Avalanche Biotechnologies

Equity Research

Quick Take: Company Update

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Price: $38.88 (06/15/2015)

Price Target: $55.00

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: AAVL
Market Cap (MM)	$992.6

Ph. IIa Demonstrates Safety And Activity, Though Doesn't Define 101's Role

The Cowen Insight

AAVL released results from AVA-101's Ph. IIa in wet AMD. '101 was safe and active, with '101 patients having improved vision and needing 50% fewer Lucentis rescue injections compared to control. However, with a median difference of only 2 Lucentis injections between '101 and control, AVA-101's role in the treatment of wet AMD will need to be defined by future studies. We remain at Outperform.

Phase IIa Data Answers Some Questions, Raises Others.

AVA-101 is in development as AAV-based gene therapy for the treatment of wet AMD. Last night Avalanche released 12 month results from AVA-101's Phase IIa trial and 36 month results from its Phase I trial. Last week, in advance of the data, we checked in with one of our consultants to understand what he hoped to see in the results. Overall, last night's data provide evidence of AVA-101's safety and activity, and that is encouraging. However, it appears to us that additional clinical development will be necessary to define AVA-101's role in treatment. Avalanche is expected to begin a Phase IIb during H2:15. With Avalanche's stock down sharply in the after-market, the current valuation could be justifed if AVA-101 is only a niche therapy in particularly hard to treat patients. We think it quite possible that there still could be a path to a meaningful market opportunity, so we remain at Outperform.

Pre-Data Check With Consultant Suggests That There Are Reasons For Optimism Based On These Results, But That AVA-101's Place In Treatment Still Must Be Defined

Last week we checked in with one of our physician consultants to discuss AVA-101's Phase IIa trial, and to better understand how he would evaluate the data.

Our consultant thinks that a clean safety profile is important given the safety of Avastin, Lucentis and Eylea. AVA-101 appeared safe and well tolerated in all datasets disclosed last night, and therefore its safety profile continues to appear acceptable.

Anti-VEGF antibodies are delivered through an intravitreal injection, but AVA-101 is delivered through a more cumbersome subretinal procedure, and therefore our consultant thinks it needs to either provide meaningfully better efficacy, or result in a significantly diminished subsequent injection burden, in order to be competitive.

AVA-101 generated clear signs of activity in last night's data. In particular, there was an 11.5 letter difference in change in best corrected visual acuity (BCVA) between '101 and control. Based on our consultants' comments, the visual acuity improvement over control, if reproduced in other studies, would itself be an important benefit. Unfortunately, a couple of datapoints raise questions about the visual acuity change. It was mostly driven by a large decrease in the 11 patient control arm (-9.3 letters) which was surprising given that patients visited their physician monthly and were getting Lucentis rescue injections in the case of OCT changes and/or worsening vision. Based on prior data our consultant expected the control patients to have stable

vision. Moreover, the change in retinal thickness trended against AVA-101 (+25mm for AVA-101 vs -56mm for control). One would expect changes in visual acuity and retinal thickness to be correlated. Therefore, while the improvement in visual acuity over control is encouraging, it is hard to have full faith in it unless it can be reproduced in larger trials.

There was a 50% decrease in the need for Lucentis rescue injections for patients on AVA-101, with '101 patients less likely to need 3 or more rescue injections compared to control patients. However, the median absolute difference in Lucentis injections given during the 12 months of the trial was only 2 (4 Lucentis injections for patients on AVA-101 compared to 6 on control). Our consultant thinks that a 50% decrease in rescue injections is meaningful, but that a decrease of just 2 injections is not. Therefore, AAVL will need to either demonstrate that patients who need more frequent Lucentis also have a 50% reduction in injections, or that the need for fewer injections persists over a long time.

Finally, our consultant hoped that a population could be defined in which 70% + of people given AVA-101 will derive benefit from the procedure. There are a number of ways to define a positive response, and therefore the proportion of patients who truly benefitted from AVA-101 in the Phase IIa is difficult determine. However, our consultant suggests that those patients who maintain or improve vision while requiring less than 50% of the rescue injections of control is a reasonable criteria. Using such a definition, 42.9% of patients in the trial "responded". Therefore, Avalanche could make a more compelling case for AVA-101 if it can define a patient population more likely to retain (or improve) vision with a decrease in the need for anti-VEGF injections.

The Phase IIa Enrolled 32 Patients With Wet AMD

The Phase IIa enrolled 32 patients age 55 and older with wet AMD, and randomized them 2:1 to high dose AVA-101 dose (10^{11} vector genomes) or control. Key inclusion criteria included subfoveal CNV secondary to AMD and with best corrected visual acuity of 20/30 or worse. Patients could not have extensive submacular scar tissue, diabetic retinopathy or retinal vascular occlusion, or cataracts. Like AVA-101's Phase I trial, the Phase IIa was conducted at the Lions Eye Institute (LEI) in Australia. During the 6-8 week ramp-up period, all subjects received two initial doses of Lucentis at Day 0 and Week 4. On Day 7, the patients in the active arm received AVA-101. Starting with Week 8 (the end of the ramp-up period), patients were offered Lucentis as a rescue therapy only on an as-needed basis. The need for rescue therapy was judged by personnel blinded to the treatment assignment in study and based on objective criteria of disease recurrence including OCT, angiography, and vision change. Subjects were assessed every four weeks for adverse events, retinal thickness, visual acuity and the need for Lucentis rescue injections. The primary endpoint of the trial was safety, and efficacy measures were collected as secondary endpoints. For safety purposes, the patients were investigated for ocular inflammation, intraocular pressure, retinal bleeding or any abnormal laboratory data. Efficacy was measured as improvements in visual acuity, reduction in retinal thickness and a reduced number of anti-VEGF (Lucentis) rescue injections.

The design of the Phase 2a was similar to AVA-101's completed Phase I, with some modest adjustments. In particular, in the Phase 2a subjects were enrolled with less advanced disease compared to Phase I, including visual acuity up to 20/30 while in the Phase I patients could have visual acuity only up to 20/80. The Phase 2a excludes patients with extensive scarring. Compared to Phase I, the patients in the Phase IIa had better visual acuity, with median baseline BCVA (ETDRS letters) of 63, compared to 36.5 in Phase I. At enrollment patients' retinas were drier, with a median baseline

center point thickness of 332.5 µm in Phase IIa compared to 549 µm in Phase I. The time since diagnosis was also less in Phase IIa, with a median of 16.2 months compared to 49.2 months in Phase I.

AVA-101 Appears To Be Safe And Well Tolerated

No patients discontinued the trial due to adverse events, and all remained in the study through the 12 month study visit. All adverse events related to drug were mild or moderate and resolved within 60 days. There were no unexpected administration-related adverse events, and any events that occurred resolved without visual sequelae. There were no serious adverse events observed. One subject in the treatment group had a non-fatal myocardial infarction, though it was classified as unrelated to therapy. There was one case of endophthalmitis in the control group.

AVA-101 Clearly Active With Improvements In Vision, And Decreased Need For Rescue Injections

The most important of the efficacy measures are changes in visual acuity, changes in optical coherence tomography (OCT) and the need for anti-VEGF (Lucentis) rescue injections.

Most encouraging, there was a difference of 11.5 letters in BCVA between AVA-101 (+2.2 letters) and control (-9.3 letters) with a 95% confidence interval of 2.3-20.7.

A significant number of AVA-101 treated patients (42.9%) improved or maintained stable vision with two or fewer rescue injections compared to subjects in the control group (9.1%). Nearly one quarter of AVA-101 patients (23.8%) experienced BCVA improvement of 10 letters with two or fewer rescue injections, compared to no one in the control group. More patients on AVA-101 also improved or maintained stable vision with </=2 rescue injections compared to subjects in the control group (42.9% vs 9.1%).

Patients treated with AVA-101 required fewer Lucentis rescue injections. The median number of rescue injections in the AVA-101 group was 2 (95% CI 1-6) compared with 4 (95% CI, 3-5) in the control group. More subjects required fewer retreatments in the treatment group compared to control (19.0% vs 9.1% with 0 injections, 33.3% vs 9.1% with </=1 injection; 52.4% vs 9.1% </= 2 injections).

Unfortunately, changes in retinal thickness favored control. Retinal thickness mean change from baseline, as reported by the site using automated segmentation was +25mm for AVA-101 treated subjects compared with -56mm in the control group (95% CI, +17 to +145mm). However, Avalanche indicated that the difference between AVA-101 and control were due largely to imbalances present at baseline that went away by week 8. OCT changes in both groups were similar between weeks 8 and 52.

AVA-101 Continues To Look Safe After 36 Months In Phase I.

Last night Avalanche also disclosed 36-month follow up data on eight subjects treated in the Phase 1 study of AVA-101. The follow-up study confirmed the benign safety profile exhibited over the first 12 months of therapy. AVA-101 was well tolerated with no significant drug-related safety concerns. This long-term follow-up included planned visits at 18 and 36 months to evaluate long-term safety. During this period, anti-VEGF rescue treatment was determined at the discretion of the subject's physician. Six of the eight subjects were available for evaluation at 36 months, four from the treatment group and two from the control arm, while two subjects withdrew from the study for reasons unrelated to study drug. For the four subjects with data available at 36 months, the mean change from baseline to month 36 was +0.5 letters and subjects received an average 0.71 rescue injections per year, in addition to the

two required Lucentis injections. Avalanche has not analyzed the number of injections needed by the control group.

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

The majority of Avalanche's market capitalization is dependent upon the success of lead candidate AVA-101. AVA-101's value could be adversely impacted should its clinical trials fail, should the regulatory agencies deny approval, or should its commercial opportunity not materialize as we project. In fact, all of Avalanche's drug candidates face clinical and regulatory risk. With the future development path depending on the evolution of clinical data, revenue forecasts are uncertain. The commercial outlook for Avalanche's candidates could additionally be altered by safety/efficacy findings, emerging competition, alterations in the medical treatment paradigm, or changes in the pricing environment. Some of Avalanche's projected market exclusivity depends on patents, which are subject to challenge by potential competitors.

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
AAVL	Avalanche Biotechnologies

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Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

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Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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Buy – The fundamentals/valuations of the subject company are improving and the investment return is expected to be 5 to 15 percentage points higher than the general market return

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Distribution of Ratings/Investment Banking Services (IB) as of 03/31/15

Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	450	58.67%	103	22.89%
Hold (b)	302	39.37%	8	2.65%
Sell (c)	15	1.96%	0	0.00%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's ratings definitions.

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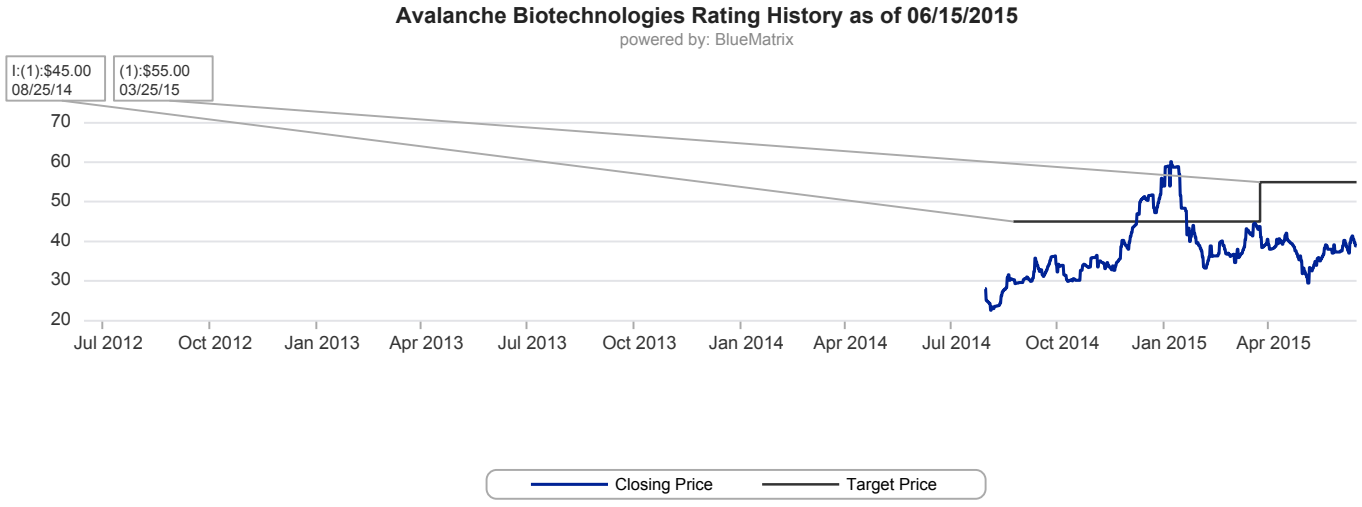

Legend for Price Chart:

I = Initiation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available | S=Suspended

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