ASGCT Abstracts Out: BLUE and AAVL Highlight Platforms

Companies Impacted in This Note			
Ticker	Price	Rating	Target
AAVL	$35.36	Buy	$60.00
BLUE	$132.12	Buy	$115.00
BMRN	$116.97	Buy	$151.00
GEVA	$102.59	Buy	$117.00

What's Incremental.
ASGCT (May 13-16, New Orleans) abstracts were **published online**. We highlight presentations on early proof-of-concept for BLUE's gene editing technology for CAR-T cells and consistent Lenti-product manufacturing for 60+ batches. For AAVL, 3 posters will showcase: 1) targeted evolution methodology, 2) Phase II AVA-101 study participant demographics and 3) preclinical data on the cone-associated disorders. We recommend investors accumulate BLUE and AAVL shares ahead of key catalysts in mid-year for both companies. Also, MPS IIIb preclinical gene therapy data has read-throughs to GEVA and BMRN.

AAVL's targeted evolution platform to be featured at the American Society of Gene and Cell Therapy (ASGCT). Abstract #316 describes a hybrid AAV variant developed by AAVL called AAV2.5T, entailing key components of AAV2 (currently used by AAVL) and AAV5 (a type less prone to immunogenicity). This vector appears effective with intravitreal injections in animal models (rodents). Furthermore, AAV2.5T does not appear to be impacted by pre-existing AAV antibodies. Abstract #202 describes an optimized vector cassette to be used by AAVL, with robust expression in cone eye cells. Investigators note these vectors could have broad utility for eye diseases such as cone-rod dystrophy, progressive cone dystrophy, Stargardt macular dystrophy, and achromatopsia.

AVA-101 Phase IIa patient demographics to be discussed at ASGCT. Abstract #394 is slated to discuss blinded patient demographics from the Phase IIa study of AVA-101 in wet AMD underway at the Lion's Eye Institute (Australia), in line with pre-annoucement at AAVL's Investor Day in March. As a reminder, for the 21 patients randomized to get AVA-101 and the 11 control patients given Lucentis injections, average best corrected visual acuity 59+15 letters. Non-naive patients had received an average of 10 anti-VEGF injections prior to trial start. Of note, these patients appear significantly milder than participants in the Phase I AVA-101 study (baseline visual acuity of 36.5 letters). Thus, we anticipate that the AVA-101 activity in the Phase IIa study would be more modest compared to the impressive +8.7 and +6.3 letters gained in the Phase I trial. New data included the following: 4 (25%) Phase II patients harbored anti-AAV antibodies at baseline; we note, however, that one participant in the Phase I trial saw improvement in vision with AVA-101 in spite of its AAV antibody-positive status at baseline.

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SEE PAGE 5 FOR REQUIRED DISCLOSURE INFORMATION

ASGCT slated to offer a glimpse into BLUE's use of PreGenEn gene editing technology for CAR T design. Abstract #685 describes the use of the megaTAL technology (obtained by BLUE through its acquisition of PreGenEn) to engineer CAR T cells. Of note, most existing CAR-T programs use lentiviral delivery systems to express the CAR cassette (thus resulting in random integration). Using the precision DNA cutting provided by mega-TAL, researchers were able to replace a specific T cell gene (CCR5) with the CAR cassette which was achieved in 60% of cells, 90% of which showed biallelic targeting (both CCR5 gene copies replaced) and correct CAR integration. The so called “targeted CAR” or tCAR-T cells showed the same preclinical anti-tumor activity as those generated using lentiviral delivery (and potentially better CAR expression control/potency). These data showcase BLUE's capabilities in the CAR-T as well as the genome editing space. This strategy is also amenable for the directed integration of functional genes into other human cells. This was demonstrated, per the abstract, where a corrected version of the mutated gene (WAS) causing the Wiskott-Aldrich syndrome) was integrated to replace the aforementioned CCR5 gene in hematopoetic stem (CD34+) cells.

BLUE will also present data supporting consistent LentiD and LentiGlobin manufacturing processes. Abstract #467 will discuss analytical data for 60+ batches of lentivirus produced using BLUE's proprietary manufacturing process (transfection of HEK293 cells with packaging plasmids, harvesting and concentration of cell medium containing the desired viral capsids). Per the abstract, process yields range between 30-60%.

Preclinical gene therapy data in MPS IIIB highlight potential read-through to GEVA's SBC-103 (but also competition for GEVA and BMRN). Abstract #172 entails preclinical data suggesting that MPS IIIB (disease where GEVA's SBC-103 is in Phase I testing; BMRN is preclinical) is also associated with metabolic disruption. Of note, investigators corrected these defects in MPS IIIB mice using systemically-delivered (intravenous administration) AAV9-NAGLU (the missing enzyme in MPS IIIB) gene therapy. These data, if recapitulated in human trials, would support GEVA's approach of using intravenous NAGLU delivery, rather than limiting enzyme expression to the nervous system (intrathecal delivery to be developed by BMRN). Thus, systemic delivery of the missing enzyme could enable correction of metabolic manifestations of this disease. Nevertheless, the key question remains whether GEVA's SBC-103 can result in meaningful enzyme accumulation across the blood-brain barrier, to address the neurological manifestations of MPS IIIB (viewed by physicians as most important for their patients). The recent WORLD conference (Biotech: Gene Therapy in the Limelight at WORLD) featured debate over the appropriate gene therapy delivery (I.V. vs. others) for neurologic-focused disorders. We believe combination approaches could be possible. On the other hand, we believe gene therapy competitive pressure for GEVA and BMRN's enzyme replacement approaches is increasing. We note that QURE is currently collaborating with Institut Pasteur on an MPS IIIB gene therapy program.

Please see ASGCT itinerary in PDF version of note.

American Society of Gene & Cell Therapy Annual Meeting Itinerary

Company	Abstract no.	Session	Presentation time	Presentation title
BMRN	385	Poster	Thursday, May 14, 5:30PM-7:00PM	Intravenous Delivery of AAV9-CMV-sFLT1 Reduces the Severity of Brain Arteriovenous Malformation Without Causing Significant Side Effects in a Mouse Model
AAVL	202	Poster	Wednesday, May 13, 5:15PM-6:45PM	pMNTC Is a Cone-Specific Regulatory Cassette Designed To Treat Cone-Associated Disorders
AAVL	316	Poster	Thursday, May 14, 5:30PM-7:00PM	Evaluating AAV Hybrid Variants for Improved Tropism after Intravitreal Gene Delivery to the Retina
AAVL	394	Poster	Thursday, May 14, 5:30PM-7:00PM	Baseline Data for Patients Participating in the Phase 2a rAAV.sFlt-1 Gene Therapy Trial for Exudative Age-Related Macular Degeneration
BLUE	467	Poster	Thursday, May 14, 5:30PM-7:00PM	Consistency of Research Grade Lentiviral Vector Manufacturing Over 60 Batches
BLUE	685	Poster	Saturday, May 16, 10:30AM-12:15PM	Efficient Targeted Gene Modification in Primary Human Hematopoietic Cells Using Co-Delivery of Nuclease mRNA and AAV Donors
SNY/Genzyme	247	Poster	Wednesday, May 13, 5:15PM-6:45PM	Characterization of Oversized rAAV Vectors for Human FVIII Gene Transfer
SNY/Genzyme	556	Poster	Friday, May 15, 5:30PM-7:00PM	Analytical Ultracentrifugation as an Approach to Characterize Recombinant AAV Vectors
SGMO	53	Oral presentation	Wednesday, May 13, 3:15PM-5:15PM	From GWAS To the Clinic: Genome-Editing the Human BCL11A Erythroid Enhancer for Fetal Globin Elevation in the Hemoglobinopathies
SGMO	54	Oral presentation	Wednesday, May 13, 3:15PM-5:15PM	Genome Editing of Primary Human $CD34^+$ Hematopoietic Stem Cells Enables a Safe Harbor Targeted Gene Addition Therapeutic Strategy for Chronic Granulomatous Disease
SGMO	55	Oral presentation	Wednesday, May 13, 3:15PM-5:15PM	AAVHSC Vectors Encoding Zinc-Finger Nucleases Mediate Efficient Targeted Integration at the Human AAVS1 Locus in CD34+ Human Hematopoietic Stem Cells
SGMO	115	Poster	Wednesday, May 13, 5:15PM-6:45PM	Correction of the Sickle-Cell Disease Mutation in Human Hematopoietic Stem/Progenitor Cells
SGMO	123	Poster	Wednesday, May 13, 5:15PM-6:45PM	Helper-Dependent Ad5/35 Vectors for ZFN Mediated Gene Editing in Hematopoietic Stem Cells
SGMO	239	Poster	Wednesday, May 13, 5:15PM-6:45PM	Preclinical Studies for the First Hematopoietic Stem Cell (HSC) Gene Editing Trial: Phase 1 Study of Beta-Thalassemia With Autologous Transplantation of Zinc Finger Nuclease-Treated HSC To Upregulate Fetal Hemoglobin
SGMO	342	Poster	Wednesday, May 14, 5:15PM-6:45PM	Gene Edition for Wiskott-Aldrich Syndrome Gene Therapy
SGMO	478	Oral presentation	Friday, May 15, 1:00PM-3:15PM	Highly Efficient Targeted Gene Addition in CD34+ Hematopoietic Stem/Progenitor Cells by Combining ZFN mRNA and AAV6 Donor Delivery
SGMO	684	Oral presentation	Saturday, May 16, 10:30AM-12:15PM	Long-Term, Multilineage Engraftment of Zinc Finger Nuclease-Edited Hematopoietic Stem Cells in Nonhuman Primates
SGMO	686	Oral presentation	Saturday, May 16, 10:30AM-12:15PM	Gene Correction of IL2RG in Human Hematopoietic Stem and Progenitor Cells
QURE	473	Poster	Thursday, May 14, 5:30PM-7:00PM	The Significance of Academia-Industry Collaboration in Translational Research: A Survey of Over 300 PIs Who Have Received Industry Funding
QURE	545	Poster	Friday, May 15, 5:30PM-7:00PM	Strong Cortico-Spinal Transduction After AAV5 Delivery into the Central Nervous System of Nonhuman Primates
QURE	664	Poster	Friday, May 15, 5:30PM-7:00PM	Improving AAV Gene Therapy Safety Analysis: Multiplex LAM-PCR Provide New Insights Into AAV Vector Integration

Sources: ASGCT Annual meeting website, STRH research

American Society of Gene & Cell Therapy Annual Meeting Itinerary continued

Company	Abstract no.	Session	Presentation time	Presentation title
ALCLS	336	Poster	Thursday, May 14, 5:30PM-7:00PM	Targeted Genome Modifications for Improved Adoptive Immunotherapy
ALCLS	419	Poster	Thursday, May 14, 5:30PM-7:00PM	Allogenic CAR T-Cells Targeting CD123 for Adoptive Immunotherapy of Acute Myeloid Leukemia (AML)
ALCLS	421	Poster	Thursday, May 14, 5:30PM-7:00PM	A Multidrug Resistant Engineered CAR T Cell for Allogeneic Combination Immunotherapy
ALCLS	717	Oral presentation	Saturday, May 16, 10:30AM	UCART19, an Allogeneic "Off-the-Shelf" Adoptive T-Cell Immunotherapy Against CD19+ B-Cell Leukemias
AGCT	199	Poster	Wednesday, May 13, 5:15PM-6:45PM	Initial Safety Evaluation of rAAV-hCNGB3 Vectors in Nonhuman Primates
AGCT	463	Poster	Thursday, May 14, 5:30PM-7:00PM	Safety and Biodistribution Study of rAAV2tYF-CB-hRS1 in RS1-deficient Mice
AGCT	470	Poster	Thursday, May 14, 5:30PM-7:00PM	Efficient Clearance of Herpes Simplex Virus Using a GMP-Compliant Method for Production of Recombinant Adeno-Associated Virus Vectors
AGCT	663	Poster	Friday, May 15, 5:30PM-7:00PM	Safety and Biodistribution Study of rAAV2tYF-CB-hRS1 in Nonhuman Primates
ReGenX	372	Poster	Thursday, May 14, 5:30PM-7:00PM	Prevalence of Anti-AAV8 Neutralizing Antibodies and ARSB Cross-Reactive Immunologic Material in MPS VI Patients Candidates for a Gene Therapy Trial
Dimension	258	Poster	Wednesday, May 13, 5:15PM-6:45PM	Universal Stem Cell Gene Therapy Platform: Broadening the Transient Epigenetic Gene Therapy Arm by Using Nuclease-Null dCas9 as an Additional Drive for Efficient Epigenetic Editing
Dimension	401	Poster	Thursday, May 14, 5:30PM-7:00PM	AAV Therapy Attenuates Respiratory Dysfunction and Glycogen Accumulation in a Murine Model of Glycogen Storage Disease Type II
Dimension	671	Poster	Friday, May 15, 5:30PM-7:00PM	Probing the Stability of rAAV Capsids and Genomic Constructs Using Differential Scanning Calorimetry in Concert With Mobile Phase Modifiers
Voyager	86	Poster	Wednesday, May 13, 5:15PM-6:45PM	Comparison of CNS Transduction by Different AAV Capsids in Mouse and Non-Human Primate
Voyager	195	Poster	Wednesday, May 13, 5:15PM-6:45PM	Comparative Analysis In Vitro of Regulatory Elements That Drive Targeted Gene Expression in Adenovirus-Associated Viral (AAV) Vectors
Voyager	502	Oral presentation	Wednesday, May 13, 5:15PM-6:45PM	Optimization of Intrathecal Delivery of AAV for Targeting the Spinal Compartment
Audentes	503	Oral presentation	Friday, May 15, 3:30PM-5:30PM	Minimally Effective Dose of Systemic AAV8-MTM1 Needed To Prolong Survival and Correct Severe Muscle Pathology in a Canine Model of X-Linked Myotubular Myopathy
Editas	124	Poster	Wednesday, May 13, 5:15PM-6:45PM	Cas9-Mediated Genome Editing in Hematopoietic Stem/Progenitor Cells
Editas	166	Poster	Wednesday, May 13, 5:15PM-6:45PM	Biophysical Characterization and Direct Delivery of S. Pyogenes Cas9 Ribonucleoprotein Complexes
Editas	348	Poster	Thursday, May 14, 5:30PM-7:00PM	Characterization of Cas9-Mediated Genome Editing in Human T Cells
Editas	560	Poster	Friday, May 15, 5:30PM-7:00PM	Therapeutic Editing of the HBB Locus Using the Endogenous HBD Locus as a Donor Template
Editas	561	Poster	Friday, May 15, 5:30PM-7:00PM	*Staphyloccocus aureus* Cas9: An Alternative Cas9 for Genome Editing Applications
Editas	687	Oral presentation	Saturday, May 16, 10:30AM-12:15PM	Therapeutic Correction of an LCA-Causing Splice Defect in the CEP290 Gene by CRISPR/Cas-Mediated Genome Editing
Adaptimmune	511	Oral presentation	Friday, May 15, 3:30PM-5:30PM	Enhanced-Affinity NY-ESO-1-Specific T Cells Exhibit Extended Functionality without Exhaustion in a Pattern of Effector and Memory Programming in Multiple Cancer Indications

Sources: ASGCT Annual meeting website, STRH research

AAVL: Valuation and Risks

Valuation

We arrive at our price target of $60 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $46.24/share to AVA-101 U.S. sales, $6.11 to AVA-101 E.U. sales, and $8.04/share to cash. We assign AVA-101 in a probability of success of 55% in the U.S. and 25% in the E.U. We assume a discount rate of 12% and a 1% terminal growth rate. We do not model for any additional indications for AVA-101 beyond wet AMD. We do not include any value for AVA-201, AVA-311, or any other follow on products in our valuation.

Investment risks

The primary investment risks for Avalanche include the following:

• **Clinical and safety risk**: Phase I results presented to date showcased some intriguing signs of activity for Avalanche's AVA-101. The limitations of these data, however, include the small number of patients, a single center whereby doctors were well familiar with subretinal injection, and participants with advanced wet AMD who experienced tremendous increases in best corrected visual acuity. There remains the risk that Phase IIa and Phase IIb data do not recapitulate earlier findings due to differences in patient baseline characteristics, variability in time of assessment and determination of whether an anti-VEGF injection is needed, variability in efficacy measurements. There also remains a risk (albeit minimal) that in vivo dosing of AVA-101 could lead to an exaggerated immune reaction, resulting in loss of anti-VEGF molecule expression of significant loss of eye tissue.
• **Regulatory risk:** No gene therapy product has been approved in the U.S. to date, and in spite of the FDA's guidance there remain questions about the appropriate study design for pivotal gene therapy trials, especially for orphan diseases. The agency may require additional information on manufacturing methodology, as well as facilities where all the moving parts of a complex therapy are generated.
• **Commercial risk:** Given the novelty of gene therapy, there remains a risk that physicians are reluctant to prescribe AVA-101 to their patients. We note the risk of AVA-101 not reaching our sales estimates due to potential pricing and reimbursement issues, lower than expected penetration, or lack of ability to effectively target the broad wet AMD market.
• **Competitive Risk:** AVA-101 is entering the established wet AMD market, where two branded products (RHHBY's Lucentis and REGN's Eylea) and off-label Avastin are competing for share of the prevalent patient pool. Furthermore, AVA-101 competes with products such as Ophthotech's Fovista and Allergan's DARPins, which offer alternatives to the current anti-VEGF standard of care. Beyond monthly or every other month injections, AVA-101 is also competing with other gene therapies, including Sanofi/Genzyme's rAAV2-sFLT01, which has also completed Phase I testing. There is a risk that AVA-101 would not capture significant share of the wet AMD market, or of the retinal vein occlusion or diabetic macular edema markets.
• **Financial and partnership risk:** Avalanche does not currently recognize any revenue related to product sales. Given the expenses associated with clinical drug development, we forecast that the company could issue additional equity to finance its activities. There remains a risk that the company's cash reserves may be significantly depleted while attempting to fulfill collaborative obligations for partner Regeneron. There is a risk that no appropriate candidates emerge from the collaboration with Regeneron, thereby jeopardizing the non-dilutive cash inflow associated with this partnership (we do not model for any revenue associated with the partnership apart from the $6.5M upfront payment).

BLUE: Valuation and Risks

We arrive at our 12-month price target of $115 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $8.52/share from Lenti-D, $98.45/share for LentiGlobin (excluding any contributions from sickle cell disease) and $8.03/share in cash, with the following assumptions: we assign Lenti-D a 75% chance of success and LentiGlobin a 90% chance of success and we assign a WACC of 11% and a 2% terminal growth rate.

The primary investment risks for bluebird include the following:

· **Lenti-D clinical risk**: Although gene therapy carries the promise of a one-time treatment round to cure a disease, it remains an unproven technology. There is a risk that the Phase II/III STARBEAM study of Lenti-D in CCALD may not exhibit any improvement over the historical and/or the contemporary natural history study. The primary endpoint of no major functional disabilities is a highly stringent one, and the new vector formulation has not yet been tested in humans, further adding to the risk of clinical failure.
· **LentiGlobin clinical risk:** The Phase I/II studies of LentiGlobin may fail to demonstrate efficacy with respect to beta-thalassemia and/or sickle cell disease patients achieving transfusion independence. Promising results from 4 patients presented to date may have been confounded by selection bias, and any baseline favorable characteristics that would have contributed to positive patient outcomes (gain of transfusion independence).
· **Safety risk**: Gene therapy studies have been discontinued in the past, with the emergence of safety signals or with the high profile of a patient's death. Given that the bluebird's lentiviral approach relies on genomic integration of the gene of interest, the risk of leukemia cannot be overruled. Emergence of any safety signal or observations of clonal expansion (leukemia precursors) may put a halt to bluebird's clinical programs.
· **Regulatory risk:** Given the lack of any preceding gene therapies approved in the U.S., the path to registration remains unclear, with guidance documents providing an incomplete framework. The contemporary natural history study for CCALD may not be sufficient to provide a "control benchmark" for Lenti-D, and the FDA may delay or decline to approve LentiD solely based on STARBEAM trial data. Timelines to potential approval of LentiGlobin may be delayed, should the agency request longer or additional patient follow up from the Northstar and HGB-206 studies.
· **Commercial and reimbursement risk:** Lenti-D and LentiGlobin may not reach our peak sales estimate due to difficulties in identifying patients with the addressable ultra-orphan disorder CCALD, or beta-thalassemia/sickle cell disease patients willing to undergo gene therapy; the estimated market size, penetration rates, product pricing and reimbursement rates may be smaller than we currently forecast). The price tag that we currently forecast, of $1.5M+ per round of treatment may raise uproar with payers.
· **Competitive risk:** With a flurry of gene therapy companies coming into play, we anticipate that bluebird may face significant competitive pressure. For LentiGlobin, bluebird may have to compete with other players in the space such as Sangamo or Acceleron (XLRN – Not covered) to recruit patients in its clinical trials. For both LentiGlobin and Lenti-D, advances in hematopoietic stem cell transplantation from non-related donors may reduce the unmet need in beta-thalassemia and sickle cell disease/CCALD
· **Exclusivity risk:** Should any of bluebird's competitors claim exclusive use of CAR T cell design and/or method of use, potential revenue streams from the Celgene collaboration could be jeopardized.

BMRN: Valuation and Risks

Valuation

We arrive at our 12-month price target of $151 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $6.05/share from Aldurazyme, $19.05/share from Naglazyme, $9.14/share from Kuvan, $39.23/share from VIMIZIM, $9.54/share from PEG-PAL, $5.43/share from BMN-701, $5.80/share from BMN-673, $4.66/share from BMN-190, $710.10/share from BMN-111, $34.54/share for drisapersen, and $6.03/share in cash, with the following assumptions: we assign a 95% chance of success to Aldurazyme, 95% chance of success to Naglazyme, 90% chance of success to Kuvan, 95% chance of success to VIMIZIM, 75% chance of success to PEG-PAL, 50% chance of success to BMN-701, 75% chance of success to BMN-673 in breast cancer, 75% chance of success to BMN-190, 35% chance of success to BMN-111, and 70% chance of success for drisapersen. We assign WACCs of 9% and 2-4% terminal growth rates.

The primary investment risks for BioMarin include the following:

- BioMarin faces clinical risk for each of their developmental stage products. In particular:
    - BMN-111 faces the risk of hypotension, or decreased blood pressure accompanied by elevated heart rate. This signal has been seen in rodents, monkeys, and humans. If severe enough, it may be viewed as an unacceptable safety risk. BMN-111 may also fail to demonstrate efficacy in the current Phase II trial

- BMN-190 faces risks relating to both efficacy and safety. Delivery of this enzyme via intracerebroventicular injections may not result in delivery of the therapeutic to all of the tissues where it is most needed, or may cause unforeseen safety issues.
- BMN-673 may fail to demonstrate efficacy in Phase III that matches the level of activity seen in Phase II trials. Additionally, unforeseen safety issues could arise due to myelosuppression.
- PEG-PAL may fail to demonstrate efficacy on the Phe lowering endpoint or either of the 2 neurocognitive endpoints (ADHD-RS and POMS) in the ongoing pivotal Phase III trial.

- Regulatory risk: Even upon successful clinical data, the FDA may not view the results as worthy of regulatory approval. In particular, we highlight the risk of certain biomarker endpoints not being suitable for FDA approval. Drisapersen is particularly exposed to regulatory risk as BLA filing is expected to complete in April 2015, and an FDA advisory committee meeting may be held thereafter.
- Commercial risk: Each product may fail to achieve revenue in line with our peak estimates in the commercial market.
- Competitive risk: The emergence of competing therapies, especially in the PARP inhibitor and MPS IIIB markets, may reduce BioMarin's market share.
- Financing risk: BioMarin has a strong balance sheet with over $1B in cash from two large convertible note series taken out in 2014. These convertible notes will increase the number of shares outstanding if exercised, thus diluting existing investors.

GEVA: Valuation and Risks

We arrive at our 12-month price target of $117 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $93.52/share for sebelipase alfa, $6.32/share for SBC-103 and $17.36/share in cash, with the following assumptions: we assign sebelipase alfa a 70% chance of success, SBC-103 a 30% chance of success and we assign a WACC of 9% and a 2% terminal growth rate.

Risks:

- **Sebelipase alfa clinical risk:** While the ARISE study of sebelipase alfa has reached its primary endpoint, as well as the majority of its secondary endpoints, there remains a risk that physicians do not regard improvement with therapy as clinically meaningful.
- **Safety signal:** Data from studies conducted to date suggest that sebelipase alfa is generally safe and well tolerated. However, should more patients experience infusion-related reactions, or any instances of anaphylactic shock caused by allergies to egg white components, it could set back the company's revenue and earnings outlook.
- **Commercial Risk:** The exact prevalence of LAL-D is difficult to estimate, and there is a risk that the true patient population is smaller than published and our estimates. Should a larger than anticipated proportion of patients decide that they do not require therapy, we believe that penetration into the targeted population could be lower.
- **Manufacturing and regulatory risk:** Sebelipase alfa would be, the best of our knowledge, the first biological therapy to be manufactured in the egg whites of transgenic chickens. Without an established precedent the company may require extensive CMC protocols and analyses for a likely FDA review. Any delays in establishing a second manufacturing facility in the U.S., or lack of ability to establish facilities ex-U.S. may negatively impact sales.
- **SBC-103 and pipeline clinical risk:** Synageva does not have any products in the clinic, aside from sebelipase alfa. There remains a risk that neither of these assets demonstrate safety and efficacy in the tested indications.
- **Exclusivity and competition risk:** Synageva is currently competing with BioMarin and other companies for MPS IIIB. Should Synageva infringe BioMarin's patents related to intrathecal enzyme delivery in any fashion, its SBC-103 development may see setbacks

Companies Mentioned in This Note

Avalanche Biotechnologies (AAVL, $35.36, Buy)
bluebird bio, Inc. (BLUE, $132.12, Buy)
BioMarin Pharmaceutical Inc. (BMRN, $116.97, Buy)
Synageva BioPharma Corp. (GEVA, $102.59, Buy)

Analyst Certification

I, Salveen Richter , hereby certify that the views expressed in this research report accurately reflect my personal views about the subject company(ies) and its (their) securities. I also certify that I have not been, am not, and will not be receiving direct or indirect compensation in exchange for expressing the specific recommendation(s) in this report.

Required Disclosures

SunTrust Robinson Humphrey, Inc. managed or co-managed a securities offering for the following companies within the last 12 months: BLUE-US and GEVA-US

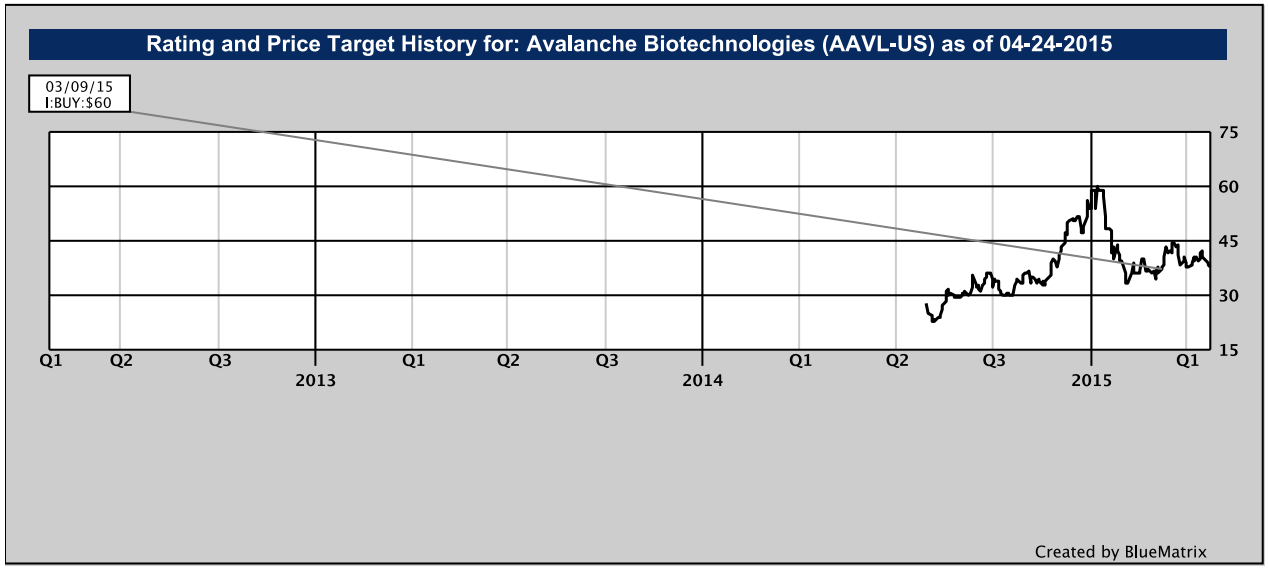
The following companies are clients of SunTrust Robinson Humphrey, Inc. and the firm has received or is entitled to receive compensation for investment banking services involving their securities within the last 12 months: BLUE-US and GEVA-US

An affiliate of SunTrust Robinson Humphrey, Inc. has received compensation for products or services other than investment banking services from the following companies within the last 12 months: BLUE-US and GEVA-US

SunTrust Robinson Humphrey, Inc. makes a market in the following companies at the time of this report: AAVL, BLUE, BMRN, GEVA

Analyst compensation is based upon stock price performance, quality of analysis, communication skills, and the overall revenue and profitability of the firm, including investment banking revenue.

As a matter of policy and practice, the firm prohibits the offering of favorable research, a specific research rating or a specific target price as consideration or inducement for the receipt of business or compensation. In addition, associated persons preparing research reports are prohibited from owning securities in the subject companies.


Rating and Price Target History for: Avalanche Biotechnologies (AAVL-US) as of 04-24-2015
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75
60
45
30
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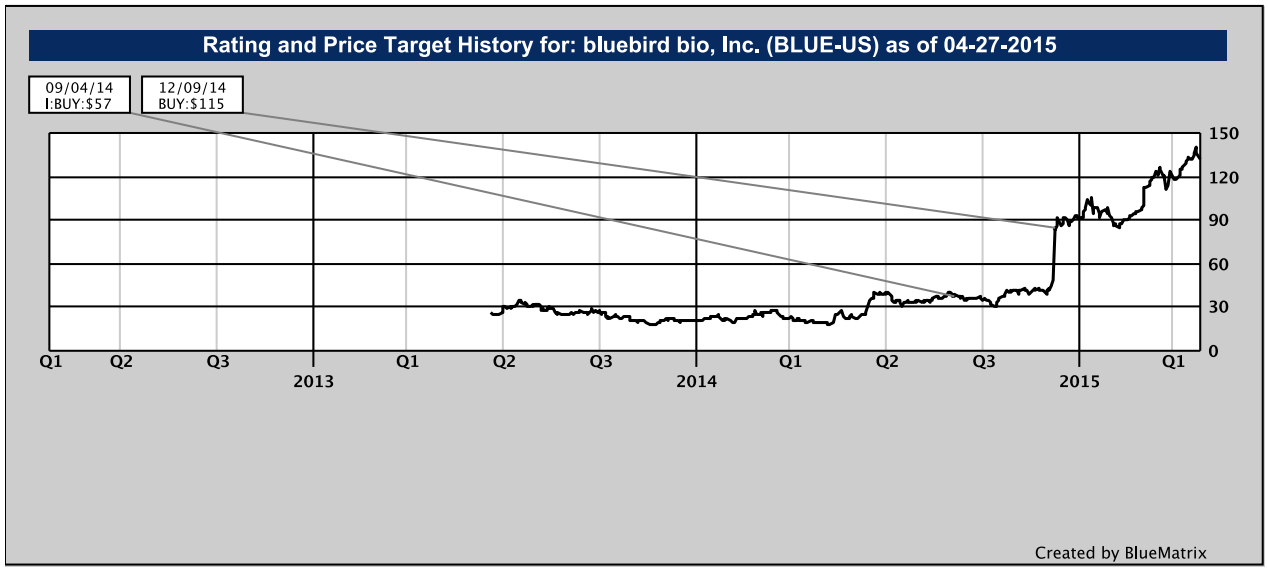
Rating and Price Target History for: bluebird bio, Inc. (BLUE-US) as of 04-27-2015
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12/09/14
BUY:$115
150
120
90
60
30
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Q1
Q2
Q3
2013
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Q3
2014
Q1
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2015
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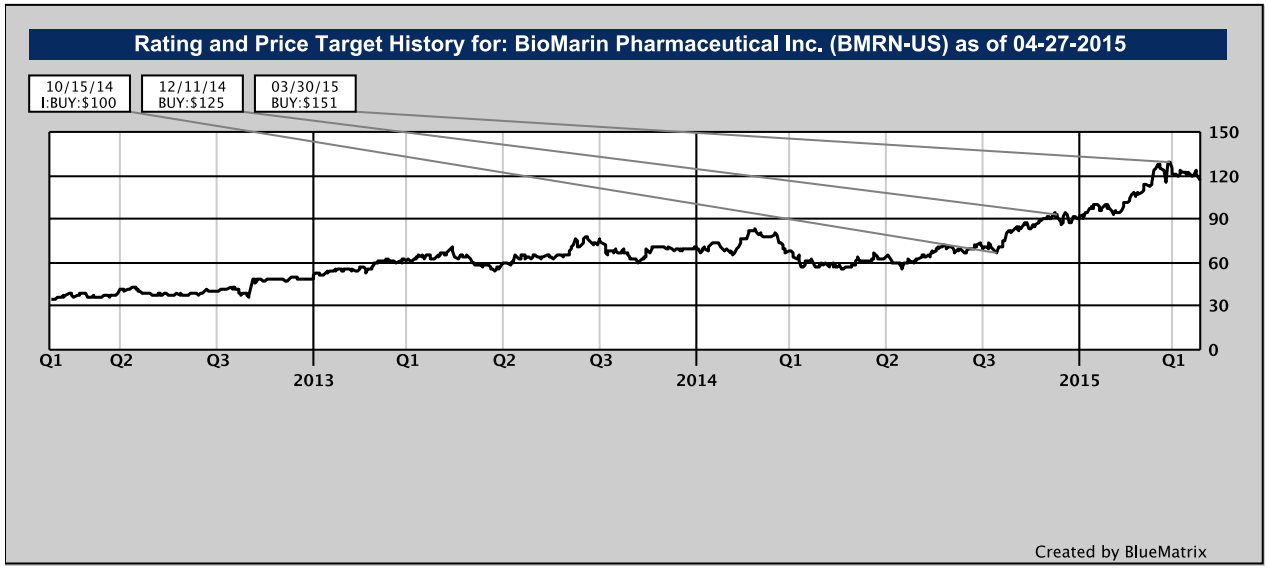
Rating and Price Target History for: BioMarin Pharmaceutical Inc. (BMRN-US) as of 04-27-2015
10/15/14
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12/11/14
BUY:$125
03/30/15
BUY:$151
150
120
90
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30
0
Q1
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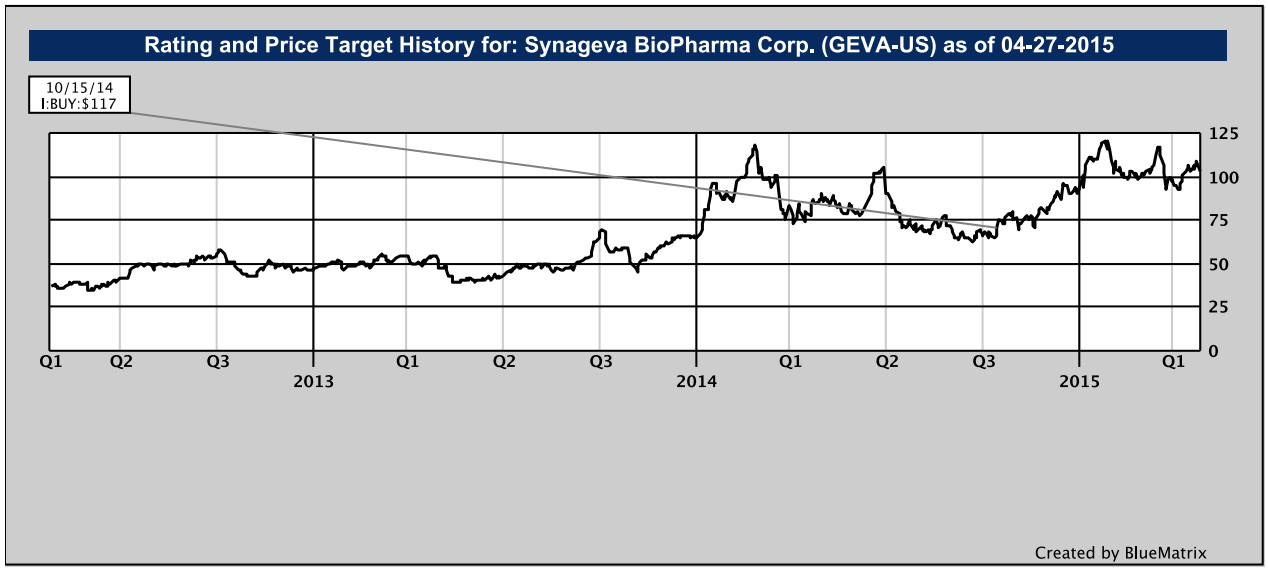
Q1
Created by BlueMatrix


Rating and Price Target History for: Synageva BioPharma Corp. (GEVA-US) as of 04-27-2015
10/15/14
I:BUY:$117
125
100
75
50
25
0
Q1
Q2
Q3
2013
Q1
Q2
Q3
2014
Q1
Q2
Q3
2015
Q1
Created by BlueMatrix

STRH Ratings System for Equity Securities

3 designations based on total returns* within a 12-month period**

- **Buy** – total return ≥ 15% (10% for low-Beta securities)***
- **Reduce** – total return ≤ negative 10% (5% for low Beta securities)
- **Neutral** – total return is within the bounds above
- **NR** – NOT RATED, STRH does not provide equity research coverage
- **CS** – Coverage Suspended

*Total return (price appreciation + dividends)
**Price targets are within a 12-month period, unless otherwise noted
***Low Beta defined as securities with an average Beta of 0.8 or less, using Bloomberg's 5-year average Beta

Legend for Rating and Price Target History Charts:
D = drop coverage
I = initiate coverage
T = transfer coverage

SunTrust Robinson Humphrey ratings distribution (as of 04/27/2015):

Coverage Universe			Investment Banking Clients Past 12 Months		
Rating	**Count**	**Percent**	**Rating**	**Count**	**Percent**
Buy	282	52.22%	Buy	103	36.52%
Neutral	246	45.56%	Neutral	48	19.51%
Sell/Reduce	12	2.22%	Sell/Reduce	3	25.00%

Other Disclosures

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