William Blair

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Avalanche Biotechnologies, Inc.

Lucentis Performance and Difficult Population Clouds Phase IIa; Phase IIb a Ways Away; Downgrading to Market Perform

- After the close Monday, June 15, Avalanche Biotech reported the top-line results of its Phase IIa trial and the 36-month follow-up from its Phase I study. The Phase IIa trial, which was powered for safety and tolerability, met the primary endpoint with no serious adverse events related to therapy observed and all adverse events related to study drug were mild or moderate and resolved within 60 days. The primary focus of investors, however, was the secondary efficacy endpoints related to visual acuity, number of rescue injections, and retinal thickness, which we believe showed mixed results. We expect detailed results at AAO in November and clarity on a potential development deal with Regeneron (REGN $499.06) for rights to AVA-101 in the near term. However, we believe the performance of Lucentis in the control arm raises more questions than answers and while we believe there is a treatment effect, considering the innovative gene therapy approach and the high bar for safety/efficacy in the VEGF class of therapies, we are downgrading shares from Outperform to Market Perform. While the next major catalyst for shares is a potential deal between both Regeneron and Avalanche, it is likely beneficial for both parties to wait until Phase IIb results to enter discussions as both parties (and the market) will likely have difficulty in valuing AVA-101 as an asset until additional results are available.

- **BCVA clouded by performance of Lucentis treatment arm.** The Phase IIa study showed a mean change in baseline best corrected visual acuity (BCVA) of 11.5 letters between the AVA-101 group (+2.2 letters) and control (-9.3 letters). On the call, management stated that the 95% confidence interval in the control arm (Lucentis PRN regimen) was between -19 letters and +0.4 letters, which was consistent with the difficult-to-treat population that was enrolled into the study. However, we are concerned with the control arm results given the breadth of anti-VEGF studies that have been performed that do not result in a 9.3 letter decrease in a treatment-as-needed population. We note the CATT two-year follow-up results that show a slight decrease (about 1-2 letters) from the Year 1 endpoint to the Year 2 endpoint, but still much higher than the results seen in Avalanche's Phase II study; however, this average was included within the wide 95% confidence interval. Also, in the company's Phase I data (although it was only four patients), the change from baseline in the control group was -3.5 letters with an average of three injections (versus the four in the Phase II study). We believe that if the AVA-101 results were compared with historical uses of Lucentis as needed in a treatment experienced population, the differences between treatment and control would not be as pronounced as those reported today.

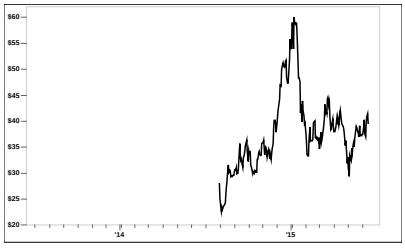
Stock Rating:	**Market Perform**
Company Profile:	**Aggressive Growth**
Price Target:	$24.00
Symbol:	AAVL (NASDAQ)
Price:	$38.88 (52-Wk.: $22-$62)
Market Value (mil.):	$1,057
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	2014A	2015E	2016E
Estimates			
EPS FY	$-2.01	$-1.92	$-2.53
CY		$-1.92	$-2.53
Sales (mil.)	1	1	0
Valuation			
FY P/E	NM	NM	NM
CY P/E		NM	NM

Trading Data (FactSet)	
Shares Outstanding (mil.)	25
Float (mil.)	17
Average Daily Volume	334,003

Financial Data (FactSet)	
Book Value Per Share (MRQ)	11.0
Return on Equity (TTM)	-38.4

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.

- **Response rate data suggests efficacy.** In the Phase IIa study, 29 of 32 total subjects enrolled in the study had received prior anti-VEGF therapy with a median of 10 prior injections. We include the baseline characteristics of both Phase I and Phase IIa trials as well as the CATT study participants in exhibit 1. One of the strongest signals coming out of the study was positive response rate data across several definitions. A significant number of AVA-101 treated subjects (42.9%) improved or maintained stable vision with ≤2 rescue injections compared with placebo (9.1%), with BCVA improvement of ≥10 letters with ≤2 rescue injections observed in 23.8% of AVA-101 treated subjects versus 0% of control subjects. We look forward to further examination of the data (and presentation at an upcoming medical conference, most likely the American Academy of Ophthalmology in November) as there may be a hyper-responder group that can be identified, and incorporated into the enrollment of further studies.

- **However, utility of Lucentis injection decreases (four in Lucentis versus two in the AVA-101 arm) and three-year Phase I data cloud the program.** The median number of rescue injections in the treatment group was two times (95% CI: 1-6 injections) versus four times (95% CI: 3-5 injections) in the control group (in addition to the two protocol-required Lucentis injections at day 0 and week 4). Rescue injections were given on the prespecified criteria of worsening vision, OCT changes, or an increase in leakage on fluorescein angiography. In exhibit 2, we show the population of patients in each group that required 0, ≤1, and ≤2 injections in the Phase IIa study. In addition, in the Phase I 36-month follow-up, subjects received an average of 0.71 rescue injections per year (in addition to the two protocol-required Lucentis injections). The Phase IIa data on rescue injections shows a decrease of two Lucentis injections between the AVA-101 group and the placebo group (Lucentis PRN), or an overall injection burden of four injections over 12 months in the AVA-101 group and six injections in the placebo group.

- **Negative retinal thickness trend in AVA-101 arm but effect beyond week 8 likely similar to Lucentis.** Retinal thickness measurements from OCT were higher in the treatment group (+25 mm) as reported by automated segmentation compared with -56 mm in the control group (CI for the difference, 17 to 145 mm). Management noted that there was an imbalance at baseline and the increases in the AVA-101 arm predominantly occurred during the Lucentis treatment period (through week 8) and were in line with the control arm through week 52. Management is conducting additional evaluations at an independent image reading center, likely because the higher thickness measurements were not consistent with the Phase I data. We also note that clinical relevance of this finding is still uncertain, as there has not been any significant correlation made between retinal thickness and efficacy.

- Phase I three-year data shows long-term safety, as four AVA-101 patients showed a mean change from baseline in BVCA of +0.5 letters, but again we note this study was primarily focused on safety. We note that this three-year follow-up has shown a decrease in efficacy from the BCVA measurements noted at the 52-week time point, when treated subjects gained an average of +7.5 letters from baseline. Although this is examining only four patients' worth of data, we note previous published studies (one in the United States and one in the United Kingdom) using the AAV2 vector in Leber's congenital amaurosis (LCA) also showed waning efficacy at three years, which led to concerns in another ocular gene therapy program in development.

- **Mixed data leaves questions likely only answered by Phase IIb, which is some time away; reducing price target from $53 to $24.** While shares are likely to open significantly off of Monday's close, we are downgrading shares of Avalanche Biotechnologies to Market Perform as we believe the totality of data leads to significant questions (namely the treatment benefit over Eylea) that will need to be addressed in the Phase IIb study, which is beyond our one-year time horizon. While shares may recover if Regeneron is to execute a large co-development partnership with Avalanche for AVA-101, we believe a more reasonable strategy for both companies is to better judge the true value of AVA-101 by executing on the currently planned Phase IIb study, which will not read out until 2017 at the earliest. We would also revisit shares as the company progresses pipeline candidates, which may produce proof of concept data in late 2016/early 2017. We believe that further analysis of the Phase IIa data at upcoming medical conferences could provide incremental upside given the population of patients that received significant visual acuity benefits from therapy and the population of patients that did not need any Lucentis rescue injections over the 52-week time course. Given Monday's results, however, we are decreasing our price target from $53 to $24 as we now assume a 33% probability of success and lower peak-year sales of $1.1 billion down to slightly over $700 million seven years after launch.

Exhibit 1
Phase IIa Baseline Characteristics Compared to Phase I

	Phase I	Phase IIa	Lucentis PRN regimen in CATT 2 Year Study*
Age (years)	79 (71-86)	79.5 (62-95)	78.4 (70.6-86.2)
Baseline BCVA (ETDRS letters)	36.5 (28-56)	63 (35-78)	61.5 (48.3-74.7)
Baseline center point thickness (µm)	549 (193-1094)	332.5 (179-816)	458 (265-651)
Number treatment naïve (n/N)	0/8	3/32	all
Previous anti-VEGF injections (for non-naïve)	11.5 (1-29)	10.5 (1-25)	6.9 (3.9-9.9)
Time since diagnosis (months)	49.2 (2-65)	16.2 (0-85)	12

all AAVL study values median (range)

*comparison is from year 1 to year 2 of therapy

Source: Company reports, Martin et al. *Ophthalmology* 2012

Exhibit 2
Phase IIa retreatment percentages

# of retreatment injections	AVA-101	Placebo
0	19.0%	9.1%
≤1	33.3%	9.1%
≤2	52.4%	9.1%

Source: Company reports

Valuation

We rate shares of Avalanche Market Perform based on the lack of near-term catalysts and uncertainty generated by the company's Phase IIa data. We continue to believe that the company has assembled a strong management team that has significant experience in the field of retinal diseases and note an intriguing (albeit very early stage) pipeline that could yield new product candidates.

Exhibit 3
Avalanche Biotechnologies, Inc.
Sum of the Parts Valuation

	Peak Sales	Discount Rate	Probability of Success	Peak Sales	Value Per Share
AVA101	$1,136	11%	33%	2024	$ 12.91
Cash Per Share					$ 10.99
NPV Value					$ 340,582
NPV Value Per Share					$ 23.90

Source: William Blair & Company L.L.C. estimates

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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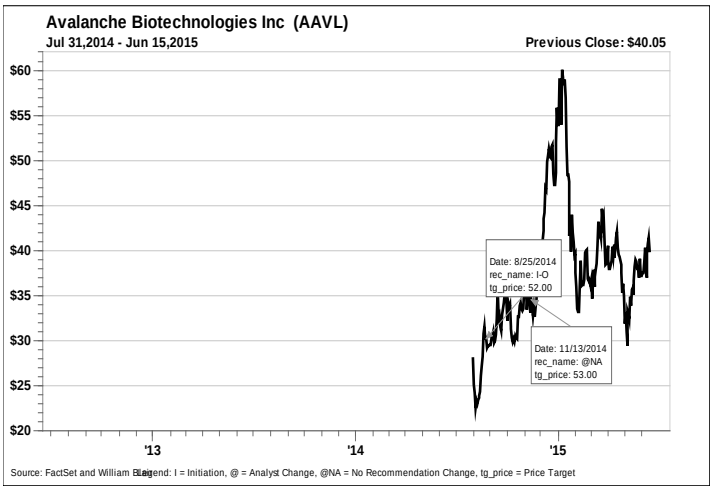
DOW JONES: 17,898.84
S&P 500: 2,094.11
NASDAQ: 5,051.10



Current Rating Distribution (as of 05/31/15)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65	Outperform (Buy)	14
Market Perform (Hold)	33	Market Perform (Hold)	3
Underperform (Sell)	1	Underperform (Sell)	0

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