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Avalanche Biotechnologies, Inc.

ARVO Wrap-Up: Gene Therapies Continue to Look Impressive Ahead of 2015 Data Sets

- We attended the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) in Denver. We focused on gene therapies under development, with companies such as Avalanche Biotechnologies and Spark Therapeutics (ONCE $59.36) presenting incremental preclinical and clinical data. The biotech sector, and in particular gene therapy companies, has recently experienced weakness (exhibit 1); however, we continue to believe in the potential for safe and efficacious gene therapies, and continue to view diseases of the eye as an immune-privileged area for clinical development.

- Dr. Elizabeth Rakoczy from the University of Western Australia presented additional data from the AVA-101 Phase I study. The presentation included new analyses of systemic VEGF levels and immune response in the six treated patients (three high dose and three low dose). Levels of serum VEGF in the small data set look in line with if not improved to Lucentis and Eylea, suggesting a lack of systemic exposure and a likely continued strong systemic side-effect profile. While one patient developed an antibody response, it was deemed transient and not associated with a safety or efficacy signal.

- Regarding Avalanche's Phase IIa data, we believe a successful study will include meeting the primary endpoint of safety and tolerability over 52 weeks with an average of 1 Lucentis rescue injection or less in the AVA-101 group (versus 3-6 in the placebo group) along with stability or minimal letter improvement in visual acuity, although the company did see an increase of 6.3 letters in the high dose in the Phase I trial. The reasoning behind our visual acuity expectations is the healthier patient population in the Phase IIa study in addition to the inclusion of primarily long-term Lucentis users who have already received a benefit in visual acuity from Lucentis, an improvement that usually plateaus over longer-term use.

- Also a topic of conversation at the conference were two articles recently published in the *New England Journal of Medicine* on follow-up studies of gene therapies used to treat Leber's congenital amaurosis (LCA), a group of inherited retinal dystrophies. The study conducted in the United States showed five- to six-year post-treatment follow-up of three patients who were given a single subretinal injection into one eye, with the contralateral eye serving as the control (Jacobson SG et al., *New England Journal of Medicine* 2015). All three patients had improvement in visual sensitivity that peaked at one to three years after treatment and declined thereafter at the same rate as the untreated retina. The second study, conducted in the United Kingdom, involved 12 patients and a single subretinal injection (including the fovea). Six of the 12 patients had improvements in visual sensitivities that peaked at 6 to 12 months after injection, but the effect declined by three years post-injection (Bainbridge JWB et al., *New England Journal of Medicine* 2015. While the durability of improvements weighed on shares of both Avalanche and Spark, we believe there are significant differences between both diseases being targeted (wet AMD for Avalanche versus LCA) and technology being employed. Even a one-year duration of effect in wet AMD would be a significant improvement over the current monthly/every-other-month dosing.

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

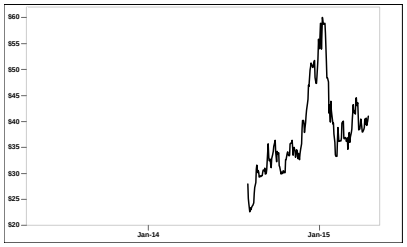
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$53.00
Symbol:	AAVL (NASDAQ)
Price:	$33.39 (52-Wk.: $22-$62)
Market Value (mil.):	$752
Fiscal Year End:	December
Long-Term EPS Growth Rate:	NA
Dividend/Yield:	None

		2014A	2015E	2016E
Estimates				
EPS	Q1	$-0.45	NA	NA
	Q2	$-2.27	NA	NA
	Q3	$-0.50	NA	NA
	Q4	$-0.46	NA	NA
	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.)	23
Float (mil.)	15
Average Daily Volume	351,380

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.0
Book Value Per Share (MRQ)	6.6
Return on Equity (TTM)	-38.4

Two-Year Price Performance Chart



Sources: FactSet, William Blair & Company estimates

- We continue to rate shares of Avalanche Outperform 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 with an impressive management team. While Avalanche 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, the company's pipeline includes multiple other compounds that may be transformational for other ocular diseases.

Exhibit 1
Gene Therapy Stock Price Performance as of May 5th, 2015

Company	Ticker	Price	Rating	Market Capitalization	Debt	Cash	EV	Week-To-Date	Month-To-Date	Quarter-To-Date	Year-To-Date
Spark Therapeutics	ONCE	$52.65	Not Rated	$1,292	$0	$75	$1,217	1.4%	3.6%	-23.4%	NA
Avalanche Biotech	AAVL	$29.44	Outperform	$665	$0	$159	$506	0.7%	4.8%	-17.6%	-38.2%
Applied Genetic Tech Corp	AGTC	$15.82	Not rated	$260	$0	$75	$184	-15.8%	-12.6%	-16.3%	-20.4%
Celladon	CLDN	$2.51	Not Rated	$59	$10	$85	($16)	-4.2%	-7.4%	-86.7%	-87.1%
uniQure	QURE	$24.70	Not Rated	$439	$20	$79	$380	12.1%	10.0%	13.3%	86.1%
bluebird bio	BLUE	$133.06	Not Rated	$3,908	$0	$474	$3,435	0.5%	4.8%	15.6%	52.2%
Gene Therapies				**$1,104**	**$5**	**$158**	**$951**	**-0.9%**	**0.6%**	**-19.2%**	**-1.5%**
Nasdaq Biotech	NBI	$3,539.59						-0.8%	2.0%	-0.8%	12.4%
Amex Biotech	BTK	$3,832.58						-0.7%	2.5%	-3.2%	12.2%
Amex Pharm	DRG	$578.14						-1.3%	-0.3%	0.9%	7.9%
Russell 2000	RUT-RUX	$1,215.42						-0.7%	-0.1%	-2.7%	1.2%
S&P500	SP50	$2,089.46						-1.3%	-0.3%	0.6%	1.0%
Indices								**-0.8%**	**1.1%**	**-2.7%**	**5.9%**

Source: FactSet

Additional Details

Dr. Elizabeth Rakoczy from the University of Western Australia presented additional data from the AVA-101 Phase I study. The presentation included new analyses of VEGF levels and immune response in the six treated patients (three high dose and three low dose). Serum, urine, and saliva concentrations of sFlt-1 and serum VEGF concentrations at different time points over the one-year follow-up showed some increases at various time points but there were no associations with AAV therapy, and the mean VEGF concentrations at every time point collected were approximately 350 pg/ml (or 0.35 ng/ml).

Since systemic exposure would be a concern given potential side effects, we note that the Lucentis label describes the pharmacokinetics of monthly intravitreal administration of 0.5 mg Lucentis that resulted in mean maximum serum concentrations of 1.7 ± 1.1 ng/mL, with maximum concentrations reached at approximately 1 day and an elimination half-life of 9 days. It also estimates a steady-state minimum concentration of 0.22 ng/mL with a monthly dosing regimen. The Eylea label describes the mean Cmax of free aflibercept in the plasma as 0.02 µg/mL or 20 ng/mL (range: 0 to 0.054 µg/mL or 54 ng/mL) and was attained in one to three days after intravitreal administration of 2 mg Eylea per eye to patients with wet AMD. Therefore, we believe that the concentrations of VEGF reported by Dr. Rakoczy are consistent with currently approved therapies and should not pose a risk in side effects that follow from systemic VEGF exposure.

In addition, the data showed an increase in anti-AAV2 antibodies in one patient (that management stated was elevated at baseline as well) and one patient (not the same as the one who had increased antibodies) who had a transient T-cell response; however, neither increases were associated with any adverse events and were most likely attributed to inter-individual variability. We continue to believe that AVA-101 is a safe and tolerable therapy heading into the near-term catalyst of Phase IIa data to be reported in mid-2015.

Regarding Avalanche's Phase IIa data, we believe a successful study will include meeting the primary endpoint of safety and tolerability over 52 weeks with an average of 1 Lucentis rescue injection or less in the AVA-101 group (versus 3-6 in the placebo group) and any letter increase in visual acuity (the company did see an increase of 6.3 letters in the high dose in the Phase Ia trial). The patients in the Phase IIa study have wet AMD in a less progressed state than the patients in the Phase Ia trial (exhibit 2). The reasoning behind our visual acuity expectations is the healthier patient population as well as the fact that patients in the studies are primarily long-term Lucentis users who have already received a benefit in visual acuity that usually plateaus, as has been shown in their clinical trial program. We believe that a reduction in the number of rescue injections is the likely most translatable outcome to larger Phase IIb and pivotal studies. As a reminder, the study is not powered to detect differences in visual acuity, although a meaningful increase in best corrected visual acuity would likely be viewed as upside, but may not translate into larger Phase IIb and Phase III trials. We also believe it will be interesting to examine the treatment-

naïve patients (although there are only four in the Phase IIa, and randomization may place several of them in the placebo group) to examine the potential of AVA-101 as a first-line therapy.

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

On Monday, two articles were published in the *New England Journal of Medicine* on follow-up studies of gene therapies used to treat Leber's congenital amaurosis (LCA), a group of inherited retinal dystrophies that are associated with blindness in early life and caused by loss-of-function mutations. The studies described in the *New England Journal of Medicine* involved long-term follow-up of patients with RPE65-associated LCA treated with AAV2 vectors. The study conducted in the United States showed five- to six-year post-treatment follow-up of three patients who were given a single extrafoveal subretinal injection into one eye, with the contralateral eye serving as the control (Jacobson SG et al., *New England Journal of Medicine* 2015). All three patients had improvement in visual sensitivity that peaked at one to three years after treatment and declined thereafter along with a loss of photoreceptors at the same rate as the untreated retina. The second study, conducted in the United Kingdom, involved 12 patients and a single subretinal injection (including the fovea). Six of the 12 patients had improvements in visual sensitivities, which peaked at 6 to 12 months after injection, but the effect declined by 3 years post-injection (Bainbridge JWB et al., *New England Journal of Medicine* 2015.

The results of these studies had direct read-through to all the gene therapy companies, particularly Spark and Avalanche, but also including those outside retinal diseases such as bluebird bio (BLUE $139.62). We believe that the Street is incorrectly bundling gene therapies, when significant differences exist in not only the diseases that are treated, but also the manufacturing process of the vectors. In our opinion, even the most directly correlated clinical program, Spark's SPK-RPE65 AAV2, is targeting a different promoter sequence in the RPE65 gene and has a differentiated protocol (from the *New England Journal of Medicine* studies) for vector manufacturing that produces an approximately 1.8-fold higher average recovery of vector, includes a surfactant that improves delivery over the published studies, and also has a reduction in DNA and protein impurities and empty capsids (Ayuso E et al., *Gene Therapy* 2010). Avalanche's Ocular BioFactory platform selects for candidates that can target specific cell layers in the retina. Therefore, we believe that the *New England Journal of Medicine* studies, while showing a three-year improvement in visual acuity (still impressive duration) and subsequent decline that was seen as a disappointing result for those expecting a one-shot lifetime therapy, should not have any read-through to Avalanche's programs or the probability of success for the Phase IIa trial.

Dr. Szilard Kiss presented an analysis of the CATT study and geographic atrophy in a follow-up from the company's analyst event at the American Academy of Ophthalmology annual meeting last year. Dr. Kiss concluded that atrophy development was not accelerated with increasing exposure to anti-VEGF, with patients receiving the most injections having the least atrophy at week 104. In addition, anti-VEGF therapy is known to improve visual acuity in patients with or without geographic atrophy. We continue to believe that geographic atrophy is part of the progression of the disease and is not associated with increased exposure to anti-VEGF therapies.

We continue to rate shares of Avalanche Biotechnologies Outperform 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 (exhibit 3). Given the breadth of Avalanche's development programs, we believe the company is positioned to enter the ranks of midcap companies in the sector, pending clinical success from AVA-101, given the innovation and large opportunities addressed by the company's pipeline.

Exhibit 3
Product Pipeline

Product Candidate	Indication	Stage of Development	Near-term Milestones	Worldwide Commercial Rights
AVA-101	Wet AMD	Phase I/II	Top line Phase 2a data mid-2015 IND filing 2H15	Avalanche
AVA-101	DME, RVO	Phase I/II	IND-enabling studies in 2015	Avalanche
AVA-201	Wet AMD (prevention)	Research	Target candidate finalization	Avalanche
AVA-322 AVA-323	Color vision deficiency	Phase I/II	IND-enabling studies in 2015 IND filing 2H16	Avalanche
AVA-311	XLRS	Phase I/II	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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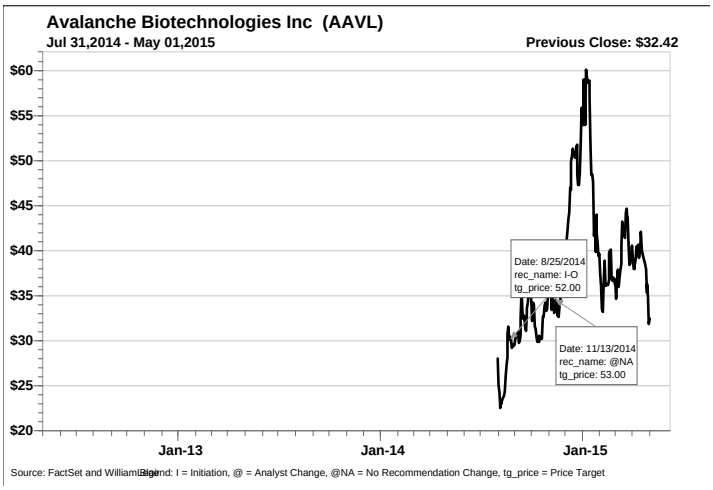
DOW JONES: 17,928.20
S&P 500: 2,089.46
NASDAQ: 4,939.33



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Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65	Outperform (Buy)	14
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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