Avalanche Biotechnologies (AAVL)

An Eye To a Cure, Initiating with a Buy and $60 PT

AAVL boasts a gene therapy platform focused on eye disorders, with lead product AVA-101 to yield randomized Phase IIa data in wet AMD in mid-2015. In addition, AVA-201 and AVA-311 (collaboration with REGN) are two preclinical products that emerged from AAVL's Ocular BioFactory platform to address wet AMD prevention and the rare eye disorder XLRS. While shares have been under pressure recently, our physician feedback suggests most concerns are likely overblown. Thus, we recommend investors step in ahead of the 03/25/15 R&D Day and mid-15 data readout (REGN has opt-in rights to AVA-101).

- **AVA-101 could disrupt and expand the ~$6B+ anti-VEGF market.** AVA-101 is an AAV-based gene therapy for wet AMD (a disease of the elderly caused by VEGF buildup which results in vision loss), designed to serve as a stable source of the naturally occurring anti-VEGF factor sFLT01 (same mechanism as REGN's blockbuster Eylea). Unlike Eylea and its competitor Lucentis which require 6-12 injections/year, AVA-101 could provide a functional cure by reducing the number of eye injections (possibly to <2/lifetime). AVA-101 could be similarly used for DME, CRVO, BRVO (additional Lucentis and Eylea ophthalmology indications).
- **Impressive and durable Phase I data sets the stage for a Phase IIa readout in mid-15.** In a Phase I Australian study, high and low dose AVA-101 (N=6 patients) resulted in a +8.7 and +6.3 letter improvement vs. control at -3.5 (N=2) at 1-year, and a stat. sig. 10-fold decrease in the number of Lucentis rescue injections. A Phase IIa study (N=32) is ongoing at the same center. Results from this study (exp. mid-15) suggesting a lower frequency of injections (at least stable BCVA) will likely support AVA-101 further development, with a Phase IIb trial poised to begin in the U.S. in H2/15.
- **KOL feedback suggests AAVL is well-positioned to address several controversies.** Although geographic atrophy (GA) emerged in patients with long term VEGF inhibition via Lucentis, KOLs believe GA is not necessarily a risk for AVA-101 since: 1) VEGF inhibition as a cause of GA has not been clearly established to date, 2) no GA was observed over 1 year in the Phase I AVA-101 study, 3) sustained but moderate VEGF inhibition using AVA-101 may be safer than broad fluctuations of anti-VEGF molecules (akin to immunosuppresant agents). Per our consultants subretinal delivery is an acceptable trade-off for fewer office visits and eye injections. Prior history of victrectomy surgery is unlikely to impact AVA-101 efficacy per clinical data. Lastly, we view AAV-based gene therapy as relatively safe and with minimal risk of immune reactions.
- **We model for $2B+ peak WW AVA-101 sales in wet AMD in 2026.** We estimate 280K and 512K patients are treated in the U.S. and E.U. for wet AMD - with peak penetration of 17% and 8%, respectively, and a conservative price of ~$22K/year in the U.S. (~$20K/year in the E.U.) corresponding to ~2 years (6 doses/year) of Eylea therapy.

Initiate Buy

Price Target: $60.00

Price (Mar. 6, 2015)	$35.96
52-Wk Range	$60.08-$22.60
Market Cap ($M)	$906
ADTV	320,874
Shares Out (M)	25.2
Short Interest Ratio/% Of Float	8.2%
TR to Target	66.9%

Cash Per Share	$8.04
Cash And Equivalents ($M)	$289.9

	2014A	2015E		2016E	
		Curr.	Prior	Curr.	Prior
EPS Adjusted					
1Q	($0.45)	($0.43)	--	--	NA
2Q	($2.27)	($0.54)	--	--	NA
3Q	($0.50)	($0.66)	--	--	NA
4Q	($0.46)	($0.72)	--	--	NA
FY	($2.46)	($2.36)	--	($3.11)	--
P/E	NM	NM		NM	
Consensus EPS Adjusted					
FY	($2.61)	($1.68)	--	($1.80)	--
Revenue ($M)					
FY	$1	$0	--	$0	--
P/Sales	906.2x	1,970.0x		7,551.6x	
Consensus Rev					
FY	$1	$0	--	$0	--

FYE Dec

Quarterly values may not add to the annual value due to rounding.

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SEE PAGE 45 FOR REQUIRED DISCLOSURE INFORMATION

Avalanche Bull/Base/Bear Scenarios

Figure 1: Bull/Bear Analysis for Avalanche

	Bear Case	STRH case	Bull Case
AVA-101 - U.S.	$4.60	$46.24	$63.06
AVA-101 - E.U.	$0.00	$6.11	$22.04
Cash/share	$8.04	$8.04	$8.04
Implied Price Target	**$12.64**	**$60.39**	**$93.14**
STRH est. scenario probability	10%	60%	30%
Price as of 03/06/2015		$35.96	
Upside/downside	*-65%*	*68%*	*159%*

Sources: Company reports, STRH research

Our base case: 60% probability. This valuation scenario reflects a 55% probability of success for Avalanche's AVA-101, an AAV-based gene therapy for wet age-related macular degeneration (wet AMD) in the U.S., where encouraging Phase I data have been gathered to date, and a 25% probability of clinical and commercial success in the E.U. Given the promising nature of these data and optimistic view of our physician consultants, we assign a 60% probability to this scenario. Our base case does not include any revenue contributions or value for the two preclinical pipeline programs, AVA-201 and AVA-311. These assumptions translate into a target of $60, 68% higher than the $35.96 closing price for Avalanche shares on 03/06/15.

Our bear case: 10% probability. This valuation scenario assumes mixed-to-negative results in the Phase IIa study of AVA-101 in wet AMD in Australia, corresponding to a 25% probability of success. This scenario also assumes a longer development process for AVA-101 and substantial competitive threat from other gene therapy players. The bear scenario assumes a 0% chance of success in the E.U., and would translate into a price target of $13, 65% below than the $35.96 closing price for Avalanche shares on 03/06/15.

A bull case for Avalanche: 30% probability. This valuation scenario would entail a 70% probability of success for AVA-101 in wet AMD in the U.S. based on promising results to date, and minimal competitive threat from other gene therapy players. This scenario would also entail a 55% probability of success for AVA-101 in wet AMD in the E.U. translating into a price target of $93, 159% higher than the $35.96 closing price for Avalanche shares on 03/06/15. Notably, our bull case scenario does not ascribe any value to the two preclinical pipeline programs, AVA-201 and AVA-311.

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We are Initiating Coverage of Avalanche with a Buy Rating and $60 PT

Avalanche is one of the most advanced players in the ophthalmology gene therapy space. Avalanche is one of a few recent entrants into the public biotech sector focused on gene therapy. Broad investor interest in the renaissance of gene therapy is evidenced by the strong performance of most of these stocks over their S1 price (BLUE +566%, AAVL +112%, CLDN +200%, AGTC +70%, and ONCE +152%). Furthermore, AAVL shares are currently down 38% off its highs at the end of December, providing an entry point ahead of pipeline visibility at the company's R&D day on March 25th 2015 and readout of the Phase IIa study of lead product AVA-101 for wet age-related macular degeneration (AMD) in mid-2015. This product consists of an adeno-associated vector-based gene therapy, with the potential to disrupt and expand the $6B+ branded anti-VEGF market. Clinical results generated to date are suggestive of activity in a small number of patients with advanced disease. A randomized Phase IIa single center study is ongoing in Australia, with results expected, as noted, in mid-2015. Given AVA-101's mechanism of action similar to anti-vascular endothelial growth factor (VEGF) biologics Lucentis and Eylea, the product could also have utility beyond wet AMD, in diseases such as retinal vein occlusion or diabetic macular edema (where Lucentis and Eylea are the standard of care). A follow-on preclinical gene therapy product AVA-201 is expected to undergo IND-enabling studies in 2015 for the prevention of high risk wet AMD. Avalanche is collaborating with Regeneron for the development of novel gene therapies for eye diseases ($8M upfront, up to $640M in potential milestones, low-to-mid single digit royalties and option to share up to 35% WW costs and profits for any two targets), with the first out of eight planned new products, AVA-311 to address the orphan disease X-linked retinoschisis (XLRS). Notably, Regeneron also retains a time-limited right to first negotiation of rights to AVA-101.

AVA-101 has demonstrated encouraging and durable proof-of-concept data in a randomized Phase I study. AVA-101 is an AAV2-based gene therapy designed to emulate a stable source of anti-VEGF biological molecules such as Lucentis or Eylea, the current standard of care of wet AMD. The disease is caused by excessive VEGF activity, which results in buildup of leaky blood vessels in the eye, and progressive loss of vision. To achieve reversal of this loss in wet AMD patients, ophthalmologists need to inject Lucentis or Eylea monthly or every other month, respectively. AVA-101 injection into a specific eye compartment (subretinal space) is designed to reduce the need for anti-VEGF injections, and therefore provide a potential functional cure for wet AMD. In a randomized Phase I study in 8 patients with advanced wet AMD conducted at the Lion's Eye Institute (Australia), AVA-101 treatment resulted in the need for 10 fold fewer Lucentis injections (0.33 injections/patient versus 3 for the control cohort) after 1 year follow up. Another measure of efficacy was improvement in best-corrected visual acuity, with 6.3 and 8.7 increase in letters from baseline with AVA-101 versus -3.5 with control. These data were viewed as encouraging by key opinion leaders with spoke with, who

believe reducing the number of anti-VEGF injections required by wet AMD patients would address a significant unmet need.

Topline results from a Phase II study of AVA-101 expected in mid-2015 to inform next steps, Phase IIb in the U.S. AVA-101 is being tested in a Phase IIa study at the LEI, with 32 patients randomized 2:1 to receive gene therapy or control. The trial is fully enrolled and topline results (including a one year follow-up portion) will report out in mid-2015. Given that patients enrolled in this trial have better baseline visual acuity (and are therefore more representative of the broad wet AMD population), we anticipate that improvement in the number of letters is likely to be more modest that in the Phase I trial. Any improvement in the secondary endpoint of BCVA may not be comparable to observations from pivotal Eylea or Lucentis trials. Investors have been trying to gauge what a potential improvement in the number of EDTRS letters could be in the Phase IIa study of AVA-101. Of note, the enrollment criteria for the Phase IIa require a history of treatment with Lucentis; thus any changes in the number of letters may not be comparable to the 6.6-10 letters gained in the Phase III trials MARINA and ANCHOR (Lucentis) and VIEW 1 and 2 (Eylea) – Lucentis/Eylea naives. Furthermore, we note baseline BCVA scores of 52-55 EDTRS letters in the pivotal trials VIEW 1 and 2, and comparable in the ANCHOR and MARINA trials. Unlike the Phase I study of AVA-101, the Phase IIa has been designed to enroll patients with scarring and visual acuity of up to 20/30 vision (corresponding to baseline ~75 letters). Thus, it is likely that baseline BCVA scores for AVA-101 are not comparable versus the pivotal Lucentis/Eylea studies, rendering potential readouts more difficult to interpret. Avalanche views the Phase IIa study as an informative path to Phase IIb testing in the U.S. (expected to begin in H2/15) rather than a binary event. Management believes that non-inferiority of AVA-101 to Lucentis could represent sufficient grounds for a Phase IIb trial, given the unmet need in wet AMD, and the approval of Eylea based on non-inferiority to Lucentis.

A number of controversies have pressured AAVL shares as of late; physician feedback suggests most are non-issues. A number of issues were brought forth by a skeptical key opinion leader at an investor event: 1) the concern that Phase I study participants were not wet AMD patients was thoroughly addressed by investigators at LEI, per Avalanche management, 2) the concern that potent VEGF inhibition via AVA-101 could cause geographic atrophy (GA: loss of vision receptors in the eye and further loss of vision), and 3) a prior history of vitrectomy (type of surgery used to remove fluid or debris from the eye) may impact the extent of VEGF inhibition. First, GA was observed in a 2-year study comparing anti-VEGF agents Lucentis with Avastin (incidence of 18% of 1024 study patients). Of note, injections with anti-VEGF standard of care result in “drying up” the fluid and blood from the central eye area (and reversal of vision loss). Key opinion leaders (KOL) we spoke with note that **“the jury is still out” whether VEGF inhibition results in GA or eye areas “dried” of blood vessels are sometimes mistaken as GA. He also believes that GA should have been readily noticeable in the 1-year Phase I AVA-101 study follow up** (based on kinetics of VEGF knockdown observed in animal models). Lack of atrophy observations at this point would suggest this risk is less of a concern. Another KOL made the analogy between VEGF inhibition and

immunosuppression. In the case of monthly Lucentis and Avastin injections, VEGF inhibition fluctuates from very potent to very low. From a safety standpoint, he believes constant, moderate VEGF suppression could be akin to moderate immuno-suppression. While short term highly potent immuno-suppression could be very deleterious of the patient, consistent low levels are generally well tolerated. Third, KOLs believe a reduction from the current 8-10 injections/year required by severe patients to 2 or fewer represent an acceptable benefit ("every time you inject the eye you are at risk of losing the eye". While AVA-101 is delivered subretinally (under the retina tissue, surgery that requires the operating room) rather than intravitreal (direct eye injections), KOLs see a favorable risk benefit ratio should 2 doses or fewer per year be needed, with no additional follow-up patient visits. Our KOL consultants believe patients having undergone vitrectomy respond just as well to anti-VEGF therapy as those without. This appears to have been a concern in the community some years ago but has been addressed through clinical data. KOLs point to data presentations and key conferences over the recent 2 years (including ARVO – the Association for Research in Vision and Ophthalmology and AAO – the American Academy of Ophthalmology).

Expect the March 25 R&D day to be a major catalyst for Avalanche. At the planned R&D Day in New York we look towards more disclosure of the basic science behind AVA-101, the broad clinical development program and next steps. The discussion will likely revolve around the unmet need, the supportive preclinical data and the types of patients addressed by the Phase IIa study underway. The company plans to discuss topics that may not be fully understood by investors, as well as frequent questions. The event will most likely include a thorough discussion of the progress on the basic science front that underpins AVA-201 and AVA-311. We believe the overhang of several controversies may be lifted, as the company and key opinion leaders will provide a broad discussion of the data and any scientific concerns.

While Avalanche is not the only player in the ophthalmology gene therapy space, we believe its approach is highly differentiated. Avalanche's AVA-101 has a direct clinical competitor with Genzyme/Sanofi's rAAV2-FLT01. While AVA-101 yields an increase in levels of naturally occurring VEGF inhibitor sFLT1, Genzyme's AAV-based therapy induces production of a single portion of sFLT1. AVA-101 appears to have a leg up in this race. A summary of Genzyme's presentation was discussed by two key opinion leaders at the Weill Cornell Medical Center (Irene Rusu and Szilard Kiss), who mentioned that biological activity was observed in "4 out of 11 expected responders as defined by the study investigators". The two authors also note that **"the response rate with AAV2-sFLT01 was significantly less than that noted with AVA-101".** In the gene therapy space, uniQure (E.U. company with the first gene therapy product to be approved in the E.U.) may compete with Avalanche as it has a preclinical wet AMD program in the works. Nevertheless, uniQure's scope appears significantly broader than eye diseases, and near term focus is on hemophilia. For rare genetic eye disorders such as XLRS, Avalanche competes with Spark Therapeutics and Applied Genetic Technologies. What differentiates the Avalanche is its manufacturing approach of using the baculovirus/Sf9 system pioneered by the National Institutes of Health, entailing a number of optimization steps. In contrast, Applied Genetic Technologies and Genzyme use herpes simplex virus vectors and baby hamster kidney cells, while Spark uses transfection and human cells. Use of the baculovirus/insect cells system allows for scalability and potentially a better

safety profile compared to the use of mammalian/human cells. Avalanche also competes with Roche and Regeneron that commercialize Lucentis, Avastin, and Eylea. However, AVA-101 could capture a significant share of these therapies, should it result in a material decrease in the number of injections needed to maintain/improve vision. A number of other companies, including Ophthotech and Allergan are developing anti-VEGF therapies for wet AMD. However, both these approaches would entail frequent injections to manage disease progression.

With its strategy of AAV-based gene therapy for ophthalmology disorders, we see Avalanche as uniquely positioned in the space. We believe that Avalanche capitalizes well on broad knowledge of AAV biology, as well as on its proprietary Ocular Biofactory platform, that allows for directed evolution and optimization of vectors. The company's approach benefits from several advantages. First, AAV vectors do not typically integrate into the patient's genome, thereby significantly reducing the risk of genomic toxicity (e.g. emergence of leukemia). Second, focus on eye diseases appears well suited to *in vivo* gene therapy, given the accessibility of this organ to procedures such as injections. (Nevertheless, for direct retinal access it appears that subretinal injections are required, rather than the more easy to administer intravitreal injections, delivery into the soft center of the eye). Third, targeting the non-dividing (post mitotic) cells of the eye ensures that the AAV-based therapy will be retained in a majority of the retinal cells, rather than be diluted away with additional rounds of cell division. Last, the eye is a relatively immuno-privileged organ, with limited interference from the immune system able to either deplete cells containing the AAV-delivered biologic or mount exacerbations against the entire organ.

We estimate peak WW revenue for AVA-101 of $2B in 2026. Based on our review of the medical literature, our discussions with KOLs and review of market research data about Lucentis presented by Roche in 2012, we estimate that ~565K patients in the U.S. have wet AMD (~150K newly incident per year), and ~322K patients are diagnosed. Treatment rate is high (~85% of the diagnosed patients) in the U.S., and 50%, 25%, and 25% of the prevalent patient pool is currently treated with Avastin, Lucentis, and Eylea (with Eylea likely to capture additional share in the future while Avastin likely to remain the dominant therapy), per our KOL feedback and Medicare compiled data (source: Holekamp et al, AJO, 2014). We assume similar prevalence numbers in the E.U., with 501K patients currently on branded therapy, but a significantly higher share on the cheaper Avastin. Uptake in ROW countries including Japan is upside to our estimates. Given the well-established regulatory path for Lucentis and Eylea, we anticipate that Avalanche would need to conduct two Phase III trials in wet AMD, which could begin by 2016 year end, with topline results in 2-2.5 years (results likely in H2/19) and launch in 2020. Per our discussions with KOLs, patients best suited to therapy are those on stable anti-VEGF injections, who require a large number (8+) of injections per year. We model uptake in Lucentis/Avastin switchers and conservatively assume peak penetration of 18% in 2026, as we anticipate competitors such as Genzyme/Sanofi could enter the market in 2020 and beyond. We assume a price for AVA-101 per patient equivalent to 2 years of Eylea, approx. 22.2K (and an 85% gross to net adjustment). This could be a highly conservative assumption, given the 2-year price of ~$47K for Lucentis; should the benefit

be striking, we anticipate Avalanche could price AVA-101 at a premium to the cost of 2 years of Lucentis. We do not currently model for any revenue for AVA-101 from indications beyond wet AMD, such as diabetic macular edema or branch retinal vein occlusion, indications included in the Eylea and Lucentis labels. We also do not include any contribution from AVA-201 or AVA-311 in our valuation.

Pipeline assets AVA-201 and AVA-311 could extend Avalanche's wet AMD franchise and diversify into orphan genetic disorders. Avalanche's follow-on anti-VEGF asset is AVA-201, a gene therapy similar to AVA-101 but amenable to intravitreal delivery (easier to achieve than subretinal for AVA-101). The product is expected to complete IND-enabling studies in 2015, for the prevention of wet AMD in high risk patients. AVA-311 is a product that emerged from the Regeneron collaboration. Preclinical data gathered to date suggests that the gene therapy could prevent vision loss upon delivery into animal models of the rare congenital disorder X-linked retinoschisis.

Avalanche has the resources to take several shots on goal. Avalanche's cash position at the end of Dec' 14 was $159M, excluding the $130.5M in proceeds from a secondary offering in Jan '15. The company has a collaboration in place with Regeneron ($8M upfront payment, $640M in milestones in addition to mow-to-mid single digits for royalties). We model for amortization of the $6.5M of the $8M upfront payment ($0.8M recognized evenly over 10 years). This amount excludes $1.5M to be recognized should Regeneron exercise the option to co-develop AVA-101. This option is slated to expire at a defined timepoint (likely around the Phase IIa data readout). We assume AVA-101 approval for wet AMD in the U.S. in 2020, and forecast revenue of $128M, $337M, and $592M for 2020, 2021, and 2022, respectively. We model for a continuing ramp-up in quarterly expense in 2015 and 2016, as the Phase IIb trial of AVA-101 begins in mid-2015 and novel products move into the clinic in 2016+. We forecast that the company will achieve profitability in 2021. The company obtained $102M through its initial public offering in August 2014, as well as $130M in a follow on offering in Jan 2015. Shares are up 123% over the S1 price based on the 03/05/15 closing price. We believe Avalanche has sufficient cash runway through 2017, and we model for two follow-on equity offerings to support continuing activities: 1) an equity offering of ~5.7M shares at $70/share in 2016, and 2) an equity offering of ~2.5M shares at $100/share in 2019, after a potential data readout from the AVA-101 pivotal studies.

Valuation

We arrive at our price target of $60 by means of a sum-of-the-parts discounted cash flow analysis, which ascribes $46.25/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 a probability of success of 55% in the U.S. and 20% 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 and 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. 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).

AAV-Gene Therapy Ophthalmology Pipeline and Two Key Near Term Catalysts

Avalanche is developing adeno-associated virus (AAV) therapies for eye diseases. Their aim is to introduce a stable source of biologic product in the appropriate eye tissue. In turn, this should enable a molecular "correction" (long-term benefit or potentially functional cure) of an acquired or genetic cellular defect. Beyond the first clinical product AVA-101 for wet age-related macular degeneration (with potential in diabetic macular edema and branch retinal vein occlusion), Avalanche's future pipeline (AVA-201 and AVA-311) is based on an integrated platform for gene therapy discovery, development, and manufacturing, called Ocular Biofactory. Next generation AAV product candidates emerging from this platform are designed for the targeted and effective delivery to the desired tissue, as well as prolonged production of the desired biologic. Avalanche is collaborating with Regeneron for the discovery and development of new product candidates with up to eight new targets (including AVA-311), using Avalanche's Ocular Biofactory, and Regeneron has a time-limited right of first negotiation for specific rights to lead candidate AVA-101.

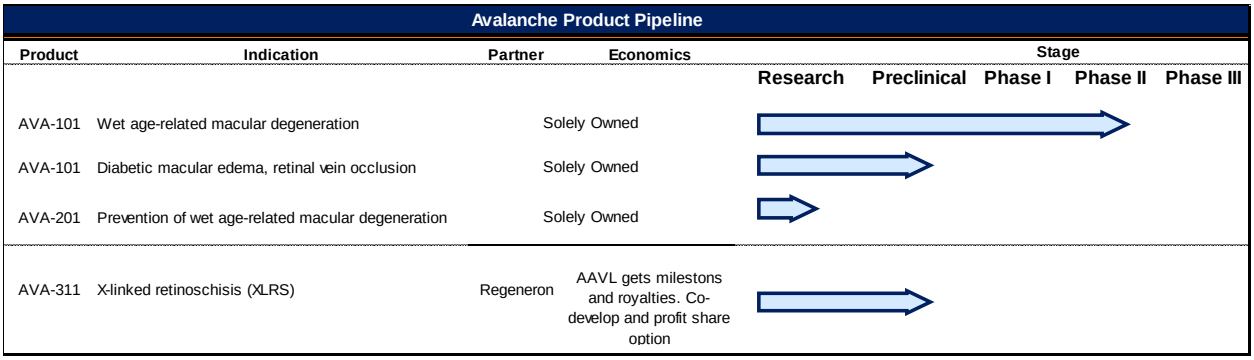
AVA-101 is an AAV-based gene therapy developed for the treatment of age-related macular degeneration, the most common cause of blindness in elderly patients. The disease is caused by buildup of leaky blood vessels, which cause degeneration of eye tissues such as the retina, resulting in lesions, scarring, and vision loss. AVA-101 is delivered into a specific eye region (subretinal injection). The drug is designed to yield tissue-targeted production of the biological molecule sFLT1 (secreted FLT1), which acts as a "natural sponge/sink" for vascular endothelial growth factor (VEGF) - VEGF depletion is the mechanism of action of the standard of care for wet AMD: Lucentis (Roche/Genentech), Eylea (Regeneron) and Avastin (Roche/Genentech). The product is in a Phase IIa randomized controlled trial underway in Australia, expected to read out in mid-2015. Based on proof-of-concept clinical data from the Phase IIa study, Avalanche could advance this program in other indications addressed by Lucentis and Eylea, such as diabetic macular edema and retinal vein occlusion.

Within Avalanche's follow-on programs - AVA-201 is slated as a potential next-generation AVA-101. AVA-201 is a next generation AAV vector construct, developed from Avalanche's Ocular Biofactory discovery platform. AVA-201 produces the same anti-VEGF molecule as AVA-101, but has an improved, customized delivery modality (intravitreal) and would be dosed earlier in the disease course of high risk wet AMD patients (prevention). We look to clarity on this program in 2015, as the company gathers additional preclinical data.

AVA-311 is a product candidate partnered with Regeneron, slated to address the orphan disease, X-linked retinoschisis (XLRS). The first product candidate subject to the Regeneron collaboration is AVA-311, a gene therapy for the treatment of XLRS, a rare retinal disease that mostly impacts boys. The disease is caused by a genetic defect

of the RS1 gene and results in “split” retina and gradual loss of vision. The product is in preclinical testing.

Figure 2: The Avalanche Pipeline



Sources: Company reports, STRH research

Figure 3: Avalanche Upcoming Milestones

Product	Timing	Indication	Event
All products	March 25, 2015	Ophthalmology - all indications	R&D Day
AVA-101	**Mid-2015**	**Wet age-related macular degeneration (wet AMD)**	**Readout of a Phase IIa study**
AVA-101	Mid-2015	Wet age-related macular degeneration	Potential Regeneron opt-in
AVA-101	H2 2015	Wet age-related macular degeneration	U.S. IND Filing
AVA-201	2015	Prevention of wet AMD	Completion of preclinical work for IND filing

Sources: Company reports, STRH research

Avalanche Aims to Revolutionize Eye Disease Treatment Using Gene Therapy

Avalanche’s focus is on developing functional cures of ophthalmologic (eye) disorders. The company’s strategy is to develop gene therapy products to address molecularly well-defined diseases. This could represent a highly disruptive approach for well-established markets such as ophthalmologic anti-VEGF, including age-related macular degeneration and diabetic macular edema (currently ~$6B+ in value for the branded therapies alone). In addition, Avalanche’s products could serve to effectively cure orphan ophthalmology diseases of high unmet need. Avalanche is leveraging an extensive academic understanding of the non-pathogenic adeno-associated virus (AAV) biology, along with a proprietary platform embodied by the Ocular Biofactory for the production of synthetic, improved AAV variants. We view a number of key strategic advantages to Avalanche’s approach in eye disorders:

1. **AAV vectors do not integrate in the genome, and therefore have limited genomic toxicity.** Unlike lentivirus approaches (such as the ones used by bluebird), AAV vectors used for gene therapy do not integrate into a patient's genome. ***This feature ensures that the risk of potential integration-related toxicities such as leukemia is significantly (if not completely) reduced***. Furthermore, AAV capsids can "infect" (or transduce, see left box) a very broad variety of human cells.

Vector: The DNA sequence encoding a virus, engineered to no longer be a pathogen but instead to carry desired genes of interest

2. **The eye is an accessible organ for direct AAV delivery.** Unlike organs such as liver or bone marrow, the eye is easily accessible and consists of highly transparent tissues. This enables for targeted and precise delivery of the gene therapy.

3. **Targeting the eye allows for prolonged production of the desired biologic agent.** AAV vectors linger within the cells that they transduce (i.e. non-pathogenic infection), as sources of biological material residing outside the chromosomes. AAV is not replicated (i.e. amplified) by human cells, in contrast to human chromosomes. This would generally be a problem for tissues consisting of rapidly growing/dividing cells. In this case, the extra-chromosomal AAV vector would only be "inherited" by a small proportion of the progeny of the originally transduced cell. ***However, the human eye consists mainly of post mitotic cells (i.e. do not need to divide and have a long life).*** Thus, once transduced with the AAV, eye cells theoretically retain the gene therapy for a prolonged period (likely years).

Transduction: Using an engineered viral particle to introduce a vector into cells of interest. Unlike infection, transduction does not result in a pathogenic event.

4. **Targeting the eye is has a low probability of eliciting a strong immune reaction.** The eye is a relatively immuno-privileged organ (i.e. immune system cells have limited access to eye tissue, given its position behind the blood brain barrier). *In vivo* delivery (directly into patient) of the packaged AAV particles into the eye is theoretically associated with a very low risk of surveillance by the immune system and therefore a low probability (although not zero) of conjuring an immune reaction. Of note, a strong immune reaction (less likely with eye treatment but more likely with heart or liver) could thwart treatment chances (eliminate transduced cells) or even endanger the patient (lead to excessive self-tissue destruction).

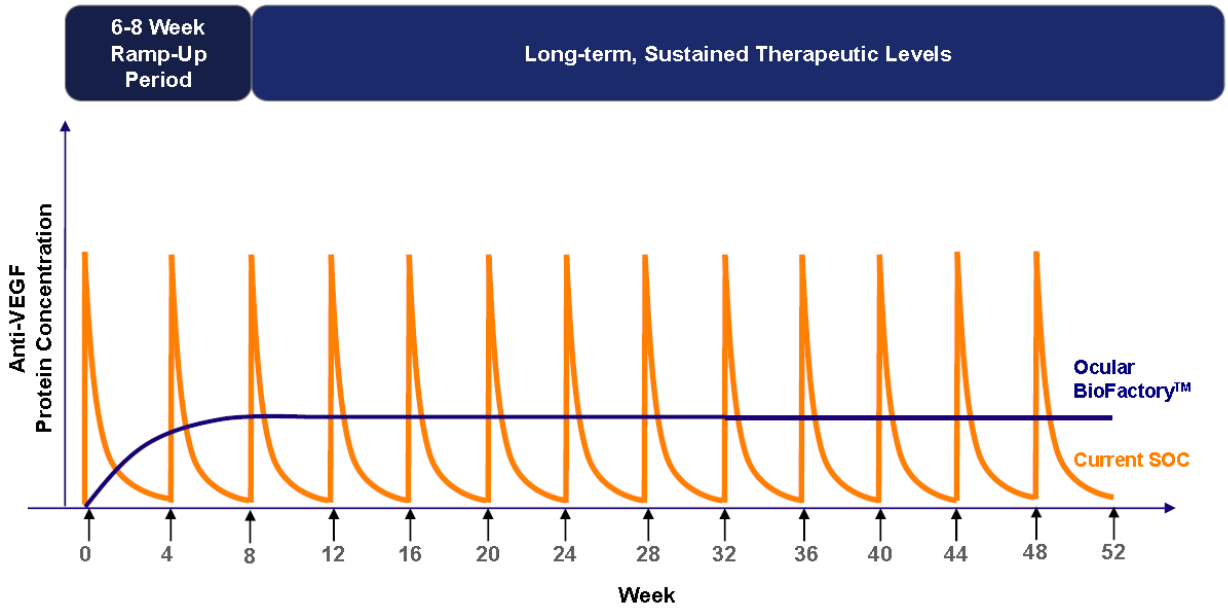
AVA-101: A Gene Therapy to Resolve the Need for Frequent Eye Injections in Wet AMD

VEGF inhibition with biologics is the cornerstone of wet AMD treatment, but unmet needs remain. Age-related macular degeneration is the primary cause of adult blindness. It is a degenerative disease of an eye tissue called macula (central portion of the retina), and the "wet", "neovascular" or "exudative" form of AMD results from abnormal blood vessel growth. Accumulation of these vessels results in leakage of watery eye fluid (subretinal fluid) and/or blood in the retina, and severely encumbered vision. Wet AMD patients suffer from debilitating vision loss and loss of ability to perform daily activities (e.g. driving, reading). Given the known biologic function of the vascular endothelial growth factor (VEGF) in blood vessel formation, treatment approaches using VEGF inhibition have revolutionized treatment of wet AMD, halting or even reversing vision loss. Standard of care for wet AMD now includes a suite of VEGF inhibitors: 1) the VEGF antibody Lucentis (Roche/Genentech), 2) off-label use of the VEGF antibody Avastin (Roche/Genentech), 3) the biologic agent Eylea (Regeneron), which includes a portion of the natural inhibitor of VEGF, soluble Fms-like tyrosine kinase-1 (sFLT1), bound to an antibody backbone. Suppression of VEGF function leads to "pruning" of leaky blood vessels and prevents new vasculature formation. However, a number of unmet needs still remain in wet AMD (discussed in a separate section below): patients require monthly or every other month injections, but get fewer than 6 injections per year due to factors such as price and convenience (source: Holekamp et al, AJO, 2014). Poor compliance results in poorly managed disease and vision loss.

AVA-101 could address some of the current limitations of Lucentis/Avastin and Eylea via gene therapy approaches for wet AMD. AVA-101 is designed to provide a stable reservoir of VEGF inhibitory molecules, thereby sparing patients the need to get frequent eye injections. AVA-101 is a gene therapy consisting of the AAV2 vector, an AAV variant derived from the first identified, naturally occurring adeno-associated virus, and most commonly used for gene therapy. A key feature of AAV vectors is their ability to persist outside of the genome (extra-chromosomally) and produce the gene of interest. In the case of AVA-101, this is sFLT1, the naturally-occurring VEGF inhibitor built into the structure of Eylea. The current standard of care entails "peaks" of VEGF inhibition, corresponding to the period immediately following injection of Lucentis, Avastin, or Eylea (Figure 4). However, as these biologic agents decay over time, the cellular balance begins to shift towards VEGF production.

AVA-101 could result in sustained production of additional (upregulation of) natural inhibitor of VEGF, and therefore stabilize cellular levels of VEGF. Thus, a one-time injection of AVA-101 is designed to introduce a lasting source of VEGF inhibition in the eye and enable constant inhibition of new blood vessel formation. To date, data generated by Avalanche suggests that AVA-101 can persist and remain productive in the retina for at least one year.

Figure 4: AVA-101 Could Allow for the Stable Production of Anti-VEGF Agent, Thereby Sparing the Need for Frequent Injections



Source: Company reports

Proof-of-Concept Data from a Controlled Phase I Study of AVA-101 Are Suggestive of Activity

The randomized Phase I trial employed a creative design to zero in on potential AVA-101 efficacy. The first clinical evaluation of AVA-101 is underway at the Lions Eye Institute, Perth, Australia. The Phase I trial enrolled 8 patients with wet AMD, to be randomized into three cohorts as follows: 3 patients to get low dose AVA-101 (1x10^10 vector genomes), 3 patients high dose AVA-101 (1x10^11 vector genomes), and 2 patients to serve as control (Figure 4).

At baseline, patients were required to be candidates for anti-VEGF, and could have received this therapy. Their disease could not have been too advanced (no extensive scarring or presentation with thick subretinal blood). Importantly, enrollment criteria did not preclude patients with prior neutralizing antibodies to AAV from participating in the study. 5 out of the 6 patients randomized to AVA-101 did not present with baseline AAV autoimmunity.

Investigators expected sFLT1 production to reach therapeutically active and continuous levels in the eye within 6-8 weeks, based on animal data. All patients had required frequent injections prior to study start, and received a Lucentis injection at Week 0, as well as another one at Week 4. Patients in the AVA-101 cohorts were given the therapy at the end of Week 1. Study participants were expected to enter Week 9 of testing with comparable levels of VEGF inhibition (assumption that it took 8 weeks for AVA-101 to

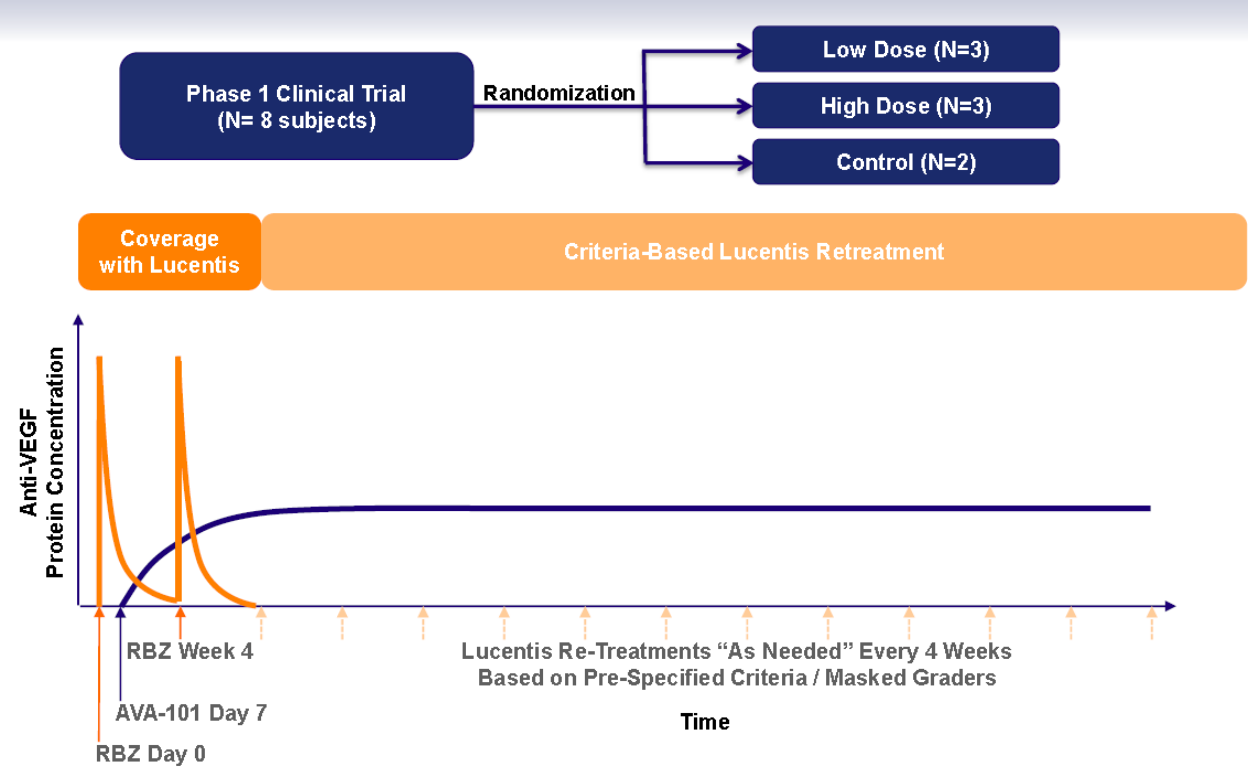
begin stable production). Starting with Week 8, patients had the possibility to get a Lucentis rescue injection.

The one year, single-blind, follow-up period was rigorously designed to detect AVA-101 activity signals. Trial participants were followed for another 44 weeks. In addition to safety measures, patients were evaluated monthly for the following efficacy measures:

- Best-corrected visual acuity (BCVA) – measured as the numbers of letters read on the ETDRS (Early Treatment Diabetic Retinopathy Study), the standard for 20/20 vision is 100.
- Choroidal neovascularization (CNV) lesion, or the degree of abnormal vessel and blood formation in the eye.
- Retinal thickness (thicker correlates with more advanced disease). This measurement is non-invasive and serves as a surrogate for disease progression.

Physicians carrying out follow-up observations were masked to the initial treatment portion, and had a number of pre-specified criteria to determine whether a Lucentis injection was needed (pro re nata, or PRN).

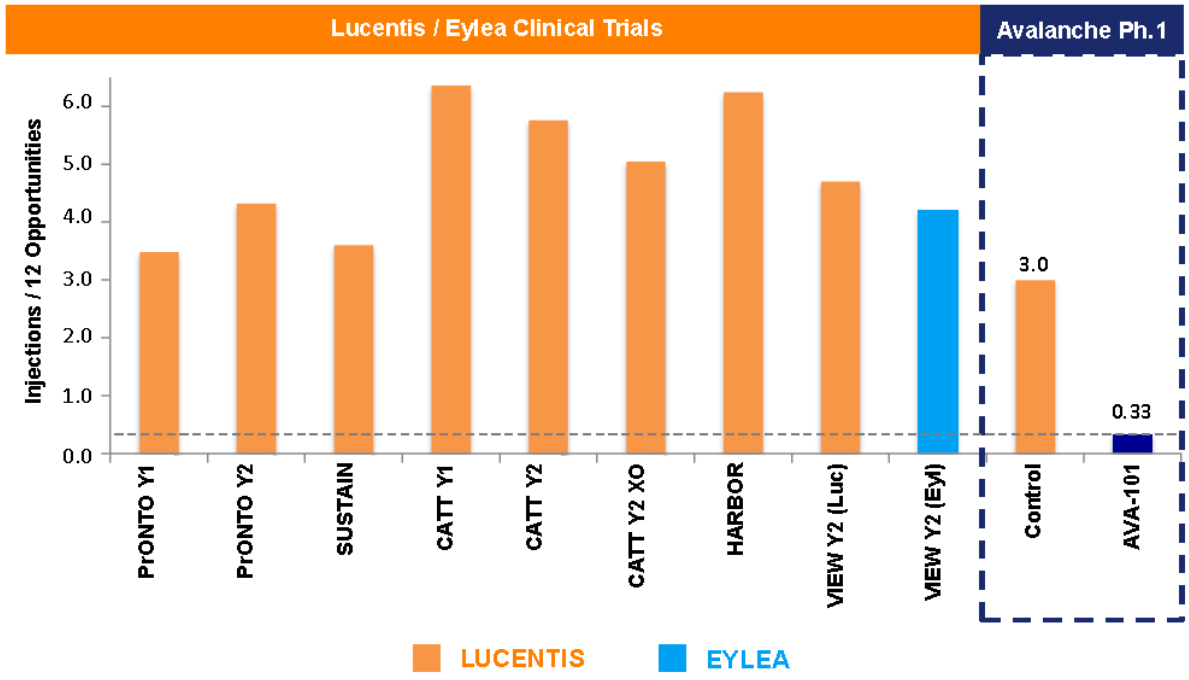
Figure 5: The Randomized Controlled Phase I Study Was Designed to Evaluate AVA-101 Efficacy Upon Lucentis (RBZ) Discontinuation



Sources: Avalanche company reports

Patients treated with AVA-101 required 10 times fewer Lucentis injections compared to control. One-year results of this Phase I trial were presented in an oral session at the Association for Research in Vision and Ophthalmology (ARVO) meeting, in May 2014. The majority of the patients treated with AVA-101 did not require rescue treatment; out of a possible 72 injections, this group was only given 2. Thus, the group received 0.33 injections/patient. This compares with 3 injections/patient received by the 2 control patients. In addition, this result was statistically significant when compared to the similar time frame of Phase III trials of Lucentis and Eylea, including CATT (Comparison of Age-Related Macular Degeneration Treatments Trial) conducted by the National Institutes of Health (NIH) to evaluate Lucentis versus Avastin.

Figure 6: AVA-101 Treatment Resulted in Statistically Significant Efficacy Compared to Historical Trials



Sources: Avalanche reports

Other measures of efficacy were suggestive of AVA-101 robust activity. In addition to fewer injections, the data presentation revealed that patients treated with AVA-101 did not experience any loss in visual activity, intraocular pressure increase, eye or systemic inflammation, or any retinal break. On the three efficacy measures listed above (BCVA, CNV, and retinal thickness), patients treated with AVA-101 appeared to fare as well/better versus on anti-VEGF injections. **On average, AVA-101-treated patients experienced improvement in BCVA, from baseline average 41.8 EDTRS letters to 49.3 letters at one year (Figure 6).**

We note, however, the limitations of this small patient dataset. Patients in the AVA-101 treatment groups had an overall better baseline visual acuity, of 41.8 letters versus 29 for the two patients in the control arm. In addition, one of the three patients given high dose AVA-101 treatment (and who harbored the highest BCVA score at baseline, of 56) experienced disease progression and a loss of 6 letters. In addition, one of the control patients did not experience any change in visual acuity from baseline. Nevertheless, we view these data as highly encouraging, given the extent of improvement of +13 and +15 ETDRS letters in AVA-101 patients with baseline BCVA of 28 and 34.

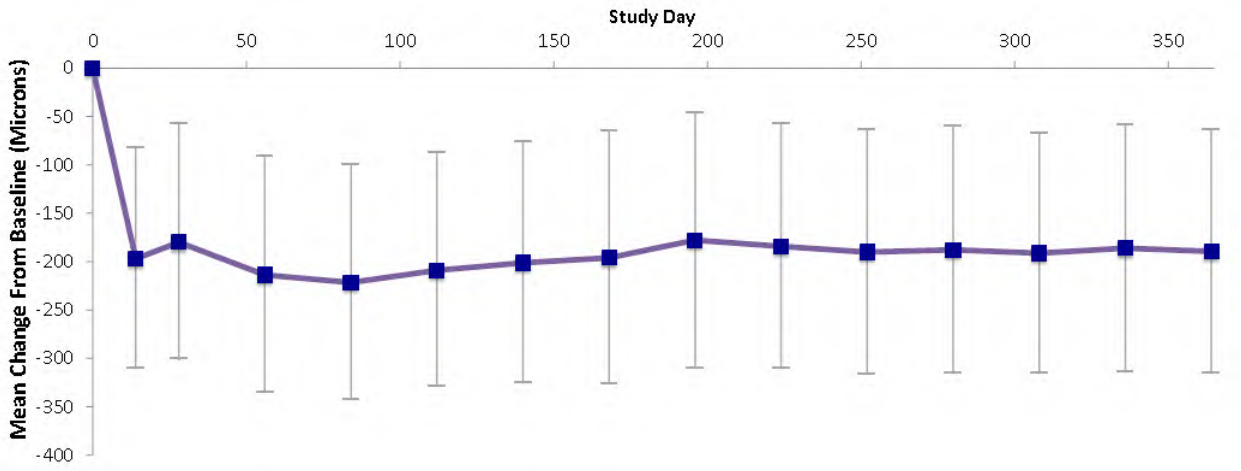
Figure 7: AVA-101 Treated Patients Experienced Vision Improvement Compared with Control

Group	Subject	Baseline Visual Acuity (ETDRS letters)	Week 52 Visual Acuity (ETDRS letters)	Change From Baseline	Change from Baseline
Low Dose	R1001	33	40	+7	+8.7
	R1002	28	41	+13	
	R1004	46	52	+6	
High Dose	R2005	56	50	-6	+6.3
	R2006	54	64	+10	
	R2008	34	49	+15	
Control	R1003	28	21	-7	-3.5
	R2007	39	39	+0	

Sources: Avalanche reports

The average retinal thickness at baseline was 552 + 132 um, and decreased to 352 + 68 um at one year (Figure 7). Notably, retinal thickness decreased with the expected increased production of sFLT1 (mediated by AVA-101 administration), and remained consistent through one year of follow up. With respect to CNV, there was a significant decrease in retinal fluid or complete lack of fluid with AVA-101 treatment. There appeared to be no atrophy in eye tissues such as the retina or choroid associated with AVA-101 therapy.

Figure 8: AVA-101 Treated Patients Experienced Improvement in Retinal Thickness



Sources: Avalanche reports

AVA-101 demonstrated a benign safety profile, with no immune exacerbations and no geographic atrophy observed. The eight study participants were evaluated at one month post injection, for any ophthalmic complications, toxicity, of systemic complications. Further, all blood counts were within baseline levels, suggesting that additional sFLT1 production did not impact blood vessel formation in other tissues and did not elicit an immune/allergic response. Only one of the 6 patients to get AAV-101 had neutralizing antibodies at baseline (not the patient with BCVA reduction). This subject experienced an increase in antibodies at day 21, while the other 5 patients saw no changes in anti-AAV antibodies. Investigators noted no correlation between drug efficacy and the presence of anti-AAV antibodies.

There were no systemic or vector-specific toxicities observed in the trial. Some of the well-known effects of VEGF inhibition (as seen with the cancer therapy Avastin) are cardiotoxicity and artherial thromboembolic events (VEGF inhibition results in “drying up” blood vessels). However, no such events were seen in patients given AVA-101, and the vector appeared to be restricted to the injected eye.

A Larger Phase IIa is Underway in Australia, to Inform a Path to Registration and Other Indications

A Phase IIa study of AVA-101 in wet AMD patients is underway, with accrual of the targeted 32 patients completed in Q2/14. The design is similar to the Phase I portion, including a 2:1 randomization to get either a single AVA-101 subretinal injection during a Lucentis ramp-up portion, or sustained Lucentis PRN. The primary endpoint is safety, while the secondary endpoints consist of:

- Retinal thickness
- Visual acuity (number of EDTRS letters)
- Need for rescue injections with Lucentis

Figure 9: A Randomized Controlled Phase IIa study is Fully Enrolled, with Topline Data Expected in Mid-2015

Sources: Avalanche reports

In contrast to the Phase I study, the Phase II trial enrolled patients with less advanced disease, with less extensive scarring and baseline visual acuity better than Phase I, representative of the broader wet AMD population.

Any improvement in the secondary endpoint of BCVA may not be comparable to observations from pivotal Eylea or Lucentis trials. Investors have been trying to gauge what a potential improvement in the number of EDTRS letters could be in the Phase IIa study of AVA-101. Of note, the enrollment criteria for the Phase IIa require a history of treatment with Lucentis; thus any changes in the number of letters may not be comparable to the 6.6-10 letters gained in the Phase III trials MARINA and ANCHOR (Lucentis) and VIEW 1 and 2 (Eylea). Furthermore, we note baseline BCVA scores of 52-55 EDTRS letters in the VIEW 1 and 2 studies, and comparable in the ANCHOR and MARINA trials. Unlike the Phase I study of AVA-101, the Phase IIa has been designed to enroll patients with scarring and visual acuity of up to 20/30 vision (corresponding to baseline ~75 letters). Thus, it is likely that baseline BCVA scores are not comparable among the different studies, rendering potential readouts more difficult to interpret.

We believe any signals would be positive and serve as basis for Phase IIb testing in the U.S. Given that patients enrolled in this trial have better baseline visual acuity (and are therefore more representative of the broad wet AMD population), we anticipate that improvement in the number of letters is likely to be more modest that in the Phase I trial. However, Avalanche views this study as an informative path to Phase IIb testing in the U.S. (expected to begin in H2/15) rather than a binary event. Non-inferiority of AVA-101 to Lucentis could represent sufficient grounds for a Phase IIb trial, given the unmet need in wet AMD, and the approval of Eylea based on non-inferiority to Lucentis. However we note that the study may not be sufficiently powered for statistical decisions.

Data are expected in mid-2015, to inform the product's path in the U.S. and other indications. Avalanche expects that safety and efficacy data from this study conducted in Australia could support the outcome of a Phase IIb study to be carried out in the U.S. starting in H2/15. This study will be randomized, controlled, multi-center, double blind,

and assess the efficacy of a single AVA-101 subretinal injection compared to standard of care anti-VEGF therapies. In addition, Australian Phase IIa data in wet AMD could serve as proof of concept for AVA-101 activity in other indications with demonstrated utility of VEGF inhibition, such as central retinal vein occlusion (CRVO) and diabetic macular edema (DME).

Clinical drug substance manufacturing for the Phase IIb is completed. Avalanche has the capability to produce AVA-101 using human as well as insect cells. AVA-101 has been successfully produced in human cells for the Phase I and IIa studies. For the following steps, the company plans to use the more scalable insect cell platform. To date, Avalanche completed the production of AVA-101 clinical drug substance required for the Phase IIb. Based on non-human primate studies of toxicology and biodistribution, this product batch appears to be well-tolerated per the company.

We Believe Avalanche is Well Positioned to Address Several Controversies

AAVL shares may have seen pressures as of late with a number of issues have been brought forth by a skeptical key opinion leader:

1) concern that Phase I study participants did not have a well-established diagnosis of wet AMD
2) concerns of atrophy caused by sustained VEGF inhibition
3) concerns that pharmacological VEGF inhibition may be impaired in patients with a history of vitrectomy (a surgery to remove a portion of the eye known as vitreous humor, to remove any blood or debris in the eye).

Per management, Phase I study investigators at the LEI have thoroughly addressed the first concern, having submitted and discussed these data in several peer-reviewed scientific forums. We spoke with other gene therapy and ophthalmology experts and discuss the other two issues as well as additional controversies below.

Can AVA-101 Lead to Vision Loss due to Geographic Atrophy?

VEGF inhibition could be associated with the emergence of retinal atrophy (loss of photoreceptors and gradual loss of vision). The Comparison of AMD Treatment Trials (CATT) multicenter study assessed head to head Lucentis and Avastin therapy. 187 (18%) of the 1024 evaluable patients in the study presented with geographic atrophy (GA) that was not present at baseline. Grunwald et at (Ophthalmology, 2014) note that the risk of GA was significantly higher with Lucentis (more potent anti-VEGF agent) than with Avastin. However, investigators concede that it is difficult to discern whether loss of vision in certain patients is due to emergence of GA or the natural course of the disease.

The KOLs we spoke with believe "the jury is still out" whether VEGF inhibition results in GA or eye areas "dried" of blood vessels resemble GA. Given the incidence of geographic atrophy in the CATT trial, investors have been concerned that potent VEGF inhibition using AVA-101 could lead to additional vision loss. While anti-VEGF injections represent the current standard of care, well-accepted within the physician community, the risk of GA cannot be ignored. However, our KOL consultants believe further investigation is required to clarify whether VEGF inhibition results in GA. Specifically, the outcome of anti-VEGF therapy is "drying up" of the abnormal blood vessels. One physicians noted that eye areas where neovascularization were reversed could resemble GA. One KOL we spoke with believes non-overlapping areas of choroidal neovascularization and atrophy would need to be documented, for a definite link to be established between anti-VEGF therapy and GA. It is difficult to distinguish if atrophy occurs in the "dried up" eye area, as a result of VEGF clearance, or is a *de novo* effect of anti-VEGF therapy. Importantly, physicians believe **GA should have been readily noticeable in the 1-year Phase I AVA-101 study follow-up.** Lack of atrophy observations at this point would suggest this risk is less of a concern.

Another KOL made the analogy between VEGF inhibition and immunosuppression. In the case of monthly Lucentis and Avastin injections, VEGF inhibition fluctuates from very potent to very low. From a safety standpoint, he believes constant, moderate VEGF suppression could be akin to moderate immuno-suppression. While short term highly potent immuno-suppression could be very deleterious of the patient, consistent low levels are generally well tolerated.

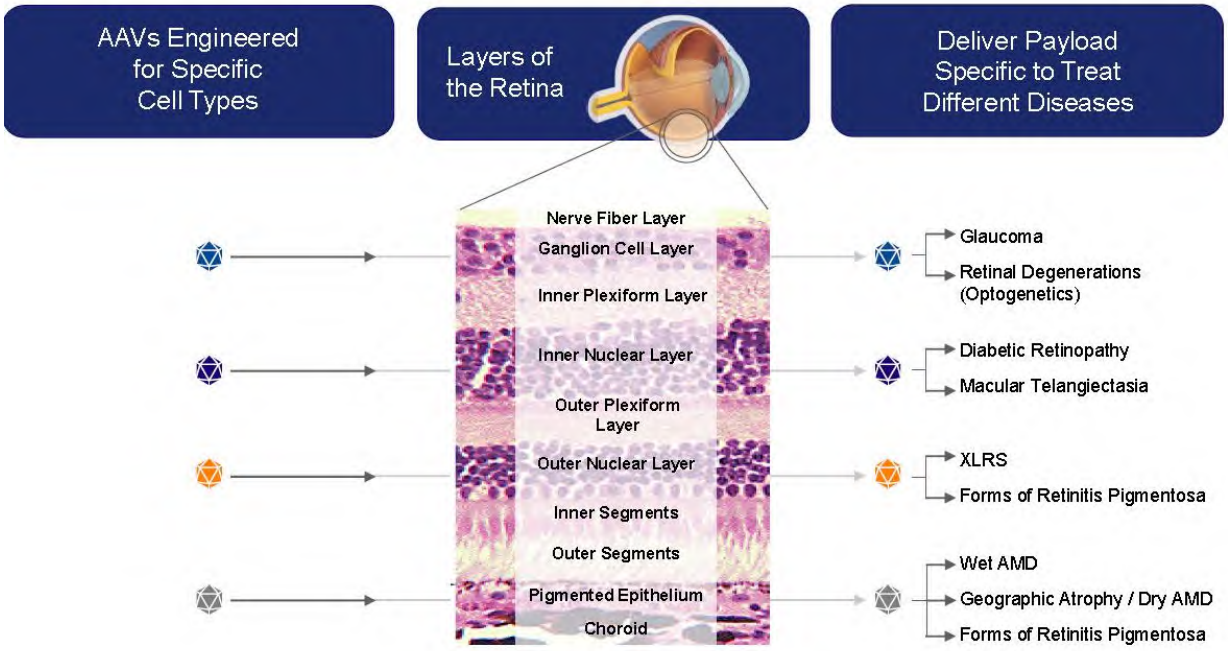
Activity of anti-VEGF therapy is likely not impacted by a history of vitrectomy

Our KOL consultants believe patients having undergone vitrectomy respond just as well to anti-VEGF therapy as those without. This appears to have been a concern in the community some year ago, but KOLs point to data presentations and key conferences over the recent 2 years (including ARVO – the Association for Research in Vision and Ophthalmology and AAO – the American Academy of Ophthalmology).

Is Subretinal Administration of AVA-101 Feasible?

Cellular barriers in the eye can prevent AAV-based therapies from effectively penetrating thick eye tissues. Experts in gene therapy that we spoke with noted significant barriers to AAV2 and AAV8-based transduction when dosed via intravitreal injection. To overcome this hurdle, Avalanche is developing a platform for more targeted delivery by engineering AAV variants and serotypes that are specific different layers of eye tissue (Figure 13). The next-generation product AVA-201 appears to have overcome the limitation of subretinal delivery, and we believe it provides Avalanche with a meaningful second shot on goal.

Figure 10: Avalanche is Developing a Platform of Novel AAVs to Enable More Targeted Delivery



Sources: Company reports

Our physician consultants suggest that the risk benefit ratio of subretinal delivery is favorable to AVA-101. We have spoken with ophthalmology experts who believe subretinal delivery is a straightforward procedure for well-trained physicians. They do note, however, the need for the operating room and anesthesia, which renders the procedure expensive and burdensome if AVA-101 would need to be re-administered. One of the KOLs noted he would be satisfied with reducing the number of patient visits per year from 6-12 to 2 or fewer. In those cases, he believes subretinal delivery would represent a minimal burden compared to the patient's need for injections and monitoring every 6-12 months. Should no re-administration of AVA-101 be required, physicians believe subretinal delivery does not pose difficulties.

Can AAV Immunogenicity Be Avoided?

One of the key limitations of *in vivo* gene therapy (the agent is administrated directly to the patient) is the propensity for immunogenicity. Tissues that are successfully transduced with AAVs could elicit strong immune responses.

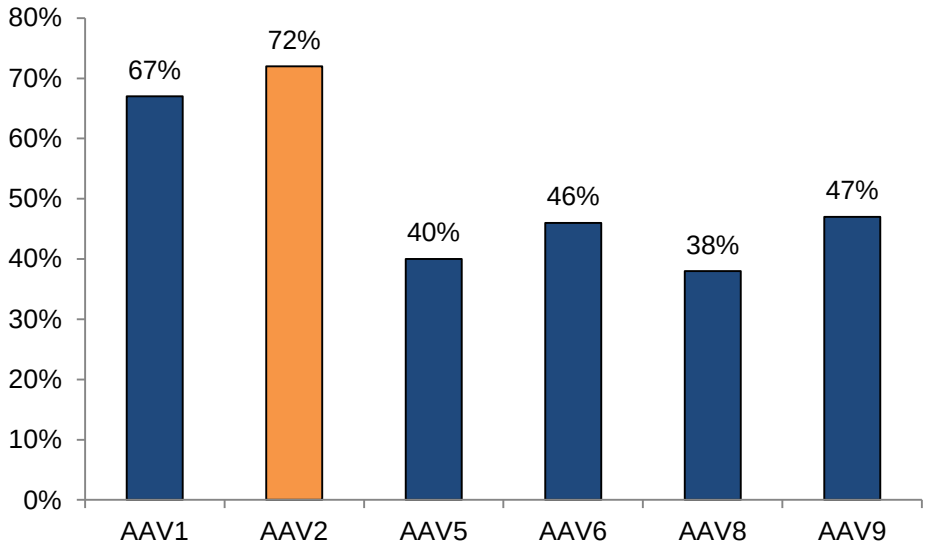
In a best case scenario, immune activation would result in inability for transduced cells to produce the desired biologic agent. This scenario would require that more therapy is administered, to boost desired levels of biologic agent. This was the case of a patient treated for hemophilia B, that experienced a decline in levels of Factor IX.

In a worst case scenario, immune activation could result in systemic destruction of transduced cells. This could be especially deleterious for the patient if affected tissue cannot be easily regenerated (i.e. heart, brain). However, we note a lesser risk for AAV-induced immunogenicity in the eye, given the immunoprivileged status of this organ.

AAV is a naturally occurring virus and humans have developed immunity against a large proportion of AAV species. Figure 14 depicts the levels of baseline immunity currently found in the broad human population. Of note, 72% of the population currently harbors antibodies against the AAV2 species, which represents the basis of Avalanche's therapy.

In addition, once the AAV capsid transduces the desired cell, the cellular degradation machinery breaks it down into small protein (peptide) components. These peptides are taken by human cells and exposed on their surface, such that they are subject to immune surveillance.

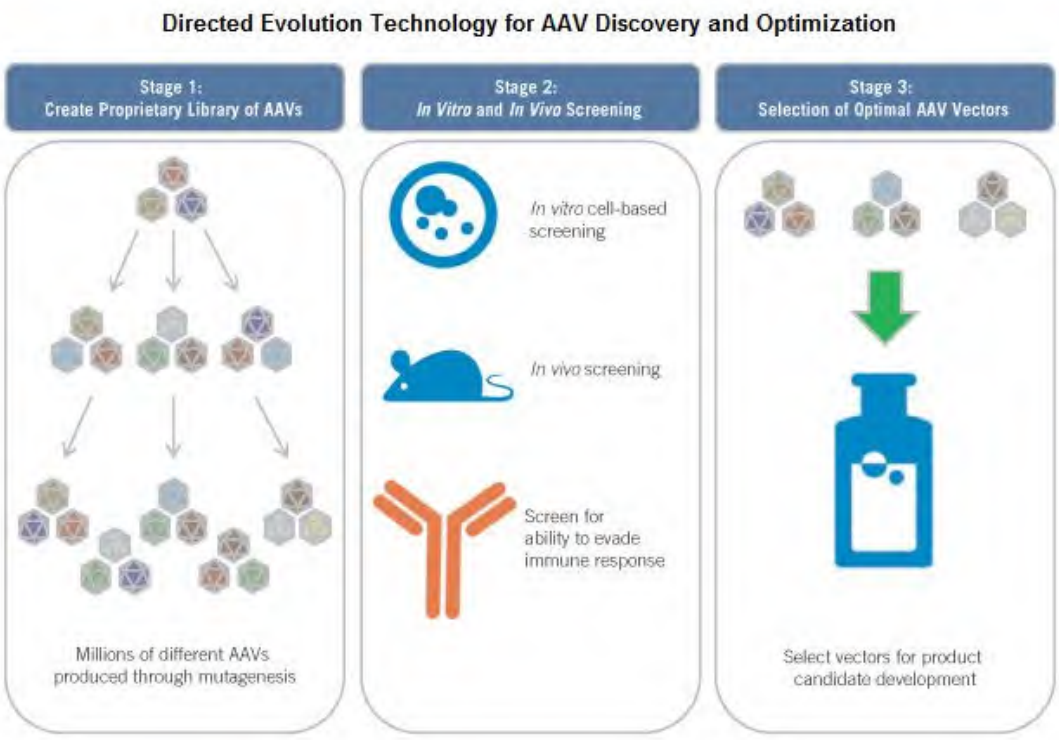
Figure 11: Different AAV Species Have High Levels of Antibodies Present in the General Population



Sources: Company reports

A key discovery was that mutating certain regions of the viral capsid renders them "less visible" to the immune system. Anecdotal evidence from scientific literature suggests that "tweaking" the small genetic code of the AAV capsid can allow it to avoid typical breakdown and presentation to the immune system. Avalanche is systematically screening for AAV species and species variants that can escape this process.

Figure 12: Avalanche's Ocular Biofactory Relies on Directed Evolution Strategies to Optimize Minimal Immunogenicity



Sources: Company reports

Is Manufacturing Using Insect Cells Safe and Scalable?

While Avalanche is comfortable using both human as well as insect cells at this point, management believes that the baculovirus/Sf9 system represents the most cost effective and easy to scale method.

First, insect cells grow in suspension (occupy an entire liquid volume available) whereas a large number of human cells may require a surface to attach to in order to remain viable. Thus, insect cells could benefit from ease of scalability and high production margins. We note, however, extensive experience and know-how held by the industry with respect to use of human or other mammalian cells for the production of biologics such as antibodies or enzyme replacement therapies.

Second, there remains a theoretical risk that Step 3 outlined above, purification of AAV from human cells, may not remove human proteins completely from the AAV mix. Depending on the nature of these proteins, they could be harmful for the recipient organ. However, we believe that this risk is minimal, again given the extensive experience within the industry of ERT/antibody use.

To Sum up: Physician Consultants Were Encouraged by the Design of AVA-101 and Believe It Would Address a Large Unmet Need

Physicians we spoke with noted the burden of monitoring and injections with anti-VEGF agents associated with wet AMD treatment. KOLs believe that administration of a stable source of VEGF in the eye would address these issues. Given the relative de-risking of the AVA-101 mechanism of action (upregulation of the sFLT1 molecule, the same outcome as delivery of Eylea), KOLs believe the therapy is well-positioned for clinical success. One KOL was highly encouraged by the significantly smaller number of Lucentis injections required by patients in the Phase I study, suggestive of potent VEGF control and reversal of leaky blood vessels in the eye. Another KOL noted that, although functional cure with a single AVA-101 dosing would be ideal, even a reduction of the number of injections with anti-VEGF therapy would represent a material improvement to the current standard of care. This physician alluded to a base case of 2 AVA-101 injections per year or fewer that he believes would be acceptable for broad uptake.

Expect the March 25 R&D Day to be a Major Catalyst for Avalanche

At the planned R&D Day in New York we look towards more disclosure of the basic science behind AVA-101, the broad clinical development program and next steps. The discussion will likely revolve around the unmet need, the supportive preclinical data and the types of patients addressed by the Phase IIa study underway. The company plans to discuss topics that may not be fully understood by investors, as well as frequent questions. The event will most likely include a thorough discussion of the progress on the basic science front that underpins AVA-201 and AVA-311. We believe the overhang of several controversies may be lifted, as the company and key opinion leaders will provide a broad discussion of the data and any scientific concerns.

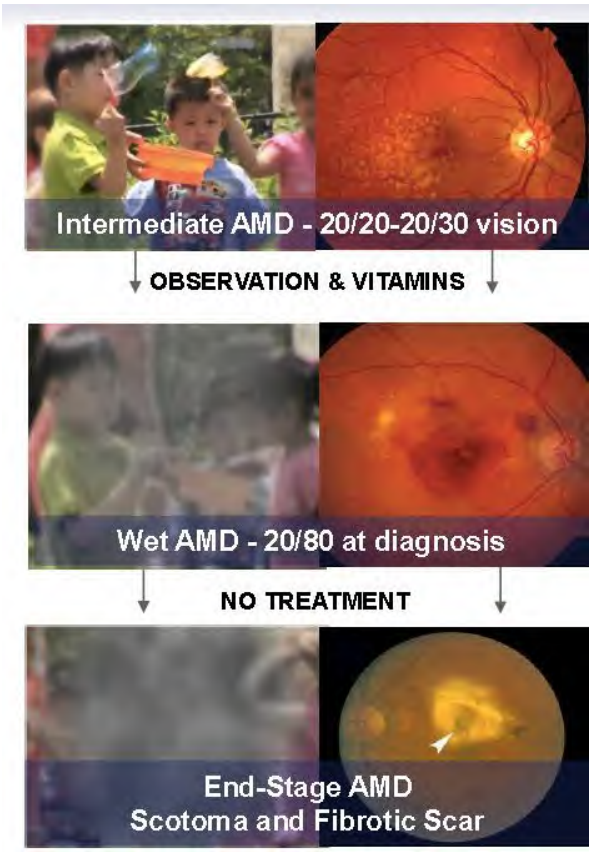
Wet AMD is a Well-Established Market but Unmet Needs Remain

VEGF Buildup Causes Leaky Blood Vessels and Vision Loss

Age-related macular degeneration is the leading cause of visual impairment in older adults. The name refers to degeneration of the central portion of the eye tissue known as the retina. The disease impacts ~1.75M U.S. individuals, but the vast majority present with milder forms. AMD is typically classified as “dry” or “wet”: dry AMD refers to retinal buildup of cellular material deposits that impair vision, while wet AMD is caused by accumulation of fluid (including blood) in the retina. The molecular mechanisms of vision loss are better understood in the case of wet AMD, whereby the vascular endothelial growth factor (VEGF) is known to play a key role in abnormal blood vessel formation.

Early AMD often presents without any symptoms, but patients with wet AMD experience a gradual appearance of distorted straight lines in the central portion of the eye (i.e. windows, doors, or other objects with straight edges are perceived as curved). This progresses to gradual loss of central vision as patients often see a dark patch in the middle of the eye known as scotoma (Figure 9). The disease begins manifesting in a single eye, however, 40%+ of patients who develop wet AMD in one eye are likely to also develop the disease in the other eye within 5 years (source: Jager et al, NEJM, 2008). Although most patients with advanced AMD do not become completely blind, their quality of life is severely impacted by significant vision loss. These patients can no longer perform daily activities such as reading, driving, or preparing meals.

Figure 13: Wet AMD Patients Experience a Rapid Loss of Vision Following Diagnosis



Source: SEC filings

Wet age-related macular degeneration is caused by VEGF buildup. Vision loss associated with wet AMD is caused by accumulation of blood and/or retinal liquid that obscures the activity of eye cells involved in vision known as photoreceptors. The abnormal liquid buildup is caused by newly-formed leaky blood vessels in the choroid portion of the eye (a process known as choroidal vascularization. A key molecule that controls novel blood vessel formation is VEGF, which binds to its receptor called VEGFR (or Flt1) and switches on a cellular cascade resulting in formation of capillary structures.

Wet AMD patients harbor excessive VEGF levels in their eye tissues. In contrast, VEGF activity in normal tissues is balanced by a number of regulator molecules, chief among which is secreted Flt1. Unlike the VEGF receptor/Flt1 which are anchored in the cellular membranes, secreted Flt1 floats in the extracellular space. sFLT1 has a high affinity for VEGF and upon their binding, VEGF can no longer bind VEGFR and the blood vessel-building cellular cascade is thus impaired.

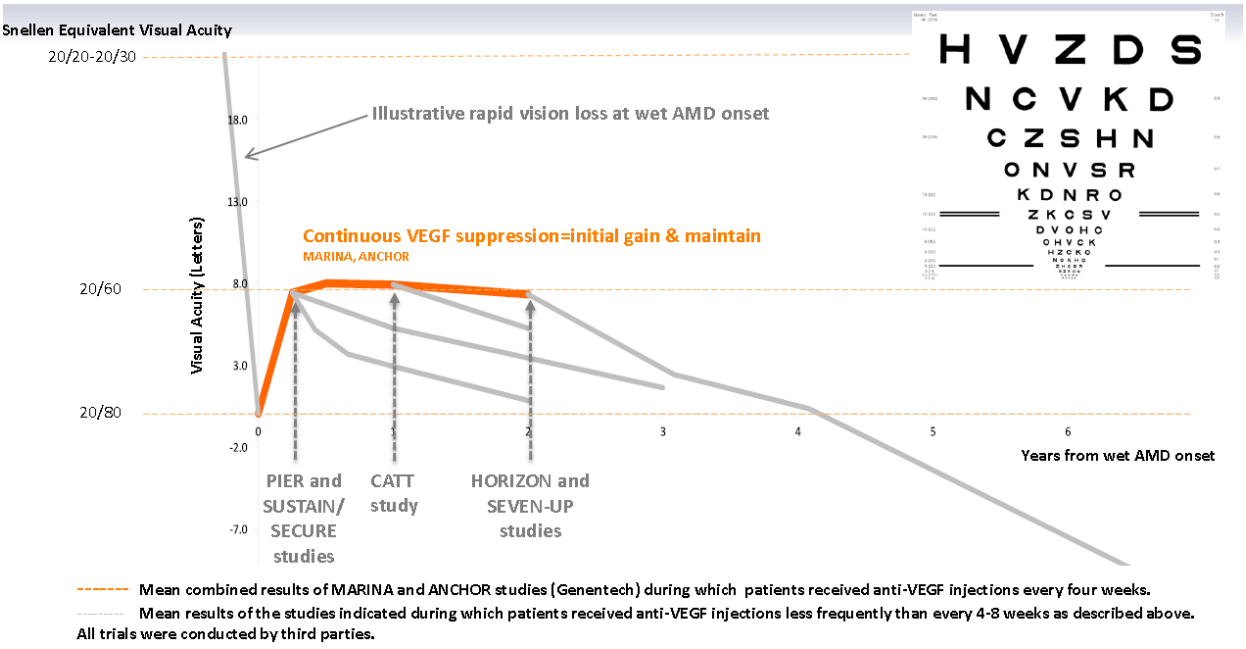
The Current AMD Standard of Care Relies on VEGF Inhibition

The history of approval and use of branded VEGF treatments is peppered with ups and downs. The advent of VEGF antibodies was hailed as a major breakthrough for cancer, but later also for ophthalmology diseases such as wet AMD, given the deleterious role played by VEGF . Prior to the approval of Lucentis in 2006, management of wet AMD was limited to slowing vision loss using approaches such as phototherapy. Treatment with monthly VEGF antibodies resulted in a partial reversal of vision loss. Lucentis shares a mechanism of action with the drug cancer Avastin but the two drugs are different molecular entities. While the monthly prices for the two drugs are similar, ophthalmologists realized that a single dose of Avastin could be compounded into multiple smaller doses for a 10^{th} of the price. Thus, Avastin off-label use in wet AMD appears to have systematically captured a ~50% share (publication of compiled Medicare records) since the early approval of Lucentis. For their part, Genentech/Roche has faced significant pressure from the medical community to formulate Avastin for ophthalmic use, and thereby to significantly reduce the cost of anti-VEGF therapy. Nevertheless, the company maintained that Lucentis was a differentiated product, and thus its price was justified. This conflict culminated with the CATT study funded by the NIH which tested head-to- head monthly Lucentis and Avastin injections, and demonstrated no significant difference between the two products.

Eylea has now surpassed Lucentis' share of branded anti-VEGF therapies in wet AMD. Per physician consultants, "every time an eye is injected there is a risk of losing that eye". Regeneron's Eylea was approved in 2011 with recommended dosing once every two months. While the product was viewed by some investors as a "me too", its differentiated design (the IgG antibody moiety coupled with structural domains of the naturally-occurring sFLT1) entailed higher VEGF binding affinity compared with Lucentis and Avastin, and therefore enabled less frequent dosing. Eylea has become a blockbuster and a strong competitor to Lucentis. On the Q4/14 EPS call Regeneron noted a 53% share (on a dollar basis) of branded wet AMD therapies for Eylea, having surpassed Lucentis. While Avastin off-label use did not diminish, a high profile incident of drug contamination during the compounding process prompted Congress to tighten regulations around drug compounding practices. To date, the branded therapy market for wet AMD remains robust (56% share of all treated wet AMD patients), given limited reimbursement from commercial payors, as a majority of these patients are covered by Medicare.

As illustrated in Figure 14, treatment with anti-VEGF agents can reverse vision loss to a certain extent. The standard of care Lucentis and Eylea have demonstrated efficacy of up to 2-3 years of treatment per follow-up in clinical trials.

Figure 14: Sustained VEGF Inhibition is Required to Stabilize Vision Loss in wet AMD Patients

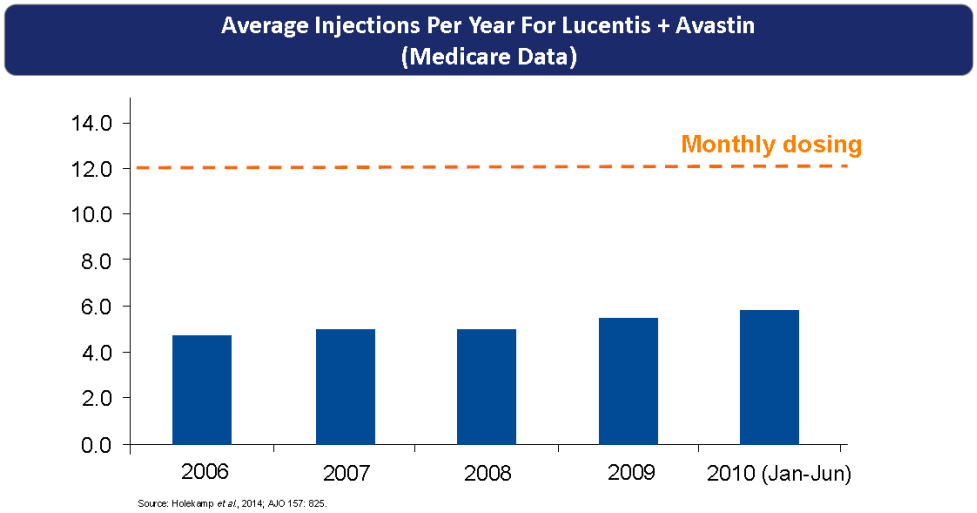


Source: Company reports

Unmet Needs Remain Due to Poor Compliance

Longer follow-up of Lucentis Phase III trials as well as of the CATT trial demonstrate that less than monthly dosing is associated, on average, with vision loss. However, real life practice entails *pro re nata* (PRN) or "as needed" injections of these drugs due to patients' desire for less frequent injections, inconveniences related to frequent travel and taking time off from work, etc. These observations are well-quantified by analyses of Medicare data (Figure 15). As levels of VEGF inhibitor peter out, deleterious VEGF is consistently produced in the eye tissues, thereby spurring growth of blood vessels and stimulating fluid build-up in the retinal space. **In contrast, AVA-101 could provide a sustained source of anti-VEGF biologic agent and prevent fluctuations.**

Figure 15: Most Wet AMD Patients Do Not Get the Recommended Number of Eye Injections



Source: Avalanche SEC filings

Investigational Agents in Development Do Not Overcome the Issue of Fluctuating VEGF Levels

Ophthotech's Fovista is a product in Phase III testing which consists of an RNA non-linear structure called an aptamer, which binds VEGF (and the cellular factor PDGF). Similar to Lucentis and Eylea, this product is aimed at sequestering functional VEGF from the retinal space. Allergan is also developing a DARPin, an antibody-mimicking protein, against VEGF. The product is currently in Phase III trials for wet AMD. Nevertheless, we view these products as add-on's to Lucentis and Eylea, to potentially prolong the interval between injections. However, similar to Lucentis and Eylea, these agents are also cleared from the patient's system and require additional injections.

We Believe Avalanche Has a Competitive Position in the Gene Therapy Space

Gene therapies in general and AAV-based approaches in particular have sparked significant interest with key opinion leader physicians and investors alike. Six new companies have conducted their initial public offerings since Jan 2013 and posted strong returns over their S1 prices. Five out of these six (83%) are using AAV for delivery. In addition, a number of larger biotech and pharma companies such as Biogen Idec, BioMarin, Pfizer, Baxter, Bayer and Regeneron (through Avalanche) are also in early stages of gene therapy development.

Figure 16: Gene Therapy Companies (non-CAR T Focused) with Recent IPOs Have Posted Strong Performance.

		S1 Price	Current Price	Returns
Applied Genetic Technologies Corp.	AGTC	$12.00	$20.34	70%
Avalanche Biotechnologies Inc	**AAVL**	**$17.00**	**$35.96**	**112%**
Bluebird Bio, Inc.	**BLUE**	**$17.00**	**$113.14**	**566%**
Celladon Corporation	CLDN	$8.00	$24.00	200%
Spark Therapeutics, Inc.	ONCE	$23.00	$58.01	152%
uniQure N.V.	QURE	$17.00	$24.62	45%

Sources: STRH Analyses

A number of private companies are also rapidly advancing their gene therapy product candidates in early clinical stages or towards the clinic.

Recent interest in gene therapy development translates into increased competition but Avalanche is on the leading edge. Avalanche competes with the following public and private companies with focus on gene therapy:

- Applied Genetic Technologies on AAV use in ophthalmology (common and orphan disorders). An rAAV2-sFLT01 partnered with Genzyme/Sanofi competes directly with AVA-101 and is in Phase I testing.
- Spark Therapeutics on AAV use in ophthalmology for orphan disorders
- uniQure on AAV use for opthalmologic indications.

AGTC/Genzyme is the closest competitor to Avalanche, with a similar strategy for wet AMD

A product similar to AVA-101 called rAAV2-sFLT01/SAR402663 is being developed by Genzyme/Sanofi, having emerged from a discovery and development collaboration with AGTC. In addition, AGTC is developing a fully owned therapy for wet AMD, and has a number of AAV-based therapies in preclinical development for orphan diseases such as X-linked retinoschisis.

There are a number of differences between Avalanche's AVA-101 and Genzyme/Sanofi's SAR402663:

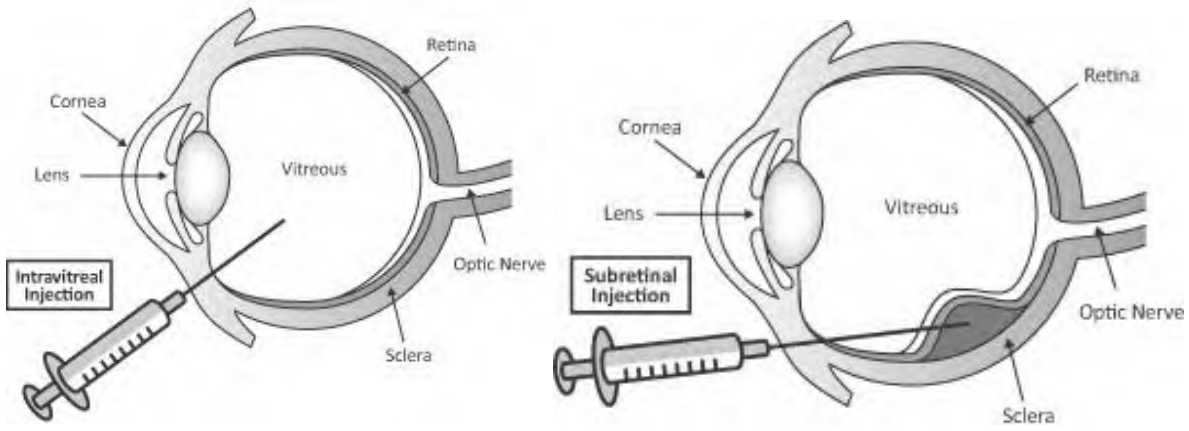
Figure 17: AVA-101 is Differentiated from SAR402663

- Both products use the AAV2 vector species, or serotype.
- Both products are designed to bind VEGF in affected tissues and counter its deleterious activity
- AVA-101 produces the entire naturally-occurring sFLT1 protein
- SAR402663 comprises a single sFLT1 portion bound to the IgG heavy chain
- AVA-101 is manufactured using insect cells transduced using a baculovirus
- SAR402663 is manufacturing using herpes-simplex virus transduced baby kidney hamster cells

Sources: STRH Analysis, SEC filings, Scientific literature

Avalanche's AVA-101 is delivered subretinally while Genzyme's SAR402663 is delivered through intravitreal injection. Anti-VEGF injections of Lucentis, Eylea or Avastin are delivered in the eye's vitreous cavity (intravitreal delivery). While these molecules benefit from a small size and get easily reach the retina, viral capsids often face difficulty crossing the thick retinal layer. Evidence to date suggests that transduction efficacy is increased upon subretinal delivery (Figure 11).

Figure 18: Subretinal Delivery Is More Precise, Albeit Demanding Surgery Compared to Intravitreal.



Sources: SEC filings

Genzyme/Sanofi's drug appears significantly behind Avalanche's AVA-101. SAR402663 is in a Phase I dose escalation trial (NCT01024998), conducted at five centers in the U.S. Four patients cohorts of four patients each were given the drug dosed at 2x10^8, 2x10^9, 6x10^9, and 2x10^10 vector genomes. The injection volume was fixed at 100uL for each injection. Patients were randomized to get one of the four doses, and the highest safe dose was elected for the second portion of the study. During the second portion of the study, patients were allowed to get at least one Lucentis injection 26 weeks post initial treatment. Results from this trial have been most recently presented at the American Society of Retinal Specialists (Sept 2014). A total of 19 patients were randomized and treated, and no safety or dose limiting toxicities had been observed.

Efficacy was assessed by evaluation of retinal thickness, conducted by an independent reading center. A summary of this presentation authored by two key opinion leaders at the Weill Cornell Medical Center (Irene Rusu and Szilard Kiss) mentioned that biological activity was observed in "4 out of 11 expected responders as defined by the study investigators". The two authors also note that **"the response rate with AAV2-sFLT01 was significantly less than that noted with AVA-101".** Nevertheless, the authors note the "clinical feasibility" of gene therapies was reinforced by these data. The timelines of SAR402663 development are not currently clear. It appears that AVA-101 Phase IIa data, if positive, would provide a robust foundation to a mid-stage development plan in the U.S. Thus, we estimate that AVA-101 has at least one year leg up ahead of SAR402663.

Our physician consultants suggest that the risk benefit ratio of subretinal delivery is favorable to AVA-101. We have spoken with ophthalmology experts who believe subretinal delivery is a straightforward procedure for well-trained physicians. They do note, however, the need for the operating room and anesthesia, which renders the procedure expensive and burdensome if AVA-101 would need to be re-administered. One of the KOLs noted he would be satisfied with reducing the number of patient visits per year from 6-12 to 2 or fewer. In those cases, he believes subretinal delivery would represent a minimal burden compared to the patient's need for injections and monitoring every 6-12 months. Should no re-administration of AVA-101 be required, physicians believe subretinal delivery does not pose difficulties.

uniQure Also Utilizes a Manufacturing Platform Similar to Avalanche but has a Broader Scope, with Near Term Focus on Hemophilia

The Dutch company uniQure has a platform of AAV-based gene therapies, and boasts the first product to be approved by a regulatory agency - Glybera, an intramuscular series of injections for the treatment of a rare disorder called lipoprotein lipase deficiency (LPLD). The product is to be commercialized by uniQure's partner Chiesi Farmaceutical, with a price of ~EUR1.1M/patient or ~$1.4M/patient.

uniQure also utilizes insect cells transduced with baculovirus for the production of AAV capsids. The company uses a similar methodology to Avalanche's baculovirus manufacturing. However, eye diseases appear to be an early program at uniQure, and we believe unlikely to enter the clinic in 2015, as the company is focusing on hemophilia in the near term. Of note, the company has two manufacturing facilities, in Lexington, MA, and in Amsterdam, NL.

Spark Therapeutics Has a Phase III Orphan Ophthalmology Program and a Broader Disease Scope

We view Spark as a potential competitor for Avalanche, within the rare ophthalmologic disorder field. Spark is developing AAV-based therapies produced using human embryonic kidney (HEK)-293 cells, a cell line commonly used in academic

laboratories. The lead product SPK-RPE65 is an AAV2-based product, designed to introduce a functional version of the RPE65 gene into pediatric patients with the rare eye disorder Leber's Congenital Amaurosis. The product is delivered via subretinal injection. Important proof-of-concept for these programs have been garnered to date in academic settings. Spark is capitalizing on this clinical experience and conducting a Phase III trial that is fully enrolled (N=24 patients). Topline data from the Phase III study are expected in H2/15.

Spark's strategic scope appears broader than eye disorders. While Spark's second program is in Phase I/II testing and is also addressing a rare eye disorder (choroideremia), the company has preclinical programs for hemophilia A and B, and neurodegenerative diseases. The company announced recently a partnership with Pfizer for the hemophilia program, with a Phase I/II study expected to begin in H1/15.

We like Avalanche's Differentiated Approach to Gene Therapy and Focus on Eye Disorders

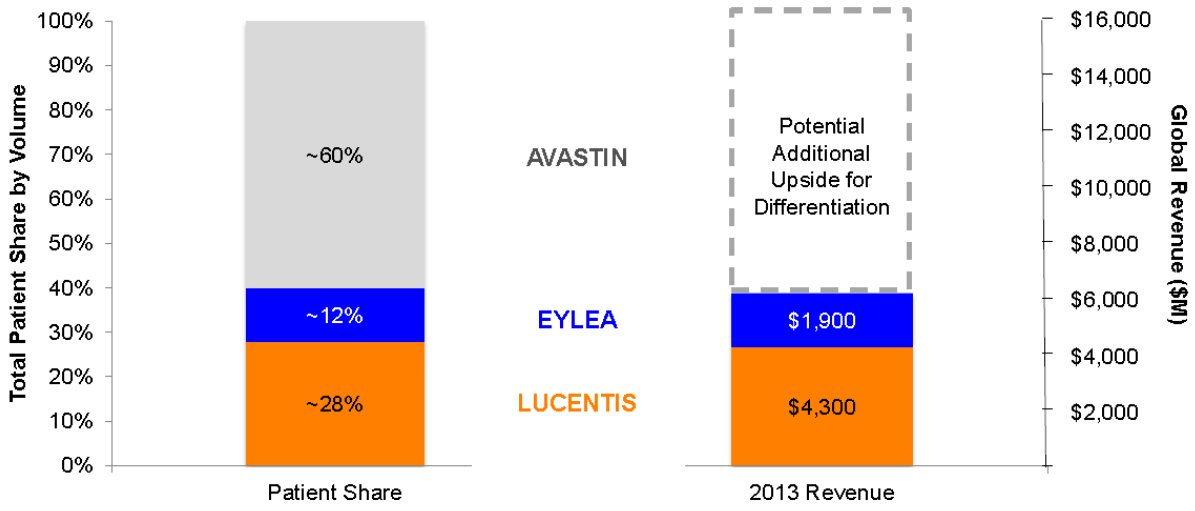
Focus on a single therapeutic area could have both advantages and disadvantages. On one hand, addressing diseases afflicting different organs can open up broad market opportunities. However, focus on a single organ could also pay out, given Avalanche's focus on large indications addressable by VEGF inhibition, such as wet AMD (anti-VEGF branded therapies were ~$6B in 2013) as well as orphan disorders. As demonstrated by Lucentis and Eylea, anti-VEGF inhibition has further utility beyond wet AMD, for broad indications such as DME and CRVO. In addition, Avalanche has a partnership in place with Regeneron, a company that successfully entered a well-established branded wet AMD market. We believe Avalanche can leverage this collaboration to uniquely tailor its clinical development, regulatory, manufacturing, and commercial strategy and leverage the partnership with Regeneron. Lastly, there appears to be space in the orphan ophthalmology space for multiple players, with a large number of genetic eye disorders currently with no approved therapies.

We Forecast $2.0B in Peak AVA-101 WW sales in 2026

Based on our review of the medical literature, our discussions with KOLs and review of market research data about Lucentis presented by Roche in 2012, we estimate that ~565K patients in the U.S. have wet AMD (~150K newly incident per year), and ~322K patients are diagnosed. Treatment rate is high (~85% of the diagnosed patients) in the U.S., and 50%, 25%, and 25% of the prevalent patient pool is currently treated with Avastin, Lucentis, and Eylea (with Eylea likely to capture additional share in the future while Avastin likely to remain the dominant therapy), per our KOL feedback and Medicare compiled data (source: Holekamp et al, AJO, 2014). We assume similar prevalence

numbers in the E.U., with 501K patients currently on branded therapy, but a significantly higher share on the cheaper Avastin. Uptake in ROW countries including Japan is upside to our estimates. Given the well-established regulatory path for Lucentis and Eylea, we anticipate that Avalanche would need to conduct two Phase III trials in wet AMD, which could begin by 2016 year end, with topline results in 2-2.5 years (results likely in H2/19) and launch in 2020. Per our discussions with KOLs, patients best suited to therapy are those on stable anti-VEGF injections, who require a large number (8+) of injections per year. We model uptake in Lucentis/Avastin switchers and conservatively assume peak penetration of 18% in 2026, as we anticipate competitors such as Genzyme/Sanofi could enter the market in 2020 and beyond. We assume a price for AVA-101 per patient equivalent to 2 years of Eylea, approx. 22.2K (and an 85% gross to net adjustment). This could be a highly conservative assumption, given the 2-year price of ~$47K for Lucentis; should the benefit be striking we anticipate Avalanche could price AVA-101 at a premium to the cost of 2 years of Lucentis. We do not currently model for any revenue for AVA-101 from indications beyond wet AMD, such as diabetic macular edema or branch retinal vein occlusion, indications included in the Eylea and Lucentis labels. We also do not include any contribution from AVA-201 or AVA-311 in our valuation.

Figure 19: AVA-101 Could Capture and Potential Expand a Portion of the Current Branded Market



Source: Company reports

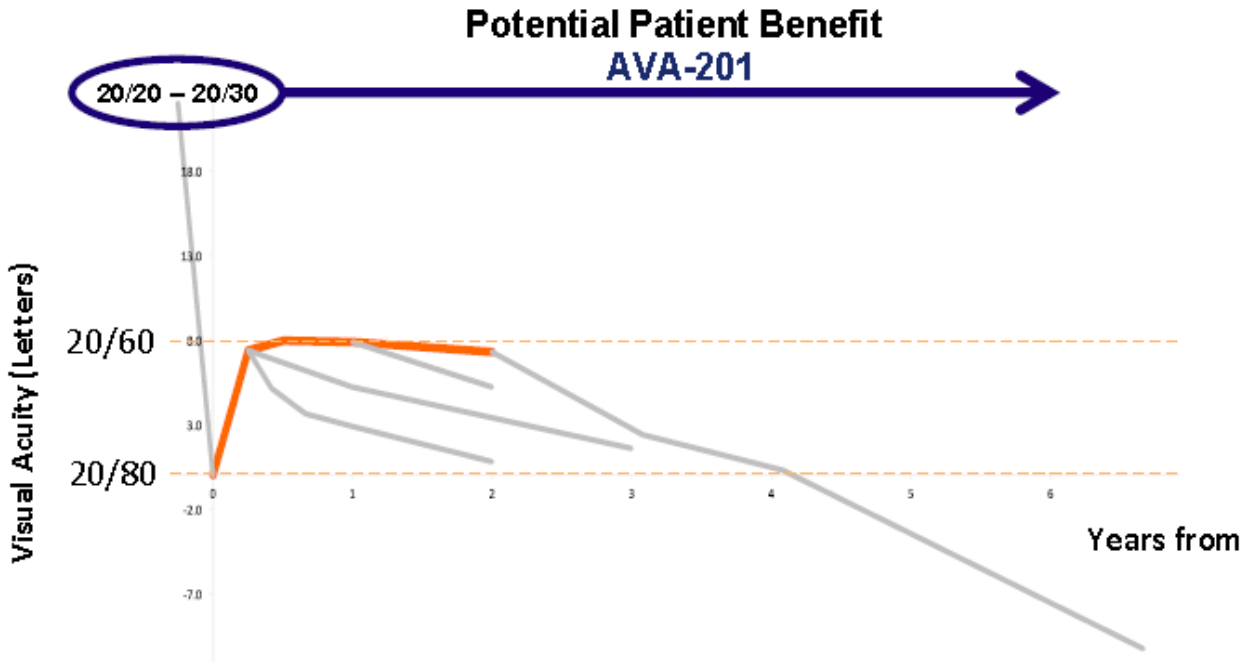
Avalanche Has a Platform of AAV-related Products for Broad and Orphan Eye Disorders

AVA-201 Could be Used as Early Intervention in Patients at High Risk for Wet AMD

AVA-201 entails the same sFLT1 anti-VEGF protein that is produced with AVA-101, but the product is designed for intravitreal injection rather than subretinal. This is achieved through Avalanche's proprietary directed evolution technology; the product should benefit from the relative ease of delivery and therefore provide Avalanche with optionality beyond AVA-101.

Avalanche is looking to use a certain panel of biologic/genetic markers, thought to predispose AMD patients to the high risk forms of the disease. The company believes that a total of 7.3 million patients at risk for wet AMD and based on their panel of genetic markers these patients could be stratified into selected population segments, amenable for preventative treatment with AVA-201 (Figure 17). As wet AMD diagnosis is typically associated with a rapid decline in vision, AVA-201 could be administered early in the disease, potentially sparing the need for any frequent anti-VEGF injections.

Figure 20: AVA-201 Could Be Suited to wet AMD Prevention



Source: Company reports

Avalanche has generated a slew of supporting preclinical data for AVA-201 in non-human primate models of wet AMD. These preclinical data have been featured in the journal *Molecular Therapy* (2005). Each animal received a single AVA-201 injection in one eye and a control vector in the other eye. 16 months later, animals were subjected to laser irradiation which causes the abnormal growth of blood vessels in the eye (choroidal neovascularization). Subjects were then evaluated at 2 and 4 weeks post irradiation. 46% of the control eyes harbored blood vessel lesions, neovascularization and fluid buildup at Week 4, while none of the treated eyes had developed abnormal blood vessels. These effects were maintained with 17 months of follow-up, with none of the treated eyes having developed degeneration.

AVA-201 is slated to begin IND-enabling studies in 2015. While Avalanche's primary focus is on advancing AVA-101, AVA-201 could provide the company with important optionality, given the next-generation nature of this product. Similar to AVA-101, the company intends to use any proof-of-activity data in wet AMD to support potential clinical testing in diabetic macular edema and central retinal occlusion, two diseases caused by abnormal VEGF activity and retinal fluid accumulation.

AVA-311 is Being Developed in Collaboration with Regeneron for X-Linked Retinoschisis

A third product in development in Avalanche's pipeline is AVA-311, and the first subject to the collaboration with Regeneron (out of 8 therapeutic targets). AVA-311 is an AAV-based gene therapy for the treatment of X-linked retinoschisis (XLRS), an orphan genetic retinal disease that impacts (with very few exceptions) boys. The disease is caused by a genetic defect of the RS1 gene, which is carried on the X chromosome (hence males are impacted since they only have a single X chromosome).

Impairment of the RS1 gene results in "split" (or schisis) of the retina, leakage of blood vessels and formation of small cysts between separated retinal layers. These cysts gradually damage the nerve tissue, resulting in gradual loss of vision that cannot be corrected with eyewear. Children with XLRS suffer from decreased central and peripheral vision. There are currently no treatment options for these patients: supplements such as vitamin A that may improve retinal cell health in other genetic disorders are not effective for XLRS, since retinal cells are mechanically disrupted rather than non-viable.

The design of AVA-311 aims to provide a permanent replacement of the RS1 gene. AVA-311 emerged from Avalanche's Ocular BioFactory platform and is using an optimized AAV backbone developed through the directed evolution methodology. The product allows for intravitreal delivery of an RS1-encoding AAV, with the aim of providing a functional cure for XLRS.

AVA-311 has demonstrated signs of activity in preclinical models of XLRS. The drug was administered to mice with defects in the RS1 gene that mimic XLRS, using a

single intravitreal injection in one eye, while the other eye was monitored as control. Animals were observed for four months, when investigators documented the following observations:

- RS1 was present in the injected eyes after 4 months, but not in control (top left panel, IF = immunofluorescence detection of the desired biologic).
- The presence of RS1 was associated with normal eye appearance, as demonstrated by two imaging techniques – fundus photography and optical coherence tomography (bottom left panels).
- RS1 delivered by AVA-311 was functional, as measured by scotopic ERC amplitude measurement (top right panel), and its function was maintained from month 1 through month 4 post-injection.
- The levels of RS1 activity delivered via AVA-311 were higher compared with other AAV vectors, such as AAV2rho-RS1 and AAV8rho-RS8.

Regeneron retains the right to opt-in for the development of AVA-311. Should Regeneron exercise its option for this program, it would retain worldwide rights while being responsible for all preclinical and clinical expenses. Avalanche would have the option to share up to 35% of the development costs and profits related to AVA-311.

XLRS represents Avalanche's foray into rare disorders, but could represent a sizeable market opportunity. The worldwide prevalence of XLRS is estimated to range between 1 in 15K to 1 in 30K (more common in European countries such as Finland and the Netherlands), corresponding to 10-21K male patients in the U.S. Avalanche believes that ~10K boys suffer from XLRS in the U.S., and we note that the higher end to prevalence estimates could be upside to investor expectations.

Avalanche Has Extensive Manufacturing Capabilities

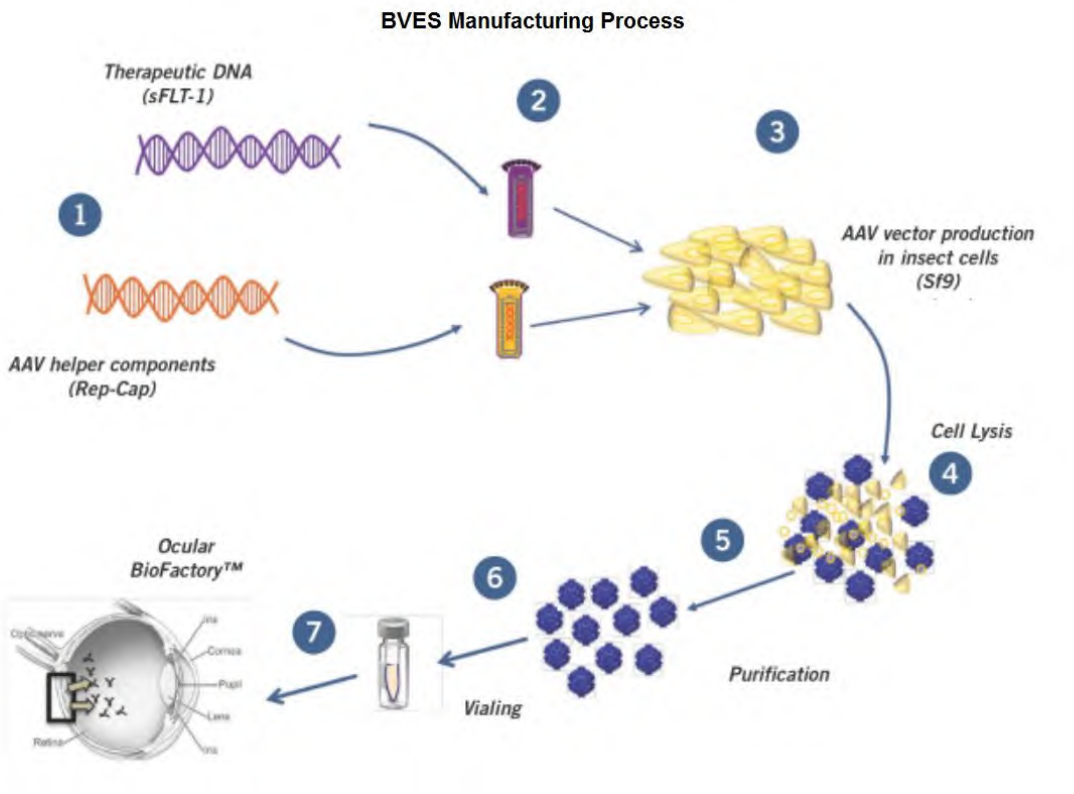
Manufacturing methodologies and scalability are key differentiation criteria among the slew of newly-emerged gene therapy companies. Production of industrial quantities of vector for gene therapy requires the following steps (illustrating Avalanche's approach in Figure 18):

1. Production of at least two DNA constructs encoding the gene of interest, as well as AAV capsid components (using well-established bacterial expansion)
2. Introduction of these DNA constructs into manufacturing-grade cells (e.g. using baculovirus transduction into insect Sf9 cells)
3. Cell disruption (lysis) and purification of therapeutic-grade AAV for *in vivo* dosing
4. Fill-and-finish of AAV vials

Gene therapy companies that have disclosed their gene therapy approaches to date utilize different methodologies for step 2, as well as different cell lines for the scalable production of AAV for therapeutic use.

While Avalanche is comfortable using both human as well as insect cells at this point, management believes that the baculovirus/Sf9 system represents the most cost effective and easy to scale method.

Figure 21 : The Avalanche Manufacturing Process Relies on AAV Vector Production in Insect Sf9 cells



Source: Company reports

First, insect cells grow in suspension (occupy an entire liquid volume available) whereas a large number of human cells may require a surface to attach to in order to remain viable. Thus, insect cells could benefit from ease of scalability and high production margins. We note, however, extensive experience and know-how held by the industry with respect to use of human or other mammalian cells for the production of biologics such as antibodies or enzyme replacement therapies.

Second, there remains a theoretical risk that Step 3 outlined above, purification of AAV from human cells, may not remove human proteins completely from the AAV mix. Depending on the nature of these proteins, they could be harmful for the recipient organ. However, we believe that this risk is minimal, again given the extensive experience within the industry of ERT/antibody use.

Intellectual Property

Avalanche owns a family of patent applications and has obtained exclusive licenses to patents that cover compositions of matter and methods of use.

The company owns patent applications related to the AVA-101 composition, unit dosages, dosing regimens, and routes of administration:

- 4 applications pending in the U.S.
- Corresponding applications pending in other countries including Australia, Brazil, Canada, Europe, Israel, Japan, South Korea, and Mexico.
- These applications would protect AVA-101 through 2033.

Avalanche also owns applications related to innovative methods to regulate gene expression in humans, in collaboration with Stanford University, with potential coverage through 2033.

The company has obtained exclusive licenses for several patent families (issued and pending applications).

Thus Avalanche has

- Rights to a U.S. patent directed to methods of treating ocular disease, including methods of use for AVA-101. The patent is co-owned by Chiron Corporation (acquired in 2006 by Novartis) and is slated to expire in 2020.
- Another U.S. patent covers the composition of matter for expression vectors that encode a soluble VEGF inhibitor, and is slated to expire in 2015.
- Exclusive rights to a family of patents and applications covering variant rAAV virions with increased infectivity, and the screening methods to identify these virions.

The company classifies its licensed patents and applications in three families, based on potential expiry dates:

1. Granted patents in Australia, Germany, France, U.K. and Spain, 3 U.S. applications and a pending application in Canada. These patents as well as any applications to issue are expected to provide coverage through 2024.
2. A second family includes a U.S. patent with 2031 expiry and a U.S. patent application with expiry in 2031.
3. A last family includes 2 pending U.S. applications (expiry in 2032 should they issue) and applications in Australia, Brazil, Europe, Israel, Japan and others.

Non-exclusive IP relates to manufacturing methods, an issued European patent and related Chinese and U.S. patent applications. All these patents would expire in 2027.

Financials

Avalanche's cash position at the end of December 2014 was $159M, excluding the $130.5M proceeds from a secondary offering in Jan 2015. In Q4 2014, AAVL reported $0.2M in revenue related to amortization of the REGN upfront payment. The company reported $10.4M in net loss attributable to common stockholders, or $0.46 per share.

The company has a collaboration in place with Regeneron ($8M upfront payment, $640M in milestones in addition to low-to-mid single digits for royalties). We model for amortization of the $6.5M of the $8M upfront payment ($0.8M recognized evenly over 10 years).

This amount excludes $1.5M to be recognized should Regeneron exercise the option to co-develop AVA-101. This option is slated to expire at a defined timepoint (likely around the Phase IIa data readout). We assume AVA-101 approval for wet AMD in the U.S. in 2020, and forecast revenue of $128M, $337M, and $592M for 2020, 2021, and 2022, respectively. We model for a continuing ramp-up in quarterly expense in 2015 and 2016, as the Phase IIb trial of AVA-101 begins in mid-2015 and novel products move into the clinic in 2016+. We forecast that the company will achieve profitability in 2021. The company obtained $102M through its initial public offering in August 2014, as well as $130M in a follow on offering in Jan 2015.

Shares are up 112% over the S1 price based on the 03/06/15 closing price. We believe Avalanche has sufficient cash runway through 2017, and we model for two follow-on equity offerings to support continuing activities: 1) an equity offering of ~5.7M shares at $70/share in 2016, and 2) an equity offering of ~2.5M shares at $100/share in 2019, after a potential data readout from the AVA-101 pivotal studies.

Management and Compensation

In our view, Avalanche management's incentives are well-aligned with shareholders. Compensation is a mix of base salary, annual cash bonus, and long-term incentive awards that include stock options (Figure 15).

The top three Named Executive Officers include the principle executive officer and the next two highest compensated officers. For 2014 the Named Executive Officers were Dr. Chalberg, Dr. Barone and Dr. Rubio. Their non-equity incentive compensation was based on a number of goals related to AVA-101, the company's pipeline and operational progress.

Figure 22: Avalanche Executives' Pay Leans Towards Options in 2014

Name and position	Salary	Bonus	Option Awards	Non-equity incentive compensation	Relocation comp.	Total
Thomas Chalberg, Jr., PhD - Chief Executive Officer	$402,917	$67,500	$935,558	$299,166	0	$1,705,141
Samuel Barone, MD - Chief Medical Officer	$176,458	$0	$1,426,733	$87,291	$3,000	$1,693,482
Roman Rubio, MD - SVP, Translational Medicine	$96,780	$0	$4,178,133	$166,791	0	$4,441,704

Source: Avalanche SEC filings

The weighting of corporate goals for the NEO's target bonus was as follows:

- 50% - Corporate – strategic transactions, financing, initial public offering, internal process
- 25% - AVA-101 – operational, program advancement, patent prosecution, quality assurance
- 10% - pipeline – technology, patent prosecution
- 15% - operational – hiring, facilities, and other operations.

For 2014 the compensation committee determined that 135% of these goals had been achieved, and enabled payment of the non-equity incentive compensation as shown in Figure 20.

SunTrust Robinson Humphrey

Avalanche Biotechnologies

(NASDAQ: AAVL)

Salveen Richter, CFA
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salveen.richter@suntrust.com

Revenue Build

($thousands, except when specified)

AVA-101 for wet age-related macular degeneration

U.S.

	FY 2013A	FY 2014A	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E
U.S. Population	316,149	319,928	321,470	323,946	326,440	328,954	331,487	334,039	336,611	339,203	341,815	344,447	347,099	349,772
%U.S. Population older than 60	*19.10%*	*19.62%*	*20.13%*	*20.65%*	*21.17%*	*21.68%*	*22.20%*	*22.72%*	*23.23%*	*23.75%*	*24.27%*	*24.78%*	*25.30%*	*25.82%*
U.S. Population older than 60	60,384	62,759	64,723	66,895	69,096	71,328	73,590	75,883	78,206	80,561	82,947	85,365	87,816	90,299
'Prevalence of wet AMD	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*	*0.90%*
No. of existing U.S. wet AMD patients	543	565	583	602	622	642	662	683	704	725	747	768	790	813
'Diagnostic rate of wet AMD	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*	*59.3%*
No. of diagnosed U.S wet AMD patients	322	335	345	357	369	381	393	405	417	430	443	456	469	482
'% of all wet AMD patients who get therapy	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*	*84.0%*
No. of wet AMD patients who get therapy	271	281	290	300	310	320	330	340	351	361	372	383	394	405
Penetration of AVA-101	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*2.0%*	*4.0%*	*6.0%*	*9.0%*	*12.0%*	*15.0%*	*17.0%*
No. of patients treated with AVA-101	0	0	0	0	0	0	0	7	14	22	33	46	59	69
Gross annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 22,200	$ 22,422	$ 22,646	$ 22,873	$ 23,101	$ 23,332	$ 23,566
Net annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 18,870	$ 19,059	$ 19,249	$ 19,442	$ 19,636	$ 19,833	$ 20,031
Total U.S. AVA-101 sales ($000s)	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ 128,387**	**$ 267,282**	**$ 417,125**	**$ 650,663**	**$ 901,773**	**$ 1,171,172**	**$ 1,378,512**

E.U.

	FY 2013A	FY 2014A	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E	FY 2021E	FY 2022E	FY 2023E	FY 2024E	FY 2025E	FY 2026E
E.U. Population	501,412	502,102	502,723	503,829	504,938	506,049	507,162	508,278	509,396	510,517	511,640	512,765	513,893	515,024
% E.U. Population older than 60	*24%*	*24.52%*	*25.03%*	*25.16%*	*25.29%*	*25.42%*	*25.55%*	*25.55%*	*25.68%*	*25.81%*	*25.94%*	*26.07%*	*26.07%*	*26.20%*
E.U. Population older than 60	120,339	123,099	125,848	126,776	127,707	128,642	129,580	129,865	130,809	131,756	132,707	133,661	133,955	134,915
'Prevalence of wet AMD	*0.90%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*	*0.900%*
No. of existing E.U. wet AMD patients	1,083	1,108	1,133	1,141	1,149	1,158	1,166	1,169	1,177	1,186	1,194	1,203	1,206	1,214
'Diagnostic rate of wet AMD	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*	*59%*
No. of diagnosed U.S wet AMD patients	642	657	672	677	682	687	692	693	698	703	708	713	715	720
'% of all wet AMD patients who get therapy	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*
No. of wet AMD patients who get therapy	501	512	524	528	532	536	539	541	545	548	552	556	558	562
Penetration of AVA-101	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0.0%*	*0.8%*	*2.0%*	*3.0%*	*4.0%*	*6.0%*	*8.0%*
No. of patients treated with AVA-101	0	1	0	0	0	0	0	0	4	11	17	22	33	45
Gross annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 20,000	$ 20,000	$ 20,000	$ 20,000	$ 20,000	$ 20,000	$ 20,000
Net annual WAC per patient	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 17,000	$ 17,000	$ 17,000	$ 17,000	$ 17,000	$ 17,000	$ 17,000
FX Impact	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Total E.U. AVA-101 sales ($000s)	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ 74,057**	**$ 186,484**	**$ 281,744**	**$ 378,360**	**$ 568,788**	**$ 763,819**

Total WW AVA-101 sales ($000s)	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ 128,387**	**$ 341,339**	**$ 603,608**	**$ 932,407**	**$ 1,280,133**	**$ 1,739,960**	**$ 2,142,331**

Source: STRH Research, Company Reports

Avalanche Biotechnologies

(NASDAQ: AAVL)

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Consolidated Income Statement

($thousands, except per share data)	FY 2014A	Mar Q1 2015E	Jun Q2 2015E	Sep Q3 2015E	Dec Q4 2015E	FY 2015E	FY 2016E	FY 2017E	FY 2018E	FY 2019E	FY 2020E
Revenue											
AVA-101	$ -	-	-	-	-	$ -	$ -	$ -	$ -	$ -	$ 128,387
% growth (QoQ or YoY)											
AVA-201	$ -					$ -					
% growth (QoQ or YoY)											
AVA-311	$ -					$ -					
% growth (QoQ or YoY)											
Other	$ -					$ -					
% growth (QoQ or YoY)											
Total product revenue						$ -	$ -	$ -	$ -	$ -	$ 128,387
Collaboration and license revenue	572	203	203	203	203	812	812	812	812	812	812
Total Revenue	$ 572	$ 203	$ 203	$ 203	$ 203	$ 812	$ 812	$ 812	$ 812	$ 812	$ 129,199
COGS	-	-	-	-	-	-	-	-	-	-	6,419
Gross profit	572	203	203	203	203	812	812	812	812	812	122,779
Operating expense											
R&D (GAAP)	16,976	7,555	9,978	12,121	13,201	42,855	72,221	98,041	118,334	132,711	143,560
SG&A (GAAP)	7,998	3,401	3,744	4,711	5,102	16,958	25,556	34,210	42,502	65,114	87,001
Total operating expense	24,974	10,956	13,722	16,832	18,303	59,813	97,777	132,251	160,836	197,825	230,561
Operating income (loss)	**(24,402)**	**(10,753)**	**(13,519)**	**(16,629)**	**(18,100)**	**(59,001)**	**(96,965)**	**(131,439)**	**(160,024)**	**(197,013)**	**(107,782)**
Interest Income (expense), net	(6)	16	20	19	18	74	122	169	129	124	116
Other income (expense), net	(70)	-	-	-	-	-	-	-	-	-	-
Change in fair value of warrant liabilities	(722)										
Total Other Income	(1,002)	16	20	19	18	74	122	169	129	124	116
Deemed dividend	(3,230)										
Income before income taxes	(25,404)	(10,737)	(13,499)	(16,610)	(18,082)	(58,927)	(96,843)	(131,270)	(159,895)	(196,889)	(107,666)
Provision for income taxes	-	-	-	-	-	-	-	-	-	-	-
Net gain (loss)	**(28,634)**	**(10,737)**	**(13,499)**	**(16,610)**	**(18,082)**	**(58,927)**	**(96,843)**	**(131,270)**	**(159,895)**	**(196,889)**	**(107,666)**
FX translation adjustment											
Net gain (loss) applicable to common shareholders	$ (28,634)	$ (10,737)	$ (13,499)	$ (16,610)	$ (18,082)	$ (58,927)	$ (96,843)	$ (131,270)	$ (159,895)	$ (196,889)	$ (107,666)
GAAP EPS (diluted)	$ (2.46)	$ (0.43)	$ (0.54)	$ (0.66)	$ (0.72)	$ (2.36)	$ (3.11)	$ (4.18)	$ (4.85)	$ (5.30)	$ (2.76)
Weighted shares outstanding basic and diluted (k)	11,651	24,779	24,902	25,027	25,152	24,965	31,118	31,429	33,000	37,151	39,008
Cash, cash equivalents and marketable securities		$ 279,151	$ 265,632	$ 249,003	$ 230,903		$ 533,938	$ 402,499	$ 242,475	$ 295,462	$ 187,680
Margin Analysis:											
Cost of product sales	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5%	5%
Product gross margin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	95%	95%
R&D (GAAP)	2968%	3722%	4915%	5971%	6503%	5278%	8894%	12074%	14573%	16344%	111%
SG&A (GAAP)	1398%	1675%	1844%	2321%	2513%	2088%	3147%	4213%	5234%	8019%	67%
Stock-based compensation expense	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Total operating expense	4366%	5397%	6760%	8292%	9016%	7366%	12042%	16287%	19807%	24363%	178%
Operating margin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-19707%	-24263%	-83%
Income tax provision	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Net margin (GAAP)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-19692%	-24247%	-83%
Y/Y change:											
Total revenue	119%	677%	150%	100%	100%	142%	100%	100%	100%	100%	15911%
AVA-101 revenue	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
R&D (GAAP)	689%	730%	222%	111%	83%	152%	69%	36%	21%	12%	8%
SG&A (GAAP)	349%	368%	151%	96%	51%	112%	51%	34%	24%	53%	34%
Stock-based compensation expense	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total operating expense	535%	570%	199%	107%	73%	140%	63%	35%	22%	23%	17%
Operating income	606%	570%	204%	109%	74%	142%	64%	36%	22%	23%	-45%
Net income (GAAP)	440%	546%	62%	101%	74%	106%	64%	36%	22%	23%	-45%
GAAP EPS (diluted)	70%	-4%	-76%	32%	56%	4%	-32%	-34%	-16%	-9%	48%
Shares outstanding - GAAP	217%	575%	578%	53%	11%	114%	25%	1%	5%	13%	5%

Source: STRH Research, Company Reports

Company Description

Avalanche Biotechnologies, Inc. is a clinical-stage biotechnology company that develops novel gene therapies to treat patients with sight-threatening ophthalmic diseases. Its products are used for the treatment of wet age-related macular degeneration and Juvenile X-linked Retinoschisis by inducing a sustained expression of a therapeutic protein with a one-time administration in the eye. The company was founded by Mark S. Blumenkranz, Thomas W. Chalberg and Steven D. Schwartz on July 17, 2006 and is headquartered in Menlo Park, CA.

Investment Thesis

Avalanche is one of the slew of new entrants in the biotech space, focused on gene therapy. Broad investor interest in the renaissance of gene therapy is evidenced by the strong performance of most of these stocks over their S1 price. Furthermore, AAVL shares are currently down off its highs at the end of December, providing an entry point ahead of visibility at the company's R&D day on March 25th 2015 and readout of the Phase IIa study of lead product AVA-101 for wet

age-related macular degeneration (AMD) in mid-2015. This product consists of an adeno-associated vector-based gene therapy, with the potential to disrupt and expand the $6B+ anti-VEGF market. Clinical results generated to date are suggestive of activity in a small number of patients with advanced disease. A randomized Phase IIa single center study is ongoing in Australia, with results expected, as noted, mid-2015. Given AVA-101's mechanism of action similar to anti-vascular endothelial growth factor (VEGF) biologics Lucentis and Eylea, the product could also have utility beyond wet AMD, in diseases such as retinal vein occlusion or diabetic macular edema (where Lucentis and Eylea are the standard of care). A follow-on preclinical gene therapy product AVA-201 is expected to undergo IND-enabling studies in 2015 for the prevention of high risk wet AMD. Avalanche is collaborating with Regeneron for the development of novel gene therapies for eye diseases, with the first product (preclinical stages) AVA-311 to address the orphan disease X-linked retinoschisis (XLRS). Notably, Regeneron also retains a time-limited right to first negotiation of rights to AVA-101.

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).

Companies Mentioned in This Note

Avalanche Biotechnologies (AAVL, $35.96, Buy)
bluebird bio, Inc. (BLUE, $113.14, Buy)
BioMarin Pharmaceutical Inc. (BMRN, $113.77, Buy)
Pfizer Inc. (PFE, $33.97, Reduce)
Regeneron Pharmaceuticals, Inc. (REGN $422.13 NR)
Roche Holding Ltd Sponsored ADR (RHHBY $32.95 NR)
Kite Pharma, Inc. (KITE $66.41 NR)
Juno Therapeutics, Inc. (JUNO $52.84 NR)
Celladon Corporation (CLDN $24.00 NR)
Spark Therapeutics, Inc. (ONCE $58.01 NR)
Applied Genetic Technologies Corp. (AGTC $20.34 NR)
uniQure N.V. (QURE $24.62 NR)
Avalanche Biotechnologies Inc (AAVL $35.96 NR)
Biogen Idec Inc. (BIIB $417.63 NR)
Novartis AG Sponsored ADR (NVS $97.46 NR)
Genzyme, subsidiary of Sanofi (SNY $47.42 NR)
Baxter International Inc. (BAX $67.73 NR)
Bayer AG (BAYN-ETR $133.65 NR)
Ophthotech Corp. (OPHT $53.19 NR)
Allergan, Inc. (AGN $233.51 NR)

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.

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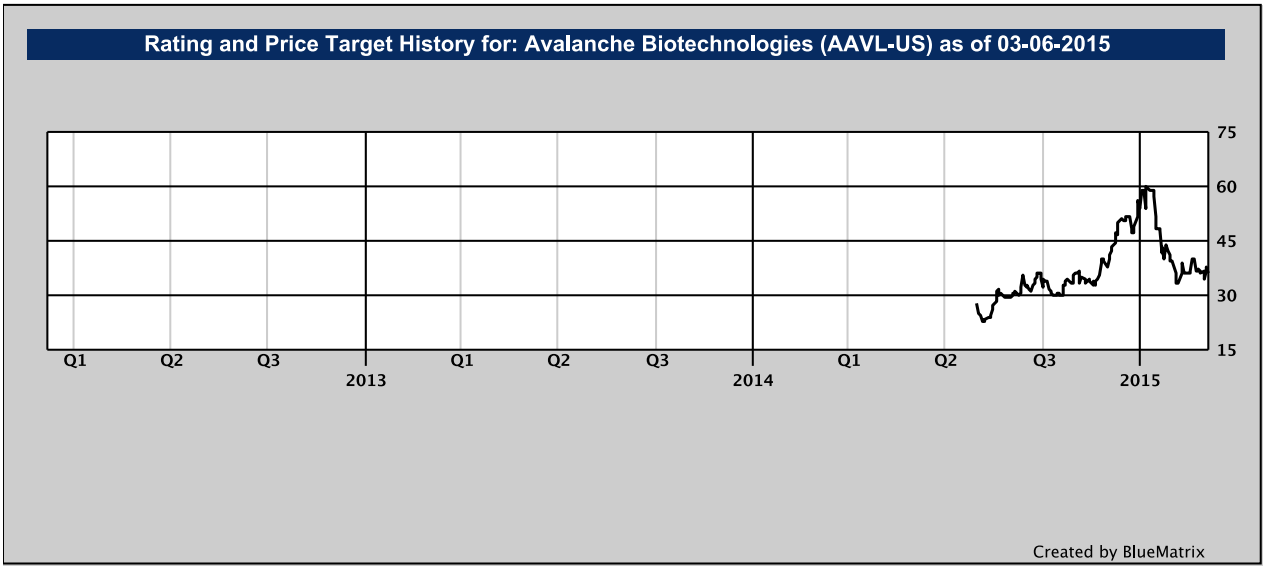

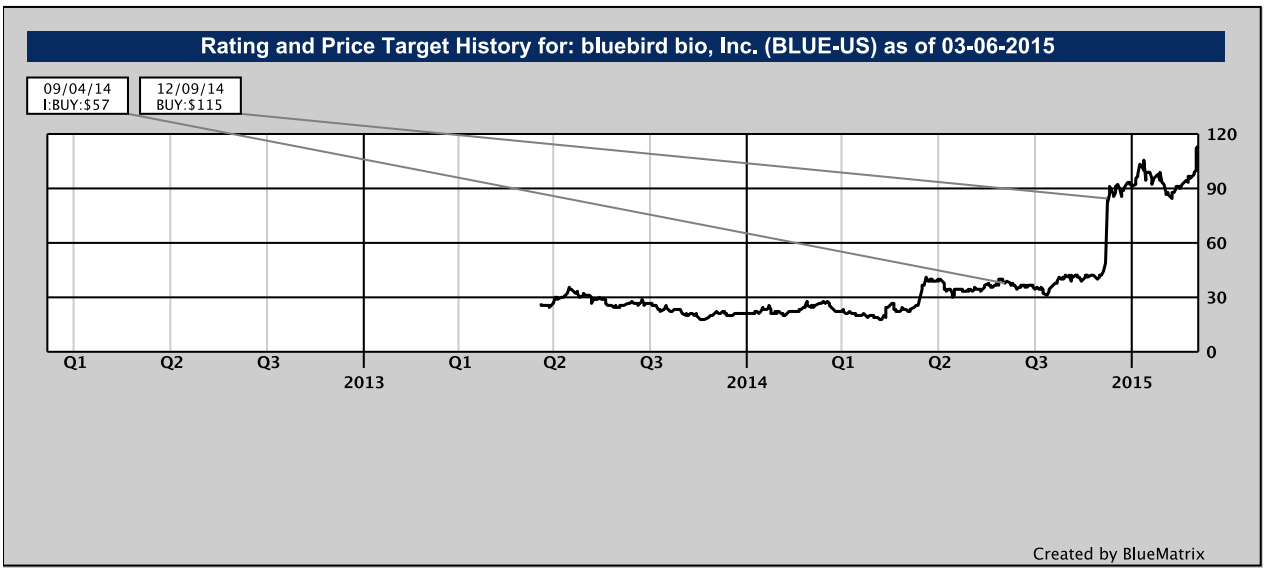

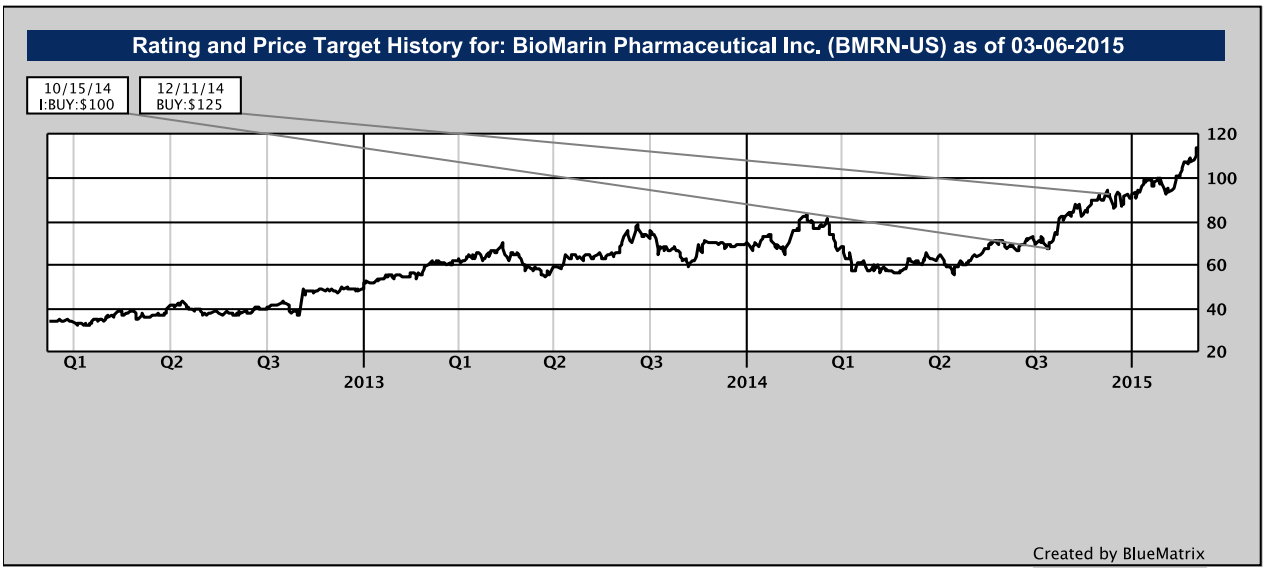

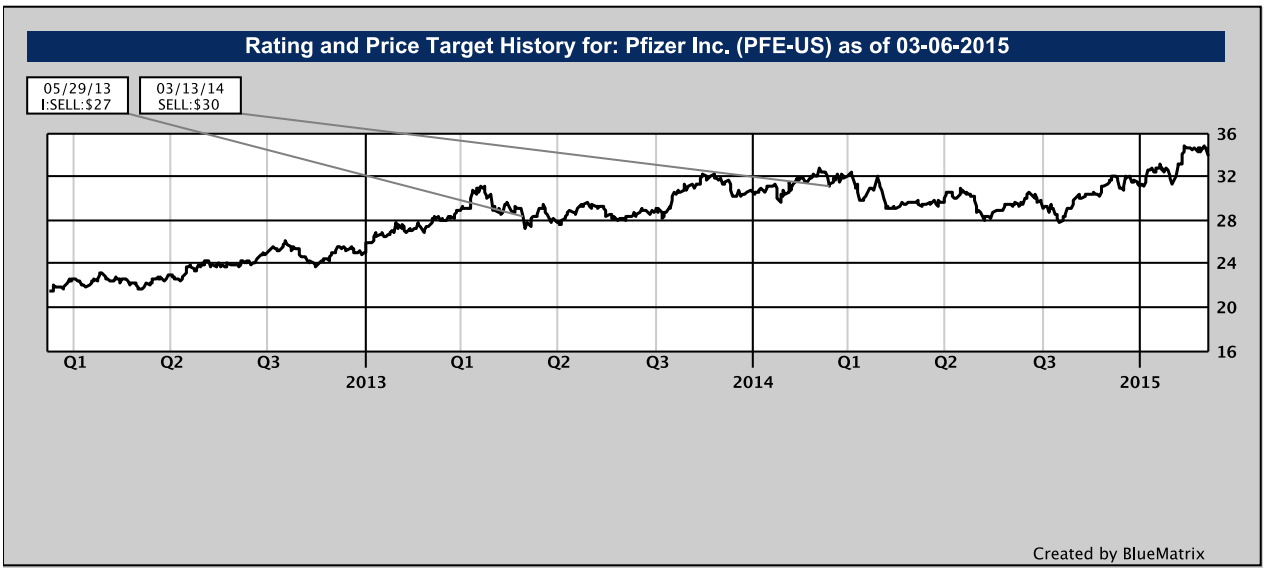

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*Total return (price appreciation + dividends)
**Price targets are within a 12-month period, unless otherwise noted
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Legend for Rating and Price Target History Charts:
D = drop coverage
I = initiate coverage
T = transfer coverage

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Coverage Universe			Investment Banking Clients Past 12 Months		
Rating	**Count**	**Percent**	**Rating**	**Count**	**Percent**
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Neutral	252	46.58%	Neutral	44	17.46%
Sell/Reduce	10	1.85%	Sell/Reduce	2	20.00%

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