Avalanche Biotechnologies (AAVL) — Overweight

Eye On The Prize; Initiating At OW, $39 PT

CONCLUSION

We are initiating coverage of AAVL with an OW rating and $39 PT. The company is among a handful of pioneers in the gene therapy field, and a leader among an even smaller group applying this technology for ophthalmic indications. Gene therapy is particularly suited for the eye given an accessible but protected target and a myriad of addressable diseases with high unmet needs. The company's lead program, AVA-101, uses an AAV-2 vector to deliver the sFlt-1 gene to the back of the eye to treat wet-AMD and other neovascular disorders. The company also has an emerging pipeline which was recently boosted by a partnership with REGN.

- **AVA-101 has achieved proof of concept:** Our conviction in this program stems from: 1) similar mechanism of action as approved standard of care therapies; 2) strong pre-clinical data; 3) small P1 study but exceptional results in "treatment addicts" supports a potent drug effect; 4) gene therapy has achieved proof of concept in other ophthalmology indications. AVA-101 offers the potential to meaningfully reduce frequency of injections (important for patient convenience and for addressing the injection burden on specialist practices) and may also improve visual outcomes.

- **Abundant opportunity in the eye**: The wet AMD (and related disorders) market opportunity is a multi-billion dollar market and growing swiftly as the population ages. Beyond wet AMD, there are dozens of monogenetic causes of blindness which could be treated by gene therapy. AAVL will be addressing a number of these disorders over time, both as part of its newly formed development partnership with REGN and on its own.

- **Questions from the roadshow**: In this report we address the most common questions investors had during the company's IPO roadshow, including: 1) implications of upcoming data from SNY/AGTC; 2) the reason we have such high conviction despite the early nature of the program; and 3) potential safety concerns of this approach.

RISKS TO ACHIEVEMENT OF PRICE TARGET

AAVL gene therapy candidates may fail to achieve target development steps.

COMPANY DESCRIPTION

AAVL is a pioneer in gene therapy, targeting ophthalmic indications.

PRICE: US$30.52
TARGET: US$39.00
DCF thru 2024, 11% discount rate, 5% growth rate

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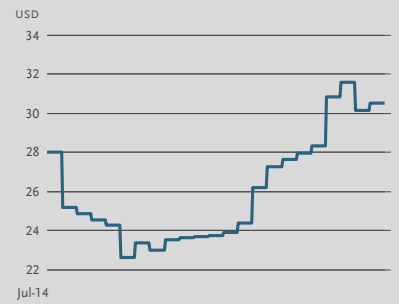
Changes	Previous	Current
Rating		Overweight
Price Tgt		US$39.00
FY15E Rev (mil)	—	US$12.0
FY16E Rev (mil)	—	US$12.0
FY15E EPS	—	US$(0.97)
FY16E EPS	—	US$(1.35)

52-Week High / Low	US$32.38 / US$22.00
Shares Out (mil)	21.0
Market Cap. (mil)	US$640.9
Net Cash Per Share	US$7.60
Debt to Total Capital	0%
Div (ann)	US$0.00
Fiscal Year End	Dec

Price Performance - 1 Year



Source: Bloomberg

YEAR	REVENUE (US$ m)						EARNINGS PER SHARE (US$)					
	Mar	Jun	Sep	Dec	FY	FY RM	Mar	Jun	Sep	Dec	FY	FY P/E
2014E	0.0A	2.0	2.0	2.0	6.0	106.8x	(0.11)A	(0.17)	(0.16)	(0.16)	(0.61)	NM
2015E	3.0	3.0	3.0	3.0	12.0	53.4x	(0.18)	(0.22)	(0.26)	(0.30)	(0.97)	NM
2016E	—	—	—	—	12.0	53.4x	—	—	—	—	(1.35)	NM

Avalanche Biotechnologies (AAVL): Snapshot

- **A leader in AAV-based gene therapies targeting the eye, AAVL is developing its lead product, AVA-101 for Wet-AMD, by targeting vascular endothelial growth factor (VEGF).**
  - Currently in a Phase IIa study, AVA-101 is mostly de-risked based on the validated target, preclinical models and the early clinical data. Phase 1 results suggest possible superiority versus the standard of care (Eylea and Lucentis).
  - Data from Phase IIa trial is expected mid-2015. AAVL plans to initiate a Phase 2b study in the US in 2H15.
  - Branded anti-VEGF market is ~$3B in the U.S., $5B+ globally. Off-label Avastin accounts for up to 50% U.S. share.
- **AAVL has a proprietary AAV-based next-generation platform for discovery and development of gene therapy vectors for ophthalmology.**
  - This technology platform encompasses discovery, development and industrialized manufacturing.
  - Manufacturing and efficient vector production may be a differentiator between gene therapy companies.
- **Partnership with REGN and other pipeline products offer significant upside.**
  - Enables expansion of AAVL's pipeline and validates the platform.
  - AAVL is pursuing pipeline programs that utilize next-generation vectors to better target various layers in the retina and potentially replace subretinal injections with intravitreal ones.

Avalanche Biotechnologies (AAVL): Company Description

AAVL is among a small handful of pioneers in the gene therapy space and among an even smaller handful of pioneers developing gene therapies for treatment of ophthalmic disorders.

The company's lead product, AVA-101, is a gene therapy for treatment of wet AMD, a form of progressive vision loss caused by growth of new, leaky blood vessels in the retina. Currently, wet AMD (and a number of related disorders) are treated by giving regular intravitreal injections of antibodies that bind to VEGF and cause regression of these leaky blood vessels. However, these therapies often require frequent administration, which is cumbersome to doctors and patients, and they often do not provide adequate disease control. AVA-101 is a gene therapy product administered subretinally to induce cells to secrete the sFlt-1 protein which binds VEGF. Preclinical data and early clinical data have established proof of concept, we believe.

Beyond AVA-101, AAVL is developing AVA-201, an optimized gene therapy for more convenient intravitreous delivery, and has a validating partnership with REGN to develop additional ophthalmic gene therapy programs. AAVL also plans to broaden its own ophthalmology gene therapy platform as the eye offers many unique opportunities for a gene therapy approach.

AAVL: Our Investment Thesis

1. **AAVL is a pioneer in gene therapy for ophthalmic applications, with a lead shot-on-goal addressing a mega-blockbuster market:**
   - AVA-101 for wet AMD has established proof of concept in preclinical/early clinical models.
   - While Phase I studies rarely provide clarity into a drug's efficacy, the rich context surrounding this study, the refractory nature of the patients and the demonstration of effect on an endpoint with minimal 'noise' is compelling to us.
   - AVA-101 has the potential to meaningfully reduce the frequency of intra-ocular injections (and potentially provide a lifetime benefit) for wet AMD patients and it also has the potential to improve visual acuity for patients who are not achieving optimal control.

2. **The market model for AVA-101/201 is easy to build:**
   - Because of the high incidence and prevalence of wet AMD (up to 100K new eyes treated each year, on top of the ~500K+ eyes in the prevalence pool), the market model for AVA-101 is much easier for investors to contemplate than rarer diseases.
   - Even limiting adoption to patients who require the most frequent (7+) injections/year still creates considerable opportunity.

3. **Modular and evolving platform:**
   - The eye offers a rich opportunity of high unmet need, with a long list of monogenic (or acquired) diseases that can be corrected by gene therapy.
   - AAVL is one of the few gene therapy companies working to further optimize its AAV vector to improve its efficiency in delivering gene candidates to the right target cells in the eye.

AAVL Valuation: Price Target $39/share

Our $39 PT represents nearly 30% potential upside from AAVL's current share price of $30.52 (as of 8/22).

- **We arrive at our PT via a DCF analysis of estimated free cash flow (modeled through 2024)**
  - Premium 11% discount rate reflects clinical/commercial risk for AAVL.
    - 5% terminal growth (18x terminal multiple) reflects the long-term outlook for AAVL's current pipeline programs and the potential gene therapy additions to the pipeline.

- **We assume:**
  - AAVL commercializes AVA-101/201 on its own in the U.S., charging $25K/injection
  - Penetration into the 'high-injection' requiring eyes reaches 45%; penetration into the 'mid-frequency injection' requiring eyes reaches 12%
  - AVA-101/201 ONLY penetrates into the disease incidence, not the prevalence (VERY conservative).
  - AAVL partners AVA-101/201 ex-U.S. for a royalty which starts at 15%.
  - REGN commercializes AVA-311 globally with launch in 2021, paying AAVL a 10%+ royalty.

By 2024, we model U.S. sales of AVA-101/201 reaching ~$500M, ex-U.S. sales reaching ~$200M and AVA-311 reaching ~$180M globally.

AAVL: Investment Risks

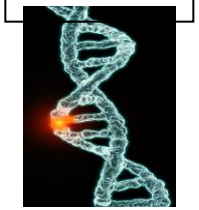
- **Gene therapy is still evolving**
  - Past mis-steps with gene therapy programs using non-optimized viral vectors led to some serious complications including death and leukemia; however, meaningful advances in the field have vastly improved the safety profile, and the eye is a confined space which limits risk of systemic side effects.
- **Clinical data for AVA-101 is early**
  - Six patients treated in Phase I study; while compelling, the small number of patients introduces risk that the results may not be replicated. That said, we believe the mechanism, approach, validation of other gene therapy approaches, refractoriness of patients studied and robust nature of the results make these results unlikely to have been generated by 'chance'.
  - Additional clinical data required to ensure no safety concerns arise.
- **Competition may emerge/intensify**
  - Other companies are pursuing gene therapy for ophthalmology indications; AGTC/SNY have a partnership for a similar gene therapy construct but are delivering it intravitreous vs AVA-101 which is being administered subretinally.
  - AGTC has a franchise of gene therapy programs for retina indications, including XLRS, which could prove competitive and potentially even block AAVL programs under Orphan Drug Exclusivity legislation in some territories.
- **Gene therapy could face regulatory or other hurdles**
  - Approval of QURE's Glybera in the EU is an important regulatory achievement for gene therapy, but all programs will be scrutinized based on the novelty of the approach.
  - Manufacturing of gene therapy, like with other biologics is complex. AAVL could experience setbacks on this front.

AAVL: Expected Upcoming Catalysts That Could Unlock Value

- **P1 data for AGTC/GENZ gene therapy for wet AMD in Sept & Oct 2014 (medical conference presentations)**
  - Competitive gene therapy program using similar protein and same vector but delivered intravitreously.
  - Seen by some investors as an 'overhang' to AAVL and by others as a potentially derisking event for the platform.
  - We do not expect results for the AGTC/Genzyme program to support ongoing development of that specific approach, but we do think it will help validate the utility of gene therapy for wet AMD. If the data are stronger than we expect it would validate the utility of intravitreal injections for wet AMD gene therapy and be a strong positive for both AGTC and AAVL, since AVA-101 could also be deployed for intravitreal delivery.
- **Phase IIa data for AVA-101 in wet AMD (mid-2014)**
  - Based on the Phase I results we expect this to be positive for AAVL.
  - Following the data, REGN has an option to sign a 45d exclusive negotiating period license, but we do not expect AAVL to partner at this time unless they get exceptional terms.
- **File IND for AVA-201, AVA-311 (2016)**
  - Will solidify AAVL as a company with a pipeline beyond AVA-101.

Background On Gene Therapy And The Role Of Viruses

- The cause of a disease can be linked to a faulty (mutated) gene.
  - Many biopharma companies develop drugs to alleviate **symptoms** of the disease
  - Gene therapy **targets** the mutated gene to **cure** the disease.

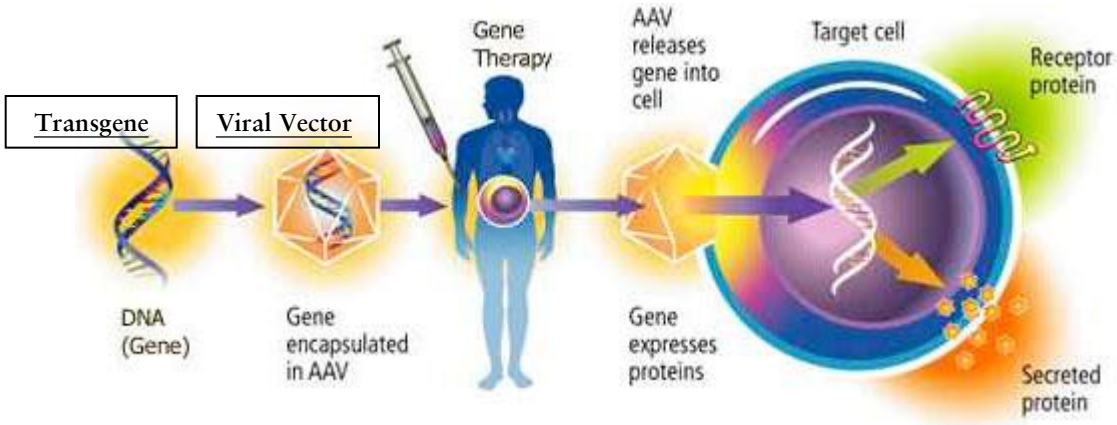


- To cure the disease, the patient needs a **properly working gene** (known as the **transgene**).
  - But how do you get the transgene into the patient? Great question- it's not easy!

- **That's where viruses come in. But these aren't just any kind of virus. These are specially engineered viruses, known as viral vectors.**
  - These viral vectors no longer have their disease causing and replicating (they can't reproduce themselves) elements. Instead, the viral vector contains the therapeutic transgene.
  - Once the viral vector is delivered to the patient, the therapeutic transgene is released, and the patient no longer has the symptoms or the cause of the disease.

The Most Common Viral Vectors

1. **Adeno-associated virus (AAV)**
   This is AAVL's vector of choice.
2. Adenovirus (rarely used)
3. Retrovirus (sometimes used)



Source: http://cisncancer.org/research/new_treatments/gene_therapy/how_it_works.html

Our Quick Thoughts On Gene Therapy

- **Area of intense focus for us**
  - We will continue to track the progress of this field closely as we believe gene therapy is the future of innovation in biotech.
  - **CLICK HERE** for our recent gene therapy primer which lays out the fundamentals of this exciting and evolving field.

- **Why we like gene therapy so much**
  - Successes to date with QURE's Glybera as well as a growing number of derisked development stage programs from academia and other companies establish proof of concept for gene therapy as a viable platform.
  - Hemophilia, Wiskott Aldrich, Childhood Cerebral Adrenoleukodystrophy, beta-thalassemia, LPL deficiency, wet AMD, Leber's Congenital Amaurosis and choroideremia all have achieved proof-of-concept in the clinic (**note the last 3 are ophthalmology indications!**)
  - Genetics is truth: If you understand the genetic basis of a disease, you can know with a high degree of confidence whether the target is the right one or not.

- **Gene therapy enables programs to de-risk even at the concept stage**
  - But not all gene therapy products are created equal.
  - Need to have an intricate understanding of the technologies and the science to determine whether there is target risk, delivery risk, regulatory risk or competitive risk.

This field is in our sweet spot for blending science, creative thinking, problem solving, trouble-shooting, and future-telling with a high degree of certainty.

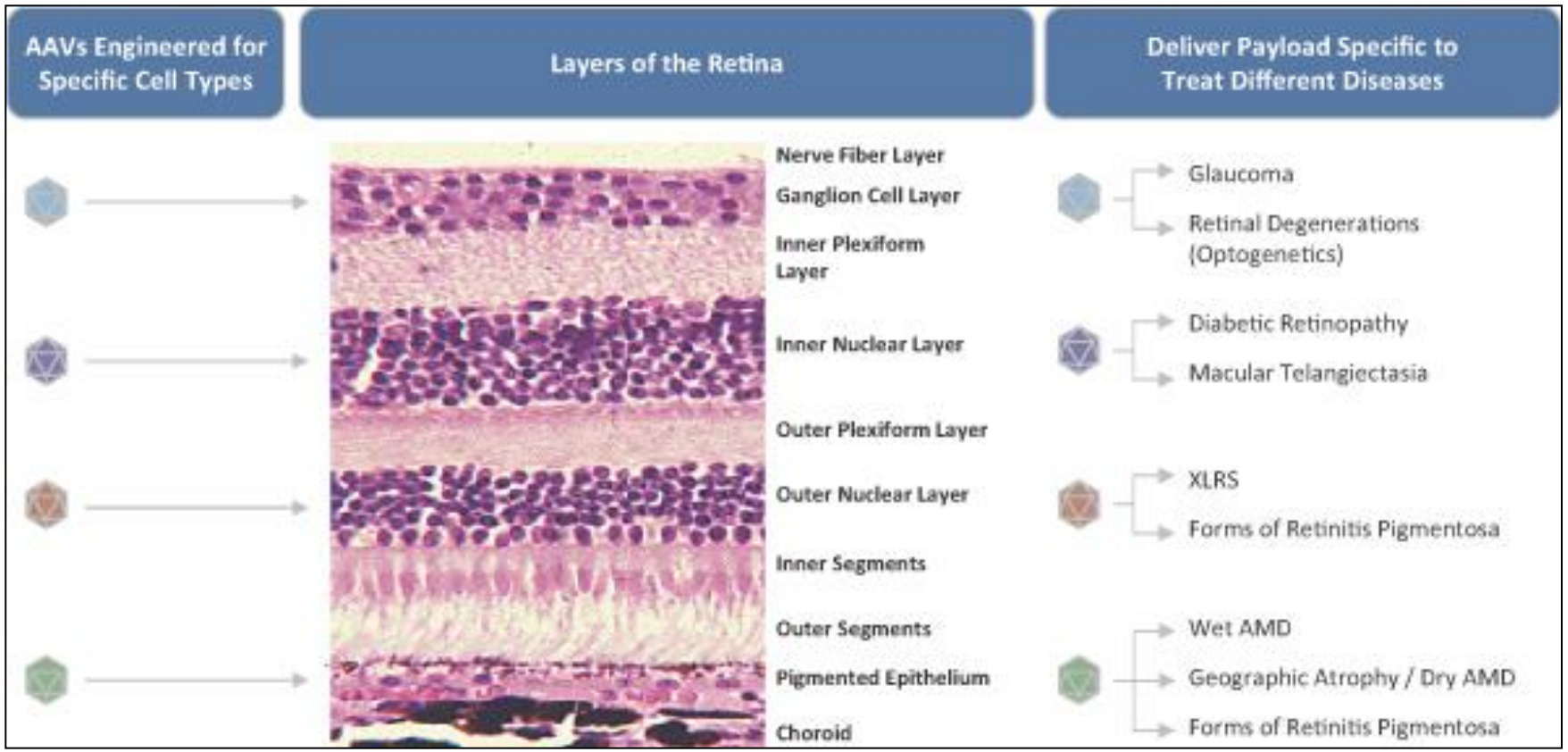
Why We Believe Gene Therapy Targeting The Eye Is De-Risked

The eye is one of the easiest and safest targets for gene therapy, given its immune-privileged nature and ability to ensure long-term expression of the therapeutic transgene.

- **Well-understood disease mechanism and endpoints.**
  - Vision loss has been extensively studied and molecular mechanisms of action are well-understood.
  - Visual acuity, visual fields, contrast sensitivity and color vision are all measurable and can be supplemented by ocular imaging.
- **Many of the targeted eye diseases are monogenic diseases.**
  - Since a number of the rare eye diseases targeted by gene therapy are caused by mutations in a single gene, the exact genetic sequence that is needed is known, thereby mitigating the uncertainty of disease biology.
- **Highly predictive animal models.**
  - The targeted eye diseases are caused by the same underlying genetic defect in humans and animals, leading to similar clinical outcomes.
- **Local delivery of the therapeutic agent.**
  - Ophthalmic gene therapy involves direct delivery to the cells affected by the disease via methods already widely used in ophthalmology. Lower doses can be used, reducing the risk of unintended effects.
- **Short time to achieve meaningful clinical data.**
  - Shorter clinical trials can facilitate rapid development.

To date, clinical success reported for wet AMD, Leber's Congenital Amaurosis and Choroideremia all validate this view.

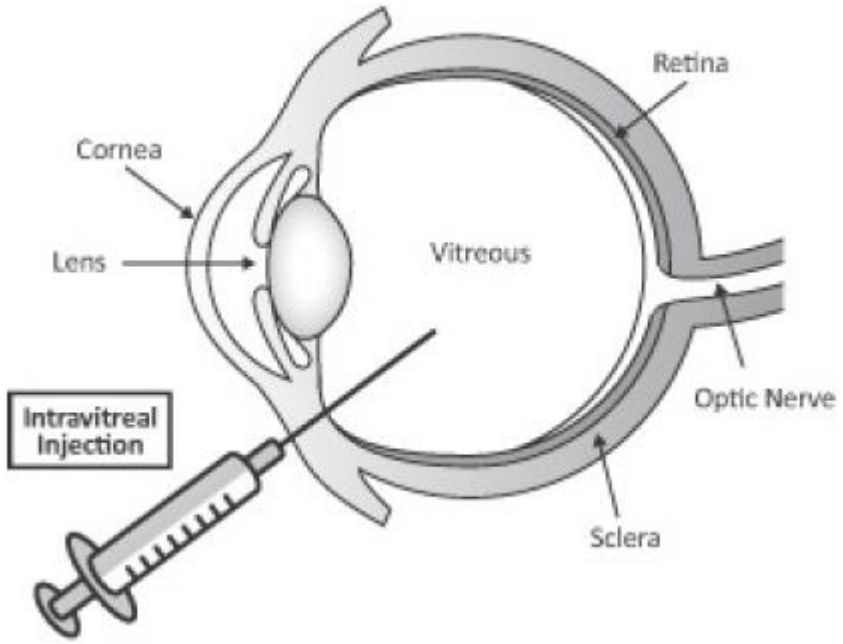
The Retina Has A Number Of Layers To Consider & Target

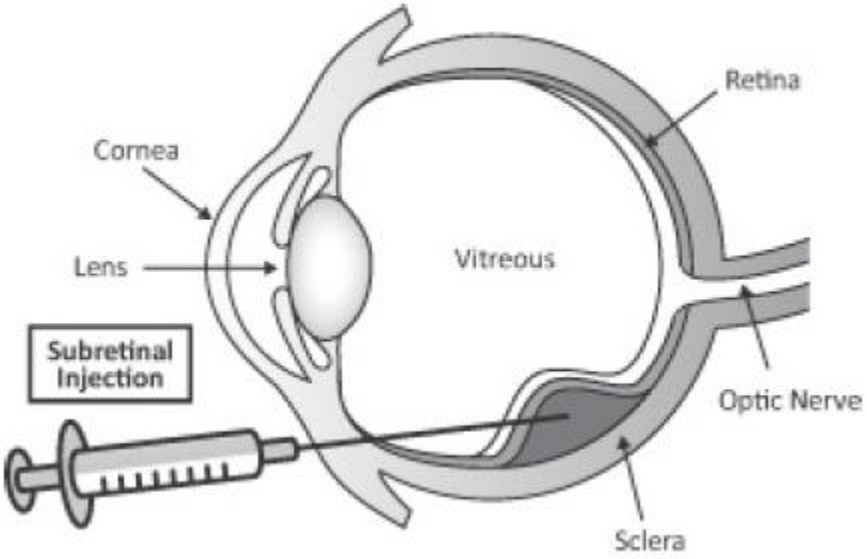


Source: AAVL S1

Different retinal diseases (genetic and acquired) affect different layers of the retina. Optimizing the viral vector so that it targets the right layer should be important for optimizing safety, efficacy and delivery.

Delivering Gene Therapy To The Eye



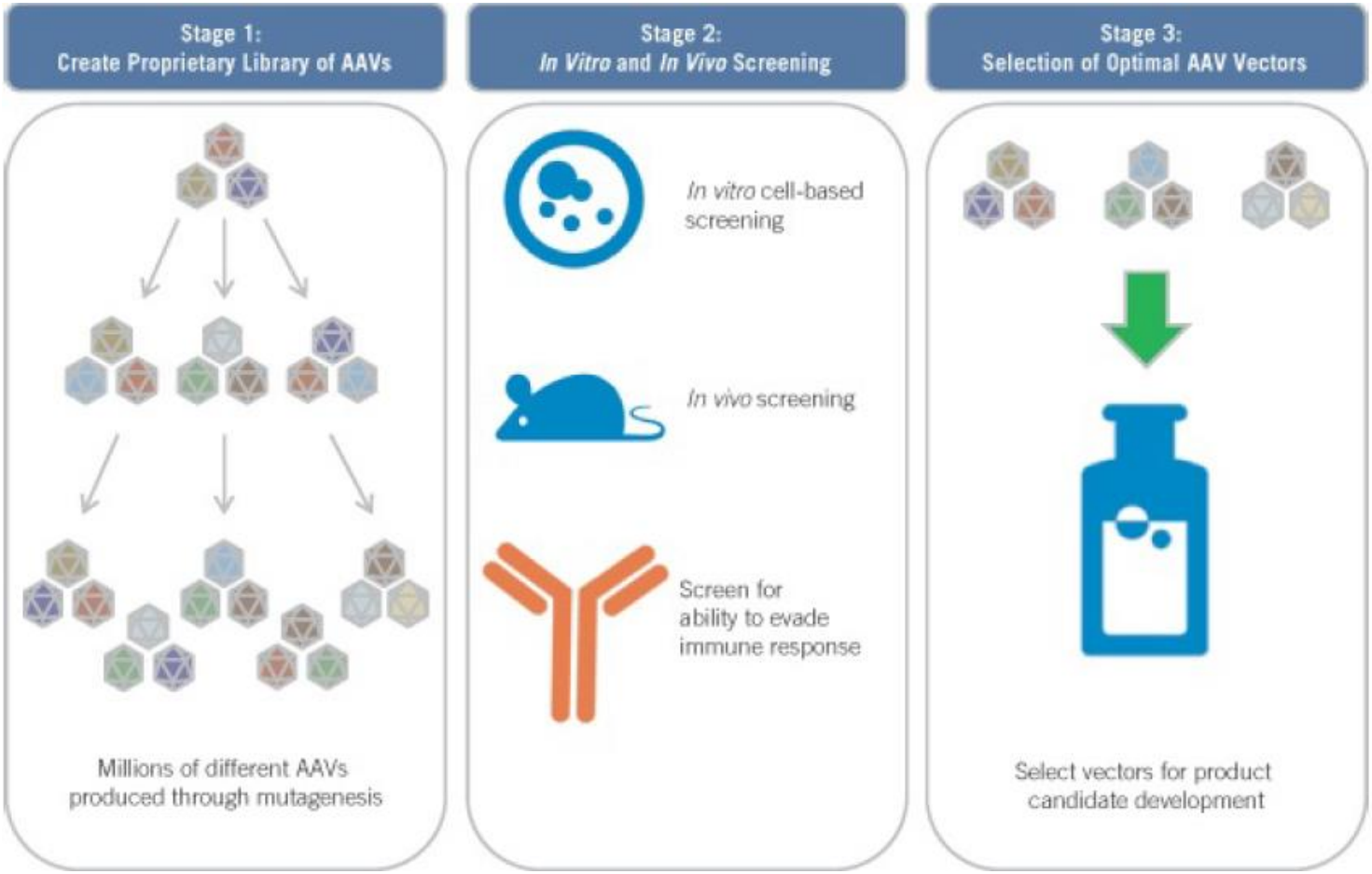


Source: AGTC S-1

Intravitreal Injection: This is a routine procedure that can be carried out in an ophthalmologist's office. The therapy is delivered to the vitreous humor, the clear gel that fills the space between the lens and the retina of the eye. Ideal procedure for delivering the product to the retinal neurons in the inner retina (closest to the lens) and photoreceptors.

Subretinal Injection: This is a short, outpatient surgical procedure, frequently performed by retinal surgeons. The therapy is delivered to the outer retina (farthest from the lens) between the photoreceptors in the outer retina and the retinal pigment epithelium. Ideal procedure for targeting the photoreceptor cells and retinal pigment epithelium cells.

AAVL's Directed Evolution Technology Gives The Platform An Edge



Source: AAVL Prospectus

AAVL's directed evolution technology allows for efficient vector discovery and optimization to deliver genes to various retina layers. Because gene therapy is a dynamic and constantly evolving field, this work is important for ensuring AAVL remains competitive; other companies are working to evolve the viral vectors toward a similar goal (AGTC, QURE with 4D Molecular Therapeutics).

All Eyes On The AAVL Pipeline

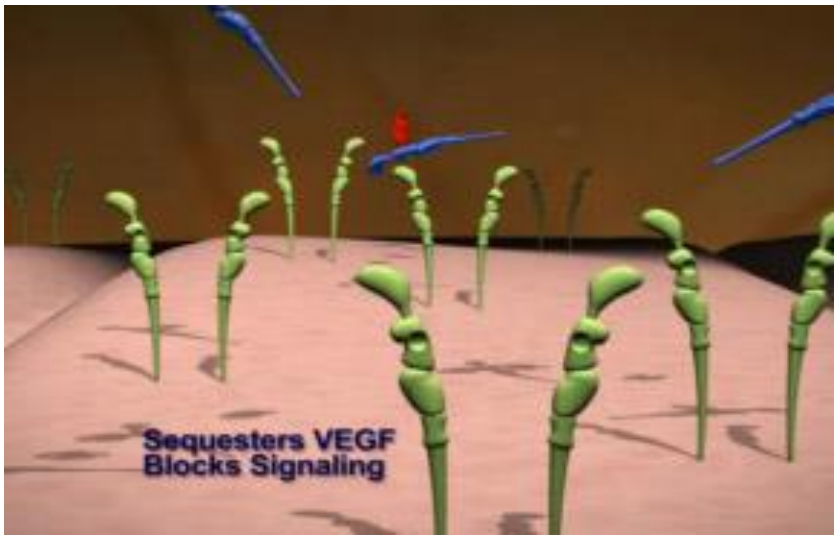
Product Candidate	Indication	Stage of Development			Near-term Milestones	Worldwide Commercial Rights
		Research	Preclinical	Phase 1 / 2		
AVA-101	Wet AMD				▪ Top-line Phase 2a data expected mid-2015 ▪ IND filing 2H 2015	Avalanche
AVA-101	DME and RVO				▪ IND-enabling studies planned for 2014 and 2015	Avalanche
AVA-201	Wet AMD (Prevention)				▪ Preclinical studies in 2014 and 2015	Avalanche
AVA-311	XLRS					Regeneron; Avalanche receives milestones and royalties and has an option to share development costs and profits

Broad Research Collaboration with Regeneron for up to 7 Additional Targets

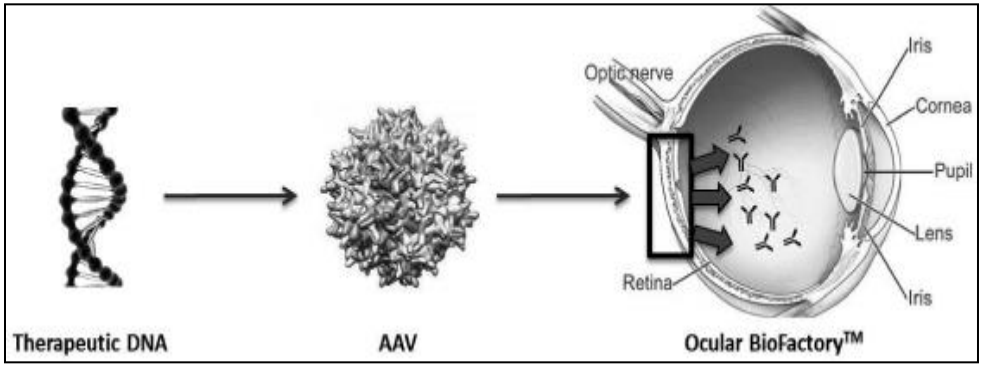
Source: AAVL Prospectus

AAVL has a modular, increasingly de-risked platform which can be easily expanded through the partnership with REGN and independently.

AVA-101 Is A Gene Therapy In Clinical Development For Wet AMD



Source: AAVL website



AVA-101 is a gene therapy that uses AAV-2 (Adeno-associated Virus) vector to deliver the gene for the soluble Flt-1 protein which binds VEGF. Mechanistically, this is similar to the approach with Lucentis and Eylea so the general premise is validated.

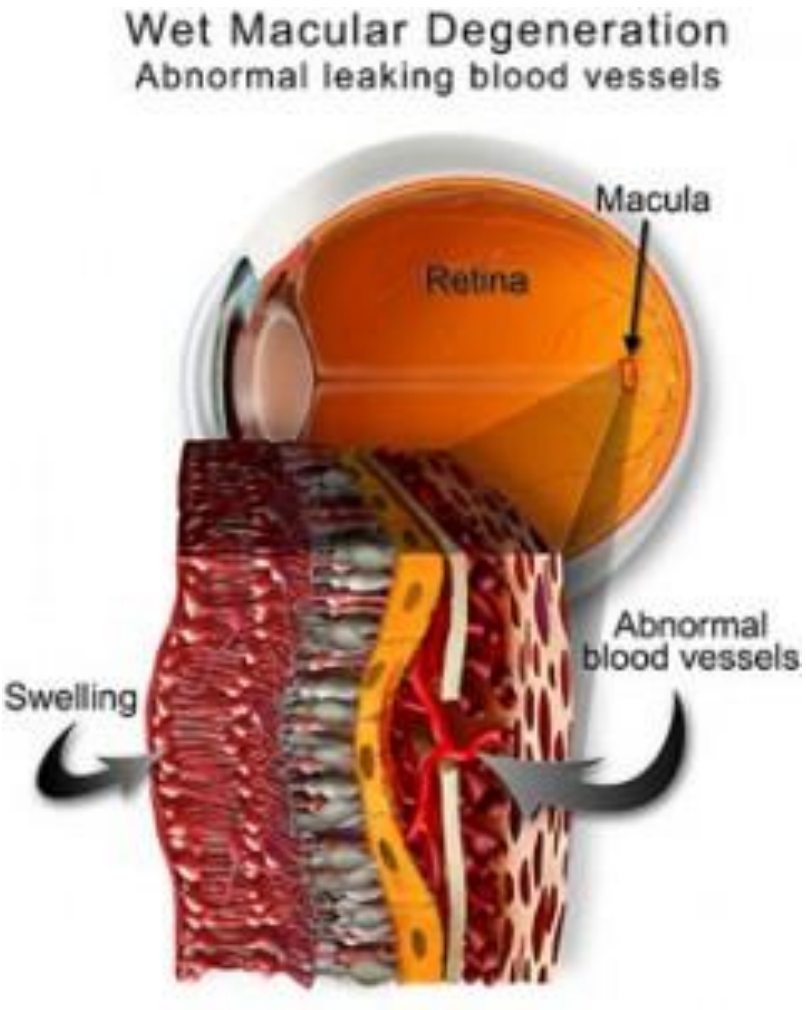
Harnessing the retina to secrete a protein via gene therapy is what AAVL coins its "Ocular BioFactory" approach.

AVA-101 is administered subretinally to target the Retina Pigmented Epithelium and photoreceptor layer (refer to prior slide on retina layers), which are the target layers for wet AMD.

Because the inner limiting membrane (ILM) of the retina acts as a barrier to most AAV serotypes, AAVL believes the intravitreous approach will not yield adequate efficacy (supported by the company's preclinical studies). AAVL is developing novel vectors which can bypass the ILM and which should have utility when delivered intravitreally. This will be an important differentiating factor for retinal-targeting gene therapy companies.

Background On Wet Age-Related Macular Degeneration (AMD)

- AMD is a retinal disease that usually affects older adults and results in a loss of vision in the center of the visual field.
- The neovascular, or wet, form of AMD results from abnormal growth of blood cells in the retina, causing blood and fluid to accumulate below the macula and lead to rapid vision loss.
- This abnormal growth of blood cells is stimulated by a protein called vascular endothelial growth factor (VEGF).
- If left untreated, the bleeding, leaking and scarring from these blood vessels eventually cause irreversible damage to the photoreceptors.
- Treatment through intravitreal injection with drugs that inhibit VEGF (ex: Lucentis and Eylea) can cause regression of the abnormal blood cells and improve vision when injected directly into the vitreous humor of the eye.
- These injections must be repeated monthly or bimonthly.
- There are ~140,000 new cases of wet-AMD per year in the US, **and the global branded market is over $5B** (excludes the off-label use of Avastin as an intravitreal injection which has nearly 50% share in the U.S.)



Source: www.may-eye-care.com

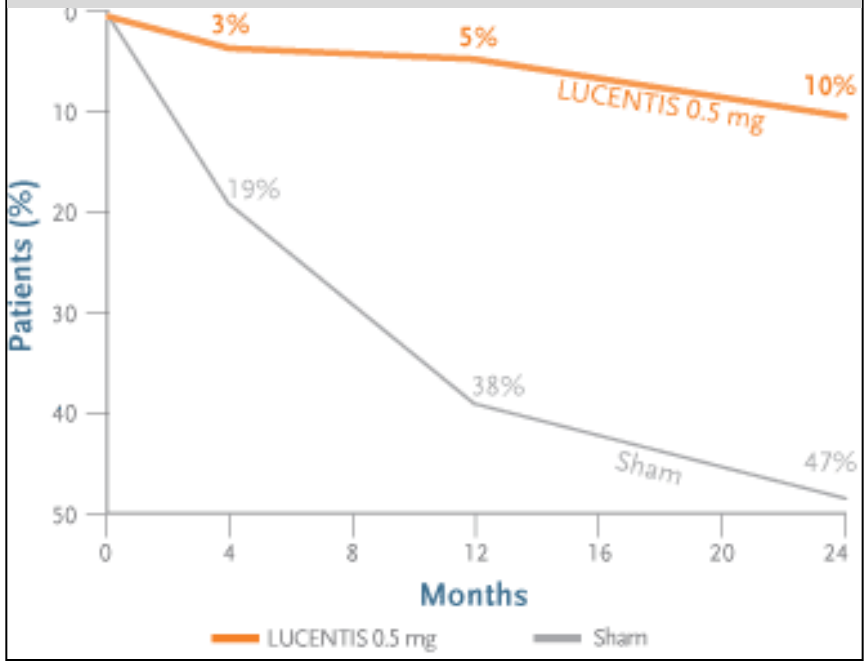
As a one-time treatment, gene therapy presents an attractive option for patients with wet-AMD.

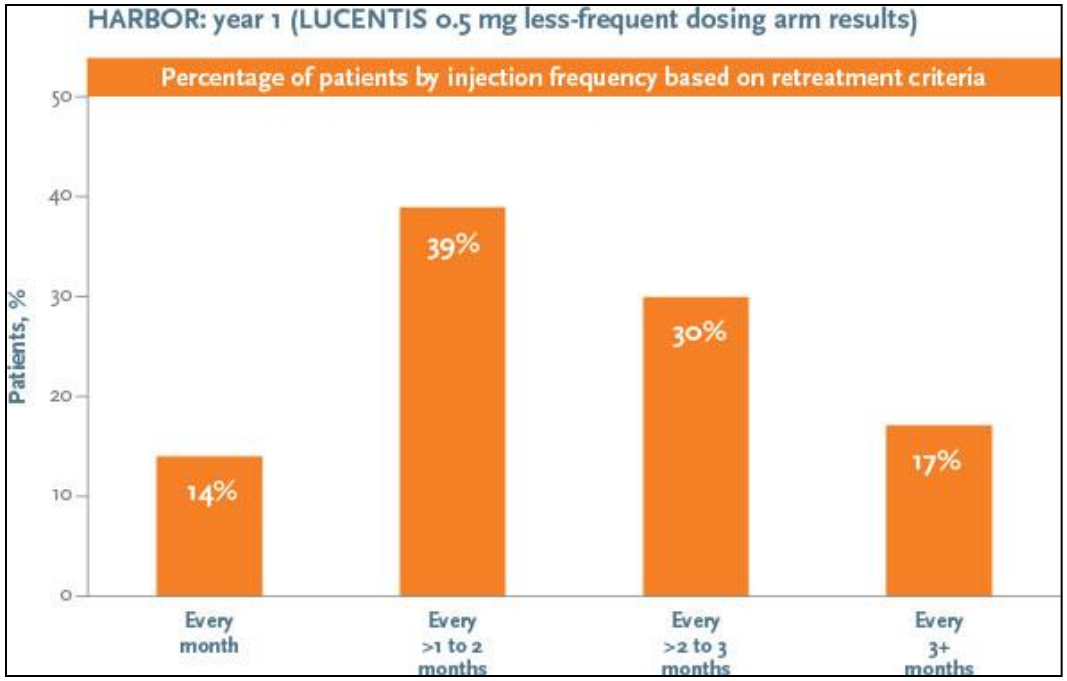
The Unmet Need In AMD And Where AAVL Fits In

- The advent of VEGF-targeting antibodies (Lucentis, Eylea, Avastin) has transformed treatment of wet AMD and led to meaningful improvements in visual acuity and slowing disease progression.

- But wet AMD is very heterogeneous
  - **While many patients have a good response to anti-VEGF therapies, an important minority continue to deteriorate despite therapy.**
  - **And many patients experience disease control, a majority still require frequent cumbersome intravitreous injections.**

RATE OF 3 LINE VISION LOSS IN HARBOR STUDY



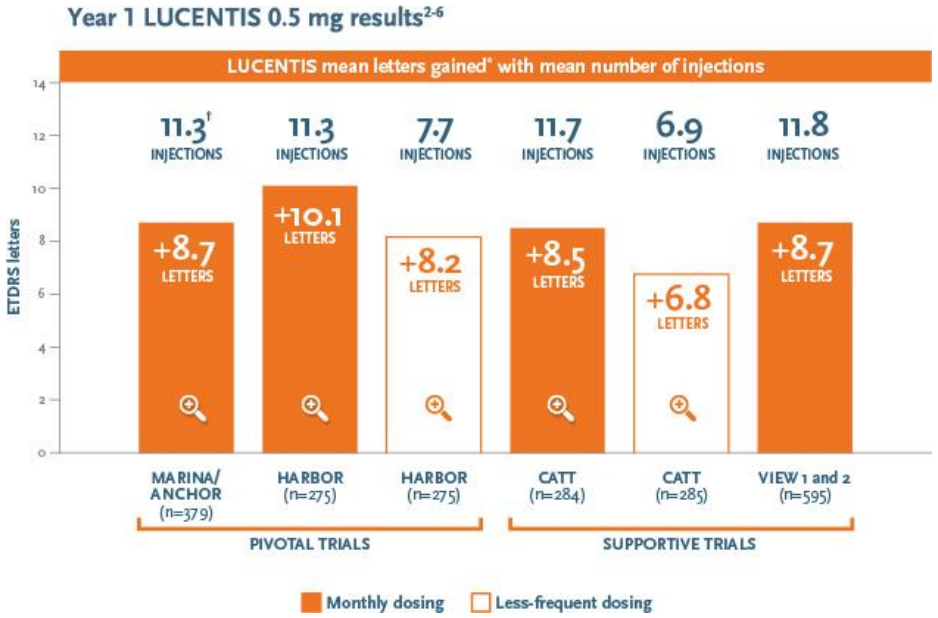


Source: Lucentis.com

There is room for improvement in both visual acuity and frequency of injections.

Less Frequent Dosing May Lead To Lesser Efficacy

- Questions have been raised about the risk of geographic atrophy (GA) with monthly injections of Lucentis versus prn injections
- Some investors questioned whether this would be a problem with AVA-101/201 since continuous anti-VEGF exposure may increase risk of geographic atrophy
- While it is a theoretical risk (although unclear if it is related to the spikes of anti-VEGF activity with the antibodies) it has not been seen to date in AVA-101 studies.
- Furthermore, as eloquently articulated in a presentation by Elizabeth Verner Cole, MD (CLICK HERE) treatment of wet AMD is a balance of risks/benefits, and some GA may be the tradeoff in exchange for optimal vision control.
- Data from the CATT study and HARBOR studies show that prn dosing which delivers less anti-VEGF therapy is also associated with worse visual outcomes.

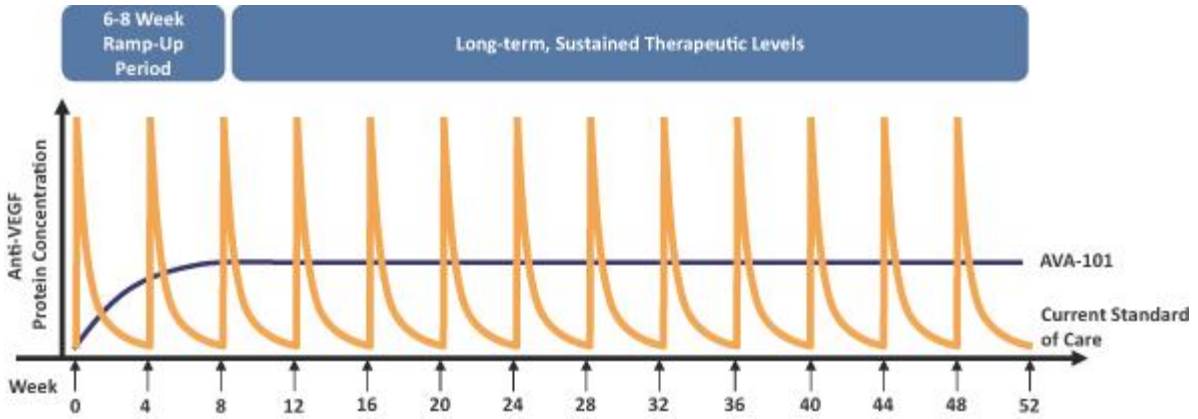


Source: Lucentis.com

By providing sustained anti-VEGF exposure, AVA-101 may lead to superior visual acuities than the current standard of care. Unclear if risk of GA will be increased, but should be offset by superior disease control.

How Gene Therapy Can Address The Unmet Need In AMD

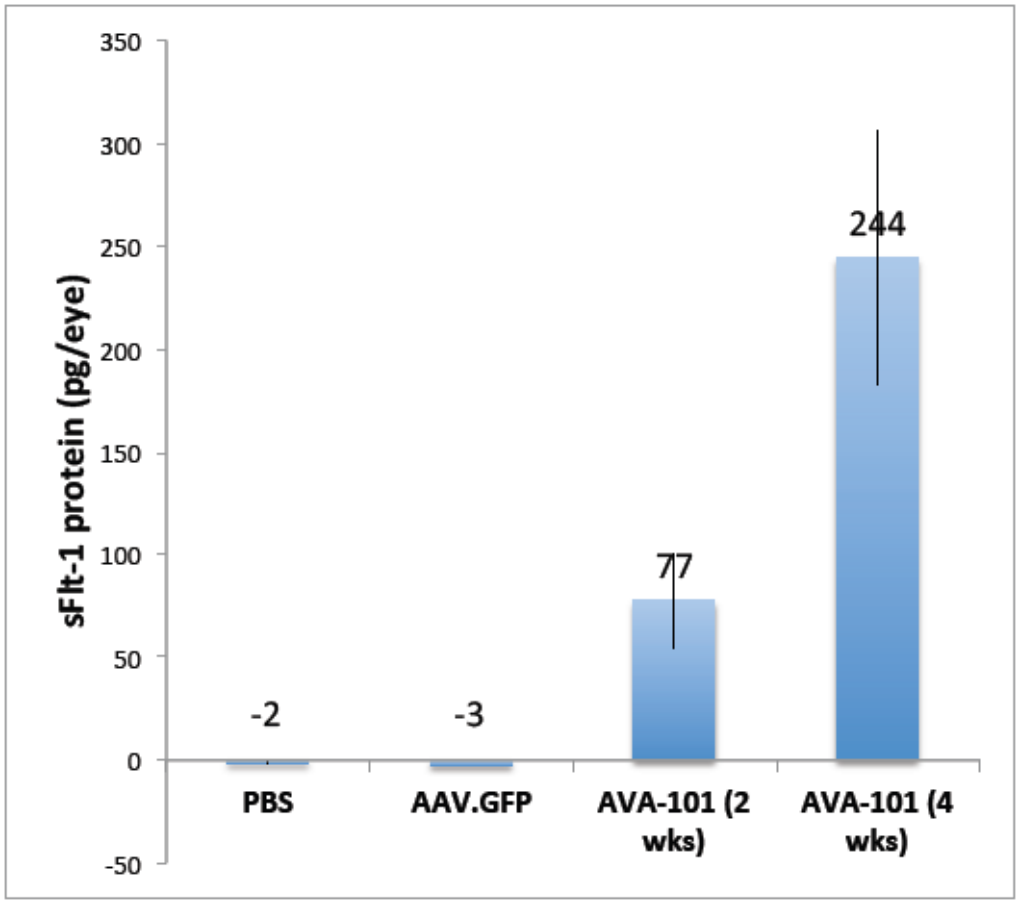
- The current anti-VEGF antibodies deliver a burst of anti-VEGF activity that rapidly declines given a short intravitreal half-life and has extended periods of time without adequate coverage.
- The prn treatment paradigm adopted by many practitioners in order to avoid the inconvenience and risk of frequent intravitreal injections waits until the patients develop evidence of disease recurrence.
- But over time, waiting for the disease to recur and then re-suppressing on this prn basis may result in inadequate long-term control because the periods of disease recurrence may be leading to a growing amount of irreversible retinal damage.
- By delivering a smoother, sustained level of anti-VEGF activity, gene therapy may both eliminate the need for repeat injections and also provide better disease control/coverage leading to improved visual acuity.



Source: AAVL S1

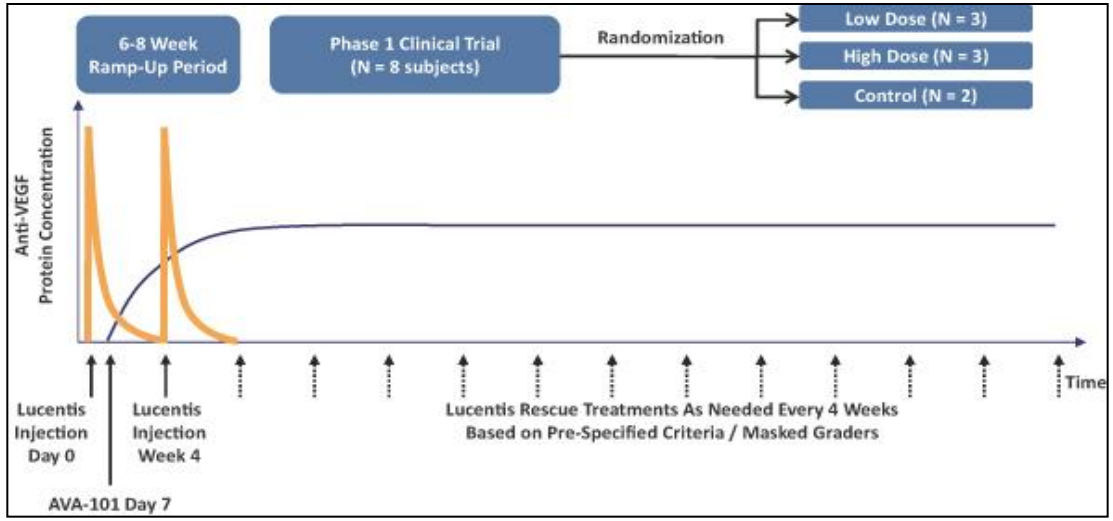
Proof-Of-Concept Has Been Established For AVA-101 In Mice...

Injection of AVA-101 into mouse eyes resulted in strong and sustained expression of the sFlt-1 protein.

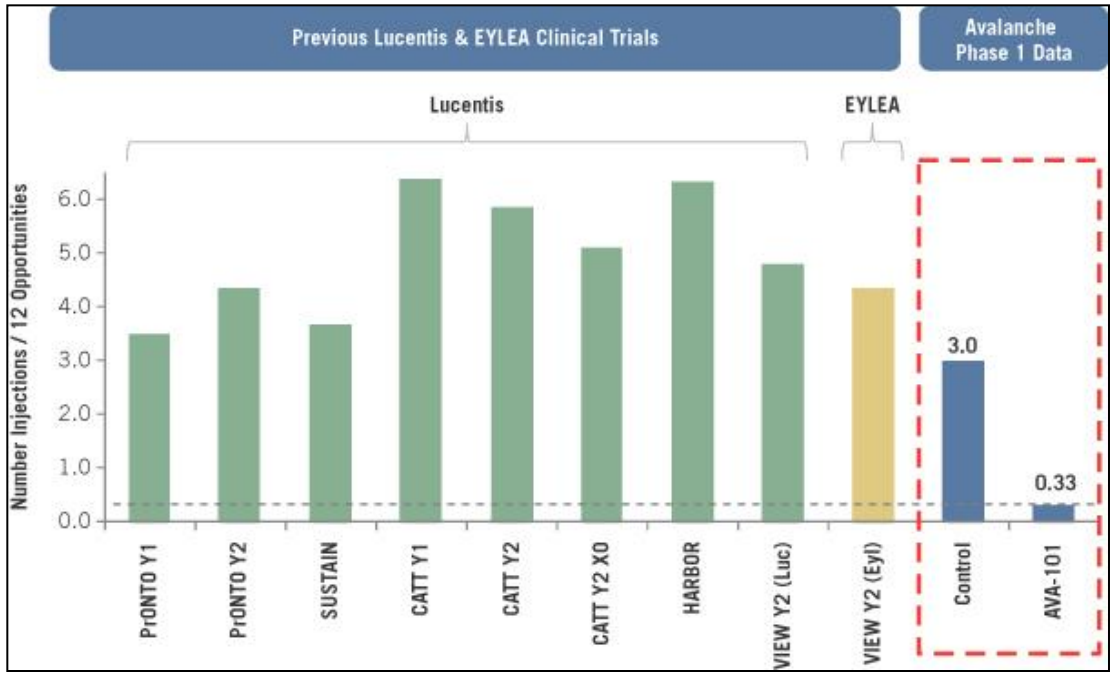


Source: AAVL Corporate Presentation

...And In Humans



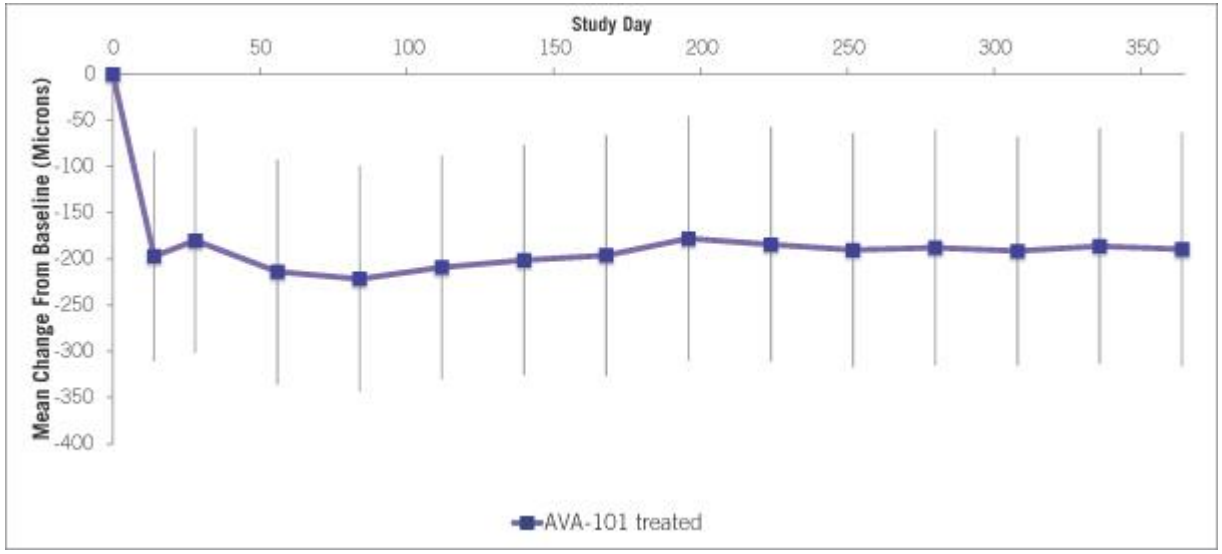
8 patients who were 'treatment addicts,' i.e. unable to wean down to less frequent intravitreous injections of Lucentis. Patients given 2 initial Lucentis doses and then AVA-101 or control and observed for need for additional injections.



After treatment with AVA-101, the need for repeat injections fell substantially! Only 2 more injections were given in the AVA-101 group, including 1 which was given very early in follow up and who subsequently needed no more injections. One of the 2 control patients had a vitreo-macular adhesion resolve spontaneously early on and did not need additional injections.

Source: AAVL S1

AVA-101 Improved OCT Imaging In Phase I As Well



Source: AAVL S1

The benefit in retinal thickness provides additional support of a physiologic effect of AVA-101. Having an objective measure to substantiate the clinical effect is noteworthy.

Treated Patients Also Had Improvement In Visual Acuity

Best-Corrected Visual Acuity

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: AAVL Corporate Presentation

Patients treated with AVA-101 in the Phase 1 trial gained visual acuity from baseline. While we place less emphasis on this endpoint since visual acuity measures tend to have much more 'noise', we do believe this could be a plausible and real signal.

AVA-101 Shown To Be Safe And Effective In Phase 1 Trial

- **Ocular safety.**
  - No drug-related adverse events.
  - Observed adverse events were as expected related to injection procedure; mild and transient.

- **Systemic safety.**
  - No arterial thromboembolic events or anti-VEGF related adverse events.

- **Vector-specific safety.**
  - No traces of the vector were found outside the injected eye.

- **Potential improvement vs. standard of care.**
  - Majority of subjects did not require re-treatment.
  - Comparable reduction in retinal thickness.
  - Trend toward improved visual acuity.

AVA-101 Now Being Evaluated In a Phase IIa Study

- **32-patient study**
  - Being conducted at Lions Eye Institute Limited in Australia (similar to Phase I)
  - Randomized to the high dose used in P1 vs control (2:1).
  - Excludes patients with extensive baseline scarring; includes patients with better baseline vision.
  - Interim reports indicate drug is well tolerated.
  - May move into DME/RVO following data.

Role of AVA-101/AVA-201

- **Burden of anti-VEGF injections becoming increasingly problematic for specialists/patients**
  - Reducing frequency of injections would represent important convenience advantage for patients and help specialists manage their over-burdened practices. Additionally, intravitreous injections carry risks so a meaningful reduction in frequency may also reduce these complications (infection, inflammation, etc).

- **Visual acuity control for many patients may be inadequate**
  - Current prn dosing (and even routine monthly/Q2 month dosing) regimens are effective for many patients, but a meaningful percentage still lose visual acuity (or fail to achieve optimal disease control).
  - AVA-101 showed a VA benefit in the Phase I study which could be reproduced in ongoing and future clinical trials which could meaningfully enhance its value-add.
  - AVA-101 may also effectively unlock other back-of-the-eye neovascular diseases such as DME (diabetic macular edema) & CRVO/BRVO (central/branch retinal vein occlusion) which together represent another multi-billion dollar commercial opportunity currently being addressed by anti-VEGF injections.

- **AVA-201 in the works to facilitate delivery**
  - Subretinal injections are more involved and can carry low risk of retinal tears/holes or hemorrhage.
  - AVA-201 is a novel AAV vector developed by AAVL to better target the retina, enabling delivery by intra-vitreous injection which is simpler.
  - Easier injection should help expand the market and potentially even enable development for preventing onset of wet AMD in high risk eyes (e.g. contralateral eye affected with additional risk factors).
  - Novel vector will improve upon intellectual property barriers for the technology.

Market Opportunities For AVA-101/201

- **Estimated AMD opportunity:**
  - 100K eyes treated/yr in the U.S.
  - US: $3B+ branded market; $6B+ if include off-label Avastin at branded prices.
  - Ex-US: $3B+ opportunity
  - **Low-hanging fruit:** AAVL market research indicates 25% of patients require 8-12 anti-VEGF injections/yr, representing a disproportionate share of value; an additional 55% require 4-7 injections/yr

- **Estimated DME opportunity:**
  - US: $1B market opportunity
  - Ex-US: $800M opportunity
  - Up to 250K new cases/yr in the U.S. but not all are treated with anti-VEGF agents.

- **Estimated Retinal Vein Occlusion opportunity:**
  - US: $500M market opportunity
  - Ex-US: $500M market opportunity
  - Up to 50K new cases/yr in the U.S.

In our model, we estimate AVA-101 reaching the market by 2020, reaching sales of ~$500M in 2024. We currently model penetration only into the wet AMD incidence, which may prove very conservative.

Next Steps For AVA-101/AVA-201

Development Path For AVA-101

- Phase 2a data: **mid-2015**
- File AVA-101 IND: **mid-2015**
- Initiate Phase 2b trial in the US: **2H15**
- Phase III: **2017/2018**
- Launch: **2020?**

Development Path For AVA-201

- IND-enabling studies: **2015**

AVA-311 and Beyond: Pipeline Also Holds Promise

- **AVA-311 for x-linked retinoschisis (partnered with REGN).**
  - Incidence of XLRS: 1:15,000 males.
  - US prevalence: 5,000-10,000+. EU prevalence comparable.
  - Congenital cause of blindness in which a defect in the retinoschisin protein causes a splitting of the retinal layers which leads to vision distortion and loss.
  - Orphan pricing opportunity.
  - **Preclinical development; early approaches with gene therapy have shown an ability to replace defective gene and correct retinal splitting in mice.**

- **Additional shots on goal to be identified.**
  - There are dozens of monogenic causes of blindness that could be targeted with gene therapy.
  - Even non-monogenic vision disturbances may be amenable to gene therapy if the platform is proven safe/effective.
  - We expect AAVL to continue to make progress advancing its current programs and also identifying new attractive opportunities with high unmet needs.

Validating Partnership With REGN

- **AVA-311 for x-linked retinoschisis already partnered with REGN**
  - Potential blockbuster opportunity.

- **Additional programs partnered with REGN**
  - REGN will develop up to eight products using AAVL's vectors, and AAVL will have the option to co-fund/profit share up to 2 of these products.
  - REGN also has the right to enter into exclusive negotiations to license AVA-101 following the Phase IIa data (although AAVL has no obligation to sign a deal)

We see the partnership with REGN as validating gene therapy for ophthalmic indications, AVA-101, and AAVL's vector evolution platform. It also highlights the 'modular' nature of gene therapy and the potential to develop multiple new programs for the eye. Also helps provide a source of funding for ongoing development.

Quick Introduction To The Competition

Gene Therapy Ophthalmology Companies				
Company	**Ticker**	**Lead Ophtho Program**	**Status**	**Comment**
Applied Genetic Technologies Corp	AGTC	XLRS	Entering P1/2	Closest competitor to AAVL, also using AAV vectors and evolving for optimal delivery. Gene therapy platform; also has a wet AMD program licensed to Genzyme/SNY but being returned.
Genzyme/Sanofi	SNY	wet AMD	P1/2	Data being presented next month; Genzyme returned the vector to AGTC but retains rights to the transgene. Despite an early first mover advantage in gene therapy, Genzyme's progress has been quite protracted and slow.
Oxford Biomedica	OX.LN	Wet AMD	P1	Genzyme/SNY decided not to pursue further efforts with lead wet AMD program (RetinoStat) but ongoing efforts with StarGen for Stargardt disease and UshStat for Usher syndrome. Oxford works with Lentivirus vector which has non-overlapping applications compared to AAVL's AAV vector.
Hemera Biosciences	Private	Wet, dry AMD	Preclinical	AAV vector to deliver CD59 gene to inhibit complement. Have identified application in dry AMD and possibly wet AMD.
Spark Therapeutics	Private	RPE65 blindness	P3	AAV vector platform also building out an ophthalomology pipeline in addition to non-ophthalmology efforts.
NighstarX	Private	Choroideremia	Entering P2/3	AAV vector gene therapy for choroideremia, program licensed from Oxford University and P1/2 data published in the Lancet.
Wet AMD Development Companies				
Company	**Ticker**	**Lead AMD Program**	**Status**	**Comment**
Regeneron	REGN	Eylea	Market	Leading wet AMD VEGF agent; REGN also has option to negotiate for AVA-101 after P2a data. Also has a PDGF antibody in P1.
Novartis	NVS	Lucentis	Market	Also has a 'next-generation' Lucentis (RTH258), single-chain VEGF antibody (ESBA1008) also being developed with Replenish delivery pump; an ex-U.S. partnership for OPHT's Fovista, a partnership with Ascendis for longer-acting Lucentis
Roche	RHGBY	Lucentis	Market	Also has RG7716 in Phase I; dual Ang-2/VEGF bispecific antibody.
Allergan	AGN	abicipar pegol (DARPin)	Entering P3 in 2015	Intravitreous VEGF-binding protein which may (or may not) offer differentiation over Eylea/Lucentis
Ophthotech	OPHT	Fovista	P3	Anti-PDGF aptamer, reported positive P2 results and now in P3 testing. Partnered with NVS ex-U.S.
Iconic	Private	hl-con1	Entering P2	Bifunctional protein which targets both choroidal neovasculature as well as immune cells to engage with the target.
PanOptica	Private	PAN-90806	Phase I	Topical anti-VEGF therapy
Ocular Therapeutix	OCUL	Anti-VEGF hydrogel	Preclinical	Unique PEG hydrogel to deliver sustained 6M release of anti-VEGF therapy

Source: Company reports

Gene therapy represents a unique value proposition in retinal diseases and AMD, although the field continues to evolve in a variety of different directions. Stay tuned…

Commercial-Scale Manufacturing Platform

Like QURE, AAVL employs insect cells, infected by a baculovirus expression vector system (BEVS).

What does that mean??

•Baculovirus is the most prominent virus known to affect the insect population and is **not pathogenic to humans.**

SAFETY

•Unlike the manufacturing process with mammalian cells, **BEVS is easily and cost-efficiently scaled up.**

EASE OF SCALE-UP

•BEVS enables the production of gene therapy, which **consistently delivers a high amount of the therapeutic effect.**

HIGH QUALITY GENE THERAPY PRODUCT

According to an article from the NIH, **"baculovirus-mediated production of AAV vectors in insect cells is especially well suited for the production of large quantities of AAV"** (R.Smith, *The American Society of Gene and Cell Therapy*, 2009).

Although similar to QURE's manufacturing approach, AAVL has developed a proprietary manufacturing method which only requires dual-infection of insect cells (in comparison to QURE's triple-infection approach), resulting in higher yields, greater efficiency, and cost savings.

Making an rAAV Vector

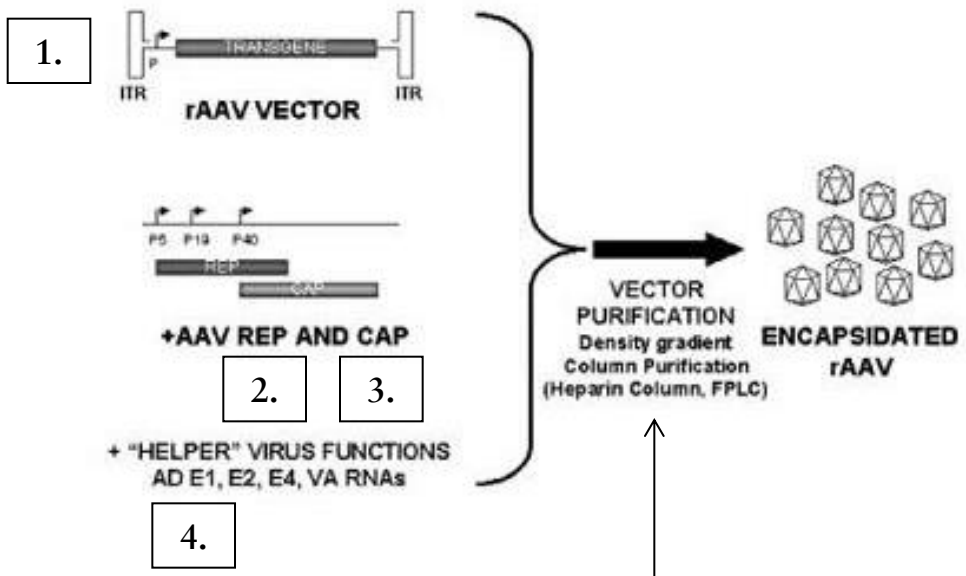
1. **The transgene**
   - Encodes the therapeutic protein.

2. ***rep* (replication) gene**
   - Contains the code for regulatory proteins involved in AAV genome replication.

3. ***cap* (capsid) gene**
   - Encodes for capsid (viral shell) proteins.

4. **Helper virus**
   - **The helper virus enables rAAV replication only during the manufacturing process.**
   - Examples are adenovirus (Ad), herpes-simplex virus (HSV), and baculovirus .

rAAV Vector Production



Source: http://www.vectorbiolabs.com/vbs/page.html?m=281

Purification (the removal of any contaminating viruses) is the most crucial step of the manufacturing process.

In the presence of the helper virus, therapeutic transgene (1) as well as the *rep* (2)and the *cap* (3) genes infect the manufacturing cells (baculovirus insect cells in the case of AAVL) to form the rAAV vector, which cannot replicate and contains the therapeutic transgene. Whereas QURE separates *rep* and *cap* into separate cassettes, AAVL combines them into one.

AAVL Has Built An Industry-Leading Team In Gene Therapy And Ophthalmology

Thomas Chalberg, PhD	**Founder and CEO**	• Genentech • Hope for Vision
Linda Bain, CFA	**CFO**	• Deloitte • AstraZeneca • Genzyme • BLUE
Samuel Barone, MD	**CMO**	• FDA • Practicing ophthalmologist
Hans Hull, JD	**VP Legal and Corporate Development**	• Heller Ehrman, LLP • Orthobond • Second Genome
Mehdi Gasmi, PhD	**VP Pharmaceutical Development**	• Chiron • Cell Genesys • Ceregene • Genethon

Source: AAVL

AAVL has built a management team that is experienced in vector technology, gene therapy for ophthalmology, as well as the manufacturing and regulatory processes for gene therapy. The strength of this team only enhances the company's upside potential and future opportunities.

Questions From The Roadshow #1: What About AGTC?

We had the opportunity to speak with a large number of investors during the AAVL IPO roadshow. The most frequently asked question was, "what about AGTC?"

- **Developing similar approach for wet AMD, licensed to Genzyme/SNY**
  - Also AAV-2, using synthetic sFlt-1 instead of natural.
  - Most important difference is using intravitreal delivery instead of subretinal.

- **Recent and pending updates for AGTC program**
  - GENZ returned the AAV-2 vector but retained the sFlt-1 transgene cassette.
  - Unclear what GENZ plans to do, but may pursue a new viral vector similar to AAVL and AGTC in order to optimize for intravitreal delivery.
  - We will get Phase I data at a medical conference in September.
  - AGTC now has the potential and plans to pursue its own optimized viral vector for intravitreal delivery.

- **Our view: Everyone can win!**
  - This is a blockbuster market opportunity even if one only considers disease incidence and not prevalence.
  - There are three main anti-VEGF products in the market currently; plenty of room for similar players.
  - If the Genzyme/AGTC data is 'very' positive, it validates the intravitreous approach and AAVL can pursue this with AVA-101 and AVA-201, so it's a positive read-through to AAVL.
  - If the Genzyme/AGTC data is negative or inadequate, it highlights the need to further evolve the AAV vector while pursuing a subretinal approach with AVA-101.
  - We do not expect the Genzyme data to be a home-run (why would they return the vector?) but it may provide additional credence to gene therapy as a platform for wet AMD.
  - AGTC may be able to re-partner its wet AMD program and re-enter the competitive race.

Will be an important program to watch but there is plenty of room for multiple players.

Questions From The Roadshow # 2: Why Are You So Confident?

We had the opportunity to speak with a large number of investors during the AAVL IPO roadshow. The second most frequently asked question was, "what gives you so much confidence with so few patients worth of data"?

- **The beauty of gene therapy is that often programs can derisk very early in development.**
  - We believe this is the case with AVA-101.
- **Proven mechanism.**
  - We know targeting VEGF is a highly effective modality for wet AMD. Eylea is also a sFlt1 construct.
- **Positive preclinical data.**
  - Animal models prove the basic science and are a high quality model for wet AMD.
- **Positive clinical data.**
  - While the patient numbers were small, the fact that they were "treatment addicts" puts them on the severe end of the spectrum, so seeing a rapid and sustained reduction in Lucentis re-injection frequency in this many patients is highly compelling.
  - One successful patient would be suggestive, but not conclusive. 6/6 is now moving toward conclusive evidence.
  - The retinal imaging findings further validate the clinical effect.
- **Validation of gene therapy for ophthalmology.**
  - Can't look at AVA-101 in a vacuum, need to appreciate that the general approach is also derisked by the experience in choroideremia and RPE65.

Despite it being early, we are comfortable that the signal represents a true clinical effect. Less certain is whether the visual acuity benefit will be repeated in P2; we suspect it will be but it's not a requisite for clinical/commercial success.

Questions From The Roadshow # 3: What About Safety?

We had the opportunity to speak with a large number of investors during the AAVL IPO roadshow. The third most frequently asked question was, "what about safety"?

- **Gene therapy is still a new platform for ophthalmology applications**
  - Ultimately will need to generate large volume of safety data, but there is a growing experience that highlights the safety of gene therapy.
  - One might consider the immunogenicity and inflammatory risks associated with the viral vector, but if they occur should be self-limited and amenable to treatment with topical steroids.
- **What happens with sustained chronic VEGF suppression?**
  - More informed investors specifically ask about risk of geographic atrophy since the CATT studies suggested patients who required the heaviest anti-VEGF exposure were the ones at increased risk of geographic atrophy (advanced form of dry AMD which can result in visual acuity loss).
  - It's unclear if the increased risk in geographic atrophy reflected a more severe underlying wet AMD condition or if it was a result of the increased requirement for anti-VEGF therapy.
  - If increased anti-VEGF injections are indeed associated with geographic atrophy it's unclear if this has to do with the high peak levels from the regular bolus injections or if it would be seen with chronic, lower levels of suppression.
  - This was not a problem in the clinical or preclinical experience with AVA-101.
  - If the visual acuity benefits of AVA-101 are reproduced, most patients would accept the trade-off of near-term vision loss for a slight risk of long-term vision deterioration.
- **There IS turning back:**
  - AAVL has developed a unique photodynamic laser software program that delivers a burst of laser activity to the retina to cause cellular proliferation which dilutes out the gene therapy effect without harming the eye. If longer-term sequelae emerge, the procedure can effectively be 'reversed.'

Questions From The Roadshow # 4: Risk/Reward?

We had the opportunity to speak with a large number of investors during the AAVL IPO roadshow. The fourth most frequently asked question was, "how do we think about the risk/reward profile"?

- **Most investors quickly appreciated the binary aspect of the opportunity:**
  - Given the size of the wet AMD market and the residual unmet need, success with AVA-101/201 as well as the pipeline could represent enormous upside.
  - The partnership with REGN was seen as providing validation and also helping emphasize the emerging pipeline opportunity so that the investment decision does not rest entirely on AVA-101/201 for wet AMD.
  - But as a new paradigm and still a single product company for the most part, investors also realized that downside could be considerable (80%+) if any of the programs stumble.
- **What's the probability of success? What's the implied probability of success?**
  - For a stock with enormous potential upside but potential for 80% downside, we believe the implied probability of success is far less than 50/50.
  - But obviously investors are risk-averse and tend to over-weight downside risks, plus the downside is a much nearer-term probability while the upside will take much longer to accrue.
  - In this type of scenario where there aren't obvious signals to worry about but the program does need to go through a full development derisking process, investors often wind up consider odds of success a 'coin toss' which in this case would have a risk/reward skewed massively to the upside.
- **How do we think about valuation?**
  - Can consider the risk/reward implied probability of success, can consider comparable companies, can also build a DCF.

We see the risk-reward as compelling as long as investors are cognizant of the risks involved with an early stage program

Questions From The Roadshow: What Wasn't Asked

We had the opportunity to speak with a large number of investors during the AAVL IPO roadshow. Interestingly, few investors focused on a couple of key questions which we think are important to consider:

- **Was the benefit in visual acuity seen in the Phase I study likely a real signal?**
  - The small study was primarily designed to evaluate whether AVA-101 could safely reduce the number of Lucentis injections in 'treatment-addicts'
  - In addition to demonstrating a significant improvement in injection frequency, there also appeared to be a gain in visual acuity with AVA-101 compared to the control arm.
  - We do not think it is a requirement for AVA-101 to improve vision over the standard of care, but if it is reproduced it would be a very important differentiating feature.
  - PRN dosing of anti-VEGF agents by definition misses some active disease because specialists are waiting for it to return before treating again. Over time, it's possible that the scarring or fibrosis from these intervals of active disease lead to poorer visual acuity, whereas perpetual exposure to anti-VEGF via AVA-101 might prevent this.
  - We'll see if it is seen in the next P2 study; since there are no expectations for success, we do not see downside to shares if it is not achieved.

- **What about the other opportunities for AVA-101/201?**
  - AAVL does intend to explore the role of these therapies in DME, RVO.
  - If AAVL succeeds in developing an intravitreous gene therapy program with AVA-201, it could unlock a large market opportunity for patients at high risk for wet AMD.
  - Waiting for AMD signs/symptoms to develop may entail waiting until some permanent vision loss has occurred. If a safe/effective method for pre-emptive this can be identified, the market could expand considerably.

AAVL: Comparable Valuation

- Best comps to AAVL in our view are gene therapy and ophthalmology companies

AAVL COMP TABLE							
Ticker	**Company**	**Description**	**Stock price**	**Mkt Cap**	**Cash**	**Shares**	**EV**
GENE THERAPY							
AGTC	AGTC	Gene therapy for ophthalmology	$18.43	$296	70	16	$226
BLUE	bluebird	Gene therapy platform, orphan dise	$35.51	$1,015	190	24	$825
QURE	uniQure	Gene therapy for orphan diseases	$11.30	$199	75	18	$124
KITE	Kite	CAR-T	$22.06	$845	185	30	$660
SGMO	Sangamo	Gene editing platform	$13.27	$905	245	63	$660
XON	Intrexon	Gene manipulation	$19.75	$1,984	425	100	$1,559
OPHTHALMOLOGY							
AERI	Aerie	Phase III glaucoma asset	$16.87	$403	65	24	$338
OCUL	Ocular Ther.	Ocular drug delivery platform	$15.80	$325	83	21	$242
OPHT	Ophthotech	Phase III wet AMD program	$36.51	$1,223	290	33	$933
Average				**$799**			**$619**
AAVL			**$30.15**	**$644**	**150**	**21**	**$494**
Upside to average				**24%**			**25%**
Sources: Company Reports, FactSet, Piper Jaffray analyst							

Source: FactSet
Pricing as of the close of 8/22/14

Our comps focus on pure-play gene therapy companies (AGTC, BLUE, KITE, SGMO, QURE), and ophthalmology companies (AERI, OCUL, OPHT).

AAVL Upcoming Catalysts				
Program	**Indication**	**Type**	**Event**	**Expected Timing**
AVA-101	wet AMD	Clinical	P1 data from AGTC/Genzyme intravitreous gene therapy study	Sept 2014 (Retina Society)
		Clinical	Additional P1 data from AGTC/Genzyme intravitreous gene therapy study	Oct 2014 (AAO)
		Clinical	P2a data, AVA-101 subretinal	Mid-2015
		Commercial	REGN 45d exclusivity to discuss licensing	Mid-2015
		Regulatory	File IND	Mid-2015
		Clinical	Start P2b study in U.S.	2H15
AVA-201	wet AMD	Clinical	File IND	2016
AVA-311	XLRS	Clinical	File IND	2016

Source: PJC and Company reports

AAVL DCF Analysis (2014-2024 CF Estimates)	
Discounted Cash Flow (DCF) Analysis	
Assumed Discount Rate (%)	*11.0%*
Terminal Growth Rate (%)	*5.0%*
Implied Terminal Year FCF Multiple	**17.5x**
NPV of FCF	**$1,005**
Cash/equiv	*$150*
Price Target	**$39**
Target valuation	$1,155
Shares Outstanding 2017E (million)	30.0

Source: PJC estimates

AAVL Valuation Sensitivity Analysis					
		Discount Rate			
		10%	**11%**	**12%**	**13%**
Terminal Growth	**3.0%**	$36	$28	$23	$18
	4.0%	$42	$33	$26	$21
	5.0%	$51	**$39**	$30	$23
	6.0%	$65	$47	$35	$27
	7.0%	$87	$59	$42	$32

Source: PJC estimates

AAVL Potential Upside From Current Levels					
		Discount Rate			
		10.0%	11.0%	12.0%	13.0%
Terminal Growth	**3.0%**	20%	(6%)	(25%)	(39%)
	4.0%	41%	8%	(14%)	(31%)
	5.0%	71%	**28%**	(1%)	(22%)
	6.0%	115%	55%	16%	(10%)
	7.0%	190%	95%	40%	6%

Source: Company Reports and Piper Jaffray.

AAVL QUARTERLY P&L											
	2013A	**1Q14A**	**2Q14E**	**3Q14E**	**4Q14E**	**2014E**	**1Q15E**	**2Q15E**	**3Q15E**	**4Q15E**	**2015E**
Product Revenue/Royalty	$0	$0	$0	$0	$0	0.0	$0	$0	$0	$0	0
Funding/milestones	0.5	0.0	2.0	2.0	2.0	6.0	3	3	3	3	12
Total Revenue	**$0.5**	**$0.03**	**$2.00**	**$2.00**	**$2.00**	**$6**	**$3**	**$3**	**$3**	**$3**	**$12**
COGS	0	0	0	0	0	0	0	0	0	0	0
% product sales	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
R&D	2	1	3	4	4	12	6	7	8	9	30
% revenue	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*
SG&A	2	1	2	2	2	6	2	2	2	2	6
% revenue	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*	*N/M*
Total operating expenses	**4**	**2**	**5**	**6**	**6**	**18**	**8**	**9**	**10**	**11**	**36**
Interest/other	-2	0	0	0	0	0	0	0	0	0	1
Pretax income	($5)	($2)	($3)	($4)	($4)	($12)	($4)	($5)	($6)	($7)	($23)
Taxes	0	0	0	0	0	0	0	0	0	0	0
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net income	**-5**	**-2**	**-3**	**-4**	**-4**	**-12**	**-4**	**-5**	**-6**	**-7**	**-23**
EPS	**($0.74)**	**($0.11)**	**($0.17)**	**($0.16)**	**($0.16)**	**($0.61)**	**($0.18)**	**($0.22)**	**($0.26)**	**($0.30)**	**($0.97)**
Shares	7	15	18	22	22	19	23	24	24	25	24

Sources: Company Reports and Piper Jaffray

Joshua Schimmer: 212-284-9322

AAVL ANNUAL PRODUCT MODEL												
	2013A	**2014E**	**2015E**	**2016E**	**2017E**	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
AVA-101 Status	P1	P2a	P2b	P2b	P3	P3	Filing	Launch	Market	Market	Market	Market
AVA-201 Status	N/A	Preclin	Preclin	P1	P2	P2	P3	P3	Filing	Launch	Market	Market
AVA-311 Status	N/A	Preclin	Preclin	P1	P2/3	P2/3	P2/3	Filing	Launch	Market	Market	Market
Wet AMD eyes/yr, U.S. (000s)	**100**	**100**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**
High frequency injection eyes	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
High frequency 101/201 penetr.	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*8%*	*20%*	*35%*	*45%*
Mid frequency injection eyes	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*
Mid frequency 101/201 penetr.	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*1%*	*2%*	*4%*	*8%*	*12%*
AVA-101/201 injections (000s)	0	0	0	0	0	0	0	0	3	8	14	20
AVA-101/201 price/Rx (000s)	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25	$25
AVA-101/201 Sales (mm)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$7**	**$83**	**$195**	**$360**	**$493**
OUS AVA-101/201 Sales (mm)	0	0	0	0	0	0	0	0	0	50	100	200
% Avalanche Royalty on OUS	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
AVA-101/201 Royalty, OUS (mm)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$8**	**$15**	**$30**
XLRS patients, W/W	20	20	20	20	20	20	20	20	20	20	20	20
AVA-311 penetration	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*1%*	*3%*	*4%*	*6%*
AVA-311 price/Rx (000s)	$150	$150	$150	$150	$150	$150	$150	$150	$150	$150	$150	$150
AVA-311 sales	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$30**	**$90**	**$120**	**$180**
% Avalanche Royalty on AVA-311	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*11%*
AVA-311 Royalty	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$3**	**$9**	**$12**	**$20**

Sources: Company Reports and Piper Jaffray

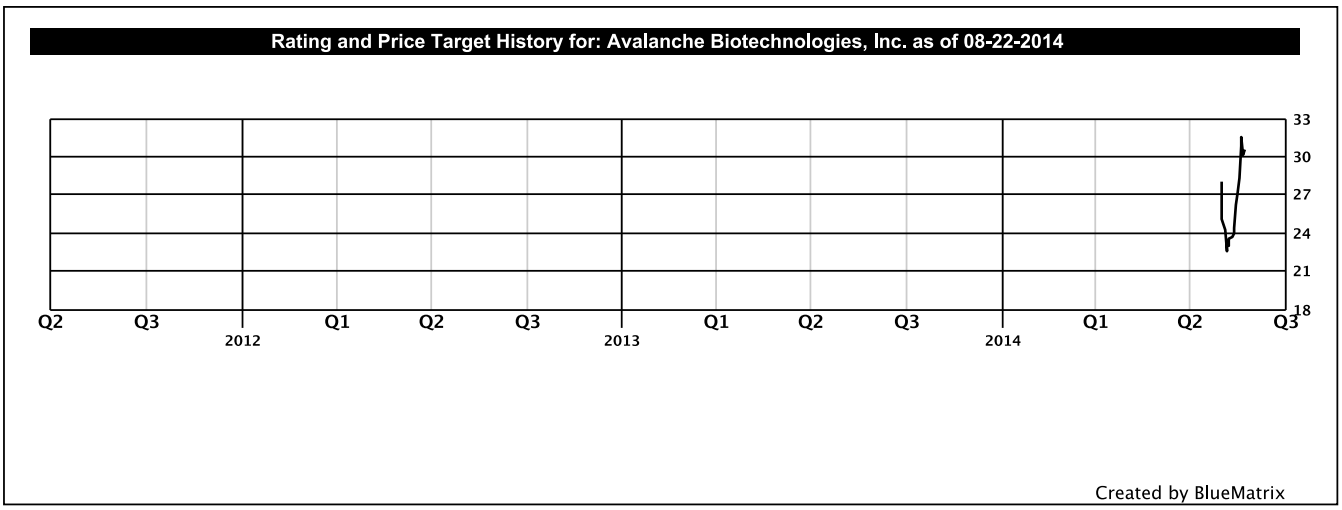
AAVL ANNUAL P&L												
	2013A	**2014E**	**2015E**	**2016E**	**2017E**	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Product Revenue/Royalty	$0	0.0	0	$0	$0	$0	$0	$7	$86	$211	$387	$543
Funding/milestones	0.5	6.0	12	12	12	12	12	12	12	12	12	12
Total Revenue	**$0.5**	**$6**	**$12**	**$12**	**$12**	**$12**	**$12**	**$19**	**$98**	**$223**	**$399**	**$555**
COGS	0	0	0	0	0	0	0	1	8	19	36	49
% product sales	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
R&D	2	12	30	40	60	80	80	65	75	80	85	90
% revenue	*N/M*	*N/M*	*N/M*	*333%*	*500%*	*667%*	*667%*	*337%*	*76%*	*36%*	*21%*	*16%*
SG&A	2	6	6	8	10	10	12	80	100	125	135	145
% revenue	*N/M*	*N/M*	*N/M*	*67%*	*83%*	*83%*	*100%*	*415%*	*102%*	*56%*	*34%*	*26%*
Total operating expenses	**4**	**18**	**36**	**48**	**70**	**90**	**92**	**146**	**183**	**224**	**256**	**284**
Interest/other	-2	0	1	1	1	1	1	1	1	2	4	6
Pretax income	($5)	($12)	($23)	($35)	($57)	($77)	($79)	($125)	($84)	$1	$147	$276
Taxes	0	0	0	0	0	0	0	0	0	0	37	69
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*25%*	*25%*	*25%*
Net income	**-5**	**-12**	**-23**	**-35**	**-57**	**-77**	**-79**	**-125**	**-84**	**1**	**110**	**207**
EPS	**($0.74)**	**($0.61)**	**($0.97)**	**($1.35)**	**($1.90)**	**($2.41)**	**($2.08)**	**($3.14)**	**($2.01)**	**$0.02**	**$2.29**	**$4.15**
Shares	7	19	24	26	30	32	38	40	42	46	48	50

Sources: Company Reports and Piper Jaffray

AAVL STATEMENT OF CASH FLOWS												
	2013A	**2014E**	**2015E**	**2016E**	**2017E**	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Net Income	-5	-12	-23	-35	-57	-77	-79	-125.43	-84	1	110	207
Depreciation	0	0	0	0	0	0	0	0	0	0	0	0
Stock based comp	1	5	8	10	12	14	16	18	20	22	24	25
Other	2	0	0	0	0	0	0	0	0	0	0	0
Change in NWC	0	-3	-4	-4	-5	-10	-15	-15	-15	-15	-15	0
Cash from operations	**-3**	**-9**	**-19**	**-29**	**-50**	**-73**	**-78**	**-122.43**	**-79**	**8**	**119**	**232**
PP&E	0	0	0	-2	-2	-2	-2	-2	-2	-2	-2	-2
Free cash flow	**-3**	**-9**	**-19**	**-31**	**-52**	**-75**	**-80**	**-124.43**	**-81**	**6**	**117**	**230**
Financing Cash	**0**	**153**	**0**	**0**	**125**	**0**	**175**	**0**	**0**	**0**	**0**	**0**
Cash start	0	0	144	125	94	167	92	187	62	-19	-13	103
Cash end	**1**	**144**	**125**	**94**	**167**	**92**	**187**	**62**	**-19**	**-13**	**103**	**334**

Sources: Company Reports and Piper Jaffray

IMPORTANT RESEARCH DISCLOSURES



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I: Initiating Coverage
R: Resuming Coverage
T: Transferring Coverage
D: Discontinuing Coverage
S: Suspending Coverage
OW: Overweight
N: Neutral
UW: Underweight
NA: Not Available
UR: Under Review

Distribution of Ratings/IB Services
Piper Jaffray

			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OW]	363	61.73	97	26.72
HOLD [N]	214	36.39	22	10.28
SELL [UW]	11	1.87	0	0.00

Note: Distribution of Ratings/IB Services shows the number of companies currently in each rating category from which Piper Jaffray and its affiliates received compensation for investment banking services within the past 12 months. FINRA rules require disclosure of which ratings most closely correspond with "buy," "hold," and "sell" recommendations. Piper Jaffray ratings are not the equivalent of buy, hold or sell, but instead represent recommended relative weightings. Nevertheless, Overweight corresponds most closely with buy, Neutral with hold and Underweight with sell. See Stock Rating definitions below.

Analyst Certification — Joshua E. Schimmer, MD, Sr Research Analyst
— Jerry Yang, Ph.D., Research Analyst

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