William Blair

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Avalanche Biotechnologies, Inc.

Analyst Day Highlights Need for AVA-101 Ahead of Phase IIa and Large Color Blindness Opportunity

- We attended Avalanche Biotech's analyst and investor day on March 25 in New York. Overall, the company gave further details on its Phase I study subjects, baseline characteristics of its Phase IIa study, a view of its regulatory development pathway, and a look into its pipeline products that are geared to address genetic disorders, such as X-linked retinoschisis (XLRS) with partner Regeneron (REGN $453.99), as well as newly announced AVA-322 and AVA-323, which are being developed in collaboration with the University of Washington to treat red-green color blindness (which effects about 10 million individuals).

- The company highlighted AVA-101's extended Phase I results and showed new Phase IIa subject baseline data. AVA-101 is a gene therapy comprising an adeno-associated virus (AAV2) vector which contains a gene encoding sFLT-1, a naturally occurring VEGF inhibitor. We continue to view the gene therapy delivery of antivascular endothelial growth factor (VEGF) by Avalanche as a best-in-class approach with the potential to be disruptive to the roughly $6 billion worldwide wet age-related macular degeneration (AMD) market. As shown in exhibit 1, new data presented at the analyst event showed a significant decrease in Lucentis injections post-therapy in patients who were already treatment experienced. The baseline characteristics of patients in the Phase IIa and Phase I study are shown in exhibit 2. When comparing the baseline characteristics from the first two studies, patients had a much higher best-corrected visual acuity (BCVA) score in the Phase IIa study than in the Phase I study, reflecting ophthalmologists' increasing comfort in allowing patients with better vision to be enrolled in the study and not restricting access to patients with severe disease. Exhibit 3 gives an example of a treatment-experienced Phase IIa subject, an 81-year-old female, who had seven prior Lucentis injections, with wet AMD with BCVA of 75 letters (20/32 vision).

- Under the current standard of care, the patient, while studied, would need 6-12 injections per year, using an as-needed treatment average of three to six intravitreal injections per year, versus AVA-101's value proposition of a single injection. While we believe OCT and visual acuity benefits are possible in the upcoming dataset, we still believe shares would react favorably under several scenarios, including an overall reduction in Lucentis rescue therapy to two doses on average (0.33 in Phase I), a subgroup of hyper-responders (given the large market), and a maintenance of vision. In addition, we would see efficacy signals in the Phase IIa as a significant proof of concept, given the more real-world patient enrollment and the reproducibility of Phase IIa results in Phase IIb and Phase III trials for previous anti-VEGF clinical programs. Dr. Samuel Barone, Avalanche's chief medical officer, outlined the potential development pathway and regulatory path of AVA-101 based on previously approved therapies. We note that Dr. Barone's previous position was with the FDA's Office of Cellular, Tissue, and Gene Therapies, which would be the subgroup Avalanche would deal with if it were to submit its products for regulatory approval.

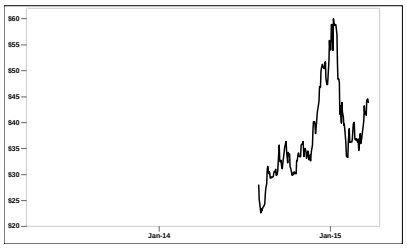
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$53.00
Symbol:	AAVL (NASDAQ)
Price:	$41.04 (52-Wk.: $22-$62)
Market Value (mil.):	$1,101
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	2014A	2015E	2016E
Estimates			
EPS FY	$-2.01	$-2.45	$-2.57
CY		$-2.45	$-2.57
Sales (mil.)	1	0	0
Valuation			
FY P/E	NM	NM	NM
CY P/E		NM	NM

Trading Data (FactSet)	
Shares Outstanding (mil.)	16
Float (mil.)	15
Average Daily Volume	299,692

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.0
Book Value Per Share (MRQ)	6.9
Return on Equity (TTM)	-34.0

Two-Year Price Performance Chart



Sources: FactSet, William Blair & Company estimates

Avalanche Biotechnologies is a biotechnology company located in Menlo Park, California, focused on developing gene-based therapies for the treatment of ocular diseases.

- The next milestones for AVA-101 include Phase IIa topline data in mid-2015, Phase I 36-month safety data presentation in the second half of 2015 (most likely at the American Academy of Ophthalmology's annual meeting on November 14-17 in Las Vegas), and Phase IIb study initiation in 2015, which will be a U.S. multicenter, sham-controlled, double-blind, dose-ranging study powered on efficacy measured by visual acuity.

- Lastly, Avalanche announced a partnership with the University of Washington to develop products for the treatment of red-green color blindness using the company's Ocular BioFactory platform, and CEO Dr. Thomas Chalberg highlighted its new products, AVA-322 and AVA-323, at the analyst event on March 25. Avalanche's approach will build on the research conducted by Drs. Jay and Maureen Neitz of the University of Washington's Department of Ophthalmology. In the University of Washington published study, two adult male squirrel monkeys showed that, after therapy with a gene encoding the M3 pigment, they could tell blue-green from gray. The authors monitored the time course of function, as well, and found that the M3-cone pigment appeared about 20 weeks after injection, and it was associated with the change in visual function (Mancuso et al. *Nature* 2009).

- At the analyst event, Dr. Neitz said that the company expects the pipeline products to enter the clinic within two years, and we believe that single-gene mutations that result in ocular dysfunctions represent diseases where AAV gene therapies could be particularly effective; the doctors stated that they are seeing efficacy using Avalanche's proprietary vectors within one month. We will eagerly watch the development of this program as red-green color blindness affects more than 10 million people in the United States, and we believe it is rare for a company of Avalanche's size to be in the lead position for not only the $6 billion wet AMD market, but also a market the size of red-green color blindness. While not discussed at the event, we believe the cone-directed therapies being developed for Avalanche in red-green color blindness could also be leveraged by the company in additional genetic disorders affecting the cone, diseases such as cone retinitis pigmentosa, cone rod dystrophy, and Stargardt's disease. We note that the color blindness program falls outside of the company's Regeneron relationship, with Avalanche holding all rights to the program.

- We continue to rate shares of Avalanche Biotechnologies with an Outperform rating and maintain our $53 price target, which is derived from conservative assumptions on AVA-101 alone. We believe that the company continues to lead in the ocular gene therapy field, and while the company has treated only a handful of patients to date with AVA-101, the proof-of-concept results are impressive with a functional cure in patients with wet AMD after prior heavy Lucentis use. In addition to the disruptive potential of AVA-101, we come away from the company's analyst day with the notion that Avalanche's pipeline compounds AVA-201, AVA-322, AVA-323, and AVA-311 hold significant promise for gene therapies to treat ocular diseases and potentially create true transformational therapies in unmet medical needs. Given the breadth of the company's development programs, we believe the company is positioned to enter the ranks of mid-cap companies in the sector, pending clinical success from AVA-101, given the innovation and large opportunities addressed by the company's pipeline.

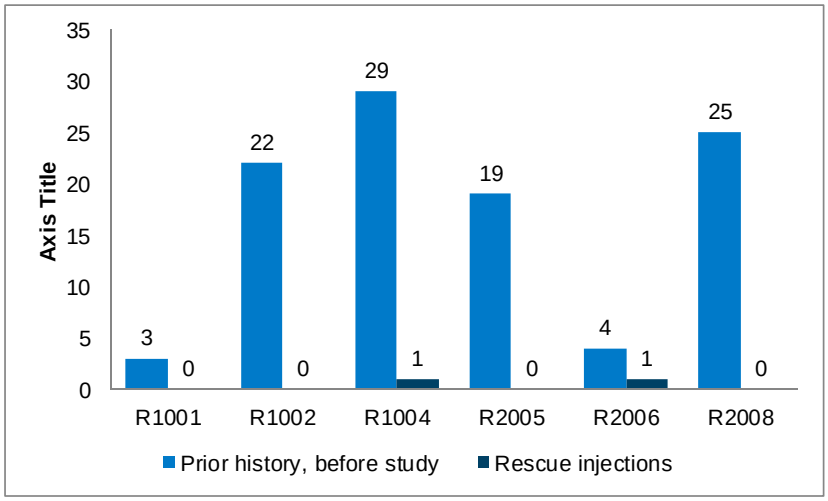
Additional Details:

Dr. David Brown began the day by speaking on the wet AMD landscape and patient burden. He initially spoke on the impact of VEGF therapy on patient lives, with the standard-of-care transition from verteporfin to ranibizumab (Lucentis) cutting blindness caused by AMD in half. However, the disease still affects 2.1 million people and given the aging population, is expected to double by 2050. Intravitreal injections will continue to represent a significant burden, considering two-thirds of AMD patients need chronic therapy, with the annual number of injections increasing over 30% every year and the total cost of intravitreal injections in 2010 nearing roughly $1.6 billion.

The next speaker, Dr. Jean Bennett, spoke specifically on the development of gene therapy and AVA-101. She highlighted the immune privilege of the eye that makes it ideal for specific delivery of AAV technology. She spoke on AVA-101 preclinical data that reversed neovascularization, which was durable to at least eight months, in a transgenic mouse model that expressed high VEGF in the retina.

Dr. Jeffrey Heier then spoke on the early results of the AVA-101 program. The Phase I study showed that AVA-101 was well-tolerated with no drug-related adverse events, inflammation, retinal tears/detachments, or localized biodistribution, and the majority of subjects did not require retreatment. Although Dr. Heier showed the visual acuity benefits in the Phase I study (which showed an average of a gain of 7.5 letters from baseline to 12 months), he noted that anatomical outcomes are more important in early phase studies, and the central retinal thickness improved and was maintained throughout the 12-month time frame in the AVA-101 Phase I study. In addition, Dr. Heier showed the prior history of anti-VEGF injections in patients who were enrolled in the Phase I study in the AVA-101 low- and high-dose groups. As shown in exhibit 1, patients had a range of 3-29 injections prior to enrollment, and these patients had an average of 0.33 injections over the 52-week course of the study.

Exhibit 1
Phase I Study Subjects Before and After AVA-101



Source: Company reports

Dr. Heier also detailed some of the baseline characteristics of the patients in the Phase IIa study, which we show in exhibit 2. Overall, patients in the Phase IIa study had a much higher BCVA score than the Phase I study, which reflects ophthalmologists increasing comfort in allowing patients with better vision to be enrolled in the study. Exhibit 3 gives an example of a treatment-experienced Phase IIa subject, an 81-year-old female, who had seven prior Lucentis injections, with wet AMD with BCVA of 75 letters (20/32 vision). Under the current standard of care, the patient would need 6-12 injections per year versus AVA-101's value proposition of one injection. We believe that if OCT and initial visual acuity benefits are seen in addition to safety and tolerability in the Phase IIb patient enrollment population, the company could see a significant increase in valuation as AVA-101 goes from a proof-of-concept therapy in six progressed patients to potentially treating more patients with a more real-world diagnosis of wet AMD.

Exhibit 2
Phase IIa Baseline Characteristics Compared to Phase I

	Phase I	Phase IIa
Age (years)	79 (71-86)	79.5 (62-95)
Baseline BCVA (ETDRS letters)	36.5 (28-56)	63 (35-78)
Baseline center point thickness (μm)	549 (193-1094)	332.5 (179-816)
Number treatment naïve (n/N)	0/8	4/32
Previous anti-VEGF injections (for non-naïve)	11.5 (1-29)	10.5 (1-25)
Time since diagnosis (months)	49.2 (2-65)	16.2 (0-85)

all values median (range)

Source: Company reports

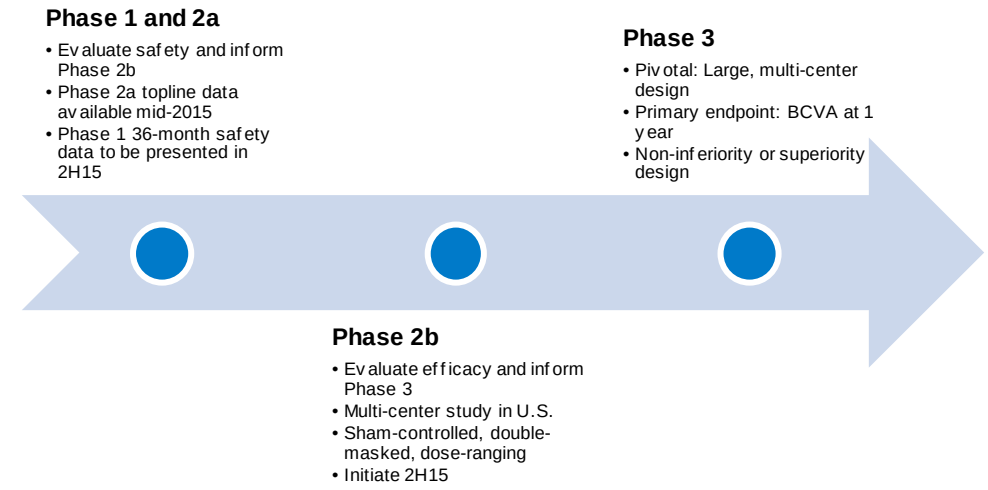
Exhibit 3
Example Phase IIa Subject

Treatment-Experienced Phase IIa Subject
81 year old female with wet-AMD
Peristent subretinal and sub-RPE fluid, PED lesion
BCVA = 75 letters (20/32)
7 Previous Lucentis injections prior to enrollment
Standard of Care = Vision Maintenance
Maintaining vision with 6-12 injections per year
Expected 30-50 injections over 5 years
55% of patients wet each month, 22% always wet with monthly therapy

Source: Company reports

Dr. Samuel Barone, Avalanche's chief medical officer, outlined the potential development pathway and regulatory path of AVA-101, based on previously approved therapies. We note that Dr. Barone's previous position was with the FDA's Office of Cellular, Tissue, and Gene Therapies which would be the subgroup Avalanche would deal with if it were to submit its products for regulatory approval. Dr. Barone showed the development plan for AVA-101, as shown in exhibit 4. It is important to note that the Phase I and Phase IIa studies are important to evaluate safety and inform the U.S. based Phase IIb study. As far as 2015 catalysts, Phase IIa top-line data should be announced in mid-2015; Phase I 36-month safety data will be presented in the second half of 2015, most likely at the American Academy of Ophthalmology's annual meeting on November 14-17 in Las Vegas; and the Phase IIb study is expected to initiate in the second half of 2015 as a multicenter, sham-controlled, double-masked, dose-ranging trial in the United States, with the primary endpoint at week 52 and patients followed out to 104 weeks.

Exhibit 4
Development Plan For AVA-101



Source: Company reports

Dr. Szilard Kiss spoke on subretinal delivery, the impact of vitrectomy, reversal of gene therapy, and AMD/atrophy. He showed an example of subretinal delivery to show the procedure. He then noted DRCR.net protocol-evaluated outcomes of eyes with diabetic macular edema with and without vitrectomy and found similar visual acuity and OCT outcomes in both groups, which provides evidence that vitrectomy plays no role in benefit or harm in patients with vitreoretinal diseases. Vitrectomy is a procedure that involves removal of the vitreous gel from the middle of the eye to give access to the subretinal space, which is needed for subretinal injection. Dr. Kiss also addressed the AMD/atrophy debate by stating that the incidence of atrophy and growth rates on anti-VEGF therapies are similar to previously published rates, and cited literature that a low level of continuous anti-VEGF therapy (which would be the case with AVA-101) does not result in peaks and troughs that may induce risk. We continue to believe that geographic atrophy is not a serious risk for gene therapy in AMD.

Red-Green Color Blindness Gene Therapy a 10-Million Patient Opportunity

Avalanche announced a partnership with the University of Washington to develop products for the treatment of red-green color blindness using the company's Ocular BioFactory platform, and CEO Dr. Thomas Chalberg highlighted its new products, AVA-322 and AVA-323, at the analyst event today. Avalanche's approach will build on the research conducted by Drs. Jay and Maureen Neitz of the University of Washington's Department of Ophthalmology. In their study on two adult male squirrel monkeys published in *Nature*, they showed that, after therapy with a gene encoding the M3 pigment, the monkeys could tell blue-green from gray. The authors monitored the time course of function as well and found that the M3-cone pigment appeared about 20 weeks after injection, and it was associated with the change in visual function. We believe this partnership represents an interesting preclinical opportunity with significant potential for Avalanche. Color blindness is a common genetic disorder that affects about 5%-8% of males and less than 1% of females (roughly 10 million patients), and is due to the absence of a single X-chromosome gene that leads to a loss of function. Normal human vision is dependent on three photopigments (trichromats) in the retina's cone photoreceptors, and those with the genetic disorder only develop two photopigments and are referred to as dichromats. Dr. Maureen Neitz stated that it expect the therapies to treat red-green color blindness to enter the clinic within two years.

Dr. Roman Rubio, the company's senior vice president of translational medicine, ended the speaker session by speaking about the now-updated product pipeline (exhibit 5). He showed new data from a rodent model treated with AVA-201, the company's pipeline product for the potential prevention of wet AMD, which had an increase in median sFlt1 concentration eight weeks post intravitreal injection, compared with AVA-101 delivered intravitreally (versus intraretinally). In addition, Dr. Rubio noted that it is currently developing a biomarker strategy, which could accelerate the clinical development plan, to identify high-risk patients. We believe this pipeline product and associated biomarker development has the potential to be even more revolutionary than AVA-101 to the field of wet AMD.

Exhibit 5
Product Pipeline

Product Candidate	Indication	Stage of Development	Near-term Milestones	Worldwide Commercial Rights
		Research Pre-Clinical Phase I/II		
AVA-101	Wet AMD		Top line Phase 2a data mid-2015 IND filing 2H15	Avalanche
AVA-101	DME, RVO		IND-enabling studies in 2015	Avalanche
AVA-201	Wet AMD (prevention)		Target candidate finalization	Avalanche
AVA-322 AVA-323	Color vision deficiency		IND-enabling studies in 2015 IND filing 2H16	Avalanche
AVA-311	XLRS		Preclinical studies ongoing	Regeneron Avalanche receives milestones and royalties and has an option to share development costs and profits

Source: Company reports

Valuation

We rate shares of Avalanche Outperform with a price target of $53. In this calculation, we assume a launch of AVA-101 in 2019, following approval early that same year. We believe peak-year sales will reach about $1.1 billion domestically. Our estimates assume a penetration of 45% into the AMD incidence and a cost of $30,000 (below the $44,000 to $46,000 cost of two years of Lucentis/Eylea). We also include minimal revenue from diabetic macular edema (DME) and retinal vein occlusion (RVO) and no revenue from outside the United States, which is likely conservative.

Risks

Risks to shares of Avalanche are similar to those of other development-stage therapeutics companies. The company faces clinical, manufacturing, and regulatory risks on its product candidates. There are additional clinical risks in developing a new cutting-edge technology. Any clinical or regulatory setbacks for the AVA-101 program or other gene therapy products in development would weigh heavily on shares.

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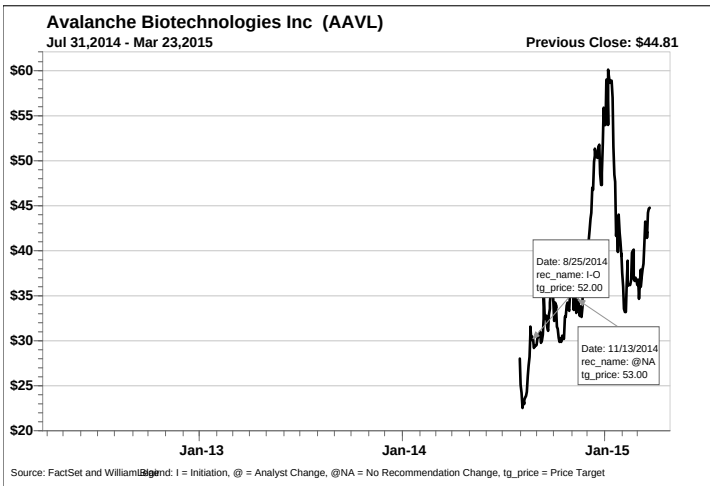
DOW JONES: 18,011.14
S&P 500: 2,091.50
NASDAQ: 4,994.73



Current Rating Distribution (as of 02/28/15)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65	Outperform (Buy)	16
Market Perform (Hold)	32	Market Perform (Hold)	2
Underperform (Sell)	2	Underperform (Sell)	0

*Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

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