COWEN
AND COMPANY

Biotechnology

Avalanche Biotechnologies

Equity Research

Initiating Coverage

August 25, 2014

Price: $30.52 (08/22/2014)

Price Target: $45.00

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: AAVL
52-Week Range:	$32.38 - 22.00
Market Cap (MM):	$651.8
Net Debt (MM):	$(0.6)
Cash/Share:	$0.15
Dil. Shares Out (MM):	25.6
Enterprise Value (MM):	$659.7
ROIC:	NA
ROE (LTM):	NA
BV/Share:	$(2.24)
Dividend:	NA

FY (Dec)	2013A	2014E	2015E
Earnings Per Share			
Q1	-	$(0.45)A	$(0.22)
Q2	-	$(0.73)	$(0.25)
Q3	-	$(0.30)	$(0.27)
Q4	-	$(0.19)	$(0.30)
Year	$(1.44)	$(1.15)	$(1.05)
P/E	NM	NM	NM
Revenue (MM)			
Year	$0.5	$0.0	$0.0
EV/S	1,319.3x	-	-

Initiation: One Stick In The Eye Is Better Than Many

The Cowen Insight

Avalanche's lead candidate AVA-101 has produced promising early data that suggests it has the potential to be a functional cure for wet AMD. Our DCF analysis implies that Avalanche is undervalued based on the promise of AVA-101 alone, with no contribution from the rest of Avalanche's pipeline. Today we are initiating coverage with an Outperform rating and a $45 price target.

A Leader In The Development Of Gene Therapies For The Eye

Avalanche has developed several technologies which allow it to create new therapeutics that address unmet needs in ophthalmology. AAVL's directed evolution technology drives the discovery of new AAV vectors engineered to target specific retinal cell types. When Avalanche's AAV vectors are injected into the eye, they create long-term "Ocular BioFactories" capable of secreting therapeutic proteins over years following a single injection.

A Single Injection Of AVA-101 Is Designed To Improve Vision And Eliminate The Need For Additional Wet AMD Therapy

Avalanche's most mature candidate, AVA-101, is designed to be a functional cure for wet AMD. One subretinal injection of AVA-101 creates an "Ocular BioFactory" that persistently secretes the natural VEGF inhibitor sFlt-1. Similar to Eylea or Lucentis, sFlt-1 binds to and neutralizes VEGF. Therefore the hope is that a single administration of AVA-101 will stop the progression of a patient's disease and eliminate the need for further therapy. AVA-101's early Phase I/II data is promising. Patients receiving AVA-101 had sustained improvements from baseline in visual acuity as compared to control, while needing substantially fewer anti-VEGF rescue injections. AVA-101 had a pristine safety profile, with no drug-related adverse events or inflammation caused by the gene therapy. AVA-101 is completing the 32-patient Phase IIa portion of the trial, from which data are expected in mid-2015. Avalanche has also advanced a second generation therapy, AVA-201, into preclinical testing. AVA-201 employs an optimized AAV vector to permit administration via an intravitreal injection. Our consultants think that a safe and effective anti-VEGF gene therapy capable of improving vision and eliminating the need for subsequent treatment will rapidly capture share of the worldwide anti-VEGF ophthalmology market, which we estimate today would be approximately $10B+ at branded prices. If successful AVA-101/201 would appear to have multi-$B potential. Avalanche owns all worldwide rights to both AVA-101 and AVA-201.

AAVL Will Collaborate With REGN To Develop AAV-Based Therapies For Up To 8 Other Targets

Included in the partnership is the preclinical candidate AVA-311, a one-time intravitreal injection for the treatment of juvenile X-linked retinoschisis (XLRS). Avalanche has an option to share up to 35% of the profits and development costs for 2 targets, and will receive tiered low to mid single-digit royalties on those for which it does not opt in.

Please see addendum of this report for important disclosures.

At A Glance

Our Investment Thesis

Avalanche's lead product AVA-101 is completing a Phase IIa study in wet AMD, from which data are expect in mid-2015. AVA-101 is a subretinal injection of AAV that delivers the naturally occurring VEGF inhibitor sFlt-1 to the back of the eye. AVA-101 could be a functional cure for wet AMD. In a Phase I/II trial, subjects given AVA-101 gained vision with minimal need for additional treatments over a year. Wet AMD is a substantial market that we estimate was approximately $8B-$10B worldwide (at branded pricing) in 2013. Even minority share could garner AVA-101 multi-$B in sales. Our DCF analysis suggests that Avalanche is undervalued based on the promise of AVA-101 alone, with no contribution from the rest of its pipeline. Today we are initiating coverage with an Outperform rating.

Forthcoming Catalysts

- Possible release of 2-year data from AVA-101's Phase I
- Results from AVA-101's Ph. IIa
- Advancement of AVA-311 and other compounds in Avalanche's collaboration with Regeneron

Base Case Assumptions

- AVA-101 has a 50% chance of being successfully developed
- Should AVA-101 be successfully developed it will achieve $300MM in revenue by 2020 and over $4B at peak
- Avalanche's other pipeline programs contribute little shareholder value

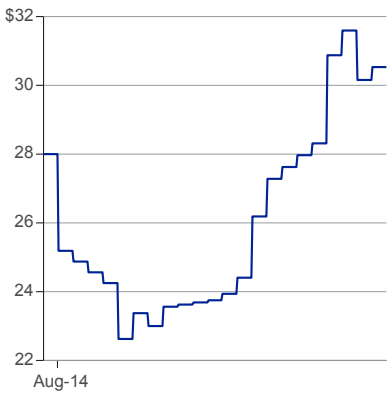
Upside Scenario

- The probability of success of AVA-101's development is materially above 50%
- Should AVA-101 be successfully developed it will achieve more than $300MM in revenue by 2020 and more than $4B at peak
- Avalanche's other pipeline programs such as AVA-311 are significant drivers of shareholder value

Downside Scenario

- AVA-101 is not successfully developed
- Even if successfully developed, AVA-101 captures little share of the wet AMD market
- Avalanche is unable to successfully develop any other pipeline programs

Price Performance



Source: Bloomberg

Company Description

Avalanche is a leader in the discovery and development of gene therapies for the eye. Avalanche has developed several adeno-associated virus (AAV) technologies, which allow it to create new therapeutics that address unmet needs in ophthalmology. Avalanche has developed a directed evolution technology for the discovery of new AAV vectors that are engineered for specific cell types, allowing Avalanche to target retinal layers and deliver payloads for diseases such as wet age-related macular degeneration (AMD), juvenile x-linked retinoschisis, and macular telangiectasia. When Avalanche's AAV vectors are injected into the eye, they create long-term "Ocular BioFactories" that secrete therapeutic proteins over years. In addition to AVA-101, Regeneron has AVA-311. AVA-311 is a one-time intravitreal injection for the treatment of juvenile X-linked retinoschisis (XLRS) which is currently in preclinical development and is partnered with Regeneron.

Analyst Top Picks

	Ticker	Price (08/22/2014)	Price Target	Rating
BioMarin Pharmaceutical	BMRN	$70.16	$95.00	Outperform
Gilead Sciences	GILD	$103.96	$105.00	Outperform
Portola Pharmaceuticals	PTLA	$25.01	$45.00	Outperform

Investment Summary

Avalanche Biotech is a leader in the discovery and development of gene therapies for the eye. Avalanche has developed several adeno-associated virus (AAV) technologies which allow it to create new therapeutics that address unmet needs in ophthalmology. Avalanche has developed a directed evolution technology for the discovery of new AAV vectors that are engineered for specific cell types, allowing Avalanche to target retinal layers and deliver payloads for diseases such as wet age-related macular degeneration (AMD), juvenile x-linked retinoschisis, and macular telangiectasia. When Avalanche's AAV vectors are injected into the eye, they create long-term "Ocular BioFactories" that secrete therapeutic proteins over years following a single injection. Avalanche's lead product AVA-101 is completing a Phase IIa study in wet AMD, from which data are expect in mid-2015. AVA-101 is a subretinal injection of AAV that delivers the naturally occurring VEGF inhibitor sFlt-1 to the back of the eye. AVA-101 could be a functional cure for wet AMD. In a Phase I/II trial, subjects given AVA-101 gained vision with minimal need for additional treatments over a year. Wet AMD is a substantial market that we estimate was approximately $8B-$10B worldwide (at branded pricing) in 2013. Even minority share could garner AVA-101 multi-$B of sales. AVA-201 is a second generation sFLT-1 gene therapy that is being developed as an intravitreal injection. In May 2014 Avalanche signed a collaboration with Regeneron to discover and develop AAV-based gene therapies against up to 8 other targets. Included in the partnership is AVA-311, a one-time intravitreal injection for the treatment of juvenile X-linked retinoschisis (XLRS) which is currently in preclinical development. Under the terms of the deal, Avalanche received $8MM upfront, and is eligible for up to $640MM in milestones. Avalanche has an option to share up to 35% of the profits and development costs for 2 targets, and will receive tiered low to mid single-digit royalties on targets for which it does not opt in. Our DCF analysis suggests that Avalanche is undervalued based on the promise of AVA-101 alone, with no contribution from the rest of Avalanche's pipeline. Today we are initiating coverage with an Outperform rating and a $45 price target.

Avalanche Upcoming Milestones

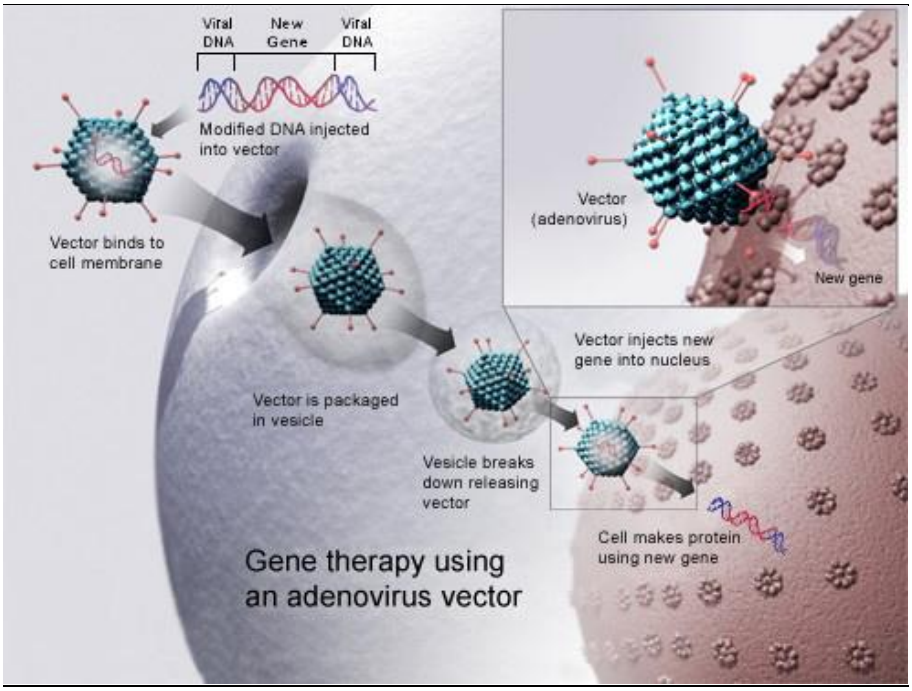
Milestone	Timing
Possible release of 2 year data from AVA-101's Phase I/II trial	H2:14
Release of data from AVA-101's Phase IIa	Mid:2015
Advancement of AVA-201 into clinical development for wet AMD	2015-16
Possible advancement of AVA-311 into clinical development for X-linked retinoschisis	2015-16
Nomination of additional targets and candidates in Avalanche's collaboration with Regeneron	2015-16

Source: Cowen and Company

Gene Therapy Has Come Of Age

Gene therapy refers to technologies that can insert genes into cells, thereby expressing the proteins encoded by the genes. Gene therapies consist of two key elements - the gene of interest, and a vector that carries the gene into the host's target cells. Over the years a number of vectors have been used, although more recently most efforts employ viruses to carry the target genes. In creating a gene therapy, most of the viral genome is replaced by the therapeutic gene of interest. This eliminates the ability of the virus to replicate and cause disease, and permits relatively large target genes to be carried. The manipulated genome is inserted into a viral vector and when the virus is given to a patient, it is taken up by the patient's cells where it delivers its DNA to the nucleus. The cell then makes the target protein using the new gene as if it were encoded by the cell's own genetic material.

Gene Therapy



Source: National Institutes of Health

Gene therapy can be used to replace damaged or missing genes, or can be used to express genes encoding proteins therapeutic for certain diseases. Gene therapy has a number of theoretical advantages over drugs and biologics as treatments for diseases. As gene therapies introduce single genes, they can be very specific, and could have few side effects. Once a person's cells have incorporated the gene, in theory the cells could produce the target protein for years, meaning that gene therapies could be very convenient and functional cures.

Ever since the dawn of molecular biology, the dream of curing genetic diseases by correcting or replacing the defective gene(s) has captivated researchers. Unfortunately, early attempts at gene therapy served to highlight that the technology had not matured enough to make the dream a reality. One notable example was an attempt to treat patients with X-linked severe combined immunodeficiency (SCID) by inserting a normal copy of the defective gene using a murine gamma-retroviral vector,

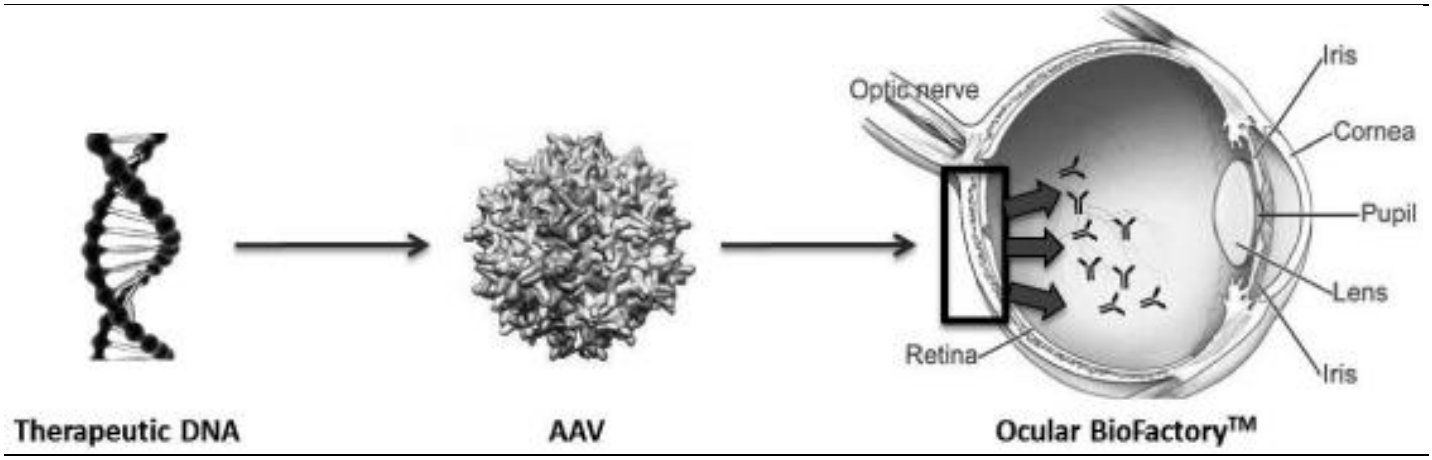
in a trial conducted from 2000 – 2002. This transgene corrected the disease, showing the promise of the approach in principle, but unfortunately the vector also caused leukemia in 5 of 20 patients. This was due to the propensity of this vector to insert near the promoter region of genes driving cellular growth, promoting the development of cancer (a process termed insertional oncogenesis). Other attempts led to little or fleeting expression of the therapeutic gene, thus having little impact on the disease.

Recent improvements in vectors and gene constructs have rapidly advanced the field, with promising clinical data having recently been reported for such diverse conditions as adrenoleukodystrophy, beta-thalassemia, chronic lymphoid leukemia, hemophilia, RPE65 blindness, and wet AMD. These advancements culminated in the first approval of a gene therapy product in 2012, UniQure's Glybera (alipogene tiparvovec) as a treatment for familial lipoprotein lipase deficiency (LPLD). In fact, with a number of promising products in clinical development, the field of gene therapy seems poised for a revolution of innovation, and to become a standard therapeutic modality.

Avalanche's Approach To Gene Therapy: The Ocular BioFactory

Avalanche's approach to treating ophthalmic diseases uses gene therapy to deliver therapeutic proteins to the eye. Using directed evolution of adeno-associated viruses (AAV) and therapeutic gene vectors, Avalanche has created the "Ocular BioFactory" technology platform. Avalanche employs AAV vectors to deliver genes encoding therapeutic proteins to cells in the retina, which enables the cells to express the protein for a sustained period of time, possibly even years.

Avalanche's Ocular BioFactory Technology Platform



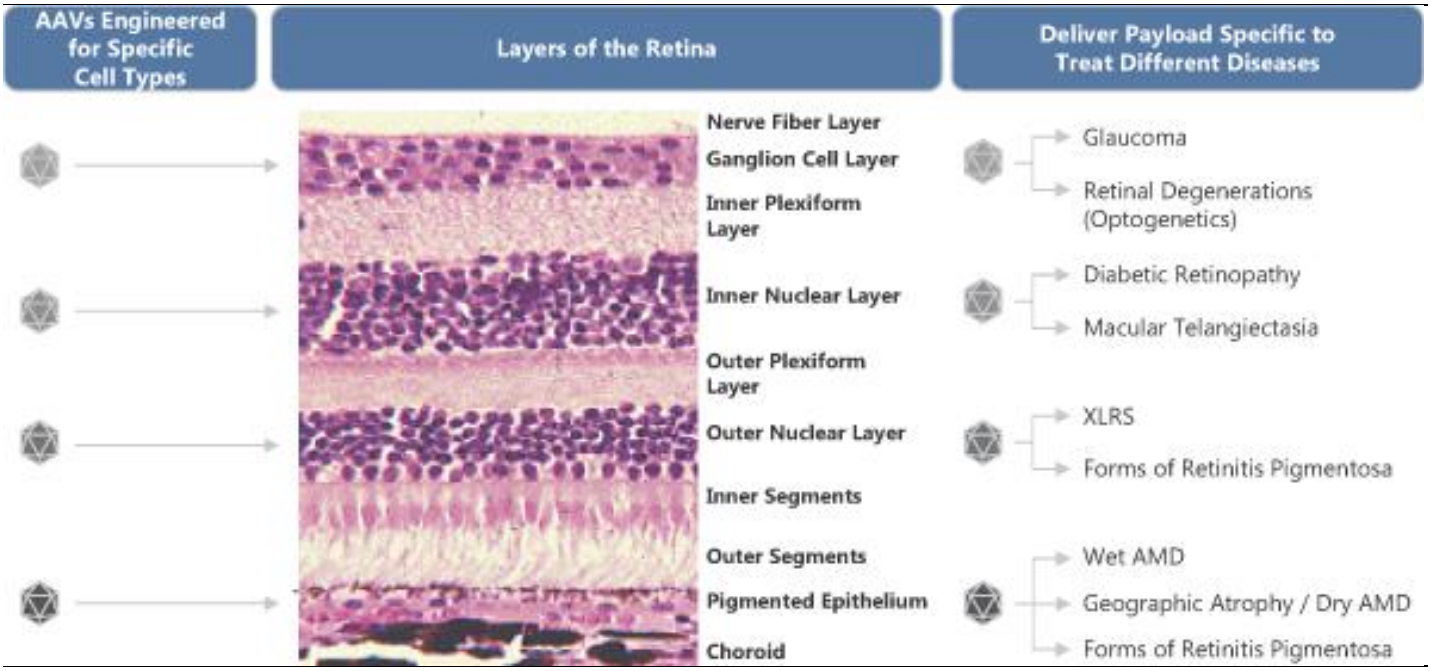
Source: Avalanche Biotechnologies

Avalanche has built its technology platform using the adeno-associated virus (AAV) as the vector to deliver the relevant genes to the eye. Avalanche has chosen AAV as its vector to deliver the therapeutic genes as AAV has a number of advantages over other viral and non-viral vectors. In particular, AAV is a naturally occurring non-pathogenic virus that is not known to cause any disease in humans. AAV vectors have low immunogenicity and elicit only a mild immune response. AAV vectors do not replicate inside the host cell, preventing their spread to unintended tissues, and they do not integrate into the host cell's genome, reducing the risk of safety issues that could come from disturbing host genes (such as those encountered in the SCID trial). AAV

vectors are also able to transduce non-dividing cells, and once incorporated into a host cell, they can drive the expression of a therapeutic protein for years. Last, AAV vectors can carry a good amount of genetic material, up to 4.5kb permitting them to target a range of indications.

Avalanche has found that the AAV2 subtype is particularly adept at infecting retinal cells, and has used AAV2 in lead candidate AVA-101. Nonetheless, Avalanche thinks that the opportunity exists to advance vector capabilities beyond what is available in the natural occurring AAV subtypes. Avalanche has developed a research engine to discover improved AAV vectors with better characteristics of cell penetration, gene delivery, protein expression and manufacturability. Avalanche is using directed evolution to develop AAV capsids which penetrate specific retinal cell types and drive very long-term expression of therapeutic proteins. Avalanche is in the process of making a library that contains millions of AAV capsids, with the expectation that some will be particularly adept at delivering genes to each of the retina's eight layers. This will allow Avalanche and collaborators to more efficiently target future therapeutics to layers of importance in various diseases.

Directed Evolution Produces Engineered Vectors That Target Specific Retinal Cell Layers



Source: Avalanche Biotechnologies

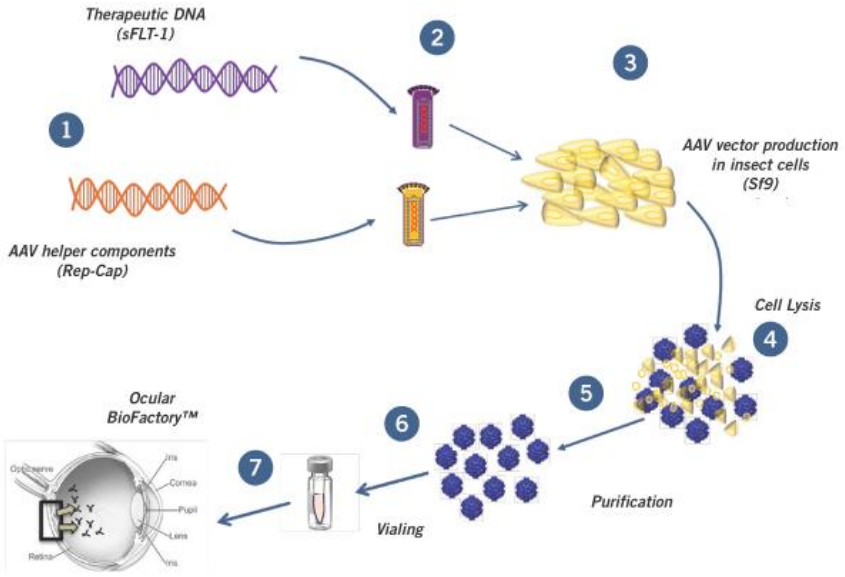
In order to create vectors optimal for product candidates, Avalanche starts by modifying genes encoding viral proteins in the laboratory. Novel combinations of these mutated genes produce millions of novel AAV vectors, each with different properties, capabilities and compositions. Avalanche then screens the AAVs for potential therapeutic benefits, such as the ability to transduce certain retinal cells, as wells as for harmful effects, such as immunogenicity. Once Avalanche has identified a pool of candidate vectors, it iterates the optimization process until it identifies a small number of ideal, engineered AAVs that are able to enter specific, targeted cell populations.

Avalanche Has Developed Industry-Leading Manufacturing Capabilities

Historically, AAV-based gene therapy programs have suffered from a lack of scalability, which has made industrial-scale manufacturing a challenge. Avalanche has developed a highly scalable manufacturing system that employs baculovirus infection of insect Sf9 cells to produce its candidates. First, insect Sf9 cells are transduced with baculoviral genomes that have been manipulated to include the AAV viral *cap* gene to produce the viral capsid, and the *rep* gene that drives replication during manufacture. These cells produce baculovirus that includes the AAV *cap* and *rep* genes in its genome. A second group of Sf9 cells is transduced with the baculoviral genome that includes the manipulated AAV genome with the target gene of interest incorporated (for AVA-101 this would be the sFLT-1 gene). These Sf9 cells produce baculovirus that includes the therapeutic gene. The two manipulated baculoviral strains then co-infect a third group of Sf9 cells. The presence of both the AAV *cap* and *rep* genes, together with the manipulated viral genome, allows the Sf9 cells to produce the therapeutic AAV viruses carrying the target gene. However, because the resulting AAV virions do not have either the *rep* or *cap* genes, they lack the ability to replicate outside of the manufacturing system. The transduced Sf9 cells are then harvested and treated with a lysis buffer solution to release the AAV vectors, which are purified to remove unwanted debris before being formulated in physiological solution and placed in vials.

Avalanche's AAV Manufacturing

BVES Manufacturing Process



Source: Avalanche Biotechnologies

Avalanche's manufacturing process has a number of advantages over traditional AAV manufacturing methods. First, it is highly scalable and efficient as it uses insect cells grown in serum-free suspension cultures, and so can produce commercial quantities. Second, since the baculovirus system uses insect cells and not mammalian cell cultures or tumorigenic cell lines, the DNA sequences of the AAV helper components are inactive in mammalian cells, lowering the risk of off-target expression. Third, Avalanche's system has high yields, which Avalanche estimates to be 100x greater than conventional AAV systems, lowering the cost of goods. Last, Avalanche's system

produces highly pure drug substances, reducing the presence of unwanted contaminants.

AMD Is A Leading Cause Of Blindness

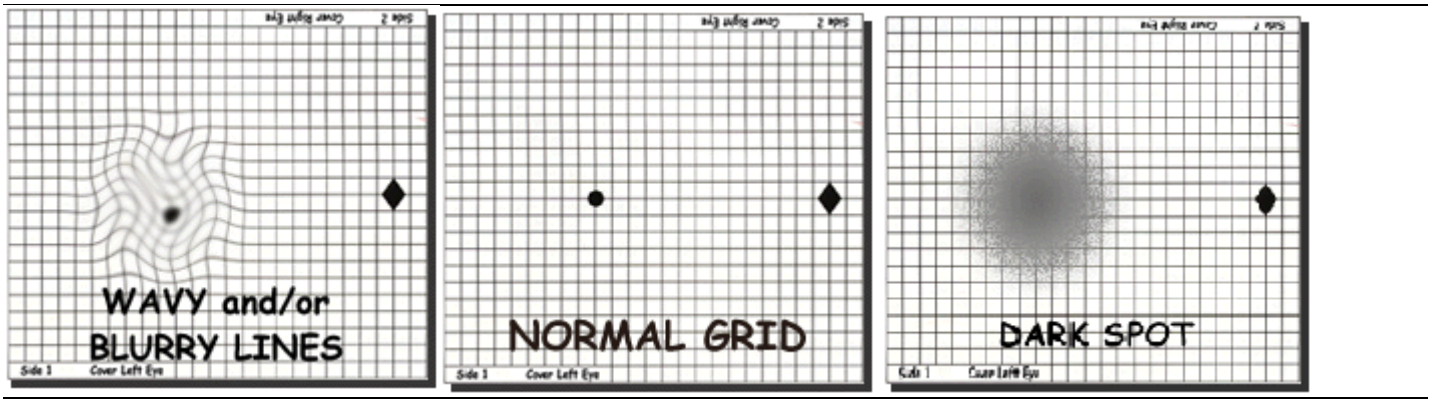
Age-related Macular Degeneration (AMD) is the leading cause of blindness in people over the age of 55. (Legal blindness is defined as a person who is only able to see 20/200 or less with glasses.) According to the National Eye Institute, more than 1MM people were diagnosed with AMD in 2009 and the annual incidence is expected to grow as the population ages.

AMD is subdivided into wet lesions (characterized by new blood vessel formation in the retina) and dry AMD (a precursor of the wet form). Approximately 15M people in the U.S. have macular degeneration, of which 10-15% have active blood vessel growth and leakage (wet AMD). The medical literature suggests there are approximately 1.5M people with wet AMD in the U.S., although Roche/Genentech estimates the size of the treatable market at approximately 180,000 patients. We estimate the U.S. AMD market opportunity at $5B+, with a similar opportunity ex-U.S. The market opportunity for wet AMD drugs has been further expanded by penetration into other back-of-the-eye conditions such as diabetic retinopathy or central retinal vein occlusion. As the population ages, the prevalence of vision loss associated with AMD is expected to nearly double by 2020.

What Is AMD?

AMD gradually destroys a person's central vision. The early stages of the disease may be barely noticeable to some, but symptoms can vary. Sometimes only one eye loses vision and the other maintains good vision for many years. Some patients have milder symptoms in both eyes that may not impair vision significantly for many years. Other frequent symptoms include distortion, or when straight lines look wavy, such as the lines on an Amsler grid (an ophthalmic diagnostic tool in the picture below) or if a doorframe or blinds look bent. Sometimes colors don't look quite right or there may be a purple or gray spot in the center vision. (See picture below.)

AMD & Amsler Grid Diagnostic Tool



Source: Cowen and Company, Macular Degeneration Foundation

Upon onset of macular degeneration, many people have trouble adjusting quickly between bright sunlight or dim light or shadows. This may be especially dangerous when driving in bright sunlight and then entering the shade or vice versa. Whereas a normal retina takes 3-5 minutes to adjust from bright light to dim (when entering a movie theater, for example), a person with macular degeneration may take 8-12 minutes or longer.

AMD Typically Starts As Slowly Progressive Dry Form

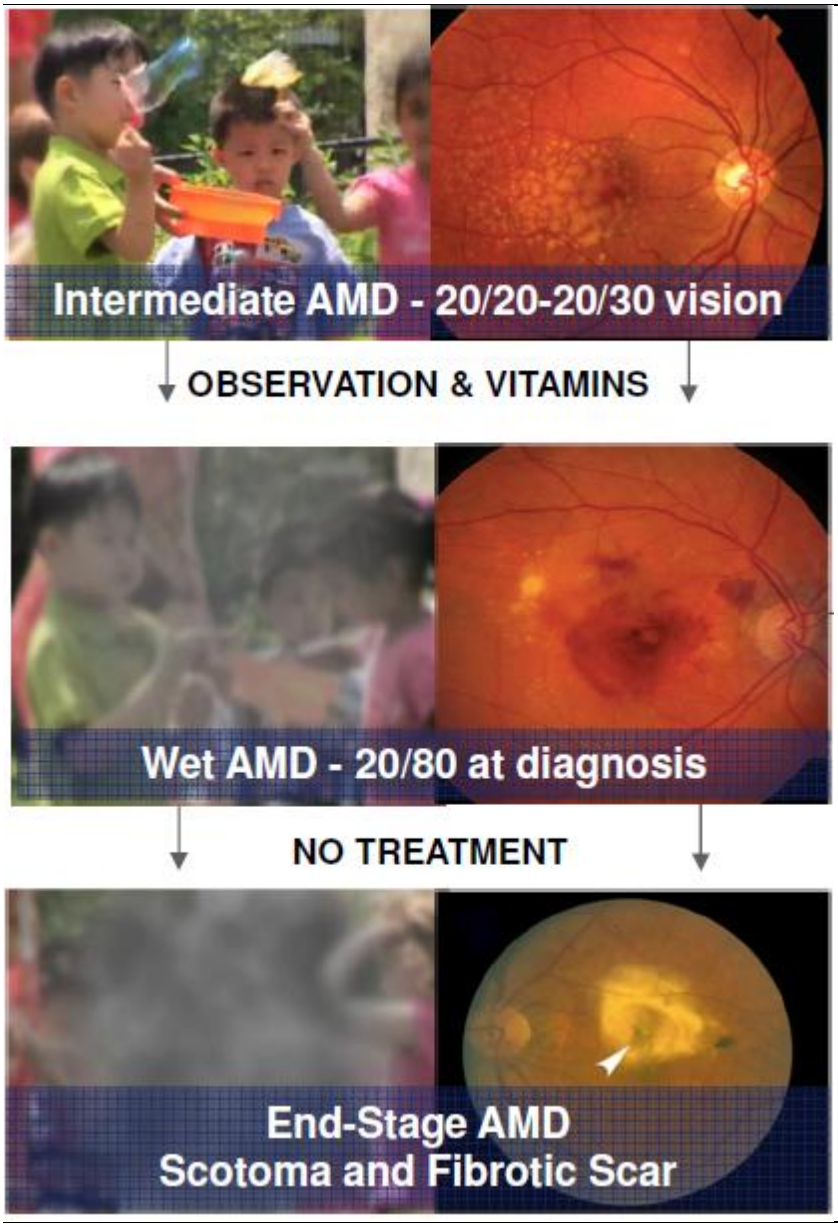
Roughly 85-90% of patients have the dry form of AMD, which involves thinning of the macular tissues and disturbances in its pigmentation. Up to 15% of AMD patients have the wet form, which can involve bleeding within and beneath the retina, opaque deposits, and, eventually, scar tissue. The wet form accounts for 90% of all cases of legal blindness in macular degeneration patients.

The dry, or atrophic, form of AMD features slowly progressive, degenerative changes in the retinal pigment epithelial cells, Bruchs membrane, and the choroid (the area beneath the retina). Many people can go for a long time with the dry form and not experience any vision problems, and when vision eventually deteriorates, it occurs gradually in the absence of wet AMD lesions. Only about 25% of people reach the stage of severe vision loss with only the dry form of AMD. Although it has been suggested that supplemental vitamins and minerals may slow the progress of the disease (as was found in the AREDS study by the NIH), more research is needed to find additional ways to prevent, slow, or cure dry AMD.

Conversion To Wet AMD Can Result In Abrupt Deterioration

About 10-15% of people who start out with the dry form progress to the wet form of AMD. As dry AMD worsens, new, fragile blood vessels grow from the outer part of the eye towards the center of the retina, known as the macula. The formation of new blood vessels (choroidal neovascularization or CNV) is characteristic of wet AMD and these vessels often leak blood and fluid, causing rapid damage to the macula and quickly leading to a loss of central vision. Wet AMD typically presents with acute-onset visual deterioration super-imposed on a background of more gradual visual deterioration characteristic of dry AMD.

AMD Progression



Source: Avalanche Biotechnologies

Etiology Of AMD Not Well Understood, But VEGF Clearly An Important Player

Any number of factors, including genetics, age, race, gender, menopause, nutrition, smoking, and exposure to sunlight, may cause AMD. Based on striking results from pan-VEGF inhibition therapy with Roche's Lucentis, it is clear that VEGF is an important driver of new blood vessel formation in the retina and conversion from dry to wet AMD. Research is ongoing to identify additional molecules that drive the wet AMD process and to better understand the pathophysiologic processes that result in VEGF overexpression.

Three Categories Of Wet AMD: Occult, Minimally Classic, and Classic

Based on the appearance of the blood vessels at the back of the eye when visualized using fluorescein angiography, wet AMD can be subdivided into predominantly classic (25%), minimally classic (35%) and occult (40%). In predominantly classic choroidal neovascularization (CNV), greater than 50% of the neovascular AMD lesion can be clearly defined, and this is generally regarded as the most aggressive subtype. In minimally classic choroidal neovascularization, 1% to 50% of the neovascular AMD lesion can be clearly defined, and this is generally regarded as the intermediate subtype in terms of progression. In occult choroidal neovascularization, none of the neovascular lesion can be clearly defined, and this is generally regarded as being the least aggressive subtype. It is helpful to think of the AMD lesion as an expanding vascular membrane which penetrates into an area underneath the retina. Angiography lights up the blood vessels in this membrane, and physicians use the angiogram to discern the outline of the membrane. However, leakage of dye from these blood vessels can obscure a physician's ability to clearly see the membrane, and the extent to which this visibility is obscured determines its classification. While it is important to identify lesion subtypes to determine eligibility for photodynamic therapy with Visudyne, the anti-VEGF therapies have utility across wet AMD subtypes, making differentiation less critical.

The Blood-Eye Barrier Can Be Bypassed With Direct Injection

The eye, like the brain, is protected from the systemic blood circulation; therefore, it is very difficult to deliver drugs into the posterior segment of the eye, particularly the retina, with sufficient concentration and reduced side effects. This is a primary reason that diseases of the posterior segment of the eye are treated by intravitreal or subretinal injections (directly into the eye), intravenous, or latero-bulbar injections, exposing the patient to pain and potential side effects. Thus, the mere location of AMD and other back-of-the-eye diseases makes it difficult for pharmaceutical/device companies to target with therapies.

Wet AMD Treatment Paradigm Evolves Rapidly

Current treatment methodologies for wet AMD include three options: anti-VEGF therapy, photodynamic therapy (PDT), and laser photocoagulation. Retina specialists are quick to adopt new therapies, often before they have undergone rigorous clinical testing or have received FDA approval. The wet AMD treatment paradigm therefore evolves rapidly and sometimes unexpectedly.

The most effective treatment for wet AMD is acknowledged to be angiogenesis inhibition. Given its vascular and progressive nature, AMD thrives on new blood vessel growth. By blocking the development of new blood vessels, researchers are hoping to cut off the supply of oxygen and nutrients and, therefore, the disease's proliferation throughout the back of the eye. Researchers have identified relevant molecular targets (e.g., VEGF) that play a key role in neovascularization in the eye.

Eyetech's Macugen, the first anti-VEGF therapy, was approved for wet AMD in 2004 and rapidly gained widespread uptake with an outstanding commercial launch. Macugen is an aptamer that binds to and inhibits activity of the VEGF165 isoform and was shown to decrease the rate of visual acuity loss in wet AMD patients versus placebo in the Phase II/III VISION trials. Macugen revenue plummeted in 2005-2007 as pan-VEGF antibodies emerged as a superior treatment option for preserving or restoring vision of wet AMD patients. Roche's Lucentis is a monoclonal antibody fragment targeting all VEGF isoforms and has set a new bar for wet AMD therapies. Data from the Phase II/III MARINA trial of Lucentis demonstrated an impressive ability

to improve visual acuity in wet AMD patients, a goal never before achieved in advanced clinical trials for this indication. Lucentis secured U.S. approval in June 2006 and EMEA approval in January 2007. The drug's U.S. launch was impressive (Roche/Genentech estimated that Lucentis achieved 55% penetration of the wet AMD market just 6 months after FDA approval), relegating Macugen and photodynamic therapy to niche market roles. While waiting for Lucentis to reach the market, retina specialists began to use off-label intravitreous Avastin, a cheap and commercially available anti-VEGF option. Even before there was Phase III data to support its use, intravitreous Avastin nonetheless captured the majority of the remaining (non-Lucentis treated) market and is the most commonly used anti-VEGF for the treatment of wet AMD. In turn, the growth of Regeneron's Eylea is the most recent example of the rapid market transformation in this market.

Physicians Expect Eylea To Capture Majority Share Of Branded Market Over The Next Several Years

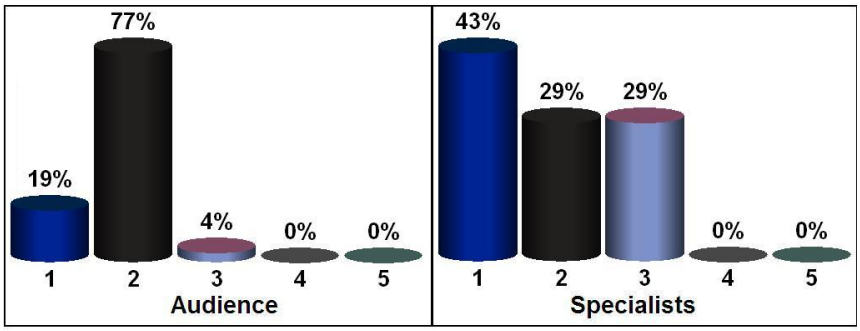
We conducted a survey of ophthalmologists in conjunction with our March 2014 Annual Health Care Conference to assess the future use of Eylea. The majority of our surveyed physicians (83%) believe that the current ratio of wet AMD patients treated with Eylea versus Lucentis is around 75%:25%, which is an increase from our October 2013 survey (50%:50%) reflecting the continued strong uptake of Eylea. Our panelists note that insurance coverage has been excellent and makes it very easy to get approval for Eylea. While established patients represent a mix of Avastin, Lucentis, and Eylea, our panelists note that new wet AMD patients are almost exclusively being started on Eylea.

In three years, many of the physicians surveyed (43%) expect the ratio of wet AMD patients treated with Eylea versus Lucentis to be close to 100%:0%, which we believe reflects the fact that the vast majority of new patients are receiving Eylea. This is up from the last October 2013, when the majority of surveyed physicians (58%) believed it would be closer to 75%:25%. However, the participants in the panel at our March 2014 conference believe that 75%:25% is probably the most accurate number as a decent amount of patients still need to be switched from one anti-VEGF therapy to another as they become refractory to treatment.

Estimated Eylea vs. Lucentis Use In Three Years, March 2014

5) In three years' time, I expect the ratio of my wet AMD patients treated with Eylea vs. Lucentis to be closest to:

1. 100% Eylea : 0% Lucentis
2. 75% Eylea : 25% Lucentis
3. 50% Eylea : 50% Lucentis
4. 25% Eylea : 75% Lucentis
5. 0% Eylea : 100% Lucentis

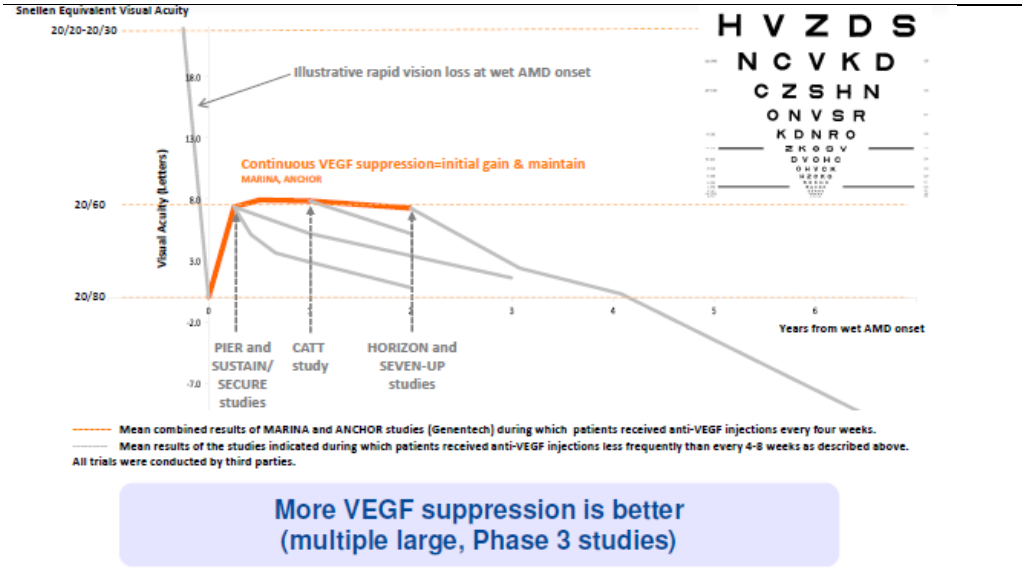


Source: Cowen and Company Health Care Conference, March 2014

Despite Success Of Anti-VEGF Injections, There Is Room For Improvement

Although the current anti-VEGF therapies Avastin, Lucentis and Eylea are widely used, our consultants note that there is still room for improvement. First, patients must stay adherent to frequent intravitreal injections in order for the disease process to be arrested. Our consultants suggest that the average Lucentis patient will need 7-9 doses per year, while the average Eylea patient may require 6-8. Therefore, patients are still required to come to their physicians' offices every 4-8 weeks, a significant time commitment for both the patients and physicians. Unfortunately several studies have shown that poor compliance leads to progressive visual loss, emphasizing the importance of good adherence.

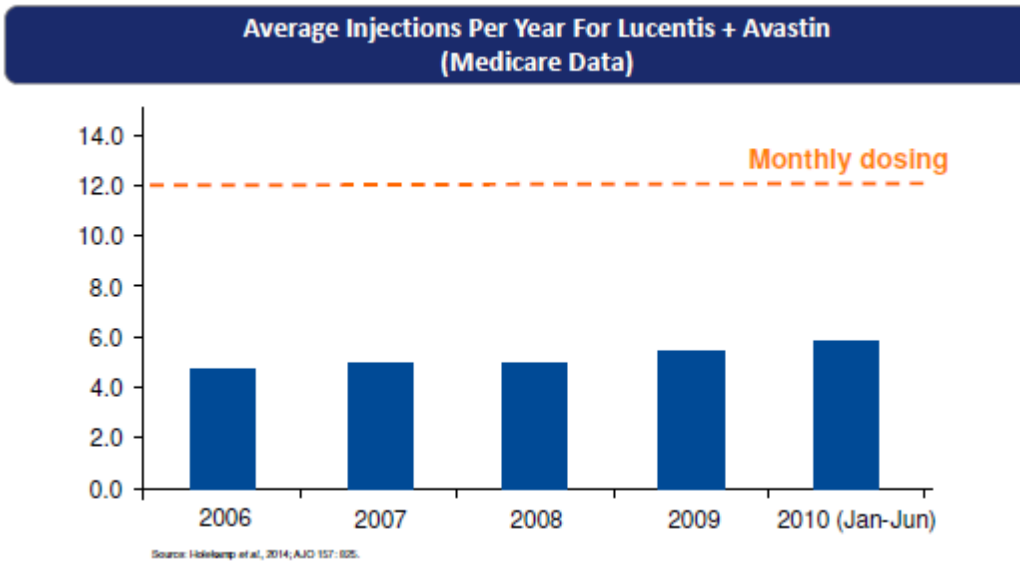
Poor Compliance Leads To Progressive Vision Loss



Source: Avalanche Biotechnologies

Unfortunately Medicare data suggest that on average patients receive fewer than the 6+ injections per year which seem necessary to maintain vision. Therefore, both physicians and patients desire more convenient therapies that can be effective with fewer injections and less monitoring. This is perhaps best exemplified by the rapidity of Eylea's launch. Despite a relatively modest improvement in convenience, Eylea has been able to rapidly capture majority share of the branded market in the U.S.

Medicare Data Suggests Patients Remain Undertreated



Source: Avalanche Biotechnologies

Second, our consultants suggest that not all patients respond to the available agents. Some say that as many as 15-20% of their populations would ideally have better control of their disease. Our physician consultants search for new options to better manage these patients, including novel VEGF inhibitors, as well as combinations with therapies targeting other molecules involved in angiogenesis.

AVA-101: Delivering A Functional Cure For Wet AMD

AVA-101 is the most advanced candidate to emerge from Avalanche's Ocular BioFactory platform. AVA-101 is designed to be a functional cure for wet AMD. One subretinal injection of AVA-101 creates an "Ocular BioFactory" that persistently secretes the natural VEGF inhibitor sFlt-1. Similar to Eylea or Lucentis, sFlt-1 binds to and neutralizes VEGF, halting the progression of wet AMD. Therefore the hope is that a single administration of AVA-101 will stop the progression of a patient's wet AMD, eliminating the need for further therapy.

AVA-101 Uses AAV2 To Deliver sFlt-1 To The Back Of The Eye

AVA-101's vector is native AAV2, and its transgene is a construct of the natural VEGF inhibitor sFlt1. Avalanche has found that native AAV2 can efficiently deliver transgenes to retinal cells. sFlt1 is a soluble, truncated form of Flt1, a VEGF transmembrane receptor responsible for propagating VEGF signaling in cells. sFlt-1 is therefore an endogenous inhibitor of VEGF signaling and angiogenesis, generated by alternative splicing. The sFlt-1 truncation includes only the VEGF binding domain (D2) of the full length factor, lacking the extracellular immunoglobulin-like domain, the transmembrane spanning region and the intracellular tyrosine-kinase domain. To date, this is the only known naturally occurring specific inhibitor of VEGF. sFlt-1 promotes inhibition by two mechanisms: (1) it binds to VEGF with high affinity (10pM), thus sequestering it, and (2) it acts as a dominant negative mutant, by forming inactive heterodimers with other VEGF receptors. *In vitro* studies have shown that binding of this truncated module to VEGF inhibited VEGF-driven angiogenesis. In animal models of cancer, expression of sFlt-1 inhibited tumor growth.

AVA-101 is administered via a subretinal injection under local anesthesia using a 23 gauge needle. It is delivered using a commercially available biocompatible cannula to create a small "bleb" by injecting 100ul. Our physician consultants suggest that this is a relatively straightforward procedure that most vitreoretinal surgeons can perform.

AVA-101 Is A Differentiated Product For The Treatment of Wet AMD

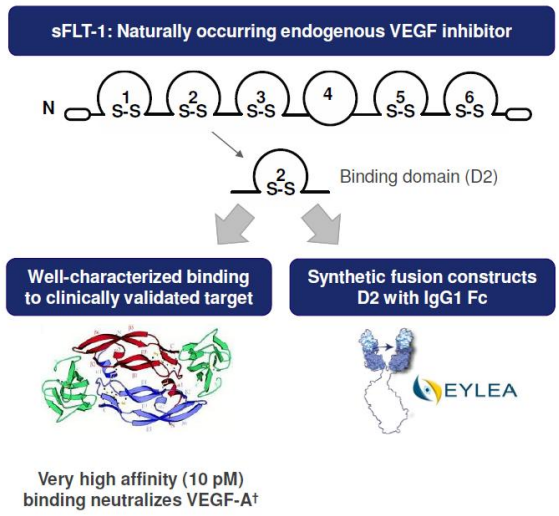
There is strong proof of concept for the use of sFlt-1 in wet AMD. In fact, the sFlt-1 VEGF binding domain is the active component of Eylea, Regeneron's blockbuster drug for treating wet AMD. In the case of Eylea, however, sFlt-1 is produced as a recombinant fusion protein outside the eye, and then administered to the eye via an intravitreal injection. Three points distinguish sFlt-1 supplied to retinal cells via gene therapy (AVA-101) vs. that supplied in the form of protein (Eylea):

1. ***Product Delivered To The Eye.*** In the case of AVA-101, the product delivered is not a recombinant protein, but rather a transgene of sFlt-1 encapsulated within the AAV2 vector. Once inside retinal cells, the transgene is expressed and the sFlt-1 protein is produced directly in and with the aid of the target cells.

2. ***Modality Of Delivery***. Unlike Eylea which is delivered by intravitreal injection, the capsid of the AVA-101 vector can only penetrate the top layers in the back of the eye, hence its administration by subretinal injection.

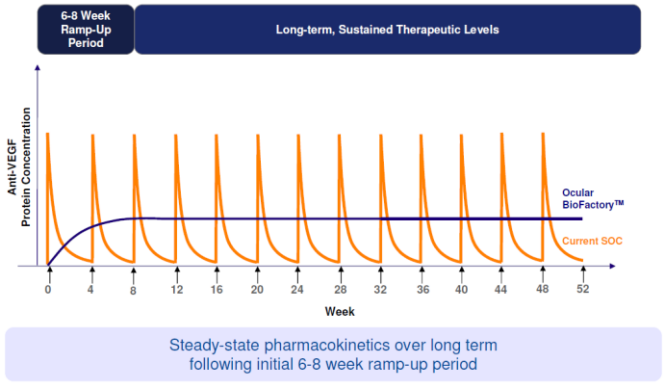
3. ***Pharmacokinetics Profile***. Most important, gene therapy delivery of sFLT-1 to the eye offers a virtually endless supply of the inhibitor. Expression of sFlt-1 from the transgene ensures a prolonged and consistent exposure of the eye to the inhibitor. This stands in contrast to the significant variations in inhibitor concentration seen with the protein VEGF inhibitors such as Eylea or Lucentis which are virtually cleared from the eye between injections. Therefore, the hope is that gene therapy will be able to manage the disease with far fewer injections.

AVA-101 Upregulates A Naturally-Occurring VEGF Inhibitor Implicated in AMD



Source: Avalanche Biotechnologies

Delivering Anti-VEGF Treatment Via Gene Therapy (AVA-101, blue line) vs. Periodic Injections Of Recombinant Inhibitor (orange peaks and troughs) Ensures Consistent Exposure



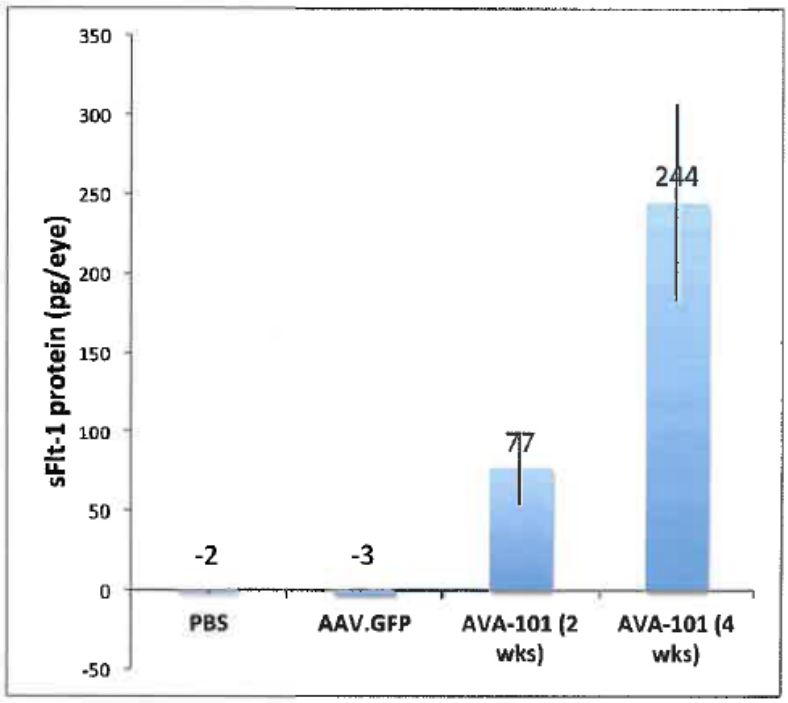
Source: Avalanche Biotechnologies

AVA-101 Has Generated Promising Preclinical Data

Preclinical studies in animal models have demonstrated that AVA-101 results in sustained, high levels of VEGF suppression, with an acceptable safety profile.

In one experiment mice were injected with either saline (n=5), the AAV vector containing GFP (a protein that has no effect on angiogenesis, n=2) or AVA-101 (n=15). Expression of sFLT-1 was seen in eyes collected from the mice at week 2, and high levels of sFlt-1 were detected at week 4. The mice studies revealed no vector-specific adverse effects. No systemic immune responses were identified, and the localized immune response in treated eyes was mild, transient and did not interfere with efficacy or safety. These experiments established proof of concept that AVA-101 can result in production of sFlt-1 in the retinas of living animals.

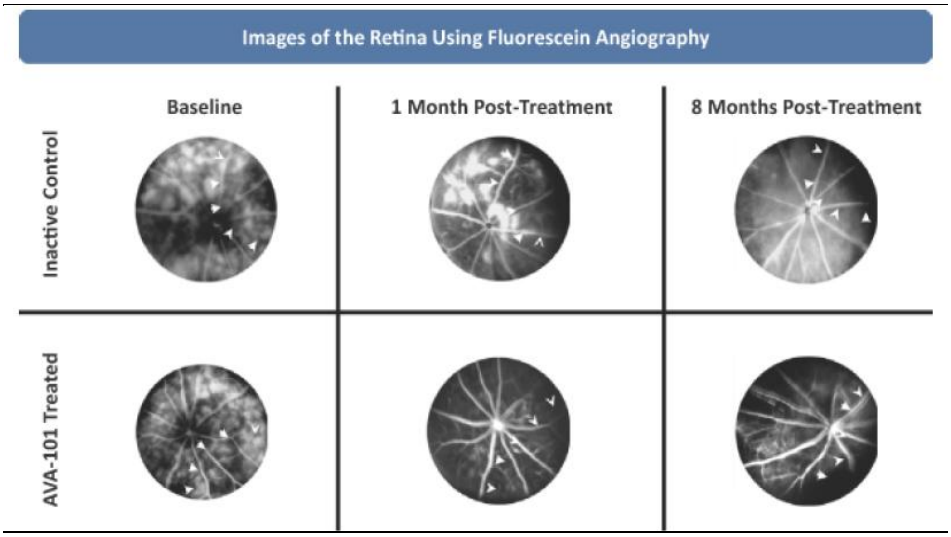
AVA-101 Results In High Levels of sFlt-1 In Mice



Source: Avalanche Biotechnologies

Avalanche also tested AVA-101 in the trVEGF029 mouse. trVEGF029 is a transgenic mouse model of VEGF-induced retinal neovascularization in which the mice express high levels of VEGF and show symptoms of retinal neovascularization, including hyperpermeability, retinal degradation, and scarring. In this experiment mice were injected with either AAV-GFP (an inactive control vector) or AVA-101, and the impact on neovascularization was assessed using fluorescein angiogram at 1, 2 and 9 months. As early as one month post treatment, AVA-101 treated eyes showed reduced neovascularization and scaring compared to inactive control and the improvements were sustained through 9 months post therapy. Moreover, confocal microscopy of sectioned eyes at 2 months demonstrated that AVA-101 preserved photoreceptors much better than control.

AVA-101 Inhibits Some Ocular Pathologies In VEGF-Induced Mouse Model Of Retinal Neovascularization



Source: Avalanche Biotechnologies

Perhaps the best animal model of wet AMD is a non-human primate model in which choroidal neovascularization is induced by laser burns on the retina of the animal. Avalanche laser-induced CNV in non-human primates, then treated one eye with AAV-GFP (an inactive control vector) and the other with AVA-101. Avalanche found that AVA-101 treatment completely prevented CNV leakage for over 17 months following a single AVA-101 injection. In comparison, eyes given the inactive controls exhibited signs of leakage. There was no evidence that sustained VEGF suppression lead to choroidal atrophy or retinal degradation. Moreover, there was no expression of sFLT-1 outside of the eye. This experiment demonstrates that a single injection of AVA-101 results in sustained and therapeutic levels of VEGF inhibition for at least 17 months.

Notably, the safety profile of AVA-101 across multiple preclinical studies demonstrated no vector-specific adverse events and no systemic immune responses. There were occasional localized immune responses in the treated eyes, but these were mild and transient and did not interfere with long-term efficacy or safety. Neither the AAV vector nor the sFLT-1 transgene were found in tissues outside of the eye.

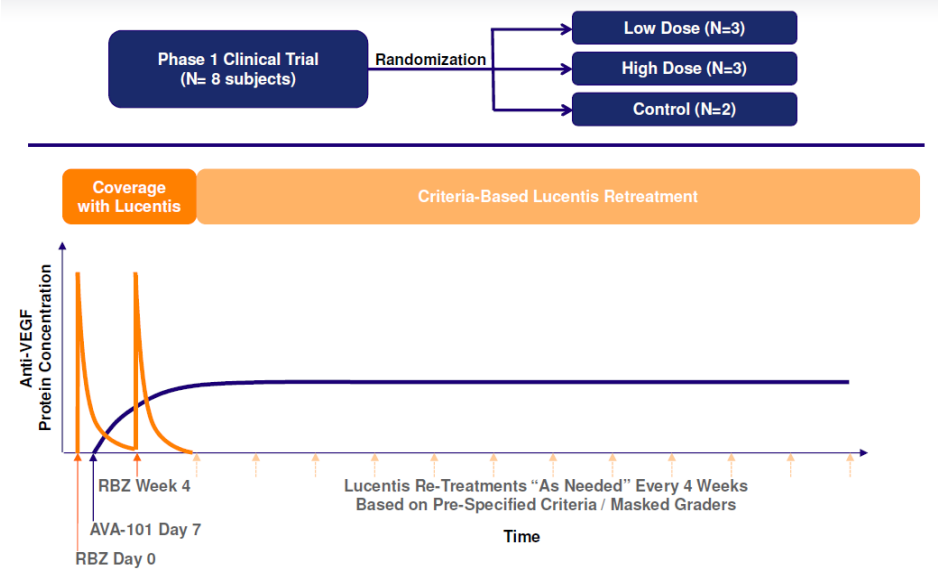
First Human Trial Of AVA-101 Was A Success, Demonstrating Prolonged Improvements In Vision After A Single Injection

In late 2011, Avalanche initiated the Phase 1 portion of a Phase 1/2a study of AVA-101 at Lions Eye Institute (LEI) in Australia. The primary outcome measures at 12 months were ophthalmic and systemic safety. Measures to assess early signs of efficacy were also made. For safety purposes, the patients were investigated for ocular inflammation, intraocular pressure, retinal bleeding or any abnormal laboratory data. Efficacy was measured as improvements in visual acuity, reduction in retinal thickness and a reduced number of anti-VEGF (Lucentis) rescue injections.

The trial enrolled 8 patients, ages 55 years or older, with confirmed neovascular leakage associated with AMD. All patients were “treatment addicts” with an established reliance on frequent anti-VEGF injections. Key inclusion criteria included

subfoveal CNV secondary to AMD and with best corrected visual acuity of 20/80 – 20/400 with 20/200 or better in the fellow eye. Also, fluorescein angiogram of the study eye must have shown evidence of a leaking subfoveal choroidal neovascular lesion. Patients could not have extensive submacular scar tissue, diabetic retinopathy or retinal vascular occlusion, or cataracts. Subjects were randomized into three groups: 2 subjects in the control arm, three in the low AVA-101 dose (10^{10} vector genomes) and 3 in the high AVA-101 dose (10^{11} vector genomes). During the 6-8 week ramp-up period, all subjects received two initial doses of Lucentis at Day 0 and Week 4. On Day 7, the patients in the active arm received AVA-101. Starting with Week 8 (the end of the ramp-up period), patients were offered Lucentis as a rescue therapy only on an as-needed basis. The need for rescue therapy was judged by personal blinded to the treatment assignment in study and based on objective criteria of disease recurrence. Subjects were assessed every four weeks for adverse events, retinal thickness, visual acuity and the need for Lucentis rescue injections.

AVA-101 Phase 1 Trial Design



Source: Avalanche Biotechnologies

The Phase 1 portion of the trial completed in April 2012. The trial revealed a pristine safety profile. There were no drug-related adverse events or inflammation caused by the gene therapy. There were mild and transient inflammatory responses related to the injection, but these were not deemed drug-related and no other eye safety concerns were raised. Consistent with the detection of the AAV vector exclusively inside the treated eye and not outside, there were no clinically significant systemic adverse events or anti-VEGF related AEs. There were no clinically significant changes in any lab values.

Patients on both AVA-101 doses had sustained improvements from baseline in visual acuity as compared to control. Twelve months after administration of AVA-101 patients on the low dose had an average improvement of +8.7 letters, and those on the high dose had an average improvement of +6.3 letters. This contrasts with control subjects who lost 3.5 letters of visual acuity from baseline. Five of the six patients who received AVA-101 improved by more than 5 letters, and three of the six AVA-101 subjects improved by more than 10 letters from baseline. Only one subject treated

with AVA-101 lost visual acuity from baseline. This patient had significant subfoveal scarring at baseline, which may have interfered with the curative process. To prevent such conditions from confounding the efficacy analysis, patients with extensive subfoveal scarring will be excluded in future trials.

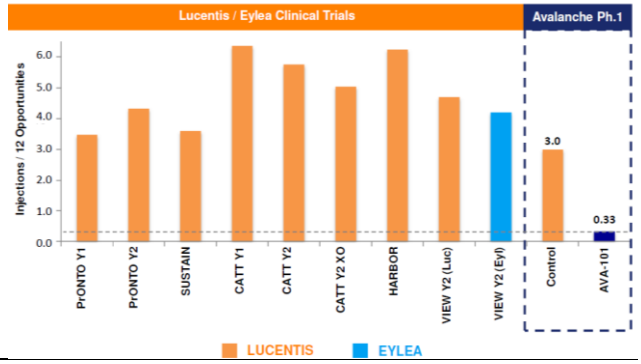
Remarkably, patients receiving either dose of AVA-101 not only had improved visual acuity, but also, over the 12 month trial period, needed on average substantially fewer rescue injections (0.33) vs. the control group (3.0). Only 2 of the 6 AVA-101 treated patients needed a Lucentis rescue injection. One patient needed one at week 12 (then no more through week 52) and the second patient needed an injection at week 52. In contrast, based on historical rates, one would expect these patients to need injections at one-quarter to one-half of their visits, similar to the rate seen in the control group (3 rescue injections per 12 visits).

Treatment With AVA-101 Improves Visual Acuity (12-Month Data)

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	

Source: Avalanche Biotechnologies

Patients Treated With AVA-101 Required Significantly Fewer Rescue Injections With Lucentis

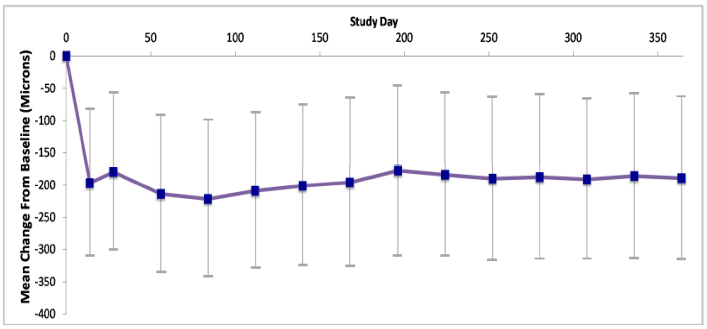


Source: Avalanche Biotechnologies

Corroborating the visual acuity improvements, measurements of retinal thickness showed meaningful decrease for all subjects treated with AVA-101. This effect was maintained for the entire year of the trial.

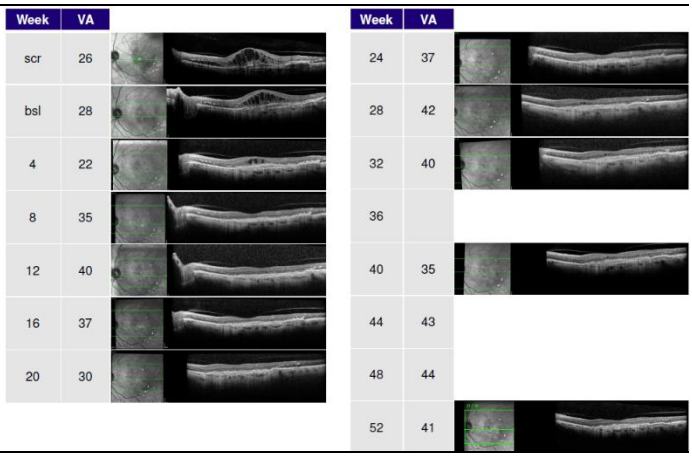
Avalanche has presented a more detailed case study of one of the AVA-101 treated subjects. The patient presented with an advanced form of wet AMD. Prior to enrollment the patient had received 24 injections of Lucentis and had a visual acuity score of 26 at screening and 28 at baseline (approximately 20/250 on the Snellen scale). Scans of the subject's retina were taken during screening, at baseline and then every four weeks for 52 weeks. At baseline, the retina contained significant fluid, leading to increase retinal thickness. The patient received doses of Lucentis at Day 0 and Week 4, as well as a low-dose of AVA-101 at Day 7. Scans at Week 8 already showed a return to normal retinal thickness levels and a seven letter improvement in visual acuity. At the end of the study (52 Weeks), visual acuity had increase by 13 letters compared to baseline, while the patient required no rescue treatment with Lucentis throughout the study.

Average Change In Retinal Thickness Of Treated Subjects



Source: Avalanche Biotechnologies

Case Study Of Subject Treated With AVA-101



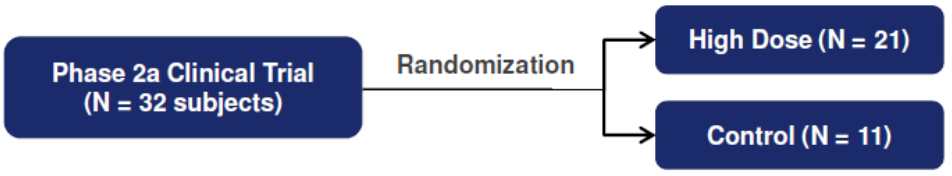
Source: Avalanche Biotechnologies

We think the data from AVA-101's Phase 1 trial establish proof-of-concept for it, and suggest that it could safely stabilize patients' vision without the need for additional anti-VEGF injections.

Data From The Ongoing Phase 2 Study Expected Mid:2015

Avalanche is currently conducting the Phase 2a portion of the AVA-101 trial. The design of the Phase 2a is similar to the Phase I, with some modest adjustments. In particular, in the Phase 2a subjects were enrolled with less advanced disease compared to Phase I, including visual acuity up to 20/30. The Phase 2a excludes patients with extensive scarring. 32 wet AMD subjects were enrolled and randomized 2:1 to high dose of AVA-101 (n=21) and control (n=11). The primary endpoint is safety and secondary endpoints include retinal thickness, visual acuity and the need for rescue injection with anti-VEGF therapy (Lucentis). The study protocol includes a similar ramp-up and re-treatment criteria as those detailed in Phase I.

Design of AVA-201's Phase 2a Trial



Source: Avalanche Biotechnologies

Avalanche released updated data from the ongoing Phase 2a trial at the ARSR meeting in mid-August. Results presented from the ongoing study suggest that AVA-101 continues to be well tolerated. Most adverse events recorded to date have been mild and not related to AVA-101 or the procedures used in the study. Importantly, inflammation levels were mild and retinal detachment or macular holes were not observed. Final data from this trial are expected in mid:2015.

The company plans to file an IND in the United States as soon as data from Phase 2a become available. Subsequently, a double-blinded, randomized, controlled Phase 2b trial to assess efficacy, safety and tolerability of a single subretinal injection of AVA-101 in subjects with wet AMD compared to standard of care anti-VEGF therapies will be undertaken in the United States in the second half of 2015. The study will include ~120 subjects and its endpoints will the similar to those in the Phase 2a trial.

In addition to wet AMD, Avalanche believes that AVA-101 may have the potential to treat other neovascular disease of the eye such as diabetic macular edema (DME) and retinal vein occlusion (RVO).

AVA-201 Has All The Benefits Of AVA-101 Delivered Via An Intravitreal Injection

AVA-201 is Avalanche's next generation anti-VEGF gene therapy product candidate, which is being developed for the prevention and treatment of wet AMD. AVA-201 carries the same therapeutic gene as AVA-101, sFLT-1. It differs, however, in the type of AAV vector used for delivery. The capsid of AVA-201 has been optimized to penetrate the inner limiting membrane (ILM) barrier that separates the retina from the vitreous body. This property permits AVA-201 to be administered more conveniently via a simple and low-risk intravitreal injection. Preclinical work in mouse eyes has shown that intravitrial injection of AVA-201 has led to high rates of transduction of retinal cells and levels of sFlt-1 protein expression comparable to those produced by subretinal AVA-101.

The convenience of intravitreal delivery of a potent anti-VEGF inhibitor, taken together with a dramatic decrease in the number of required injections, positions AVA-201 to not only extend Avalanche's franchise, but to also expand the addressable market opportunity. Avalanche believes that AVA-201's properties make it appealing as a prophylaxis treatment for those at high risk of developing AMD. The prophylaxis market could be substantial. According to the CDC, approximately 7.3 million Americans are at high risk of developing wet AMD although Avalanche expects that only those patients in the highest risk category, defined through a combination of clinical and genetic factors, would be willing to pursue prophylaxis treatment.

There Are A Number Of New Agents In Development For Wet AMD

Historically, the treatment of wet AMD has rapidly evolved, as physicians have been quick to adopt new therapies with the potential for better efficacy or improved convenience. Visudyne was launched by QLT in 2000 and was used widely in conjunction with laser therapy. However, Visudyne and photodynamic therapy (PDT) were quickly supplanted by anti-VEGF-based treatments as they were seen to be more effective at controlling vision loss. Macugen (anti-VEGF aptamer) was launched by Eyetech in 2004 based on Phase III data showing that about 70% of patients who received Macugen experienced no significant vision loss. Macugen was soon replaced by Avastin and Lucentis after Lucentis's June 2006 approval as the anti-VEGF antibodies were thought to be significantly more potent. In Lucentis's Phase III trials 95% of patients experienced no significant vision loss over two years. Most impressive, approximately one-third of patients reported visual improvement, the first demonstration of improvement in vision of wet AMD patients. More recently, REGN's Eylea has quickly gained share of the market based on a more convenient, less frequent administration profile, and the perception that it is somewhat more potent than Lucentis and Avastin.

There are a number of new wet AMD agents in development, and therefore it seems likely that the treatment paradigm will continue to evolve. These agents fall largely into three categories: longer-lasting or less-invasive anti-VEGFs, biologic approaches that seek to be "curative" following a single administration, and novel mechanisms that are to be used in combination with anti-VEGFs.

New Agents In Development For Wet AMD

Company	Technology	Stage
	Longer Lasting Or Less-Invasive anti-VEGF's:	
Allergan/Molecular Partners	DARPin	Phase II
ForSight/Genentech	Slow release pump	Phase I/II
PanOptica	Anti-VEGF eye drop	Phase I
Replenish/Alcon	Slow release pump	Phase I
OnDemand	Laser-release packets	Pre-clinical
Ocular Therapeutix	Drug-loaded slurry	Pre-clinical
	Biologic Approaches That Seek Functional Cures	
Avalanche	AAV2-delivered sFLT-1	Phase I/II
Genzyme/Sanofi	AAV2-delivered sFLT-1	Phase I/II
Neurotech	Immortalized cell line that secretes factors	Phase I/II
Oxford Biomedica	Lentivirus RetinoStat (angiostatin/endostatin)	Phase I
	Novel Mechanisms In Combination With Anti-VEGF	
Ophthotech	Anti-PDGF	Phase III
Iconics	Tissue Factor	Phase I
Regeneron	Anti-PDGF	Phase I
Regeneron	Anti-ANG2	Phase I

Source: Cowen and Company

The most direct competitor to Avalanche's AVA-101 and AVA-201 is the gene therapy program from Genzyme/Sanofi. Genzyme/Sanofi is also seeking to deliver a sFLT-1 construct using the naturally occurring AAV2 vector, and therefore the approaches of Avalanche and Genzyme/Sanofi are quite similar. Nonetheless, the programs have two key differences which are likely to produce distinct clinical profiles. First, while Avalanche is delivering the naturally occurring sFlt-1 protein (with a unique 31 amino acid terminus), Genzyme is delivering a synthetic conjugate comprised of sFlt-1 domain 2 and an IgG1Fc domain. Second, and more important, the two preparations differ in their route of administration. Whereas Genzyme/Sanofi delivers its through an intravitreal injection, Avalanche delivers AVA-101 through a subretinal injection. Avalanche has indicated that it has attempted to deliver AAV2 by both intravitreal and subretinal injections, and has found that subretinal delivery results in more consistent expression and higher amounts of protein. Therefore, based on Avalanche's experience, it would seem that AVA-101 is more likely to result in a highly potent preparation. That being said, intravitreal injections are certain easier than subretinal, and therefore should Genzyme achieve sufficient potency, it would enjoy a convenience advantage.

Consultants Desire Yet More Convenient Options For Wet AMD

Our wet AMD physician consultants continue to desire therapeutics that can manage the condition with fewer injections and/or better potency. With the "average" patient returning for an injection every 6-7 weeks, the current paradigm is relatively inconvenient for the patients and their caregivers. Our consultants say that they and their staff spend much of their time giving anti-VEGF injections, and would like to be

free to perform other (perhaps more interesting or lucrative) procedures. Moreover, our consultants note that as many as 10-20% of their patients are not adequately managed by the current anti-VEGF options, and therefore there is also a need for more potent alternatives to help better manage the disease in refractory patients.

Our consultants have been impressed by the preclinical data supporting the delivery of sFLT-1 via AAV2, saying that it has quite convincingly established that gene therapy is able to reduce VEGF levels and control choroidal neovascularization in animal models of wet AMD. They are therefore intrigued by the possibility that gene therapy could result in a functional cure of wet AMD.

Our consultants think that AVA-101's early clinical data is persuasive, and convincingly demonstrates (albeit in a small number of patients) that AVA-101 is able to inhibit neovascularization, improve vision, and abrogate the need for future anti-VEGF treatments after just a single administration. Our consultants think that the safety profile produced thus far has been acceptable, with no signs of drug-induced inflammation or other safety problems. Our consultants find it particularly comforting that there is no evidence for expression of the transgene outside of the eye, as long term systemic expression could lead to risk for anti-VEGF cerebrovascular and cardiovascular side effects.

As noted in the preceding section, Genzyme/Sanofi is developing a similar AAV2/sFLT-1 therapeutic for wet AMD. Our consultants think that ultimately Avalanche and Genzyme/Sanofi's programs will be clinically differentiated given the differences in transgene and administration. While clinical trial results are not yet mature enough to permit a definitive comparison, our consultants think it likely that Avalanche's subretinal delivery will result in more consistent and more robust expression of sFLT-1, resulting in advantages in efficacy and potency. They think that the subretinal injection is likely to produce a more reliable distribution of the transgene, as the inner limiting membrane (the boundary between the retina and vitreous body) is probably a barrier that will prevent AAV2 delivered intravitreally from reaching the retinal cells in sufficient concentration to result in high expression levels.

In fact, data from a non-human primate study of Genzyme's preparation published by MacLachlan et al. in the journal *Molecular Therapy* in 2011 provided evidence for inconsistent expression levels of sFlt-1 from intravitreally delivered AAV2. In the preclinical study, a wide range of expression levels, ranging as high as tenfold, were observed in the nonhuman primate eyes even within dose groups. Although the exact reason for the variability was not determined, MacLachlan et al hypothesize it could be related to the injection of the vector into the "highly viscous vitreous which might impede diffusion to transducing sites within the eye." Moreover, MacLachlan et al. also found that the injection of AAV2 into the vitreous induced mild to moderate inflammation in most of the animals (14 of 18), which generally persisted for 5 months after the injection but could last up to 15 months. The authors determined that this inflammation was due to the presence of AAV2 in the vitreous, and not the expression of the sFlt1 protein. The authors postulated that injection of AAV into the viscous vitreous could act as a depot driving persistent inflammation. Therefore, injections of AAV into the vitreous may also carry a higher risk of durable inflammation.

All that being said, should Genzyme be able to produce sufficient expression using intravitreal injections in humans, its preparation would have a convenience advantage. A subretinal injection is more akin to minor surgery than a simple injection, and therefore is a somewhat more complicated procedure than an intravitreal injection. Nonetheless, our consultants note that subretinal injections are frequently conducted by vitreoretinal surgeons to deliver molecules such as tissue plasminogen activator

(TPA) for the treatment of retinal vascular occlusions. They typically have a very low complication rate when done by a skilled and trained vitreoretinal surgeon. Though more cumbersome than an intravitreal injection, subretinal injections are relatively straightforward procedures conducted under local anesthesia in the outpatient setting.

While impressed by the data produced by AVA-101 thus far, and generally convinced of the efficacy of AVA-101, our consultants think more must be learned about its safety profile in longer and larger studies in order for the program to be fully de-risked. One concern has been prominently highlighted by our consultants. They will be particularly vigilant to look for signs of geographic atrophy caused by too robust anti-VEGF inhibition in future datasets. While consistent VEGF suppression offers clear convenience advantages over intermittent injections, some worry that there could be risks associated with it, too. Work in animal models has implied that the elimination of VEGF in the eye could lead to geographic atrophy, an advanced form of dry AMD that is manifested by the degeneration of retinal pigment epithelial cells (RPE) followed by the death of photoreceptors and loss of vision. In particular, results in mice that were engineered to produce only an insoluble form of VEGF demonstrated that VEGF signaling is required for the maintenance of a normal retina function. In humans treated for wet AMD, however, it is harder to tease apart whether a VEGF-blockade causes geographic atrophy or the loss of vision is part of the natural course of the underlying dry AMD pathology, and thus far no clinical evidence exists that chronic VEGF suppression in wet AMD patients leads to geographic atrophy or other degenerative changes. Avalanche has seen no evidence of geographic atrophy in any of its preclinical, non-human primate, or human trials. Nonetheless, Avalanche notes that should sFLT-1 BioFactory expression need to be “turned down”, in pre-clinical studies it has been demonstrated that AAV expression can be silenced following a laser procedure. Laser treatment stimulates cell division and due to its non-replicative and non-integrative nature, the AAV vector is lost when cells divide.

Should AVA-101 be successfully developed as a single injection functional cure for wet AMD, our consultants think it would have wide appeal for those patients who need frequent anti-VEGF injections. They think many patients would want to have the single subretinal injection, and then be virtually cured of their disease, with no need for additional treatments. They also note that chronic, long-term suppression may help to control disease that is currently refractory to anti-VEGF injections. Finally, as the reimbursement for intravitreal injections has been decreasing in recent years, our consultants suggest that there could be a financial incentive for physicians to perform the subretinal procedure.

Avalanche’s Intellectual Property Position Is Strong, Allowing Both Market Access And Exclusivity For AVA-101

Avalanche has been aggressive at applying for patents to protect its AAV vectors, manufacturing processes, and therapeutic products. Avalanche has 27 pending patent applications in the United States and corresponding foreign territories, and Avalanche’s university collaborators have filed an additional 18. Thus far 12 patents have issued to Avalanche or to its licensors. AVA-101 specifically is protected by issued patents through 2020, and by pending applications should they issue until 2033.

In particular, Avalanche owns a family of patent applications that are directed to AAV-based compositions and methods for treating or preventing eye diseases associated with neovascularization. These applications relate to the AVA-101 composition, dosing regimens, routes of administration and various unit dosages. For example, Claim 80 of

application WO 2013173129 claims " A method for treating or reducing ocular neovascularization in a human subject, comprising: administering subretinally a pharmaceutical composition comprising a pharmaceutically effective amount of a recombinant virus comprising a nucleic acid encoding soluble Fms-related tyrosine kinase-1 (sFlt-1) protein to a human subject in need of a treatment." Four of these applications are pending in the U.S., one application is pending in Taiwan, and one is pending under the Patent Cooperation Treaty (PCT) which should result in applications in various territories outside of the U.S. Avalanche expects patents from this family to expire in 2033.

Avalanche has exclusively licensed from the Regents and Chiron US patent 6,943,153. This patent claims methods of treating ocular diseases that relate to AVA-101. Specifically, the patent claims "A method of inhibiting angiogenesis in a diseased eye of a subject, comprising, administering intraocularly a recombinant adeno-associated virus (rAAV) gene delivery vector which directs the expression of an anti angiogenic factor, such that administration of said vector inhibits neovascularization of the diseased eye." This patent will expire in 2020.

Avalanche has exclusively licensed several families of patents and applications that relate to variant rAAV virions having desirable characteristics, such as increased infectivity, as well as novel methods to screen for such variants. These patents generally expire between 2024 and 2031.

In addition to its formal patents, we would expect Avalanche's products to have 12 year of data exclusivity following approval as they are biologics. Moreover, we suspect that gene therapy products will face only limited biosimilar competition as we think it will likely be many years until the FDA approves an interchangeable gene therapy product. Therefore we expect Avalanche's products will have viable commercial lives long after the expiration of their patents.

Wet AMD Is A Multibillion-Dollar Opportunity

Combined worldwide sales of Regeneron/Bayer's Eylea and Roche/Novartis' Lucentis were nearly $6B in 2013. Moreover, we estimate that approximately as many patients are prescribed compounded versions of Roche's Avastin as Eylea and Lucentis, implying that worldwide demand for anti-VEGF therapies for ocular indications was approximately $10B+ in 2013.

U.S. revenue of Avastin and Lucentis was $2.9B in 2013, of which we estimate approximately $2B was from wet AMD itself. This equates to approximately 1MM Eylea and Lucentis injections for wet AMD, and 1.5MM injections overall. If one assumes that each wet AMD eye receives an anti-VEGF injection every 6-7 weeks, this would imply that in the U.S. there were between 115K and 135K eyes treated for wet AMD with the branded therapies in 2013, and perhaps 230K – 270K eyes treated overall, as our consultants suggest that compounded Avastin maintains approximately 50% share of the market.

Our consultants suggest that a product capable of controlling the progression of wet AMD after a single injection will provide significant convenience advantages over the current generation of anti-VEGF antibodies, and may also be better able to control disease not managed by the currently available anti-VEGF antibodies. Therefore, such a product would be differentiated and able to capture significant share of the market. Moreover, the launches of Macugen, Lucentis and Eylea have demonstrated that vitreoretinal surgeons will aggressively adopt new, innovative products.

In our opinion, potent and well tolerated anti-VEGF gene therapy that is capable of producing high levels of consistent and long-term VEGF suppression would clearly address a multi-$B opportunity. Moreover, we think that AVA-101's adoption will be rapid should its profile continue to suggest that it could be a functional cure, capable of potently and safely suppressing VEGF over a long period of time.

Our consultants suggest that on average patients will receive an Eylea injection about once every 7 weeks, implying 14-15 injections over a 2-year period. At an average cost per injection of $1,850, this implies an average cost of Eylea over 2 years of $25.9K - $27.8K. We have assumed that Avalanche prices AVA-101 approximately equivalent to the cost of two years of Eylea, or at about $25K per treatment course.

We project that Avalanche's AVA-101 will be launched in 2020 after completing Phase IIa, Phase IIb, and Phase III trials. We project it will achieve $300MM in worldwide revenue in 2020, equating to about 12K eyes on therapy, approximately 10% of the current U.S. branded market, and 5% of the U.S. market overall. We project that AVA-101 will rapidly capture share of the market, achieving over $4B at peak.

Worldwide Anti-VEGF Market Model

	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E
U.S. Wet AMD								
Prevalence of wet AMD ('000's)	454	476	500	525	552	579	608	638
% diagnosed & clinically significant	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
# diagnosed patients	361	381	400	420	441	463	486	511
% of diagnosed patients that are treated with anti-VEGF agents	*95%*	*96%*	*96%*	*96%*	*96%*	*96%*	*96%*	*96%*
# treated patients	343	364	384	403	424	445	467	490
% AVA-101 penetration							*0%*	*2%*
# patients receiving AVA-101 each year ('000)							0	8
AVA-101 price per treatment course ($'000)							25	25
U.S. AVA-101 Sales In Wet AMD ($MM)							**$0**	**$200**
% Avastin penetration	*41%*	*36%*	*35%*	*35%*	*35%*	*36%*	*37%*	*38%*
# patients receiving Avastin each year	141	130	136	141	147	158	171	184
Average # vials per patient per year	5.6	5.5	5.5	5.5	5.5	5.5	5.5	5.5
% Lucentis penetration	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
# patients receiving Lucentis each year	69	73	77	81	85	89	93	98
Average # vials per patient per year	5.6	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Lucentis price per dose	$1,950	$1,950	$1,950	$1,950	$1,950	$1,950	$1,950	$1,950
U.S. Lucentis Sales In Wet AMD ($MM)	**$748**	**$781**	**$824**	**$865**	**$909**	**$954**	**$1,002**	**$1,052**
% Eylea penetration	*39%*	*44%*	*45%*	*45%*	*45%*	*44%*	*43%*	*42%*
% penetration of non-Avastin market	*66%*	*69%*	*69%*	*69%*	*69%*	*69%*	*68%*	*68%*
# patients receiving Eylea each year	134	161	172	182	192	198	203	208
Average # vials per patient per year	5.4	5.2	5.2	5.2	5.2	5.2	5.2	5.2
Eylea price per dose	$1,850	$1,850	$1,850	$1,850	$1,850	$1,850	$1,850	$1,850
U.S. Eylea Sales In Wet AMD ($MM)	**$1,334**	**$1,549**	**$1,650**	**$1,750**	**$1,850**	**$1,900**	**$1,950**	**$2,000**
U.S. Diabetic Macular Edema								
# Diagnosed Diabetes Patients in U.S. ('000)	20,103.7	20,485.7	20,874.9	21,271.5	21,675.7	22,087.5	22,507.2	22,934.8
# DME patients in the U.S.	382.0	389.2	396.6	404.2	411.8	419.7	427.6	435.8
% Treated	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
# DME Patients treated in U.S.	191.0	194.6	198.3	202.1	205.9	209.8	213.8	217.9
% Avastin penetration	*1.8%*	*2.0%*	*2.2%*	*2.4%*	*2.4%*	*2.4%*	*2.4%*	*2.4%*
# patients receiving Avastin each year	3	4	4	5	5	5	5	5
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
% Lucentis penetration	*40.1%*	*38.0%*	*36.0%*	*34.0%*	*32.0%*	*30.0%*	*28.0%*	*26.0%*
# patients receiving Lucentis each year	77	74	71	69	66	63	60	57
Average # vials per patient per year	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Lucentis price per dose	1,170.0	1,170.0	1,170.0	1,170.0	1,170.0	1,170.0	1,170.0	1,170.0
Lucentis U.S. DME Sales ($MM)	**$538**	**$519**	**$501**	**$482**	**$463**	**$442**	**$420**	**$398**
% Eylea penetration	*1.2%*	*3.5%*	*10.2%*	*13.4%*	*15.1%*	*15.7%*	*16.3%*	*16.5%*
# patients receiving Eylea each year	2	7	20	27	31	33	35	36
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Eylea price per dose	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0
Eylea U.S. DME Sales ($MM)	**$50**	**$150**	**$450**	**$600**	**$690**	**$730**	**$775**	**$800**
U.S. Retinal Vein Occlusion								
# RVO patients in the U.S. ('000)	196.8	198.8	200.7	202.8	204.8	206.8	208.9	211.0
% Treated	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
# RVO Patients treated in U.S.	68.9	69.6	70.3	71.0	71.7	72.4	73.1	73.8
% Avastin penetration	*14.5%*	*15.0%*	*15.5%*	*15.5%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*
# patients receiving Avastin each year	10	10	11	11	11	12	12	12
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
% Lucentis penetration	*14.5%*	*15.0%*	*15.5%*	*15.5%*	*15.5%*	*15.5%*	*15.5%*	*15.5%*
# patients receiving Lucentis each year	10	10	11	11	11	11	11	11
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Lucentis price per dose	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0
Lucentis U.S. RVO Sales ($MM)	**$234**	**$244**	**$255**	**$257**	**$260**	**$263**	**$265**	**$268**
% Eylea penetration	*1.6%*	*3.2%*	*4.8%*	*6.3%*	*6.9%*	*7.5%*	*7.5%*	*7.5%*
# patients receiving Eylea each year	1	2	3	5	5	5	5	6
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Eylea price per dose	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0
Eylea U.S. RVO Sales ($MM)	**$25**	**$50**	**$75**	**$100**	**$110**	**$120**	**$121**	**$122**
Lucentis U.S. Sales ($MM)	**$1,520**	**$1,544**	**$1,580**	**$1,605**	**$1,631**	**$1,658**	**$1,687**	**$1,717**
Eylea U.S. Sales ($MM)	**$1,409**	**$1,749**	**$2,175**	**$2,450**	**$2,650**	**$2,750**	**$2,846**	**$2,922**
AVA-101 U.S. Sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$200**

Source: Cowen and Company

Worldwide Anti-VEGF Market Model (Cont.)

	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
ex-U.S. Wet AMD								
Prevalence of wet AMD ('000's)	681	715	750	788	827	869	912	958
% diagnosed & clinically significant	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*	*80%*
# diagnosed patients	541	572	600	630	662	695	730	766
% of diagnosed patients that are treated with anti-VEGF agents	*95%*	*96%*	*96%*	*96%*	*96%*	*96%*	*96%*	*96%*
# treated patients	514	546	576	605	635	667	700	735
% AVA-101 penetration								*1%*
# patients receiving AVA-101 each year ('000)								4
AVA-101 price per treatment course ($'000)								25
ex-U.S. AVA-101 Sales In Wet AMD ($MM)								**$100**
% Avastin penetration	*59%*	*52%*	*48%*	*47%*	*47%*	*47%*	*47%*	*47%*
# patients receiving Avastin each year	302	282	278	285	299	314	329	346
Average # vials per patient per year	5.6	5.5	5.5	5.5	5.5	5.5	5.5	5.5
% Lucentis penetration	*34%*	*32%*	*30%*	*28%*	*26%*	*24%*	*22%*	*22%*
# patients receiving Lucentis each year	175	175	173	169	165	160	154	162
Average # vials per patient per year	5.6	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Lucentis price per dose	$1,950	$1,950	$1,950	$1,950	$1,950	$1,950	$1,950	$1,950
ex-U.S. Lucentis Sales In Wet AMD ($MM)	**$1,908**	**$1,874**	**$1,854**	**$1,817**	**$1,772**	**$1,717**	**$1,653**	**$1,735**
% Eylea penetration	*7%*	*16%*	*22%*	*25%*	*28%*	*28%*	*29%*	*29%*
% penetration of non-Avastin market	*17%*	*34%*	*42%*	*47%*	*52%*	*54%*	*57%*	*57%*
# patients receiving Eylea each year	37	90	126	151	176	189	201	214
Average # vials per patient per year	5.4	4.7	4.3	4.3	4.3	4.3	4.3	4.3
Eylea price per dose	$1,850	$1,850	$1,850	$1,850	$1,850	$1,850	$1,850	$1,850
ex-U.S. Eylea Sales In Wet AMD ($MM)	**$370**	**$780**	**$1,000**	**$1,200**	**$1,400**	**$1,500**	**$1,600**	**$1,700**
ex-U.S. Diabetic Macular Edema								
# Relevant Diabetes Patients	20,103.7	20,485.7	20,874.9	21,271.5	21,675.7	22,087.5	22,507.2	22,934.8
# DME patients	382.0	389.2	396.6	404.2	411.8	419.7	427.6	435.8
% Treated	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
# DME Patients Treated	191.0	194.6	198.3	202.1	205.9	209.8	213.8	217.9
% Avastin penetration	*1.8%*	*2.0%*	*2.2%*	*2.4%*	*2.6%*	*2.6%*	*2.6%*	*2.6%*
# patients receiving Avastin each year	3	4	4	5	5	5	6	6
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
% Lucentis penetration	*8.9%*	*10.6%*	*11.7%*	*13.2%*	*14.9%*	*16.7%*	*18.6%*	*17.6%*
# patients receiving Lucentis each year	17	21	23	27	31	35	40	38
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Lucentis price per dose	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0
Lucentis ex-U.S. DME Sales ($MM)	**$398**	**$482**	**$541**	**$626**	**$718**	**$820**	**$932**	**$897**
% Eylea penetration	*1.4%*	*2.2%*	*5.3%*	*8.9%*	*12.0%*	*12.9%*	*14.3%*	*15.7%*
# patients receiving Eylea each year	3	4	11	18	25	27	31	34
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Eylea price per dose	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0
Eylea ex-U.S. DME Sales ($MM)	**$60**	**$97**	**$235**	**$400**	**$550**	**$600**	**$680**	**$761**
ex-U.S. Retinal Vein Occlusion								
# RVO patients ('000)	196.8	198.8	200.7	202.8	204.8	206.8	208.9	211.0
% Treated	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
# RVO Patients treated	68.9	69.6	70.3	71.0	71.7	72.4	73.1	73.8
% Avastin penetration	*14.5%*	*15.0%*	*15.5%*	*15.5%*	*16.0%*	*16.0%*	*16.0%*	*16.0%*
# patients receiving Avastin each year	10	10	11	11	11	12	12	12
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
% Lucentis penetration	*14.5%*	*15.0%*	*15.5%*	*15.5%*	*15.5%*	*15.5%*	*15.5%*	*15.5%*
# patients receiving Lucentis each year	10	10	11	11	11	11	11	11
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Lucentis price per dose	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0	1,950.0
Lucentis ex-U.S. RVO Sales ($MM)	**$234**	**$244**	**$255**	**$257**	**$260**	**$263**	**$265**	**$268**
% Eylea penetration	*2.6%*	*10.6%*	*12.2%*	*15.9%*	*18.9%*	*21.8%*	*24.6%*	*27.5%*
# patients receiving Eylea each year	2	7	9	11	14	16	18	20
Average # vials per patient per year	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Eylea price per dose	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0	1,850.0
Eylea ex-U.S. RVO Sales ($MM)	**$40**	**$163**	**$190**	**$250**	**$300**	**$350**	**$400**	**$450**
Lucentis ex-U.S. Sales ($MM)	**$2,540**	**$2,600**	**$2,650**	**$2,700**	**$2,750**	**$2,800**	**$2,850**	**$2,900**
Eylea ex-U.S. Sales ($MM)	**$470**	**$1,040**	**$1,425**	**$1,850**	**$2,250**	**$2,450**	**$2,680**	**$2,911**
AVA-101 ex-U.S. Sales ($MM)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$100**
Y/Y Growth (%)								
Lucentis WW Sales ($MM)	**$4,060**	**$4,144**	**$4,230**	**$4,305**	**$4,381**	**$4,458**	**$4,537**	**$4,617**
Eylea WW Sales ($MM)	**$1,879**	**$2,789**	**$3,600**	**$4,300**	**$4,900**	**$5,200**	**$5,526**	**$5,833**
AVA-101 WW Sales ($MM)							**$0**	**$300**

Source: Cowen and Company

Avalanche Will Collaborate With Regeneron To Develop AAV-Based Therapies For Up To 8 Other Targets

In May 2014, Avalanche entered into a broad research collaboration and license agreement with Regeneron. The collaboration deal covers eight novel candidates produced by the Ocular BioFactory platform, including AVA-311. The remaining seven candidates cannot be from among those Avalanche is already working on (e.g., AVA-101 and AVA-201). Avalanche has the right to choose to co-develop two of the targets for a 35% share of the worldwide development costs and profits. To date, Avalanche has received an initial payment of $8.0MM and is eligible for reimbursement of additional collaboration research costs. For each of the eight products, Avalanche is eligible to receive up to $80MM in development and regulatory milestone payments, for a combined of $640MM in potential milestone payments, as well as low to mid single-digit royalties on worldwide net sales of collaboration product candidates.

The collaboration does not include an agreement for AVA-201, but it does include a clause giving Regeneron a time-limited right of first negotiation for certain rights to AVA-101. Avalanche owns exclusive rights to develop and commercialize AVA-101 worldwide, but for a short window of time after the Phase IIa trial data become available, Regeneron can offer deal terms to Avalanche. Avalanche is not required to accept the terms of the offer.

AVA-311 Expands The Franchise To X-linked Retinoschisis

Juvenile X-linked Retinoschisis (XLRS) is a recessively inherited bilateral vitreoretinal dystrophy that has an early onset manifested in young males. It is an orphan indication with high unmet need affecting 1:15,000 males (approximately 10K – 12K men and boys in the U.S.). XLRS is caused by a defect in the RS1 gene which encodes a small protein (24 kDa) that assembles into an oligomer, retinoschisin, the precise function of which remains elusive. Retinoschisin may play a role in cell adhesion, as suggested by the presence of a conserved discoidin domain, frequently encountered in this family of protein. To date, over 190 RS1 mutations have been reported in the RS1 gene, but the majority of XLRS patients carry missense mutations involving conserved amino acids in the discoidin domain. Based on the phenotypes observed, retinoschisin is clearly required for maintaining the integrity of photoreceptor cells.

Patients present with impaired visual acuity, but secondary complications include retinal detachment, vitreal hemorrhage and glaucoma with neovascularization. Clinically, the severity of the symptoms varies among patients, and the diagnosis includes an abnormal ocular fundus, characteristic amplitude loss of the ERG b-wave (a key determinant of disease progression), and family history consistent with X-linked inheritance.

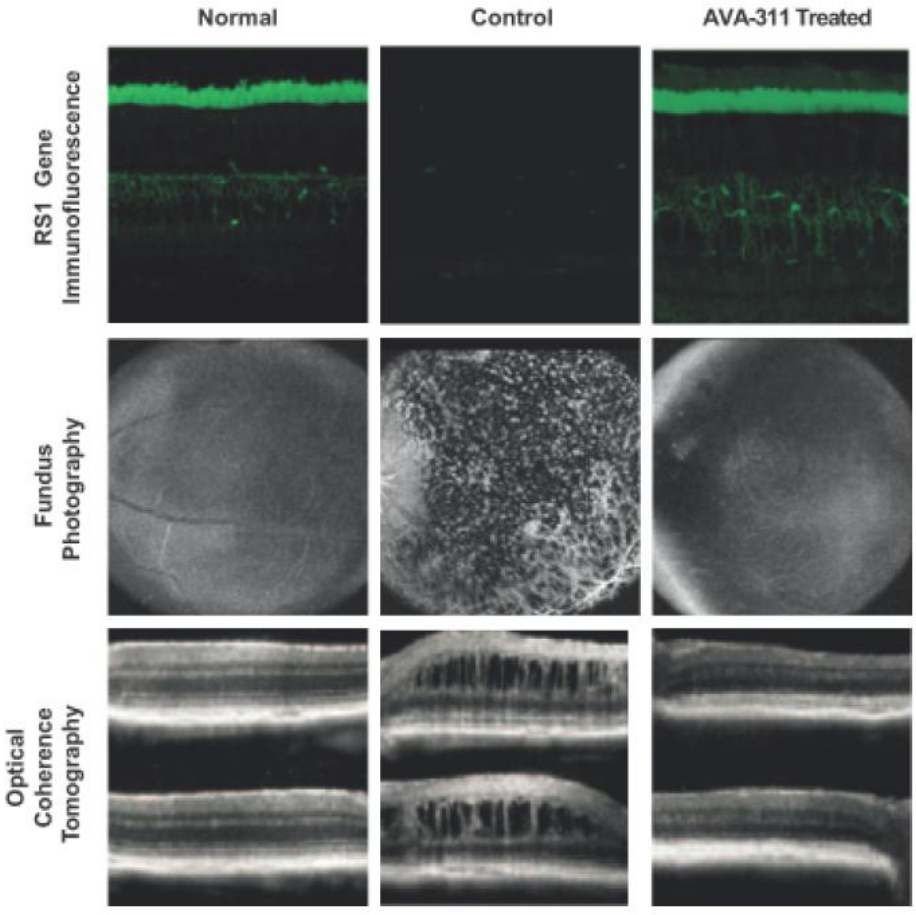
AVA-311 is a preclinical candidate designed to treat XLRS. The AVA-311 capsid has been optimized using the directed evolution technology to penetrate photoreceptor cells after an intravitreal injection as such cells undergo degeneration in the absence of a functional RS1 gene product. AVA-311 delivers a wild-type copy of the malfunctioning RS1 gene. As the virus is administered intravitreally, it has the potential to infect a number of retinal cell populations as it diffuses through. To ensure that the RS1 gene is only expressed in the target cell, it is controlled by a rhodopsin (rho) promoter which turns on transcription only in photoreceptor cells. Therefore, the construct chosen for future development is named 7m8-rho-RS1. Work undertaken in Avalanche's collaborating labs has shown that 7m8-rho-GFP leads to specific expression in photoreceptors and not in other retinal cell types.

AVA-311 Was Shown To Be Effective In A Mouse Model of XLRS

In mouse models of XLRS, the homolog of retinoschisin (Rs1h) is ablated, resulting in a condition that closely mimics the human disease. The retina of these mice is highly disorganized and characterized by cavities in the inner retina. A progressive loss of rod and cone photoreceptors takes place, peaking at 18 days after birth. Similar to what is seen in human patients, there is a reduction of the b-wave of the electroretinogram under both dim and bright light.

To test the efficacy of AVA-311, mice were given a single intravitreal injection in one eye, while the other was left untreated. Mice were then monitored for four months. AVA-311 treated eyes exhibited high levels of RS1 protein expression localized to the photoreceptors in the outer segments of the retina. Levels were comparable to those found in normal eyes. Importantly, AVA-311 restored the anatomy and appearance of a normal retina. Treated eyes also exhibited significant improvements in retinal function as measured with electroretinography (ERG) after one month. This improvement was maintained over 4 months. Conversely, retinal function in untreated eyes was lower and continued to decline over the four-month period.

AVA-311 Corrects Defects In A Mouse Model Of XLRS



Source: Avalanche Biotechnologies

Avalanche and Regeneron are conducting additional preclinical studies of AVA-311. They are further optimizing and characterizing the 7m8-rho-RS1 transgene so that it results in optimal protein expression. They plan to conduct additional experiments in rodents, followed by PK/PD evaluations in non-human primates. Avalanche and Regeneron are also scaling the GMP manufacturing process, and conducting IND-enabling toxicology studies. Avalanche and Regeneron have not provided guidance as to when AVA-311 could enter human clinical testing.

Avalanche Appears Undervalued Based On A Heavily Risk-Adjusted DCF

To value Avalanche, we have incorporated our estimates into a discounted cash flow (DCF) analysis. We project a 2020 launch for AVA-101. We project that sales will grow from $300MM in 2020 to $4.7B at peak in 2030. Notably, we assume that sales fall precipitously after AVA-101's patents expire in 2030. However, this is likely a conservative assumption since AVA-101 is a biologic. Not only will it have 12 years of data exclusivity after approval in 2020, but we think it is also unlikely to face true, small-molecule like generic competition upon the expiry of its patents. Therefore, we think it will likely have a longer commercial life than we are giving it credit. Moreover, we model no revenue from the other members of Avalanche's pipeline, including AVA-311 and the other compounds in the Regeneron collaboration.

We assume 50% COGS at the time of AVA-101's launch, declining to 30% COGS over time. We conservatively assume that Avalanche's R&D will ramp through AVA-101's commercial life. We assume that SG&A will ramp into the launch of AVA-101, at which time we project it will approach $200MM ($175MM). We assume that SG&A will remain at 20% of AVA-101's sales through its commercial life. We assume that Avalanche will have a 35% tax rate immediately upon breaking into profitability in 2021.

To these assumptions we apply a 12% discount rate, and a -10% terminal growth rate. Such a DCF would imply that Avalanche is worth $93 today. However, with AVA-101 so early in development, we feel it is necessary to risk adjust our DCF to reflect the myriad clinical, regulatory and commercial risks that AVA-101 still faces. Therefore we assign a 50% probability of success to our DCF. This yields a fair value of $47 to Avalanche today. After rounding, we are initiating coverage of Avalanche with an Outperform rating and a $45 price target.

Avalanche DCF Analysis

Financial Year End	12/31/2014
Valuation Date	8/18/2014
Discount Rate	**12.0%**
Terminal Growth Rate	**-10.0%**

Avalanche: DCF Valuation

$MM	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
AVA-101						0	300	1800	2700	3375	3713	3898	4093	4298	4513	4738	4738	711
Growth (%)							*#DIV/0!*	*500%*	*50%*	*25%*	*10%*	*5%*	*5%*	*5%*	*5%*	*5%*	*0%*	*-85%*
License, Milestone and Grant Revenue	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Growth (%)																		
Total Revenues	**0**	**0**	**0**	**0**	**0**	**0**	**300**	**1800**	**2700**	**3375**	**3713**	**3898**	**4093**	**4298**	**4513**	**4738**	**4738**	**711**
Growth (%)									*50%*	*25%*	*10%*	*5%*	*5%*	*5%*	*5%*	*5%*	*0%*	*-85%*
COGS	**0**	**0**	**0**	**0**	**0**	**0**	**150**	**630**	**810**	**1,013**	**1,114**	**1,169**	**1,228**	**1,289**	**1,354**	**1,421**	**1,421**	**213**
COGS as a % of sales							*50%*	*35%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
R&D	**10**	**21**	**28**	**45**	**75**	**95**	**105**	**180**	**270**	**338**	**371**	**390**	**409**	**430**	**451**	**474**	**474**	**71**
R&D as a % of Revenues							*35%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
SG&A	**4**	**6**	**10**	**25**	**75**	**150**	**175**	**360**	**540**	**675**	**743**	**780**	**819**	**860**	**903**	**948**	**948**	**142**
SG&A as a % of Revenues							*58%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Operating Income	**-14**	**-28**	**-38**	**-70**	**-150**	**-245**	**-130**	**630**	**1080**	**1350**	**1485**	**1559**	**1637**	**1719**	**1805**	**1895**	**1895**	**284**
Tax	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**221**	**378**	**473**	**520**	**546**	**573**	**602**	**632**	**663**	**663**	**100**
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
NOL/Tax Assets Utilized																		
Tax rate																		
Taxes Paid	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**221**	**378**	**473**	**520**	**546**	**573**	**602**	**632**	**663**	**663**	**100**
Approx Free Cash Flow	**(14)**	**(28)**	**(38)**	**(70)**	**(150)**	**(245)**	**(130)**	**410**	**702**	**878**	**965**	**1,014**	**1,064**	**1,117**	**1,173**	**1,232**	**1,232**	**185**
Years	0.37	1.36	2.37	3.37	4.37	5.36	6.37	7.37	8.37	9.36	10.37	11.37	12.36	13.36	14.37	15.37	16.36	17.36
Discount Factor	0.96	0.86	0.76	0.68	0.61	0.54	0.49	0.43	0.39	0.35	0.31	0.28	0.25	0.22	0.20	0.18	0.16	0.14
NPV of Cash flows	**(13)**	**(24)**	**(29)**	**(48)**	**(91)**	**(133)**	**(63)**	**178**	**272**	**304**	**298**	**280**	**262**	**246**	**230**	**216**	**193**	**26**

Terminal Value Calculation

Final year FCF	185
Perpetual Growth Rate	-10.0%
Terminal Value	**756**
Discount Factor	0.14
Present Value of Terminal Value	**106**
Present Value of Cash Flows	**2,116**
Enterprise Value	**2,221**
Add: Net cash	165
Market Value	**2,387**
Fully Diluted Shares Outstanding	25.6
Value per Fully Diluted Share	**$93.23**
Probability of success	50.0%
Value per Fully Diluted Share	**$46.62**

Source: Cowen and Company

Avalanche Quarterly P&L ($MM)

	Q1:14A	Q2:14E	Q3:14E	Q4:14E	2014E	Q1:15E	Q2:15E	Q3:15E	Q4:15E	2015E
AVA-101	-	-	-	-	-	-	-	-	-	-
License, Milestone and Grant Revenue	0.0	-	-	-	-	-	-	-	-	-
Total Revenue	0.0	-	-	-	-	-	-	-	-	-
COGS	-	-	-	-	-	-	-	-	-	-
R&D	0.9	2.0	3.5	3.7	10.1	4.2	5.0	5.6	6.3	21.1
SG&A	0.7	0.8	1.1	1.3	3.9	1.5	1.6	1.6	1.7	6.4
Other	-	-	-	-	-					-
Operating Expenses	1.6	2.8	4.6	5.0	14.0	5.7	6.6	7.2	8.0	27.5
Operating Income / (Loss)	(1.6)	(2.8)	(4.6)	(5.0)	(14.0)	(5.7)	(6.6)	(7.2)	(8.0)	(27.5)
Interest Income	-	0.1	0.1	0.1	0.3	0.1	0.1	0.1	0.1	0.4
Interest Expenses	(0.0)	(0.0)	(0.0)	-	(0.1)	-	-	-	-	-
Other Income (Expense)	(0.0)	-	-	-	(0.0)	-	-	-	-	-
Pretax net income	(1.7)	(2.7)	(4.5)	(4.9)	(13.8)	(5.6)	(6.5)	(7.1)	(7.9)	(27.1)
Taxes	-	-	-	-	-	-	-	-	-	-
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
GAAP Net Income	(1.7)	(2.7)	(4.5)	(4.9)	(13.8)	(5.6)	(6.5)	(7.1)	(7.9)	(27.1)
GAAP EPS	**$ (0.45)**	**$ (0.73)**	**$ (0.30)**	**$ (0.19)**	**$ (1.15)**	**$ (0.22)**	**$ (0.25)**	**$ (0.27)**	**$ (0.30)**	**$ (1.05)**
Diluted Shares Outstanding (MM)	3.7	3.7	15.0	25.6	12.0	25.7	25.9	26.0	26.1	25.9

Source: Cowen and Company

Avalanche Annual P&L ($MM)

	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E
AVA-101	-	-	-	-	-	-	-	300.0
License, Milestone and Grant Revenue	0.5	-	-	-	-	-	-	-
Total Revenue	0.5	-	-	-	-	-	-	300.0
COGS	-	-	-	-	-	-	-	150.0
R&D	2.2	10.1	21.1	27.5	45.0	75.0	95.0	105.0
SG&A	1.8	3.9	6.4	10.0	25.0	75.0	150.0	175.0
Other	-	-	-	-	-	-	-	-
Operating Expenses	3.9	14.0	27.5	37.5	70.0	150.0	245.0	430.0
Operating Income / (Loss)	(3.5)	(14.0)	(27.5)	(37.5)	(70.0)	(150.0)	(245.0)	(130.0)
Interest Income	-	0.3	0.4	0.3	0.5	0.5	1.9	1.0
Interest Expenses	(0.1)	(0.1)	-	-	-	-	-	-
Other Income (Expense)	(1.7)	(0.0)	-	-	-	-	-	-
Pretax net income	(5.3)	(13.8)	(27.1)	(37.2)	(69.5)	(149.5)	(243.1)	(129.0)
Taxes	-	-	-	-	-	-	-	-
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
GAAP Net Income	(5.3)	(13.8)	(27.1)	(37.2)	(69.5)	(149.5)	(243.1)	(129.0)
GAAP EPS	**$ (1.44)**	**$ (1.15)**	**$ (1.05)**	**$ (1.40)**	**$ (2.30)**	**$ (4.90)**	**$ (6.85)**	**$ (3.35)**
Diluted Shares Outstanding (MM)	3.7	12.0	25.9	26.6	30.2	30.5	35.5	38.5

Source: Cowen and Company

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

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

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

Investment Risks

Biotechnology:

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

Risks To The Price Target

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

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
AAVL	Avalanche Biotechnologies
BMRN	BioMarin Pharmaceutical
GILD	Gilead Sciences
PTLA	Portola Pharmaceuticals

Analyst Certification

Each author of this research report hereby certifies that (i) the views expressed in the research report accurately reflect his or her personal views about any and all of the subject securities or issuers, and (ii) no part of his or her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed in this report.

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Cowen and Company, LLC and or its affiliates make a market in the stock of Avalanche Biotechnologies, BioMarin Pharmaceutical, Gilead Sciences and Portola Pharmaceuticals securities.

Avalanche Biotechnologies and Portola Pharmaceuticals have been client(s) of Cowen and Company, LLC in the past 12 months.

Cowen and Company, LLC and/or its affiliates expect to receive, or intend to seek, compensation for investment banking services in the next 3 months from Avalanche Biotechnologies.

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Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

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Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

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

Cowen Securities, formerly known as Dahlman Rose & Company, Rating System until May 25, 2013

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

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Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

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Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	417	58.57%	94	22.54%
Hold (b)	279	39.19%	7	2.51%
Sell (c)	16	2.25%	0	0.00%

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

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Avalanche Biotechnologies Rating History as of 08/22/2014

powered by: BlueMatrix

BioMarin Pharmaceutical Rating History as of 08/22/2014

powered by: BlueMatrix

Gilead Sciences Rating History as of 08/22/2014

powered by: BlueMatrix

Portola Pharmaceuticals Rating History as of 08/22/2014

powered by: BlueMatrix

Legend for Price Chart:

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

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