this process is often choppy (state-by-state). We would expect that presence of a therapeutic option (particularly a high-profile option such as a gene therapy) would drive awareness of the disease and make patients easier to find.
- **How will payors react?:** We have yet to see how payors will react to an anticipated seven-figure price tag, and we look to Glybera's expected E.U. launch in 2013 for color. However, we expect payors will reimburse at these levels, given: 1) it is a one-time charge given the curative nature of gene therapy; 2) it may be spread out over several years (we assume three) or paid on achievement of specific therapeutic milestones; 3) payors have some comfort with high-priced therapies for ultra-orphan disorders (particularly Alexion's Soliris at ~$440K/year or weight-based ERTs that

can cost >$500K annually); and 4) bluebird is laying the groundwork via ongoing conversations with payors.

- **Regulatory risk:** The requirements to achieve approval for a gene therapy product in the U.S. are unknown. Additionally, the FDA has questions on the robustness of the CCALD natural history trial, and may not accept it as a comparison against the Lenti-D-treated population. Given the severity of the diseases and preliminary guidance from the FDA that notes that healthy volunteer gene therapy trials may not be necessary, we expect that results for either Lenti-D or LentiGlobin that compare favorably to a natural history trial over 24 months would be sufficient for approval. However, we look to evolution of the field for guidance.
- **Competitive threats from other gene therapies…:** Several other gene therapy platforms are under development. Notably, Sangamo is developing a gene therapy system to treat β-thalassemia and sickle cell via activation of the fetal-globin gene (INDs expected in 2014; see page 22). Given the single-gene nature of these diseases and the potential to be treated with *ex-vivo* approaches, we expect more competitors to emerge, particularly for β-thalassemia and SCD (large market opportunities). Academic centers have been working on transcription activator-like effector nucleases (TALENs), a similar technique to target specific genetic sequences – however, we are not aware of use of any TALENs outside academic settings.
- **…or improvements on existing therapies:** Although our physician feedback indicates that they would offer Lenti-D to all their patients with CCALD (without a matched donor) and LentiGlobin to more severe ß-thalassemia patients, other therapies could emerge that alter this dynamic. Specifically, improvements in HSCT (particularly for patients without sibling matched donors) would represent a competitive threat to both Lenti-D and LentiGlobin. For ß-thalassemia, advances in oral chelation or other therapies (e.g., Acceleron's TGF-ß ligand trap in Phase 2) that increase the number of treatment options could negatively impact uptake of LentiGlobin.

WE ESTIMATE PEAK WW REVENUE TO BLUEBIRD OF $1.2B IN 2026

We assume the Phase 2/3 Lenti-D trial in CCALD will demonstrate safety and efficacy that compares favorably to the natural history trial. From ~18 months to enroll the trial post-initiation in late 2013 and 24 months of follow-up, we assume full data in mid-2017, regulatory filings in YE17 and launches in mid-2018 (U.S.) and early 2019 (E.U.). Per conversations with management and given the ~$1.6M (£1M) expected pricing of Glybera for the less-severe disease lipoprotein lipase deficiency (LPLD), we assume launch pricing of $1.75M in the U.S. and E.U. ($1.5M in 2013 with 3% annual increases is $1.74M at launch in 2018), with 3% annual price increases in the U.S. We note that LPLD has a prevalence of ~1/1M, but patients can live into adulthood.

We assume bluebird will commercialize Lenti-D alone in the U.S. and E.U. and model for peak penetration of 82% (U.S.) and 76% (E.U.) into the eligible population (newly-progressing CCALD patients without a matched sibling donor) of ~60 boys/year (U.S.) and ~80/year in the E.U., for peak sales of $212M in 2028. Given the high cost of each individual therapy and conversations with management, we assume payors will pay over the course of three years, for peak revenue recognized by bluebird of $207M in 2028.

For LentiGlobin in ß-thalassemia, we expect preliminary interim data from one or both Phase 1/2 trials in late 2014, pivotal trial initiation in early 2016, data in mid-2019, regulatory filings by YE19 and launches in mid-2020 (U.S.) and early 2021 (E.U.). We have greater confidence in ß-thalassemia (vs. SCD) given the proof of concept data, and we only model into ß-thalassemia.

We model into ~100 and ~1.5K births/year in the U.S. and E.U., respectively, and ~1K and ~16K patient populations (greater in the E.U. due to genetic makeup). We assume penetration into the bolus of affected patients, with steady-state penetration into newly-affected patients, with peak penetration into patients with newly-diagnosed ß-thalassemia of 57% (U.S.) and 46% (E.U.) in 2028, and peak penetration into existing cases of 9.1% (U.S.) and 7.2% (E.U.) in 2022 and 2023, respectively. From launch pricing of $1.5M (lower than Lenti-D due to the larger patient population and less severe nature of the disease) and revenue paid to bluebird over three years, we arrive at peak LentiGlobin sales of $1.06B in 2025 and peak revenue to bluebird of $1.04B in 2026.

Although vector manufacturing cost is expected to decrease to < $10K, this should be a minimal portion of COGS vs. costs associated with transduction and testing, and model for COGS at launch of 25% of net sales with gradual decreases to 18% at steady-state. We model for 10 sales reps / 2 commercial leaders each in the U.S. and E.U. for Lenti-D and 10 sales reps / 2 commercial leaders (U.S.) and 20 sales reps / 4 commercial leaders (E.U.) for LentiGlobin.

For both Lenti-D and LentiGlobin, a quicker path to registration, higher pricing, deeper penetration, larger eligible patient population, lower COGS, or geographic expansion represent potential upside to our numbers.

CLINICAL DEVELOPMENT PATH FOR THE TWO LEAD PRODUCTS

Pivotal Phase 2/3 trial of Lenti-D in CCALD to kick off in late 2013

bluebird plans on initiating ALD-102, a pivotal Phase 2/3 trial of Lenti-D in CCALD in late 2013 following IND activation in April 2013. This uncontrolled trial will be run in the U.S., U.K. and France and aims to enroll 15 patients to obtain data from at least 12. Patients with a mutant copy of the *ABCD1* gene who do not have a matched sibling donor will be followed until they demonstrate disease progression (MRI or gadolinium enhancement). The primary endpoint will be the number of patients with no major functional disabilities (MFD) at 24 months – as measured by a neurologic function score (NFS). Specifically, bluebird identified six MFDs that measure profound neurological defects: 1) loss of communication; 2) cortical blindness; 3) tube feeding; 4) total incontinence; 5) wheelchair dependence; and 6) complete loss of voluntary movement. While 25% (1 of 4) CCALD patients previously treated with Lenti-D would have developed a MFD, bluebird expects that they will demonstrate better results (i.e., fewer than 25% of patients developing a MFD), given improvements in vector transfection ability. Secondary endpoints include overall survival, MFD-free survival, individual NFS components, Loes score and gadolinium-enhancement resolution (all at 24 months). On the safety side, the trial will monitor the success and kinetics of HSCT engraftment, autologous transplant mortality (at 100 and 180 days post-transplant) and measures of insertional mutagenesis (e.g., clonal dominance; must be tied to elevated WBC counts to stop trial). Inclusion

criteria will be CCALD-diagnosed patients without a matched donor who are 15 years old or younger with NFS <1, Loes score between 0.5-9 and evidence of gadolinium enhancement.

Given the absence of a control arm in the Phase 2/3 trial, bluebird conducted a natural history trial (ALD-101) that surveyed 137 CCALD patients (72 untreated, 65 treated with allogeneic HSCT). The key takeaway from the ALD-101 study is that three measurements are used most frequently to measure CCALD progression: 1) neurological functional score (NFS), which includes the six MFDs used in the primary endpoint of the Phase 2/3 trial as well as nine other measurements in a 25-point score; 2) Leos score, which measures the degree of brain abnormalities in a 34-point score; and 3) gadolinium (Gd) enhancement, which measures degradation of the blood-brain barrier. Other key findings of the ALD-101 trial are: 1) untreated CCALD patients have median overall survival of 7.7 years (in line with published literature); 2) baseline disease severity predicts survival; 3) MFDs are correlated to Gd enhancement; 4) Gd enhancement is a predictor of neurologic progression; 5) HSCT can stabilize disease progression; and 6) HSCT is accompanied by morbidity and mortality. We note that the FDA does not see ALD-101 as being "sufficiently robust to serve as a conventional historical control group and as a basis of comparison against the results of the ALD-102 Study" – management has noted that ALD-101 was designed with input from the FDA and EMA, and was intended to guide endpoints chosen for the pivotal trial (not as a matched-case).

There are two less severe forms of ALD: adult cerebral ALD (ACALD) and adrenomyeloneuropathy (AMN). Given that ACALD and AMN are caused by mutations in *ABCD1* – the same gene that causes CCALD – Lenti-D treatment has the potential to cure these diseases as well. ACALD has disease progression on par with CCALD but develops later (~15 years of age) with an incidence rate ~15% of CCALD, and AMN is less severe (~40% develop serious cerebral disease; average age of onset is 28) but with an incidence rate 100-150% that of CCALD. While bluebird is examining ACALD in pre-clinical trials, the path to registration is not clear and we do not include either ACALD or AMN in our models.

Two Phase 1/2 LentiGlobin trials are on tap

bluebird has started one Phase 1/2 trial in France (HGB-205) using LentiGlobin, and will initiate another Phase 1/2 trial (HGB-204) in the U.S. in mid-2013. The French trial is a continuation study to the LG001 trial that demonstrated early efficacy in two ß-thalassemia patients, but uses a newer version of the LentiGlobin vector. It aims to enroll 7 patients with ß-thalassemia and SCD between the ages of 5-35 who are eligible for HSCT but do not have a matched donor. ß-thalassemia patients in this trial must have been transfused over the last two years, and SCD patients must not have response to hydroxyurea, with one additional risk factor (e.g., recurrent veno-occlusive crises or acute chest syndromes). Efficacy endpoints include transfusion requirements (per month and per year) and number of in-patient hospitalization days at 6, 12 and 24 months post-treatment. Safety endpoints include measurements of engraftment, transplant-related mortality, presence of vector that is able to replicate, detection of insertional mutagenesis site and overall survival. The U.S. trial will initiate in mid-2013 and is for patients with ß-thalassemia only (bluebird will file an NDA for patients with SCD in 2014). This trial will be open to adult patients (18-35 year old) with otherwise similar entry requirements to the ß-thalassemia patients in the French trial, and efficacy measured via production of

≥2 g/dL transgenic ß-globin from 18-24 months post-treatment. Exploratory efficacy endpoints will include transfusion requirements, and safety endpoints similar to that in the French trial. bluebird expects to use data from one or both of these trials in late 2014/early 2015 to make a decision on a pivotal trial (potentially only data from levels of engraftment; transfusion data may not be mature).

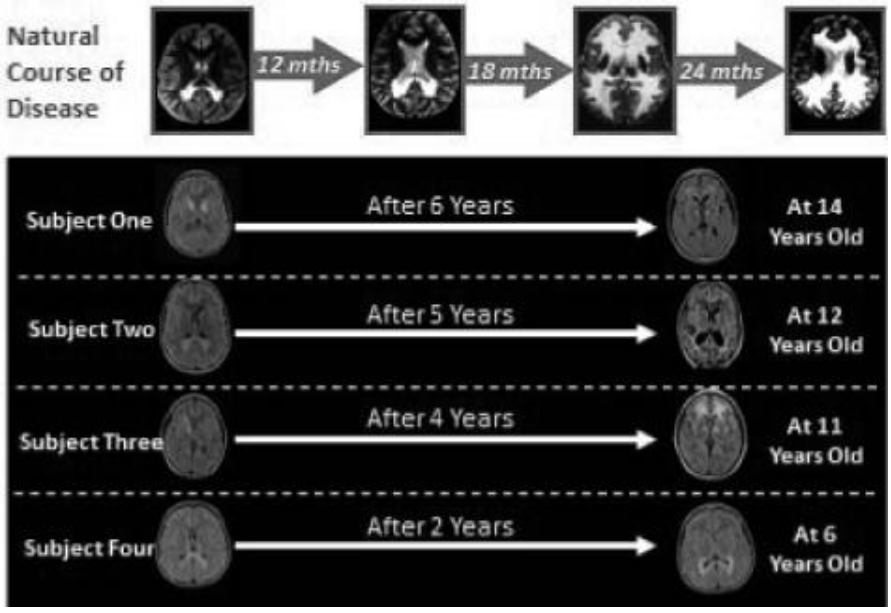
CLINICAL EXPERIENCE WITH LENTI-D AND LENTIGLOBIN IS LIMITED BUT STRIKING

To date, four patients have been treated with an earlier version of Lenti-D and three with a version of LentiGlobin. Particularly in CCALD, the ability of therapy to halt progression of a disease with few good treatment options is quite striking. Specifically, three patients demonstrated initial disease stabilization, with all four achieving long-term stabilization. None of the patients developed permanent clonal dominance (precursor to the primary safety concern of leukemia). Although we note the data in ß-thalassemia is not as strong (one of three patients failed to engraft; only one of the two remaining patients achieved transfusion independence), the shortcomings may be due to a previous form of the vector with less-effective transfection – and we expect clarity on this issue in the two Phase 1/2 trials.

Lenti-D halted CCALD progression in four patients in a Phase 1/2 trial

In the Phase 1/2 Lenti-D trial, three of four patients had Loes score (CNS disease measurement) stabilization (at months 16, 30 and 30 post-treatment). The fourth patient had persistent gadolinium enhancement and lost some cognitive ability (reasons are unknown; his disease may have been too advanced), but did demonstrate disease stabilization by month 33. All four patients had stable disease at the last time points (months 24, 64, 75 and 54, respectively). *See Figure 3.*

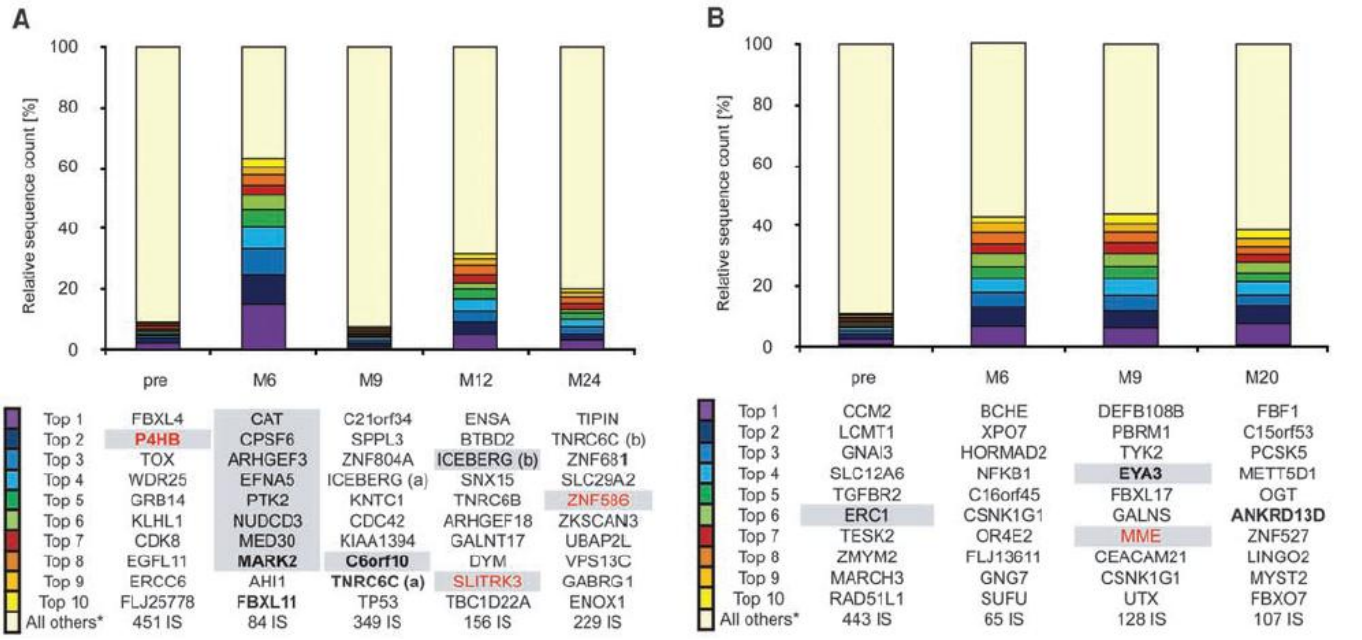
Figure 3: Four patients demonstrated disease stabilization following lentiviral treatment



Source: Company report

On the key safety concern of leukemia, no evidence of clonal dominance was observed in any of the four patients (*See Figure 4*). No other gene therapy-related safety signal was noted, and no graft-versus-host disease was seen following treatment.

Figure 4: Lenti-D treatment has not been shown to cause clonal dominance

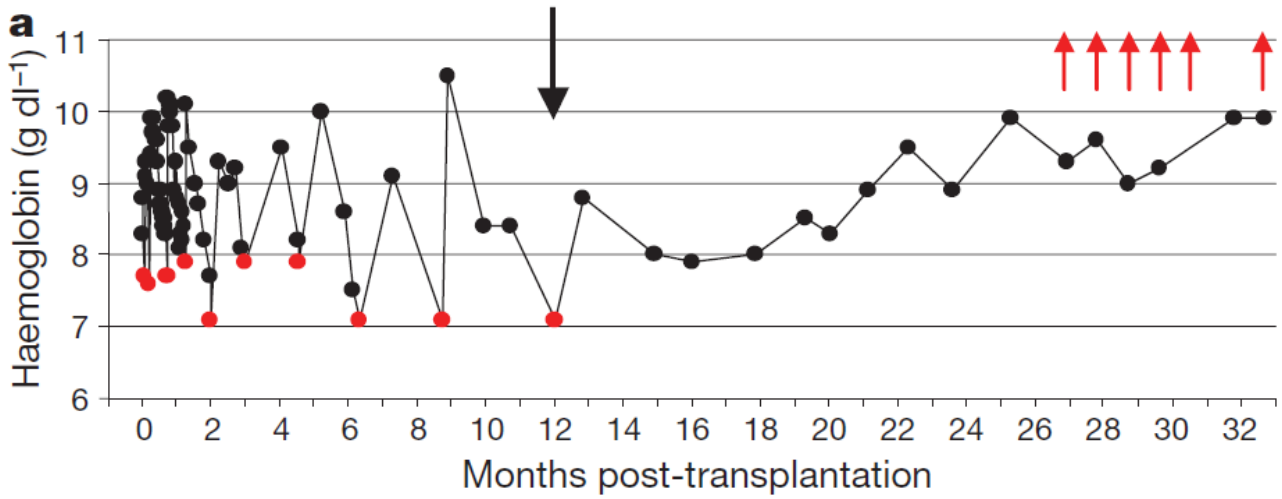


Source: *Science,* 2009

LentiGlobin Phase 1/2

Three patients with ß-thalassemia have been treated with a previous version of the LentiGlobin vector in a Phase 1/2 trial (one other patient, Subject One, was enrolled but not treated due to complications that affected eligibility). Of the three treated patients, Subject Two was treated with 0.93M cells/kg (below protocol requirement of 3M cells/kg and below current standards) and failed to engraft. Subject Three received a dose of 3.9M cells/kg, demonstrated engraftment at day 29 post-treatment and achieved transfusion independence at one year. *See Figure 5* – red dots indicate regular transfusions; black arrow indicates final transfusion; red arrows indicate phlebotomies). This patient has maintained transfusion independence for six years.

Figure 5: LentiGlobin treatment eliminated the need for transfusions in Subject Three

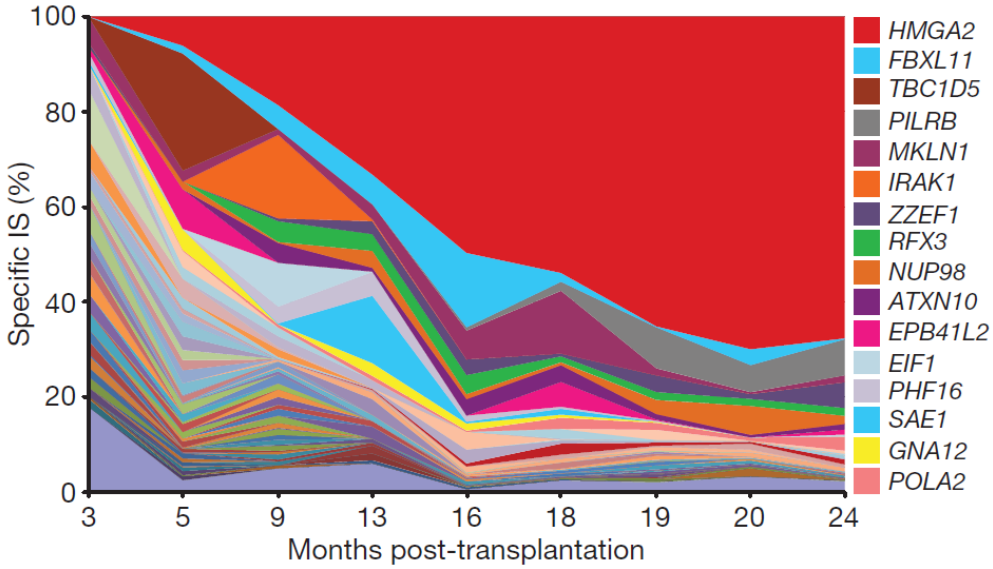


Source: *Nature,* 2010

Subject Four was treated with 4.3M cells/kg, engrafted and expressed the transformed ß-globin. However, this patient continues to require regular transfusions, likely due to lower-than-expected levels of ß-globin expression. bluebird attributes this to the patient's age (Subject Four was 23 years old when treated, vs. Subject Three at 18 years old) and the prior version of the vector (transduction with the newer version demonstrated 3x higher levels of expression in stored cells).

In contrast with Lenti-D, clonal dominance was observed in one ß-thalassemia patient (Subject Three) treated with LentiGlobin – specifically, cells with an integration in the *HMGA2* gene demonstrated increasing prevalence over the first 24 months post-treatment (*see Figure 6*). However, this was not determined to be a pre-leukemic event given that relative expression of the clone plateaued after ~20 months and expression was only in the red blood cell lineage (not found in white blood cell progenitors). More importantly, prevalence of clones with this integration has decreased over time and is no longer the more prevalent clone. Although we cannot exclude the possibility of a leukemic event as a result of LentiGlobin treatment, we see the risk as minimal and within the context of a favorable risk:benefit profile.

Figure 6: Subject 3 developed signs of clonal dominance following LentiGlobin treatment



Source: *Nature*, 2010

CELGENE PARTNERSHIP ON CAR T CELLS PROVIDES A PATH FORWARD FOR CANCER TREATMENT

In March 2013, bluebird announced a partnership with Celgene to develop a gene therapy approach to construct chimeric antigen receptor (CAR) T cells to target cancer. CAR T are patient-specific T cells (a type of white blood cell) that have been modified via gene therapy to express a protein that will recognize a wide variety of cancers – newer generation engineered CAR T cells also contain a domain to activate and sustain themselves in vivo. Clinical trials of CAR T cells have been conducted in various cancers, including ovarian cancer, renal cancer, lymphomas, leukemias and neuroblastoma – Novartis announced a partnership with the University of Pennsylvania in 2012 on CAR T cells for treatment of B cell cancers. We look to further clinical development of both programs to determine how they will differentiate from each other.

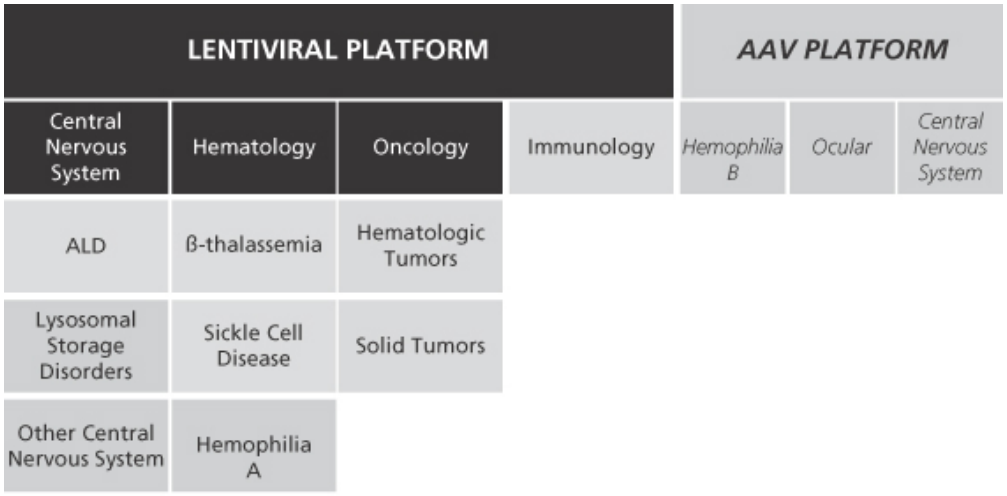
bluebird's partnership with Celgene includes a $75M upfront payment and lasts for three years (Celgene can extend the partnership twice with additional payments: once for two years and again for one year). bluebird is responsible for R&D through Phase 1, and Celgene would have an exclusive worldwide license to products developed from the collaboration. Each product would be eligible for up to $225M in fees and milestone payments, as well royalties to bluebird from the mid-single digits to mid-teens.

Given the preliminary stage of the CAR T development program, we do not model for any product sales deriving from the partnership (although we do include recognition of the $75M upfront amortized over three years).

GENE THERAPY HAS THE POTENTIAL TO BE DISRUPTIVE ACROSS MULTIPLE DISEASES

bluebird sees its gene therapy platform as applicable to a wide variety of indications, including any disease that could be treated by adding a gene into hematopoietic stem cells. Specifically, opportunity exists for lentiviral treatment of CNS diseases, hematology, oncology and immunology (*See Figure 7*). bluebird is also developing an adeno-associated virus (AAV)-based gene therapy system – although development is early, they intend to use this platform for *in vivo* applications.

Figure 7: bluebird's gene therapy platform has multiple opportunities



Source: Company report

Gene therapy has demonstrated efficacy in pre-clinical models of several diseases – particularly in lysosomal storage disorders (LSDs), due to the well-understood biology of the diseases, the monogenic (single-gene) nature and the ability to restore function with <100% of normal protein levels. *In vivo* approaches have been used to treat models of MPS VII (mice and dogs), Fabry disease (mice), MPS I (mice and dogs), LINCL (mice, rats, monkeys), and Sandhoff disease (mice and cats). We note that immune response (cells expressing the foreign protein are recognized and destroyed) can be problematic with this approach. *Ex vivo*, a mouse model of metachromatic leukodystrophy has been corrected with genetically modified HSCs and a mouse model of MPS I and a cat model of alpha-mannosidosis have been corrected via bone marrow transplant. In hemotology, hemophilia A (often caused by mutations in the factor VIII gene) is potentially addressable via gene therapy – we note BioMarin licensed a factor VIII gene therapy program from University College London and St. Jude Children's Hospital in February. Gene therapy also has shown promise in oncology (see below) – highlighting the diverse set of conditions that have the possibility to be addressed via gene therapy. Although all these approaches may not be successful, we believe gene therapy has the potential to be a highly disruptive technology due to the one-time treatment and potential across multiple indications.

We expect regulators to be receptive to gene therapy

Physicians note that while the FDA has traditionally viewed gene therapy as an academic pursuit, there has been a tonal shift recently to a view of a possible registration path (uniQure will reportedly file Glyberra with the FDA in H2/13-14). They characterize this change as a benefit for gene therapies, which we believe is reinforced by the recent publication of Center for Biologics Evaluation and Research (CBER)/Office of Cellular, Tissue, and Gene Therapies (OCTGT) draft guidance on design for early-phase gene therapy trials. In the guidance, the FDA notes that there has been "increasing interest and activity" in gene therapies, and emphasizes the need for a risk/benefit analysis. It also notes that some toxicities "may be expected and acceptable," notes that healthy

volunteer trials are likely not acceptable, acknowledges that blinded trials may not be desirable and addresses patient-specific products (like bluebird's ex-vivo approach; mostly with respect to the timeframe of product manufacturing). Although we note this is a non-binding draft, and we look to guidance on later-stage trial design, we view the publication of the guidance as a positive for gene therapy in general and for bluebird in particular given the comments are in-line with bluebird's approach.

SEVERAL COMPETITIVE GENE THERAPY APPROACHES ARE ON THE HORIZON

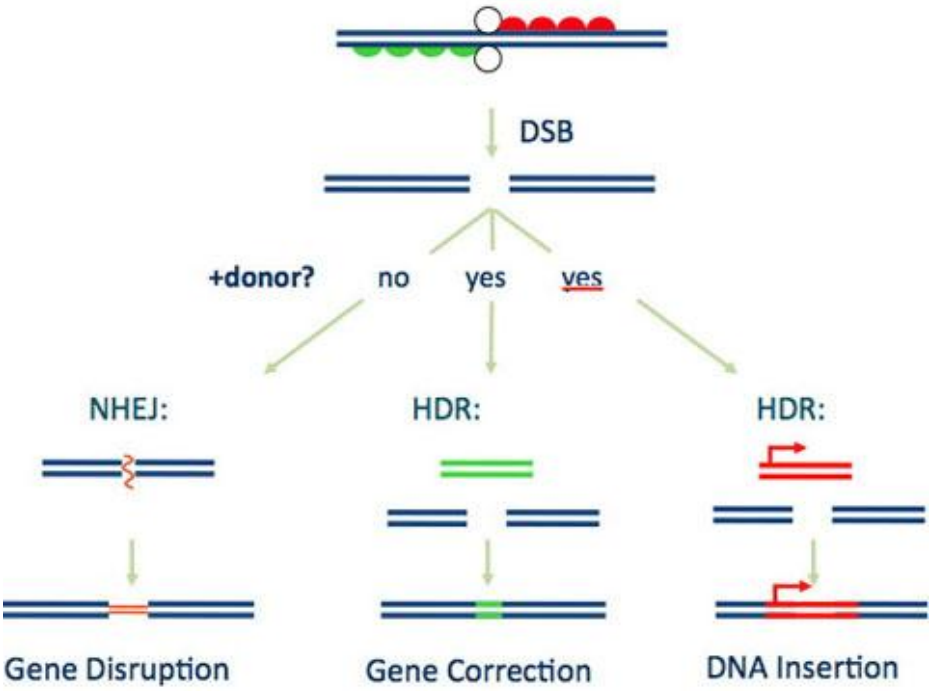
Another gene therapy technique uses adeno-associated virus-based vectors

The adeno-associated virus (AAV) has been used in several gene therapy clinical trials. AAV-based vectors vary from lentiviral-based vectors in that they use single-stranded DNA (versus RNA in lentiviruses), integrate into a specific site in the genome (versus randomly), and can carry less genetic information (~4K bases versus ~8.5K). Glybera, approved in the E.U. in 2012 for treatment of lipoprotein lipase deficiency (LPLD) is based on an AAV, and is delivered *in vivo* into a patient's muscles. Another use of AAV is for treatment of a rare genetic type of blindness (Leber's congenital amaurosis), which was shown to be able to restore some eyesight function from work published by the University of Naples and University College London. bluebird also has expertise with AAV-vectors and may pursue development on this front, particularly for *in vivo* gene therapy approaches.

Sangamo plans on taking zinc finger protein nucleases for treatment of β-thalassemia and SCD, among others, into the clinic

Sangamo BioSciences (SGMO) is developing a gene therapy platform based on zinc finger protein nucleases (ZFNs) with both *in vivo* and *ex vivo* approaches. A zinc finger can be engineered to recognize a specific DNA sequence – ZFNs pair a zinc finger with a domain to cut DNA in a specific location that can be repaired from a donor template. Depending on the design, the gene can be knocked out or modified (i.e. "fixed" back to a working copy; *see Figure 8*).

Figure 8: Zinc finger nucleases



Source: Sangamo BioSciences

In practice, ZFNs demonstrate better efficacy when knocking out genes, which is the approach used in Sangamo's lead program, SB-728 for patients infected with HIV. Sangamo is also developing ZFNs for use in HSCs for treatment of β-thalassemia and SCD, and recently received a $6.4M grant from the California Institute for Regenerative Medicine to take a gene therapy product through Phase 1. Although Sangamo's approach (activate the fetal gamma globin gene in HSCs ex vivo) may vary from bluebird's, it would target the same population and could produce similar clinical outcomes. We look to clinical progress (IND expected in 2014) for greater color on the likelihood of success of this program. Sangamo is also developing an *in vivo* approach to treat lysosomal storage disorders (LSDs; data presented in Gaucher, Pompe, Hunter and Hurler), and plans on filing two LSD-related INDs in 2015. We note that in our diligence, physicians had questions on the commercial viability of ZFN-based approaches due to concerns on efficiency of genetic targeting.

TALENs are similar to ZFNs but further behind

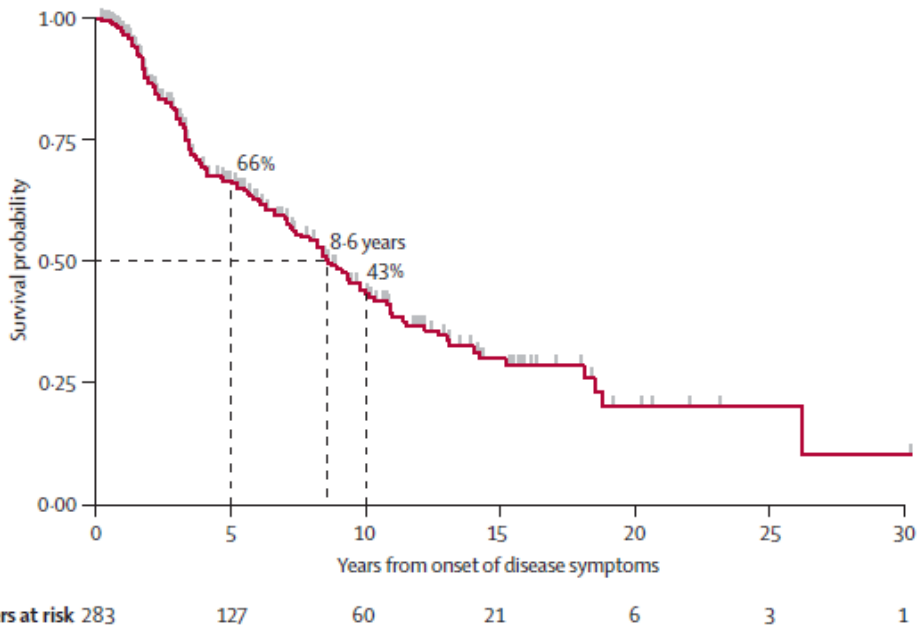
A downside to using zinc finger domains is that engineering zinc fingers to recognize a DNA sequence can be difficult, time-consuming and not necessarily specific to one sequence of DNA. Like zinc fingers, transcription activator-like effector nucleases (TALENs) recognize specific DNA sequences, but can be constructed more quickly and are thought to be more specific for particular DNA sequences. We note that more pre-clinical work on delivery systems and on off-target effects (binding the wrong sequence of DNA) is required before TALENs can enter the clinic, and we are not aware of use of any TALENs outside academic settings.

GETTING UP TO SPEED ON BLUEBIRD'S DISEASES…

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is a genetic (X-linked) disease caused by mutations in the *ABCD1* gene. These mutations result in a dysfunctional ALDP protein, which inhibits proper breakdown of very long chain fatty acids (VLCFA). These acids will build up throughout the body, but have their greatest impact in the central nervous system, where they cause an inflammatory response and subsequent demyelination (breakdown of a protective sheath surrounding nerve cells). Several types of ALD have been described, sorted by disease severity (no genotype-phenotype correlation has been identified): the least severe form, adult cerebral ALD (~2-5% of ALD cases) usually presents between the ages of 20 – 50 as a psychiatric disorder (e.g. schizophrenia, paranoia). An intermediate form of the disease, adrenomyeloneuropathy (AMN; ~40 – 46% of ALD) appears, on average in the late 20s, and involves difficulty in walking (with potential progression to wheelchair) and behavioral changes. The most severe form is childhood cerebral ALD (CCALD; ~30-35%), which presents between the ages of 2 – 15 and is typically first noticed due to behavioral and learning defects. However, CCALD will quickly progress if untreated, leading to seizures, coordination and muscle function deterioration and vegetative state within ~2 years after diagnosis. bluebird found 55% overall survival (OS) at 5 years and median survival of 7.7 years in untreated CCALD patients in its natural history trial, in-line with published literature: 66% 5-year OS and 8.6 year median survival *(Lancet Neurology,* 2007 – s*ee Figure 9*).

Figure 9: CCALD patients have a poor prognosis without HSCT

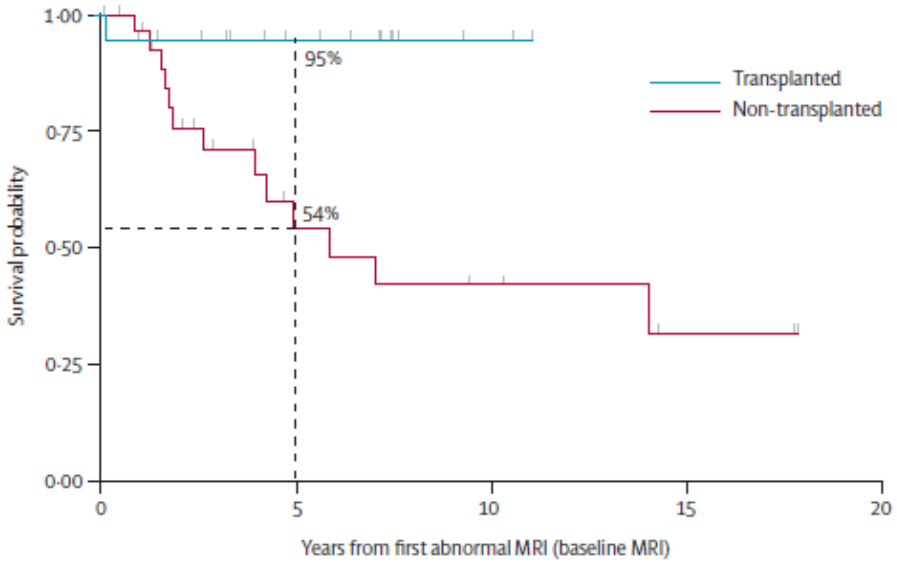


Source: *Lancet Neurology*, 2007

The only proven therapy to treat CCALD is hematopoietic stem cell transplant (HSCT), where a patient's bone marrow is ablated and allogeneic stem cells (taken from a donor,

usually a sibling) are infused into the patient. If successful, these cells engraft (grow and replicate), and prevent further disease progression, but any damage done to the brain prior to HSCT is irreversible. Although the mechanism by which the new cells stop progression is not fully understood, it is thought to involve brain microglia (cells in the brain that are derived from bone marrow). Although there are several risks to HSCT (particularly from the myeloablation and graft-versus-host disease), it is associated with a strong survival advantage in patients with early-stage disease – per the bluebird natural history study, the 5-year OS is 74% in patients treated with matched donor HSCT – although we note published OS rates in patients with early-stage disease (neurological deficit score of 0 or 1; MRI severity score < 9) are higher (95% in *Lancet Neurology*, 2007*;* 92% in *Blood*, 2004 – *see Figure 10*).

Figure 10: Stem cell transplant demonstrates a survival improvement in early-stage patients



Source: *Lancet Neurology*, 2007

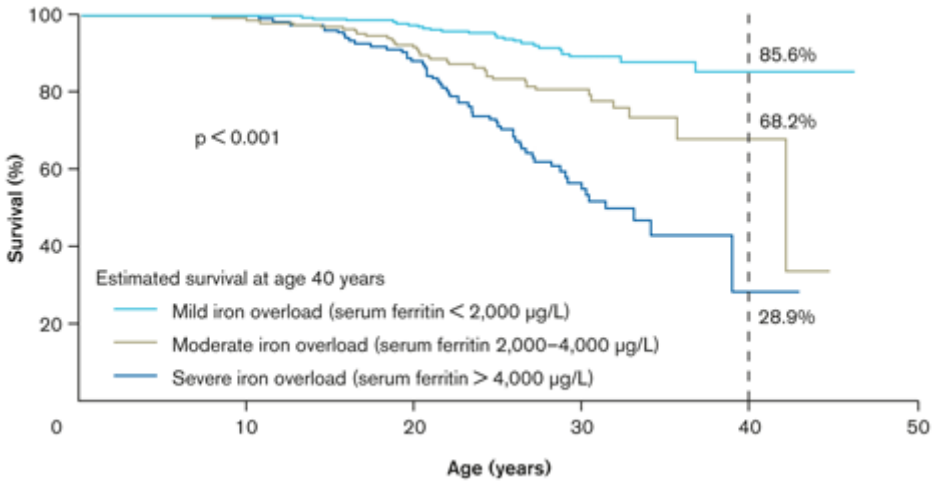
Treatments other than HSCT have not proven effective: although some publications cite a mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's Oil) as having the potential to prevent progression in asymptomatic ALD patients, no benefit on survival has been associated with its use. A Phase 2 investigator-initiated trial is ongoing in AMN patients examining the potential of antioxidants (N-acetylcysteine, lipoic acid and vitamin E) to examine efficacy, safety and biomarkers – however, no clinical benefit has been demonstrated to date.

Thalassemia and sickle cell disease

Thalassemia and sickle cell disease (SCD) are genetic diseases caused by mutations in the genes that encode the hemoglobin (Hb) protein. Hb, which carries oxygen in red blood cells, is generally formed of four subunits: two of the α type and two of the β. A similar

gene, fetal hemoglobin (HbF), is produced by the fetus in utero, but HbF production shuts off ~6 months after birth, allowing adult Hb production to take over. While thalassemia can be caused by defects in the genes that encode any of these subunits, SCD is caused by two copies (homozygous) of a specific mutation in the β gene. As a result of these mutations, Hb aggregates unnaturally, causing red blood cells to "sickle," or acquire a distorted shape. These deformed cells damage blood vessels and are destroyed, causing anemia and reduced Hb levels of 6-8 g/dL (normal levels are 12-17 g/dL). Mutations in any of the α or β genes can cause thalassemia – mutations in the β gene cause β-thalassemia, where the Hb has a reduced capacity to carry oxygen. β-thalassemia severity depends on the nature of the mutation – the most severe case (β-thalassemia major) is associated with Hb levels < 7g/dL. If untreated, β-thalassemia major is usually fatal before five years of age, but life expectancy can be extended to ~15-20 (with regular blood transfusions). Chelation in addition to transfusions can improve survival to the ~30s+, depending on the degree of iron overload (*see Figure 11*). Median life expectancy for SCD patients is in the 50s.

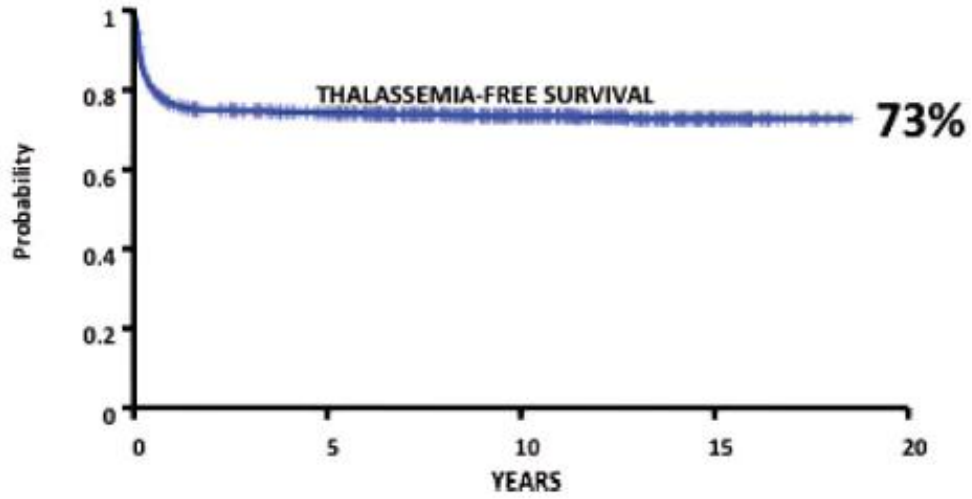
Figure 11: Iron overload causes death in β-thalassemia patients



Source: *Iron Health Alliance*

While the standard of care for β-thalassemia is transfusions and chelation, some patients are also treated with allogeneic HSCT. Prognostic indicators have been developed (based on chelation quality, hepatomegaly and presence of liver fibrosis) that can stratify patients into high-risk (70% OS) and low-risk (94% OS) groups, with overall thalassemia-free survival from matched sibling HSCT at ~73% (*see Figure 12*). Although some HSCT transplants are performed in for β-thalassemia patients with matched unrelated or mismatched related donors are performed, results are in-line to worse (65% - 97% OS and 65% OS, respectively).

Figure 12: HSCT has long-term curative potential for thalassemia



Source: *Blood*, 2010

Folic acid is also used to treat β-thalassemia and SCD, although it has not demonstrated improvements in RBC count or transfusion intervals. Several drugs have been linked to upregulation of the fetal hemoglobin gene (HbF), which could stand in for the disrupted β-globin gene. These include 5-azacytidine, decitabine, butyrate derivatives, 2,2-dimethylbutyric acid and hydroxyurea (HU). Although there is pre-clinical and preliminary data for several of these compounds (and HU is typically used for treatment of SCD), we are not aware of any company-sponsored late-stage clinical trials for any of these compounds.

…AND THE GENE THERAPY LANDSCAPE

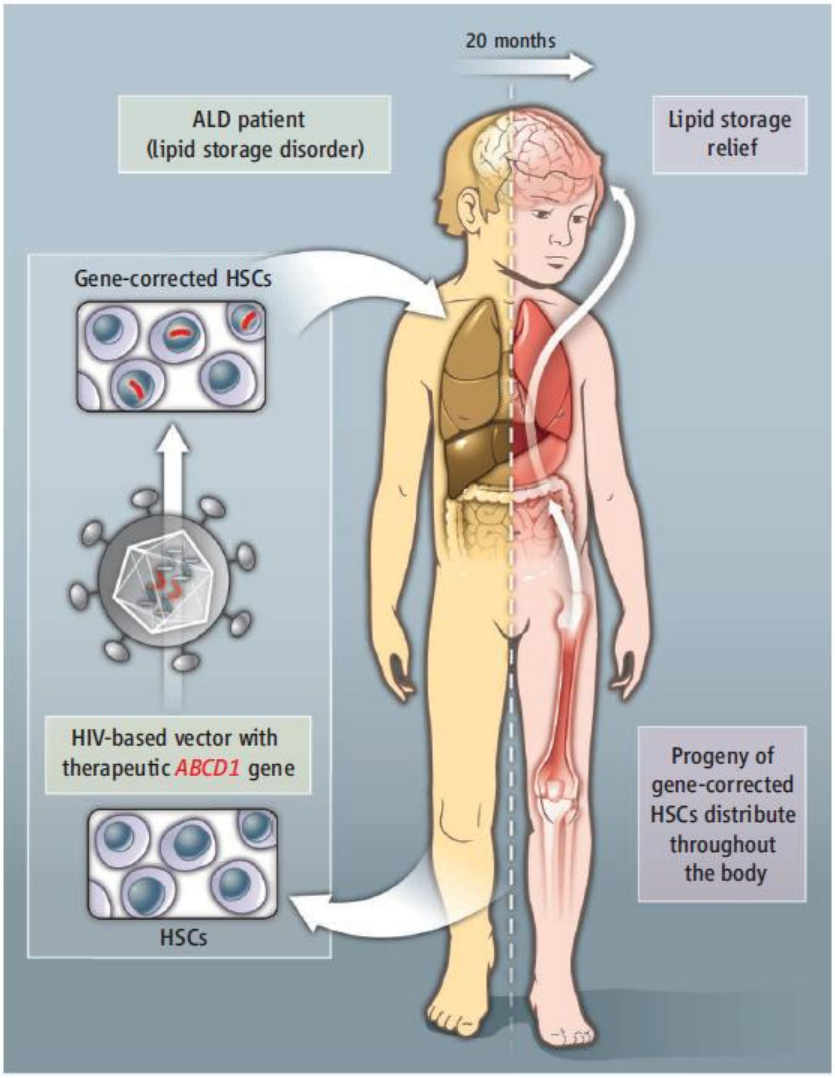
Changing a patient's own genes has long held the promise of a one-time curative therapy, but technical problems have historically been limiting. The first success came in treatment of severe combined immunodeficiency disease (SCID) – a disease characterized by the near absence of immune function, caused by mutations in one of several genes. SCID has several characteristics that make it amenable to gene therapy, including a well-understood genetic cause, clinical history of curative treatment via stem cell transplants, and an amplification effect whereby a few healthy cells can regenerate the immune system. However, the vector used in some academic clinical trials caused several cases of leukemia, which led to the death of one treated patient. This highlights the importance of vector design and risk:benefit analyses in gene therapy.

bluebird uses lentivirus-based vectors

bluebird's gene therapy platform uses vectors based on the lentivirus (given the capability of the virus to replicate has genetically eliminated, the resulting product is referred to as a vector), a HIV-based retrovirus (uses RNA as the genetic code) with the ability to infect non-dividing cells. On infection, the vector will translate its RNA into DNA and integrate randomly into the host's genome (s*ee Figure 13*). bluebird uses its

lentiviruses to infect hematopoietic stem cells (HSCs) *ex vivo* (outside the body), which give rise to all lineages of blood cells. Theoretically, any disease caused by monogenic (single gene) defects in blood cells, or diseases that can be treated by adding a new gene into blood cells, could be treated with this approach. Although one limitation to lentiviruses is the length of the genetic code it can carry (~8.5K bases), this is more than sufficient for β-thalassemia (~1K) or CCALD (~4K). A challenge in this technique is making sufficient numbers of vectors, which can be measured via a ratio of active:inactive particles produced: while bluebird produced a 1:5000 active:inactive particle ratio initially, they currently have the ability to produce 1:200-300, with the goal of getting to 1:100-200 for commercial-scale production.

Figure 13: Schematic of CCALD treatment with Lenti-D



Source: *Science*, 2009

Leukemia is the primary safety concern with lentiviral vectors

Concerns for leukemia as a result gene therapy was heightened following the report of two cases of T-cell leukemia following retroviral treatment of twenty infants with severe combined immune deficiency (SCID). Although the trial initially appeared to be quite successful (9 of 10 patients in an initial trial achieved immune reconstitution), five patients developed T-cell leukemia three years post-treatment caused by a retroviral insertion near the *LMO2* that drove its inappropriate transcription. Analysis of this trial led to the development of several strategies to reduce the risk of leukemic transformation: 1) utilization of a vector that will delete its enhancer and promoter on insertion (self-inactivating vector; SIN); 2) utilization of cell-specific enhancers/promoters, so vectors specific to one cell lineage (such as erthryocytes to treat β-thalassemia) will not be active in other lineages; 3) use of promoters that require specific small molecules for activation; 4) insertion of insulators that will prevent enhancers from activating adjacent genes; 5) addition of a 'suicide gene' that could be activated on development of leukemia; and 6) site-directed insertions, to avoid regions that are known to cause leukemia. While all of these strategies are not necessary, bluebird uses SINs that produce a 100-1000x reduced ability to immortalize cells *in vitro.* Another possible risk is via immune response to the vector – one patient with ornithine transcarbamylase deficiency treated with an adenovirus developed multi-system organ failure and died, attributed to cytokines release in response to components of the vector. We note that no patient has demonstrated an immune response to bluebird's vector. Although the risk of leukemia transformations or a severe immune response cannot be eliminated, we like the risk/reward profile of the vector, particularly in the new form, especially given the severe nature of CCALD and β-thalassemia/SCD, and note that leukemia is treatable (four of five patients in the SCID trial who developed leukemia were cured).

A secondary risk to the gene therapy process is the myeloablation (treatment with chemotherapy or radiation) to remove endogenous bone marrow cells prior to re-infusion of the transformed HSCT. By destroying the bone marrow, patients become strongly immunosuppressed, which carries the risk of infection. However, myeloablation is also required in the standard-of-care CCALD treatment of HSCT (in bluebird's natural history trial of CCALD patients, the most common serious adverse event of patients treated with HSCT was infection, in 29% of patients). Net-net, Lenti-D has a favorable safety profile particularly given the risk of graft-versus-host disease (~42% of HSCT patients developed GVHD per the bluebird natural history trial; 12% of patients developed severe/acute GVHD per *Blood*, 2004, causing 4% mortality). Given an acute GVHD rate of 20% in matched HSCT for β-thalassemia, we look to the Phase 1/2 trials for color on the risk/reward of LentiGlobin in this indication.

INTELLECTUAL PROPERTY

bluebird owns or has licensed over 250 patents related to vectors, vector systems and manufacturing. These include licenses that cover both Lenti-D and LentiGlobin from the Pasteur Institute (expiration 2019-2023 in the U.S., 2019-2020 ROW), the Research Development Foundation (expiration 2021-2023 WW). bluebird has WW patent applications that cover composition of matter and methods for Lenti-D that expire in 2032, and for LentiGlobin that expire in 2031. Both therapies would be covered by

orphan exclusivity (including pediatric exclusivity), for a period of 7.5 years (U.S.) and 12 years (E.U.), and by biologic exclusivity for a period of 12 years. In addition, bluebird has numerous unpatented and proprietary methods for vector manufacturing that it views as critical for high rates of transfection.

FINANCIALS

In Q1/13, bluebird reported net revenue of $1.1M ($1.0M from the Celgene collaboration and $0.1M from research and licensing fees) and a net loss of $6.5M, or $(19.94) per share. The company had 328K shares outstanding, not including 6.8M shares related to the IPO, 16.4M shares from conversion of preferred stock, 3.8M shares from options, 440K shares from warrants and 1.3M shares from an incentive plan, for a fully-diluted share count of 29.1M shares.

We model for a Lenti-D launch in mid-2018 (U.S.) and early 2019 (E.U.), providing peak sales of $221M in 2028. For LentiGlobin, we model for launches in mid-2020 (U.S.) and early 2021 (E.U.), with peak revenue to bluebird of $1.06B in 2025 on penetration into both the bolus of existing patients and newly diagnosed patients. We assume payors will reimburse bluebird for the cost ($1.75M for Lenti-D; $1.5M for LentiGlobin) of the drugs evenly over the course of three years, for peak net revenue to bluebird of $1.23B in 2026. We model for the company to achieve profitability in 2021.

As of March 31, 2013, bluebird had $131.8M in cash and equivalents, including $73.9M of the Celgene upfront yet to be recognized, but not including ~$103.5M raised in the IPO for a cash balance of ~$235.3M. We believe bluebird's cash balance is sufficient to fund operations into early 2017 and we model for an equity offering of $200M in mid-2016 (5M shares at $40/share), although future milestones from the Celgene partnership may provide an infusion of cash.

Figure 14: Lenti-D and LentiGlobin revenue builds

Revenue Model - Lenti-D

Childhood cerebral adrenoleukodystrophy (CCALD) market

U.S.

	FY 2011A	FY 2012A	Mar 1Q13A	Jun 2Q13E	Sep 3Q13E	Dec 4Q13E	FY 2013E	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E	FY 2027E	FY 2028E
Number of births - U.S. ('000)	4,039	4,060	4,068	4,076	4,084	4,092	4,080	4,117	4,154	4,191	4,229	4,267	4,305	4,344	4,383	4,423	4,462	4,503	4,543	4,584	4,625	4,667
Incidence of CCALD	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*
Rate of CCALD patients eligible for Lenti-D	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
Total number of eligible new cases of CCALD	56	56	*14*	*14*	*14*	*14*	56	57	57	58	58	59	59	60	60	61	62	62	63	63	64	64
Market penetration into eligible CCALD	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*10.8%*	*42.2%*	*58.9%*	*66.3%*	*71.0%*	*75.6%*	*78.6%*	*80.9%*	*81.5%*	*81.6%*	*81.7%*
Total number of CCALD patients on Lenti-D	-	-	-	-	-	-	-	-	-	-	-	6	25	35	40	43	47	49	51	52	52	53
Gross cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,750,000	$1,802,500	$1,856,575	$1,912,272	$1,969,640	$2,028,730	$2,089,592	$2,152,279	$2,216,848	$2,283,353	$2,351,854
Net cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,487,500	$1,532,125	$1,578,089	$1,625,431	$1,674,194	$1,724,420	$1,776,153	$1,829,437	$1,884,320	$1,940,850	$1,999,076
Total U.S. Lenti-D sales ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 9,455	$ 38,395	$ 55,693	$ 65,152	$ 72,511	$ 80,241	$ 86,701	$ 92,742	$ 97,099	$ 101,036	$ 105,132
Total U.S. Lenti-D revenue recognized by bluebird ($'000) 3	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 3,152	$ 15,950	$ 34,514	$ 53,080	$ 64,452	$ 72,634	$ 79,817	$ 86,561	$ 92,181	$ 96,959	$ 101,089

E.U.

	FY 2011A	FY 2012A	Mar 1Q13A	Jun 2Q13E	Sep 3Q13E	Dec 4Q13E	FY 2013E	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E	FY 2027E	FY 2028E
Number of births - E.U. ('000)	5,446	5,474	5,512	5,534	5,556	5,577	5,545	5,600	5,656	5,713	5,770	5,828	5,886	5,945	6,004	6,064	6,125	6,186	6,248	6,311	6,374	6,437
Incidence of CCALD	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*	*0.0017%*
Rate of CCALD patients eligible for Lenti-D	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*
Total number of eligible new cases of CCALD	80	80	*20*	*20*	*20*	*20*	81	82	83	84	85	85	86	87	88	89	90	91	92	92	93	94
Market penetration into eligible CCALD	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*34.2%*	*48.5%*	*61.1%*	*70.5%*	*72.3%*	*73.4%*	*74.8%*	*75.7%*	*76.1%*	*76.3%*
Total number of CCALD patients on Lenti-D	-	-	-	-	-	-	-	-	-	-	-	-	30	42	54	63	65	67	68	70	71	72
Gross cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,750,000	$1,750,000	$1,750,000	$1,750,000	$1,750,000	$1,750,000	$1,750,000	$1,750,000	$1,750,000	$1,750,000
Net cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,487,500	$1,487,500	$1,487,500	$1,487,500	$1,487,500	$1,487,500	$1,487,500	$1,487,500	$1,487,500	$1,487,500
Total E.U. Lenti-D sales ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 43,882	$ 62,853	$ 79,974	$ 93,201	$ 96,536	$ 98,985	$ 101,881	$ 104,138	$ 105,736	$ 107,074
Total E.U. Lenti-D revenue recognized by bluebird ($'000) 3	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 14,627	$ 35,579	$ 62,237	$ 78,676	$ 89,904	$ 96,240	$ 99,134	$ 101,668	$ 103,918	$ 105,649

TOTAL Lenti-D sales - WW ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 9,455	$ 82,277	$ 118,547	$ 145,126	$ 165,711	$ 176,777	$ 185,686	$ 194,624	$ 201,237	$ 206,771	$ 212,206
TOTAL Lenti-D revenue recognized by bluebird - WW ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 3,152	$ 30,577	$ 70,093	$ 115,317	$ 143,128	$ 162,538	$ 176,058	$ 185,695	$ 193,849	$ 200,878	$ 206,738

Revenue Model - LentiGlobin

β-thalassemia market

U.S.

	FY 2011A	FY 2012A	Mar 1Q13A	Jun 2Q13E	Sep 3Q13E	Dec 4Q13E	FY 2013E	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E	FY 2027E	FY 2028E
Number of births - U.S. ('000)	4,190	4,211	4,219	4,228	4,236	4,245	4,232	4,270	4,309	4,347	4,386	4,426	4,466	4,506	4,546	4,587	4,629	4,670	4,712	4,755	4,798	4,841
Incidence of β-thalassemia major	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*	*0.0024%*
Total number of patients born with β-thalassemia major	99	100	*25*	*25*	*25*	*25*	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115
Rate of newly-diagnosed β-thalassemia patients eligible for LentiGlobin	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Market penetration into new cases	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*6.1%*	*20.1%*	*32.2%*	*41.5%*	*48.5%*	*55.3%*	*56.6%*	*57.0%*	*57.2%*
Number of newly-born β-thalassemia patients treated with LentiGlobin	-	-	-	-	-	-	-	-	-	-	-	-	-	5	16	26	34	40	46	48	49	49
Total U.S. population ('000)	311,590	313,151	*313,777*	*314,405*	*315,034*	*315,664*	314,720	317,552	320,410	323,294	326,204	329,140	332,102	335,091	338,107	341,150	344,220	347,318	350,444	353,598	356,780	359,991
Prevalence of β-thalassemia major	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*	*0.0003%*
Rate of existing β-thalassemia patients eligible for LentiGlobin	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Total number of non-new cases of β-thalassemia major	248	249	*250*	*250*	*251*	*251*	250	253	255	257	260	262	264	267	269	271	274	276	279	281	284	286
Number of non-new, untreated β-thalassemia patients	248	249	*250*	*250*	*251*	*251*	250	253	255	257	260	262	264	267	263	248	228	210	198	191	187	185
Market penetration into non-new, untreated cases	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*2.1%*	*6.8%*	*9.1%*	*8.7%*	*7.0%*	*5.1%*	*3.4%*	*2.2%*	*0.9%*
Number of non-new β-thalassemia patients treated with LentiGlobin	-	-	-	-	-	-	-	-	-	-	-	-	-	6	18	23	20	15	10	6	4	2
Number of non-new β-thalassemia patients treated to date ('000)								-	-	-	-	-	-	6	24	46	66	81	91	97	101	103
Total number of β-thalassemia patients treated with LentiGlobin	-	-	-	-	-	-	-	-	-	-	-	-	-	10	34	49	54	55	56	54	53	51
Gross cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,500,000	$1,545,000	$1,591,350	$1,639,091	$1,688,263	$1,738,911	$1,791,078	$1,844,811	$1,900,155
Net cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,275,000	$1,313,250	$1,352,648	$1,393,227	$1,435,024	$1,478,074	$1,522,417	$1,568,089	$1,615,132
Total U.S. LentiGlobin sales ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 13,369	$ 44,858	$ 66,037	$ 75,187	$ 78,921	$ 83,409	$ 82,695	$ 82,662	$ 82,184
Total U.S. LentiGlobin revenue recognized by bluebird ($'000) 3	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 4,456	$ 19,409	$ 41,421	$ 62,027	$ 73,381	$ 79,172	$ 81,675	$ 82,922	$ 82,514

E.U.

	FY 2011A	FY 2012A	Mar 1Q13A	Jun 2Q13E	Sep 3Q13E	Dec 4Q13E	FY 2013E	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E	FY 2027E	FY 2028E
Number of births - E.U. ('000)	5,446	5,474	5,512	5,534	5,556	5,577	5,545	5,600	5,656	5,713	5,770	5,828	5,886	5,945	6,004	6,064	6,125	6,186	6,248	6,311	6,374	6,437
Incidence of β-thalassemia major	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*	*0.0274%*
Total number of patients born with β-thalassemia major	1,492	1,500	*378*	*379*	*381*	*382*	1,519	1,534	1,550	1,565	1,581	1,597	1,613	1,629	1,645	1,662	1,678	1,695	1,712	1,729	1,746	1,764
Rate of newly-diagnosed β-thalassemia patients eligible for LentiGlobin	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Market penetration into new cases	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*13.0%*	*25.6%*	*33.1%*	*39.0%*	*44.3%*	*45.1%*	*45.8%*	*46.4%*
Number of newly-born β-thalassemia patients treated with LentiGlobin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	160	319	417	496	569	585	600	614
Total E.U. population ('000)	508,857	511,406	*512,429*	*513,454*	*514,481*	*515,510*	513,969	518,594	523,262	527,971	532,723	537,517	542,355	547,236	552,161	557,131	562,145	567,204	572,309	577,460	582,657	587,901
Prevalence of β-thalassemia major	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*	*0.0031%*
Rate of existing β-thalassemia patients eligible for LentiGlobin	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Total number of non-new cases of β-thalassemia major	3,960	3,980	*3,988*	*3,996*	*4,004*	*4,012*	4,000	4,036	4,072	4,109	4,146	4,183	4,221	4,259	4,297	4,336	4,375	4,414	4,454	4,494	4,535	4,575
Number of non-new, untreated β-thalassemia patients	3,960	3,980	*3,988*	*3,996*	*4,004*	*4,012*	4,000	4,036	4,072	4,109	4,146	4,183	4,221	4,259	4,297	4,194	4,002	3,754	3,527	3,373	3,279	3,234
Market penetration into non-new, untreated cases	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*3.3%*	*5.5%*	*7.2%*	*7.1%*	*5.5%*	*4.0%*	*2.6%*	*1.7%*
Number of non-new β-thalassemia patients treated with LentiGlobin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	142	231	288	267	194	135	85	55
Number of non-new β-thalassemia patients treated to date ('000)								-	-	-	-	-	-	-	142	372	661	927	1,121	1,256	1,341	1,396
Total number of β-thalassemia patients treated with LentiGlobin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	302	550	705	762	763	720	685	669
Gross cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,500,000	$1,500,000	$1,500,000	$1,500,000	$1,500,000	$1,500,000	$1,500,000	$1,500,000
Net cost per treatment per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$1,275,000	$1,275,000	$1,275,000	$1,275,000	$1,275,000	$1,275,000	$1,275,000	$1,275,000
Total E.U. LentiGlobin sales ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 385,321	$ 700,876	$ 898,619	$ 971,935	$ 972,544	$ 917,724	$ 873,532	$ 852,716
Total E.U. LentiGlobin revenue recognized by bluebird ($'000) 3	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 128,440	$ 362,066	$ 661,605	$ 857,143	$ 947,699	$ 954,068	$ 921,267	$ 881,324

TOTAL LentiGlobin sales - WW ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 13,369	$ 430,180	$ 766,913	$ 973,805	$1,050,856	$1,055,953	$1,000,419	$ 956,194	$ 934,900
TOTAL LentiGlobin revenue recognized by bluebird - WW ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 4,456	$ 147,849	$ 403,487	$ 723,633	$ 930,525	$1,026,871	$1,035,743	$1,004,188	$ 963,838

TOTAL revenue recognized by bluebird - WW ($'000)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 3,152	$ 30,577	$ 74,549	$ 263,166	$ 546,615	$ 886,171	$1,106,583	$1,212,567	$1,229,591	$1,205,066	$1,170,576

Source: Company reports, Canaccord Genuity estimates

Figure 15: bluebird income statement

($thousands, except per share data)

	FY 2011A	FY 2012A	Mar 1Q13A	Jun 2Q13E	Sep 3Q13E	Dec 4Q13E	FY 2013E	FY 2014E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E
Revenue																	
Lenti-D (CCALD) Total Revenue	$ -	$ -	-	-	-	-	$ -	$ -	$ -	$ -	$ -	$ 3,152	$ 30,577	$ 70,093	$ 115,317	$ 143,128	$ 162,538
Lenti-D - U.S.	-	-	-	-	-	-	-	-	-	-	-	3,152	15,950	34,514	53,080	64,452	72,634
Lenti-D - E.U.	-	-	-	-	-	-	-	-	-	-	-	-	14,627	35,579	62,237	78,676	89,904
LentiGlobin (β-thalassemia) Total Revenue	$ -	$ -	-	-	-	-	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 4,456	$ 147,849	$ 403,487	$ 723,633
LentiGlobin - U.S.	-	-	-	-	-	-	-	-	-	-	-	-	-	4,456	19,409	41,421	62,027
LentiGlobin - E.U.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	128,440	362,066	661,605
Total other revenue	$ 882	$ 340	1,127	6,250	6,831	6,831	$ 21,040	$ 27,325	$ 27,325	$ 7,533	$ 1,163	$ -	$ -	$ -	$ -	$ -	$ -
Total Revenue	$ 882	$ 340	$ 1,127	$ 6,250	$ 6,831	$ 6,831	$ 21,040	$ 27,325	$ 27,325	$ 7,533	$ 1,163	$ 3,152	$ 30,577	$ 74,549	$ 263,166	$ 546,615	$ 886,171
COGS	-	-	-	-	-	-	-	-	-	-	-	788	6,727	14,910	47,370	98,391	159,511
Gross profit	882	340	1,127	6,250	6,831	6,831	21,040	27,325	27,325	7,533	1,163	2,364	23,850	59,639	215,796	448,224	726,660
Operating expense																	
R&D (GAAP)	11,409	17,210	5,284	6,285	6,753	7,788	26,110	28,083	29,533	31,503	33,593	35,605	37,504	39,481	41,502	43,550	45,503
SG&A (GAAP)	4,615	6,846	2,324	2,864	3,358	4,391	12,937	14,431	15,538	17,011	25,715	27,280	34,731	42,202	44,283	46,189	48,200
Total operating expense	16,024	24,056	7,608	9,149	10,111	12,179	39,047	42,514	45,071	48,514	59,308	62,885	72,235	81,683	85,785	89,739	93,703
Operating income (loss)	**(15,142)**	**(23,716)**	**(6,481)**	**(2,899)**	**(3,280)**	**(5,348)**	**(18,008)**	**(15,189)**	**(17,746)**	**(40,981)**	**(58,146)**	**(60,521)**	**(48,385)**	**(22,044)**	**130,011**	**358,485**	**632,957**
Other (expense) income, net	(456)	46	(63)	5	6	6	(45)	6	4	6	10	8	6	5	12	37	91
Net gain (loss)	**(15,598)**	**(23,670)**	**(6,544)**	**(2,894)**	**(3,273)**	**(5,342)**	**(18,053)**	**(15,183)**	**(17,742)**	**(40,975)**	**(58,136)**	**(60,514)**	**(48,379)**	**(22,039)**	**130,023**	**358,523**	**633,047**
Income Tax Provision	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	43,023	202,575
Net loss applicable to common shareholders	$ (20,591)	$ (3,613)	$ (6,544)	$ (2,894)	$ (3,273)	$ (5,342)	$ (18,053)	$ (15,183)	$ (17,742)	$ (40,975)	$ (58,136)	$ (60,514)	$ (48,379)	$ (22,039)	$ 130,023	$ 315,500	$ 430,472
GAAP EPS (diluted)	$ (171.59)	$ (13.79)	$ (19.94)	$ (0.92)	$ (0.14)	$ (0.23)	$ (1.42)	$ (0.63)	$ (0.73)	$ (1.52)	$ (1.96)	$ (2.02)	$ (1.60)	$ (0.72)	$ 4.07	$ 9.57	$ 12.39
Weighted shares outstanding basic and diluted	120	262	328	3,137	23,566	23,684	12,679	23,921	24,160	26,902	29,671	29,968	30,267	30,570	31,946	32,978	34,734
Margin Analysis:																	
Cost of product sales	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	25%	22%	20%	18%	18%	18%
Product gross margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	75%	78%	80%	82%	82%	82%
R&D (GAAP)	nm	469%	469%	101%	99%	114%	124%	103%	108%	418%	2890%	1130%	123%	53%	16%	8%	5%
SG&A (GAAP)	nm	206%	206%	46%	49%	64%	61%	53%	57%	226%	2212%	866%	114%	57%	17%	8%	5%
Stock-based compensation expense	nm	18%	62%	12%	12%	13%	15%	13%	15%	64%	480%	198%	23%	11%	3%	2%	1%
Total operating expense	nm	nm	nm	146%	148%	178%	186%	156%	165%	644%	5102%	1995%	236%	110%	33%	16%	11%
Operating margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	49%	66%	71%
Income tax provision	nm	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	12%	32%
Net margin (GAAP)	nm	nm	nm	-46%	-48%	-78%	-86%	-56%	-65%	-544%	-5001%	-1920%	-158%	-30%	49%	58%	49%
Y/Y change:																	
Total revenue	nm	nm	nm	nm	nm	nm	nm	30%	0%	-72%	-85%	171%	870%	144%	253%	108%	62%
Lenti-D revenue	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	870%	129%	65%	24%	14%
LentiGlobin revenue	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm	3218%	173%	79%
R&D (GAAP)	nm	51%	37%	nm	nm	nm	52%	8%	5%	7%	7%	6%	5%	5%	5%	5%	4%
SG&A (GAAP)	nm	48%	71%	nm	nm	nm	89%	12%	8%	9%	51%	6%	27%	22%	5%	4%	4%
Stock-based compensation expense	nm	0%	-13%	nm	nm	nm	297%	14%	17%	14%	16%	12%	13%	14%	12%	10%	10%
Total operating expense	nm	50%	46%	nm	nm	nm	62%	9%	6%	8%	22%	6%	15%	13%	5%	5%	4%
Operating income	nm	57%	26%	nm	nm	nm	-24%	-16%	17%	131%	42%	4%	-20%	-54%	-690%	176%	77%
Net income (GAAP)	nm	-82%	3%	nm	nm	nm	400%	-16%	17%	131%	42%	4%	-20%	-54%	-690%	143%	36%
GAAP EPS (diluted)	nm	-92%	-30%	nm	nm	nm	-90%	-55%	16%	107%	29%	3%	-21%	-55%	-665%	135%	30%
Shares outstanding - GAAP	nm	118%	47%	nm	nm	nm	4739%	89%	1%	11%	10%	1%	1%	1%	4%	3%	5%

Source: Company reports, Canaccord Genuity estimates

APPENDIX: IMPORTANT DISCLOSURES

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Distribution of Ratings:
Global Stock Ratings
(as of 28 June 2013)

	Coverage Universe		IB Clients
Rating	#	%	%
Buy	568	59.1%	36.6%
Speculative Buy	58	6.0%	60.3%
Hold	288	30.0%	11.1%
Sell	47	4.9%	6.4%
	964*	100.0%	

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Canaccord Genuity Research Disclosures as of 15 July 2013

Company	Disclosure
bluebird bio	1A, 2, 3, 5, 7

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