COMPANY NOTE

Initiating Coverage

USA | Healthcare | Biotechnology

August 25, 2014

Jefferies

Avalanche Biotechnologies (AAVL)

Initiate at Buy: AAVL Gene Therapy Has Disruptive Potential in Wet AMD

BUY
Price target $40.00
Price $30.52

EQUITY RESEARCH AMERICAS

Key Takeaway

AAVL shares hold significant promise based on PI data with AVA-101 observing meaningful VA improvements and durable responses in wAMD patients, which supports a favorable outlook for the PIIa study expected in mid-'15. A successful outcome would further validate AAVL's gene therapy platform. Further upside may come from 2 additional programs, AVA-201 for wAMD prevention and AVA-311 for XLRS, in preclinical development. We initiate with a Buy rating and $40 PT.

Jefferies was joint book-running manager in AAVL's IPO in July 2014.

AVA-101 Offers Curative Potential in wAMD: AAVL's lead candidate is AVA-101, a one-time subretinal injection which offers durable remission for pts with wAMD. AVA-101 induces the retinal cells to produce sFlt-1, a naturally occurring VEGF inhibitor and clinically validated target. AVA-101 has shown impressive efficacy and safety results from 8 pts from its PI study. Mean VA improvement in the +12.2 and +9.8 letters for the low- and high-dose, respectively, v. control at wk 52. Impressively, fewer pts on AVA-101 required Lucentis re-tx relative to the control (0.33 v. 3.0, respectively) ($p<0.001$). Moreover, the effect appears durable lasting >12 mos, and potentially for many years. The PIIa trial has enrolled 32 pts, and we await topline data in mid-'15. AAVL also has potential to expand into DME and CRVO.

AVA-101 Role in Wet AMD: Anti-VEGF therapy dominates as the preferred tx of choice in wet AMD with current U.S. market size of ~$7-8B. AVA-101 could potentially displace regular anti-VEGF injections and could be preferred tx of choice in wAMD. We estimate AVA-101 may launch in 2020 and could generate a risk-adjusted $600M in peak U.S. sales (assuming 70% discount) in wAMD. Additional sales may also come from two add'l indications, CRVO and DME, which could generate $725M in risk-adjusted peak U.S. sales. Ex-U.S., we estimate peak risk-adjusted royalties of $120M, and do not include potential upfront payments/ milestones from an ex-U.S. partnership.

Additional Early-Stage Opportunities: AAVL is also developing AVA-201 for wAMD prevention, designed to deliver the sFlt-1 gene but with a different AAV vector. AVA-201 has demonstrated efficacy through prevention of choroidal neovascularization in primates. AAVL is also developing AVA-311 for XLRS in preclinical stages. We do not yet model these products, which represent upside.

Valuation/Risks

Our $40 PT is DCF-based. Risks include clinical, manufacturing, competitive, regulatory, and commercial.

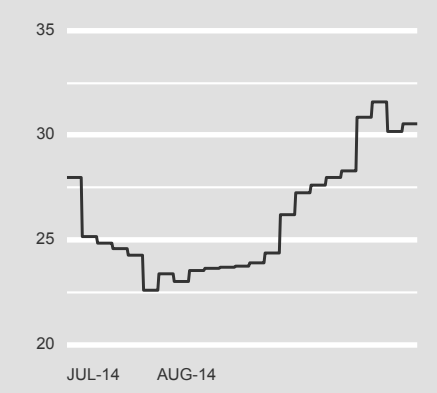
Financial Summary	
Net Debt (MM):	($159.9)
Long-Term Debt (MM):	$0.0
Cash & ST Invest. (MM):	$159.9
Cash/Share:	$6.01
Cash (MM):	$159.9

Market Data	
52 Week Range:	$32.38 - $22.00
Total Entprs. Value (MM):	$651.9
Market Cap. (MM):	$811.8
Shares Out. (MM):	26.6
Float (MM):	5.3
Avg. Daily Vol.:	NA

USD	Prev.	2013A	Prev.	2014E	Prev.	2015E	Prev.	2016E
Rev. (MM)	--	0.5	--	0.0	--	2.0	--	0.0
EV/Rev		NM				NM		
EPS								
Mar	--	--	--	(0.11)A	--	--	--	--
Jun	--	--	--	(0.08)A	--	--	--	--
Sep	--	--	--	(0.14)	--	--	--	--
Dec	--	--	--	(0.27)	--	--	--	--
FY Dec	--	(1.45)	--	(0.61)	--	(0.72)	--	(0.79)
FY P/E		NM		NM		NM		NM

Biren Amin *
Equity Analyst
(212) 284-8162 bamin@jefferies.com
Hugo Ong, Ph.D. *
Equity Associate
(212) 323-3364 hong@jefferies.com
* Jefferies LLC

Price Performance



Avalanche Biotechnologies

Buy: $40 Price Target

THE LONG VIEW

Scenarios

Target Investment Thesis

- Positive outcome for AVA-101 in PIIa trial for wAMD in mid-2015, and subsequent PIIb trial and PIII program
- We expect U.S. approval of AVA-101 for wAMD in 2020 and peak sales of $602M by 2026 (risk-adj)
- We expect AVA-101 expansion into DME and CRVO in 2022 and peak sales of $716M by 2026 (risk-adj)
- DCF-based PT: $40

Upside Scenario

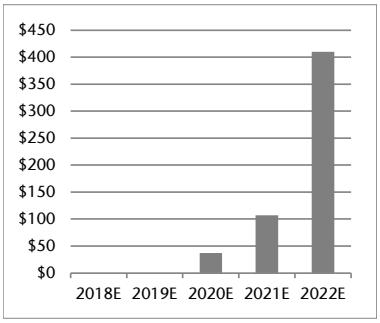
- De-risked AVA-101 program through Phase II/III trial datasets for wAMD, DME and CRVO
- DCF-based PT: $135
- Successful development of AVA-201 for wAMD (prevention) and AVA-311 for XLRS
- DCF-based PT: $250

Downside Scenario

- Negative outcome for AVA-101 in DME and CRVO
- DCF-based PT: $19
- Negative outcome for AVA-101 in all ophthalmic diseases
- Cash-based PT: $6

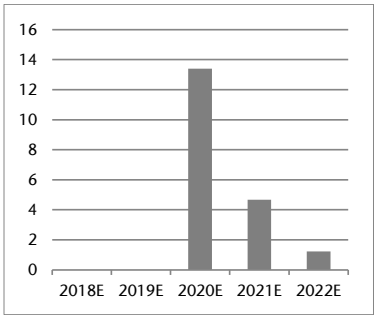
Long Term Analysis

Revenue (millions)



Source: Company data; Jefferies estimates

Enterprise Value (EV)/Sales



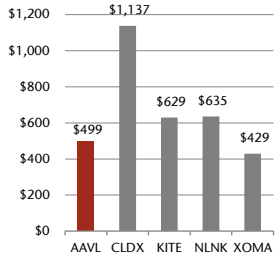
Source: Company data; Jefferies estimates

Other Considerations

We consider small-cap and mid-cap biotech companies with late-stage programs to continue to be attractive targets for partnering or M&A partnering with large-cap biotech and pharma companies, which we believe will be a driving factor for performance in the biotech sector 2014-2015.

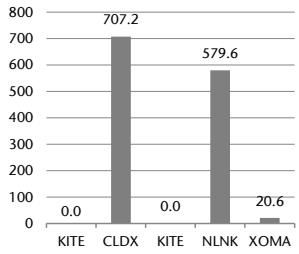
Peer Group

Group EV



Source: Factset, Jefferies estimates

Group EV/2014E Sales



Source: Factset, Jefferies estimates

Recommendation / Price Target

Ticker	Rec.	PT
AAVL	**Buy**	**$40**
CLDX	Buy	$31
KITE	Buy	$35
NLNK	Buy	$34
XOMA	Buy	$9

Catalysts

- Topline data for AVA-101 for Phase IIa trial in mid-2015
- IND filing for wAMD in H2 2015
- Initiation of Phase IIb trial in H2 2015

Company Description

Avalanche Biotechnologies, Inc. is a biotechnology company focused on the discovery and development of novel gene therapies for sight-threatening ophthalmic diseases. It has leveraged its gene therapy platform, Ocular BioFactory, to create a pipeline of product candidates. AAVL's lead candidate is AVA-101 for wet AMD, which is a gene therapy product that utilizes AAV2 to deliver the gene for sFlt-1, a naturally-occurring VEGF inhibitor. AVA-101 has generated proof-of-concept data in eight patients in a Phase I trial. AAVL may also expand AVA-101 into DME and CRVO. AAVL is also developing AVA-201 for wAMD (prevention) and AVA-311 for juvenile X-linked retinoschisis (XLRS).

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Executive Summary

Avalanche Biotechnologies is a biopharmaceutical company focused on the discovery and development of novel gene therapies for sight-threatening ophthalmic diseases. It has leveraged its gene therapy platform, Ocular BioFactory, to create a pipeline of product candidates. AAVL's lead candidate is AVA-101 for the treatment of wet AMD, which is a gene therapy product that utilizes AAV2 as its vector to deliver the gene for sFlt-1, a naturally-occurring VEGF inhibitor. Wet AMD is an established market of $3.5-4.0 billion per year in the U.S. (on branded products alone) where cost and treatment burden are high, and AVA-101 may be able to differentiate as a single-injection with long and durable responses. To date, AVA-101 has generated impressive proof-of-concept data in eight patients in a Phase I trial with meaningful improvements in mean visual acuity and duration of >12 months. The Phase IIa trial has enrolled 32 patients, and we await topline data expected in mid-2015 to confirm earlier findings. Assuming the trial is successful, AAVL may also expand AVA-101 into DME and CRVO which are also significant markets. Success in AVA-101 would also validate AAVL's gene therapy platform that would bode well for its developing pipeline, including AVA-201 for wAMD (prevention) and AVA-311 for juvenile X-linked retinoschisis (XLRS). We are initiating AAVL with a Buy rating and $40 PT.

- **It's Prime Time for Gene Therapy.** AAVL's proprietary Ocular BioFactory platform uses gene therapy to enable the patient's own cells via an AAV-vector to continuously express the desired therapeutic protein for a durable period of time. Historically, viral vectors have had a tumultuous journey given their potential for infection, insertional mutagenesis, and/or acquired immune response. But the eye is an immune-privileged site and significant strides have been made in the field that now make gene therapy a clinically viable strategy, and AAVL is taking the lead in vascular ophthalmic diseases with products that can be delivered with only a single-injection and have curative potential. AAVL's BioFactory platform consists of two key proprietary components: novel vector screening and optimization system (directed evolution) and an industrialized manufacturing process. Through directed evolution, AAVL can generate a diverse library of millions of AAV variants through mutagenesis and screen the variants in multiple in vitro and in vivo tests to identify the optimal variant. AAVL's proprietary baculovirus expression system (BVES) is efficient and scalable, with production yields up to 100x greater than those obtained by conventional AAV production system. AAVL's BVES system allows it to manufacture commercial grade production for large markets such as wAMD. Lastly, although no gene therapy product has yet been approved in the U.S., the FDA has published guidance for gene therapy products for retinal disorders that helps provide regulatory clarity for this technology.

- **AVA-101 Offers Curative Potential in wAMD.** AAVL's lead candidate is AVA-101, a one-time subretinal injection which offers a potential cure (i.e. durable remission) for patients with wAMD. As a gene therapy product, AVA-101 induces the patient's own retinal cells to produce sFlt-1, a naturally occurring endogenous VEGF inhibitor. Given the experience of REGN's (REGN, $341.51, Hold) Eylea and (ROG VX, CHF265.90, Buy) Lucentis, VEGF is a clinically validated target for the treatment of wAMD. Given current trajectories of Eylea and Lucentis into 2014, we approximate the U.S. branded anti-VEGF market for wAMD to be ~$3.5-4.0 billion. Including off-label Avastin (if Avastin were at branded price), the anti-VEGF market for wAMD is ~$7.0-8.0 billion, which is a substantial market for AVA-101. To date, AVA-101 has shown impressive efficacy and safety results from eight patients from its Phase I study. Mean visual acuity (VA) improvement from baseline in the low-dose group

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

was +8.7 letters at week 52 and +12.2 letters relative to the control. For the high-dose, the improvement was +6.3 and +9.8 letters, respectively. Impressively, fewer patients on AVA-101 required Lucentis re-treatment relative to the control (0.33 v. 3.0, respectively), and the result was statistically significant on a small number of patients. Moreover, the benefit appears durable with effects lasting >12 months in the eight patients to date, and potentially for many years. The Phase IIa trial has enrolled 32 patients, and we await topline data expected in mid-2015 to confirm earlier findings. We also see upside in other vascular ophthalmic diseases as DME and CRVO.

- **Additional Early-Stage Opportunities Are Available To AAVL:** AAVL is also developing AVA-201 for wAMD prevention, which is designed to deliver same sFlt-1 expressing gene as AVA-101 but uses a different AAV vector delivery method optimized through AAVL's directed evolution platform. AVA-201 has demonstrated efficacy through long-term prevention of choroidal neovascularization in non-human primates, and remains to be corroborated in human trials. Though early stage, AVA-201 has the same disruptive potential to the wAMD market as AVA-101. AAVL is also developing AVA-311 for juvenile X-linked retinoschisis in preclinical stages. We do not yet include AVA-201 or AVA-311 in our model, and represent upside to our estimates.

Valuation

We arrive at our $40 price target based on a DCF valuation model, which assumes a WACC of 14%, terminal growth rate of 0% and outstanding shares of 26.8 million, driven by sales of AVA-101. We assume market entry for AVA-101 for wet AMD in 2020 assuming positive data from a Phase III program. We estimate peak sales of $4.4 billion in the U.S. by 2026 for ophthalmic diseases including wet AMD, DME, and CRVO on an unadjusted-basis. If we apply a 70% risk discount to reflect the clinical risk of the AVA-101 program, we estimate $1.3 billion in U.S. sales by 2026. Additionally, we expect $79 million in royalty revenue for the same indications in 2026 using an 70% risk-discount.

AAVL's initial target population for AVA-101 will be wAMD. We estimate peak sales of $2.0 billion in the U.S. by 2026 for wAMD on an unadjusted-basis. Applying a 70% risk discount to reflect the clinical risk of the AVA-101 program, we estimate $602 million in U.S. sales by 2026. AAVL intends to expand AVA-101 into CRVO and DME, and we assume market entry for these indications in 2022. For CRVO, we estimate peak U.S. sales of $510 million (unadjusted) and $153 million in 2026 (70% risk-discount). For DME, we estimate peak U.S. sales of $1.9 billion (unadjusted) and $573 million by 2025 (70% risk-discount).

For rest-of-world (ROW), we estimate peak sales of $783 million for wAMD by 2025 (unadjusted). We assume a 20% royalty for ROW sales and a 70% risk discount, translating to peak royalty revenue $47 million in 2025. For CRVO, we estimate peak ROW sales of $292 million in 2026 (unadjusted). Assuming a 20% royalty and 70% risk-discount, we estimate peak ROW sales of $18 million in 2026. For DME, we estimate peak ROW sales of $1.0 billion by 2025 (unadjusted). Under the same assumptions as wAMD and CRVO, we estimate peak ROW sales of $60 million in 2025 in DME.

At this time, we do not model AVA-201 for wAMD or AVA-311 for juvenile X-linked retinoschisis (XLRS), and these products represent upside. We expect R&D expense to reach $12 million by YE 2014, increasing to $55 million by 2026 as AAVL ramps up clinical development of AVA-101 into DME and CRVO, AVA-201 and AVA-311. We expect SG&A expense to be $2.9 million by YE 2014, increasing to $43 million by 2026. We include $25 million in launch expenses for AVA-101 in 2021, risk-adjusted by 70%.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 1: DCF sensitivity analysis

Equity Value	Price/Share
$1,528.2	$56.95
$1,277.4	$47.60
$1,074.9	**$40.06**
$910.7	$33.94
$777.0	$28.96

Source: Jefferies estimates

Risks

Clinical Failure: As with all companies in biotechnology and pharmaceuticals developing treatments of the future, a clinical failure can lead to delays in approval or possibly discontinuation of programs.

Regulatory Failure: The FDA could determine the Biologic Licensing Application is inadequate for AVA-101 for wet AMD and could delay approval. Furthermore, to date the FDA has not approved any gene therapy products for any indication. There is therefore no historical precedence for approval of such products, and the FDA may deem AAVL's clinical package for AVA-101 as insufficient for approval. Any delays in approval timelines could impact our earnings estimates, price target, and/or rating.

Commercial Failure: We currently estimate peak sales of $4.4 billion in the U.S. by 2026 for ophthalmic diseases including wet AMD, DME, and CRVO on an unadjusted-basis. If we apply a 70% risk discount to reflect the clinical risk of the AVA-101 program, we estimate $1.3 billion in U.S. sales by 2026. Additionally, we expect $79 million in royalty revenue for the same indications in 2026 using an 80% risk-discount. Our estimates may rely on the success of the company/partners to receive drug reimbursement from private/public payors.

Manufacturing Risks: AAVL relies on its proprietary baculovirus expression system (BVES) to produce its gene therapy products, including AVA-101. AAVL believes its BVES is efficient and scalable, with production yields up to 100x greater than those obtained by conventional AAV production system, allowing it to manufacture commercial grade production for large markets as wet AMD. If AVA-101 is approved, AAVL will need a consistent and reliable process, while limiting contamination risks, for manufacturing these candidates on large-scale for the approved patient population. Any supply or manufacturing disruption could negatively impact AVA-101 supply and sales.

Competitive Risks: Other companies are rapidly developing gene therapy product candidates in various stages of clinical development for ophthalmic diseases including wet AMD that may compete with AVA-101. If any of these product candidates have an improved therapeutic profile over AVA-101 and is approved, AVA-101's growth trajectory in the marketplace, even if approved, could be adversely impacted.

Financing Risks: We expect AAVL to have adequate cash through the majority of AVA-101's clinical development, and we model an $80 million equity raise on 2 million shares in 2019. AAVL may need additional dilutive financing to fund the potential U.S. launch of AVA-101 and its R&D programs in additional indications.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Company Overview

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Exhibit 2: Company Pipeline

Drug	Mechanism of Action	Indication	Development Phase
AVA-101	Anti-VEGF through gene delivery	Wet AMD	Phase I/IIa
		DME and RVO	IND-enabling studies in 2014-2015
AVA-201	Anti-VEGF through gene delivery	Wet AMD (prevention)	IND-enabling studies in 2015
AVA-311	RS1 gene delivery	Juvenile X-linked Retinoschisis	Preclinical
AVA-322 and AVA-323	Undisclosed	Undisclosed genetic diseases	Preclinical studies in 2014 and 2015

Source: Company data.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 3: Key Upcoming Milestones.

Product	Indication	Event	Date
AVA-101	**Wet AMD**	Genzyme Phase I data for AAV2-sFlt01 (competitor) at AAO	October 2014
		Topline data from Phase IIa trial (n~40; low-dose v. high-dose v. control; 1 EP: no sign of unresolved ophthalmic complications, toxicity or systemic complications)	Mid-2015
		REGN time-limited option to first negotiation for certain rights to AVA-101	~Mid-/Q3 2015
		IND filing for wAMD	H2 2015
		Initiation of Phase IIb trial	H2 2015
		Initiation of pivotal Phase III trial	2017
		Topline data for Phase III trial	2019
		U.S. filing	2019
		U.S. approval/launch	2020
		ROW approval/launch	2021
	CRVO	Initiation of IND-enabling studies	2014-2015
		U.S. approval/launch	2022
	DME	Initiation of IND-enabling studies	2014-2015
		U.S. approval/launch	2022
AVA-201	**Wet AMD**	Initiation of IND-enabling studies	2015
		Initiation of Phase I study	2015
AVA-311	**XLRS**	REGN option to share in development costs and profits	TBD
AVA-322 and AVA-323	**Undisclosed genetic diseases**	Preclinical studies	2014-2015

Source: Company estimates, Jefferies.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

AVA-101

Wet AMD and Other Ophthalmic Diseases

Gene Therapy Technology for the Eye with Curative Potential

AAVL is developing a gene therapy technology platform for vascular ophthalmic diseases, which represents one of the most exciting developments in ophthalmology. AAVL's Ocular BioFactory platform utilizes adeno-associated viruses (AAV) to deliver a therapeutic gene in the eye that leads to robust and durable responses. Historically, viral vectors have had a tumultuous journey given their potential for infection, insertional mutagenesis, and/or acquired immune response. But the eye is an immune-privileged site and significant strides have been made in the field that now make gene therapy a clinically viable strategy, and AAVL is taking the lead in vascular ophthalmic diseases with products that can be delivered with only a single-injection and have curative potential.

AAVL's lead candidate is AVA-101 for wet age-related macular degeneration (wAMD), an established U.S. market of ~$3.5-4.0 billion. The standard-of-care for wAMD is treatment with anti-VEGF therapies, including REGN's Eylea, Roche's Lucentis, and Avastin (off-label). Treatment burden is high with these agents with injections needed every 4-8 weeks taken chronically and AVA-101 has the potential to differentiate with only a single-injection. AVA-101's early data in eight patients from the Phase I study has been impressive with notable improvements in VA of +10-12 letters relative to the control and with responses that are durable ≥12 months. Notably, far fewer patients on AVA-101 required Lucentis re-treatment v. patients on control. AAVL has completed enrollment of 32 patients in the Phase IIa study, and we await data from these patients in mid-2015 to confirm earlier findings. AAVL also intends to initiate a Phase IIb trial in the U.S. in H2 2015. In May 2014, REGN and AAVL entered into a broad collaboration to jointly develop and commercialize novel gene therapy products based on AAVL's Ocular BioFactory platform for the treatment of ophthalmologic diseases. AAVL is eligible to receive contingent payments upon certain milestones and low-to-mid-single-digit royalties on worldwide net sales of collaboration product candidates. REGN has a time-limited right of first negotiation for certain rights to AVA-101 for wAMD upon completion of the Phase IIa trial.

Assuming a positive Phase III program, we estimate AVA-101 can enter the wAMD market in 2020. We estimate peak sales of $602 million in the U.S. by 2026 for wAMD using a 70% risk-discount. For rest-of-world (ROW), we estimate $31 million in 2025 in peak royalties (assuming 20% royalty) using an 80% risk-discount. Following the Phase IIa results for wAMD and assuming positive data, AAVL may follow with expansion into DME and CRVO. In DME, we assume market entry in 2022 and estimate peak U.S. sales of $573 million in 2025 using a 70% risk-discount. For ROW, we assume market entry in 2022 peak ROW sales of $40 million in 2025 (assuming 20% royalty) using an 80% risk-discount. For CRVO, we assume market entry in 2022 and estimate peak U.S. sales of $153 million in 2026 using a 70% risk-discount. For ROW, we assume market entry in 2022 and estimate peak ROW sales of $11.7 million in 2026 (assuming 20% royalty) using an 80% risk-discount.

U.S. Market Opportunity in Ophthalmic Diseases

U.S. Market Opportunity in Wet AMD. The overall prevalence of wAMD in the U.S. population 40 years and older is estimated to be 1.47%, with 1.75 million people having AMD (National Eye Institute. Statistics and Data: Prevalence of Age-related Macular Degeneration in the United States, *Archives of Ophthalmology*, 2004, 122, 564-572). Prevalence of AMD increases dramatically with age and the number of people with AMD is expected to increase by 50% to 2.95 million in 2020. Our base assumption for the

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

number of wAMD patients is ~2.7 million in 2020, of which we believe 414k (~16%) may receive treatment. We estimate 166k (40%) of those patients are receiving Avastin as treatment, while the remaining 248k may be receiving branded anti-VEGF treatment, including REGN's Eylea and Roche's Lucentis. We assume a 5% y/y growth in the wAMD population, but because AVA-101 is potentially curative, we also remove patients as they are treated with AVA-101 out of the wAMD population pool.

The market opportunity in wAMD is potentially substantial for AVA-101. Eylea and Lucentis are currently the standard-of-care for wAMD. In 2013, U.S. Eylea sales were $1.4 billion (+68% y/y). REGN expects U.S. Eylea sales to be $1.7-1.8 billion in 2014 (including potential benefit from DME and BRVO). U.S. Lucentis sales for 2013 were 1,689 million CHF (+15% y/y), or ~$1.86 billion (which includes DME and BRVO). Given current trajectories into 2014, we approximate the U.S. branded anti-VEGF market for wAMD to be currently ~$3.5-4.0 billion. Branded anti-VEGF represents ~50% of total anti-VEGF market. Thus, including off-label Avastin (if Avastin were at branded price), the anti-VEGF market for wAMD is ~$7.0-8.0 billion.

AVA-101 is in a Phase IIa trial with data expected in mid-2015. A Phase IIb trial is also planned in H2 2015. A Phase III program could be initiated potentially in 2017 and assuming positive results in 2019, we believe AVA-101 could reach market in 2020. By 2030, we expect ~46 million wAMD patients to be treated with AVA-101 (~40% market penetration of wAMD patients receiving anti-VEGF treatment). Eylea costs ~$1,850 an injection in the U.S. for a total cost of ~$11-12k annually (assuming ~6 injections per year). For AVA-101, we estimate that the cost per treatment will be ~$25k per injection, which we believe is justifiable given that AVA-101 leads to a very durable response, potentially translating to significant costs savings over the long-haul. We estimate peak sales of $2.0 billion in the U.S. by 2026 for wAMD on an unadjusted-basis. If we apply a 70% risk discount to reflect the clinical risk of the AVA-101 program, we estimate $602 million in U.S. sales by 2026.

For rest-of-world (ROW), Bayer (BAYN GR, €99.05, Buy) estimates 2.2 million wAMD patients outside of the U.S. (OUS), and we estimate this number could reach 2.8 million by 2020. We assume market ROW in 2021. We assume a lower cost for AVA-101 OUS at $15k per injection. We estimate peak sales of $783 million by 2025 (unadjusted). We assume a 20% royalty for ROW sales, thus translating to $157 million in royalty revenue (on an unadjusted basis). Applying an 80% risk discount to reflect a higher risk than the U.S., we estimate peak royalty revenue $31 million in 2025.

CRVO. Central retinal vein occlusion (CRVO) is a retinal vascular disorder in which there is a blockage of the main vein in the retina and causes the walls of the vein to leak blood and excess fluid into the retina. When the fluid collects in the macula, vision can become blurry. AAVL is planning IND-enabling studies in CRVO in 2014-2015. Assuming a successful Phase III program, we model AVA-101 U.S. market entry into CRVO in 2022. As in wAMD, we assume an annual cost of $25k per injection and assume that one injection can lead to durable responses. As a result, once a patient is treated with AVA-101, we remove the patient from the total available CRVO patient population. We estimate peak U.S. sales of $510 million by 2026 with a penetration rate of 34% (unadjusted). If we apply a 70% risk discount to reflect the risk of the clinical program, we estimate U.S. peak sales of $153 million in 2026.

For ROW, we assume market entry in 2022 and an annual cost of $15k per injection. We estimate peak ROW sales of $292 million in 2026 at a penetration rate of 30%. We assume a royalty of 20%, translating to royalty revenue of $58 million in 2026. Apply an 80% risk discount, we estimate peak ROW sales of $11.7 million in 2026.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

DME. Diabetic macular edema (DME) is one of the leading causes of blindness in most developed countries, and with an increasing number of individuals with diabetes the incidence of DME is expected to continue to rise. Studies suggest DME may affect up to 7% of people with diabetes (Ding, J. et al., *Curr Diab Rep*, 2012, 346-354). In 2020, we estimate 318k patients receiving treatment. AAVL is planning IND-enabling studies in DME in 2014-2015. Assuming a successful Phase III program, we model AVA-101 U.S. market entry into DME in 2022. As in wAMD, we assume an annual cost of $25k per injection and assume that one injection can lead to durable responses. As a result, once a patient is treated with AVA-101, we remove the patient from the total available DME patient population. We estimate peak U.S. sales of $1.9 billion by 2025 at a penetration rate of 27% (unadjusted). If we apply a 70% risk discount to reflect the risk of the clinical program, we estimate U.S. peak sales of $573 million in 2025.

For ROW, we assume market entry in 2022 and an annual cost of $15k per injection. We estimate peak ROW sales of $1.0 billion by 2025 at a penetration rate of 25%. We assume a royalty of 20%, translating to royalty revenue of $201 million in 2025. Applying an 80% risk discount, we estimate peak ROW sales of $40 million in 2025.

About AAVL's Ocular BioFactory Platform

AAVL's proprietary Ocular BioFactory platform uses gene therapy to enable the patient's own cells to continuously express the desired therapeutic protein for a durable period of time. AAVL's BioFactory platform consists of two key proprietary components: novel vector screening and optimization system (directed evolution) and an industrialized manufacturing process. Through directed evolution, AAVL can generate a diverse library of millions of AAV variants through mutagenesis and screen the variants in multiple *in vitro* and *in vivo* tests to identify the optimal variant. AAVL's proprietary baculovirus expression system (BVES) is efficient and scalable, with production yields up to 100x greater than those obtained by conventional AAV production system. AAVL's BVES system allows it to manufacture commercial grade production for large markets such as wAMD.

AAV as a Vehicle for Gene Delivery. Gene delivery is possible through either viral or non-viral approaches, and each has its respective advantages and disadvantages. Non-viral approaches include injecting naked DNA (simple and cheap, but has low efficiency and expression), oligonucleotides (such as antisense oligonucleotides, siRNA, and double-stranded oligodeoxynucleotide but has only transient expression), lipolexes (complexes of liposome with DNA which may have high efficiency but has possible toxicity), and nanoparticles (small nanoparticles that are <500 nm that have large capacity and high loading densities but may be costly and have quality control issues). The advantage of viral vectors v. non-viral vectors is that they are more efficient with respect to cell delivery. Historically, viral vectors have had a tumultuous journey given their potential for infection, insertional mutagenesis, and induction of an innate and/or acquired immune response. However, many of the difficulties associated with viral vectors are being overcome, leading to several candidates with promise in the clinical setting. For example, in 2012, the EMA granted approval to uniQure's (QURE, $11.30, Buy) Glybera for lipoprotein lipase deficiency (orphan disease), which uses an AAV-1 vector to deliver the lipoprotein lipase gene. Glybera is the first gene therapy product to be approved in the Western world. The characteristics and disadvantages of various viral vectors are highlighted in Exhibit 4.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 4: Characteristics of various viruses used in gene delivery techniques

Vector	Characteristics	Disadvantages	Examples of Investigated Indications
Adeno-associated virus (AAV)	**Single-stranded DNA virus** **Infects dividing and non-dividing cells** **Can hold up to 5 kb packaging capacity**	**Limited packaging capacity**	**Age-related macular degeneration** **Malignant melanoma** **Cystic fibrosis**
Adenovirus	Double-stranded DNA virus Can hold up to 30 kb packaging capacity High transduction efficiency	Immune response Transient gene expression	HIV Prostate cancer Lung cancer
Retrovirus	Infects both dividing and non-dividing cells Can hold up to 7.5 kb packaging capacity High transduction efficiency	Insertional mutagenesis Requires cell division	SCID-X1 HIV Glioblastoma
Lentivirus	Subclass of retroviruses Infects dividing and non-dividing cells High transduction efficiency	Insertional mutagenesis Risk of replication competent HIV	Mucopolysaccharidosis type VII HIV-1
Herpesvirus	Double-stranded DNA virus Infects neurons Can hold up to 50 kb packaging capacity High efficiency	Inflammatory and immune response	Malignant melanoma Glioma Neuroblastoma

Source: Han, Z. et al., *Investigative Ophthalmology & Visual Science*, 2011, 52, 6, 3051-3059 (adapted); Jefferies.

AAVL uses the adeno-associated virus (AAV) to deliver their therapeutic gene. AAV is the most widely used vector for ocular gene delivery because it mediates long-term transgene expression and elicits minimal immune responses. Furthermore, AAV is non-pathogenic and non-replicative on its own, making it ideal for gene delivery applications. Gene transfer vectors derived from AAV are non-inflammatory, non-integrative and promote long-term expression. Also, the eye is immune privileged, thus minimizing the potential for host immunity or systemic safety issues.

AAV is a small (25 nm), non-enveloped virus that contains a single-stranded DNA genome packaged in an icosahedral capsid comprised of three structural Cap proteins: VP-1, -2, and -3. It belongs to the family *Parvoviridae* and is placed in the genus *Dependovirus*, largely because infection occurs only in the presence of a helper virus (adenovirus or herpes virus). To transduce cells, the AAV vector enters the cell and delivers its single-stranded DNA to the nucleus, where it is converted to double-stranded DNA prior to transcription. These viruses insert genetic material at a specific site on chromosome 19.

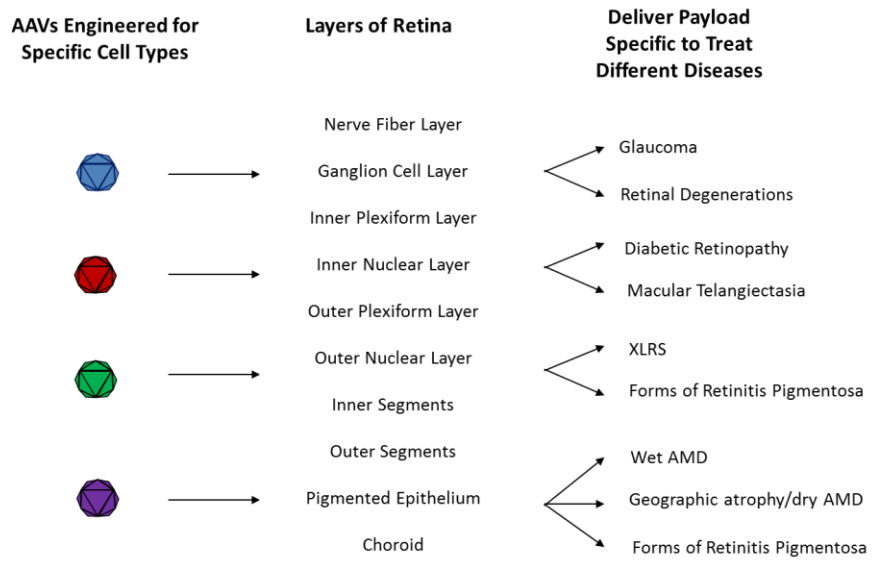
There are twelve human serotypes (AAV-1 through -12), which exhibit differing tissue tropism. The most frequently studied serotype is AAV-2, which preferentially infect a number of cell types, including those found in the retina. AAVL uses the AAV-2 serotype for AVA-101.

Key regulatory concerns related to gene therapy include: 1) chromosomal integration of a vector/gene which could cause cancer; 2) capacity of a vector for latency/reactiviation which may lead to chronic infection/unnecessary gene expression; 3) capacity of a vector for inadvertent replication after complementation by viruses which may lead to chronic infection or biodistribution to non-target tissues/organ; 4) replication incompetence or competence of a vector; or 5) unwanted immunogenicity due to persistent gene expression.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

AAVL Can Create Diverse Libraries of AAV Through Directed Evolution. Through directed evolution, AAVL can generate a diverse library of millions of AAV variants through mutagenesis and screen the variants in multiple *in vitro* and *in vivo* tests to identify the optimal variant. Depending on the disease, AAVL can create proprietary AAV variants that are optimized to target different layers of the retina, which constitute different potential therapeutic targets (Exhibit 5). Directed evolution is an unbiased approach and does not require a thorough understanding of AAV's structure-function biology to find a highly effective variant. The alternative approach is through rationale design which can also yield AAV with unique properties but this approach requires intimate understanding of the biochemical interactions involved.

Exhibit *5*: AAVL's Ocular BioFactory platform can engineer specific AAV-types through directed evolution that can target different layers of the retina to treat different diseases



Source: Company presentation (adapted); Jefferies

One of the limitations of AAV in gene delivery is the size of the gene it is able to accommodate (up to 5 kb packaging capacity). This characteristic could limit some future applications if the therapeutic gene that needs to be expressed is too large.

Gene is Delivered Through Subretinal Injection. Because of the blood/retina barrier, it is not possible to inject AAV intravenously to achieve gene transduction in the retina. Therefore, injection must occur directly into the eye. Intravitreal injections are possible, but efficient gene expression may be a concern. Instead, AVA-101 is delivered through subretinal injection. AVA-101 is delivered through a 23-41 gauge cannula, 3-port PPV setup and may be delivered with local anesthesia. The surgeon creates a small "bleb" by injecting 100 µL. The patients must also undergo a victrectomy (surgical procedure that removes the vitreous gel from the middle of the eye). A victrectomy can be performed by well-trained retina specialists to remove blood/debris from the eye, or remove scar tissue which may be impacting vision. The retinal surgeon performs the procedure by make several small incisions a few millilitres in length on the sclera (the white outer coating of the eye) and the procedure is typically conducted with retinal detachment repair, macular hole surgery, and macular membrane peel. At times, patients

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

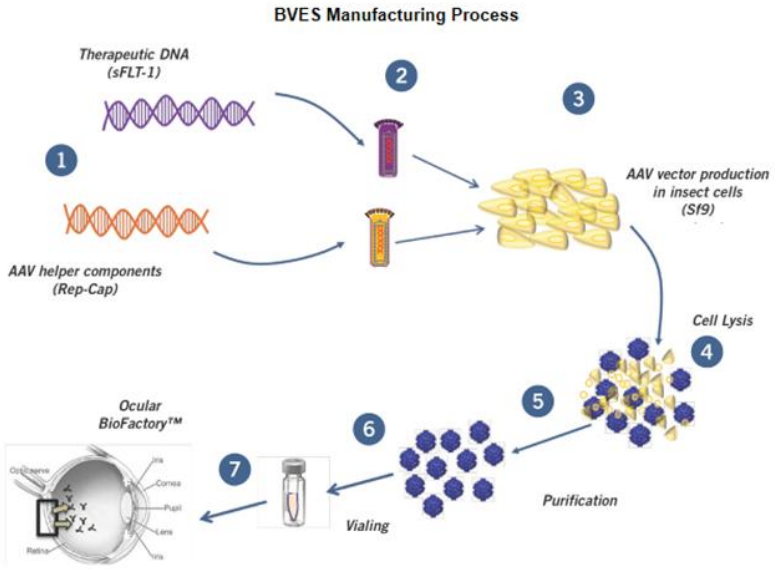
may be administered a small gas bubble or silicone oil to keep the retina in place. Patients are expected to wear an eye shield for up to 7 days post-procedure. Risks related to vitrectomy include: infection, bleeding, retinal detachment, cataract formation, and intraocular pressure. The vitrectomy and subretinal administration takes about 30-60 minutes. In the eight patients in the Phase I study, all patients undergoing gene therapy underwent a vitrectomy approximately 1 week after the first Lucentis dose.

AAVL Will Utilize the Baculovirus Expression System (BVES) to Produce AVA-101. AAVL will utilize the baculovirus expression system (BVES) in Sf9 cells to produce AVA-101. BVES is efficient and scalable, with production yields up to 100x greater than those obtained by conventional AAV production system (high number of particles per cell, producing many thousand doses per manufacturing run), thereby minimizing the cost of goods (COGS). BVES does not use mammalian cell cultures or tumorigenic cell lines, and the DNA sequences used in production are inactive in mammalian cells, providing reduced risk of off-target expression. BVES is a validated process and has been used for several FDA- and EMA-approved vaccines and gene therapy products, such as FluBlok, Cervarix, and Glybera. AAVL's BVES system allows it to manufacture commercial grade production for large markets as wAMD. BVES's advantages over rAAV produced in HEK 293 cells include potential scalability to 200L, and may also replicate the vector DNA more efficiently than HEK 293 cells. AAVL is currently working with Lonza (LONN VX, CHF101.40, Hold) to further scale/establish its manufacture process for commercial use.

The BVES manufacturing process can be described in several steps (Exhibit 6). First, the process begins with two DNA constructs, one encoding the sFlt-1 gene and the other encoding AAV helper components encoding the AAV capsid and for replication of vectors. Second, each DNA construct is inserted into the genome of a baculovirus to create two types of recombinant baculoviruses. Third, the two baculoviruses are made to transduce insect cells which produce large amounts of AAV vectors containing the sFlt-1 gene. Fourth, the transduced cells are harvested and treated with a lysis buffer solution to burst the insect cells and release the AAV vectors. Fifth, the AAV vectors are purified. Sixth, the vectors are formulated in a physiological solution and stored in vials. Lastly, the drug product is used to create an Ocular BioFactory for the treatment of wAMD.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 6: Baculovirus Expression System (BVES) Manufacturing Process



Source: Company presentation; Jefferies.

Key Learnings From Glybera Regulatory Review On Manufacture Related Issues. We evaluated the Glybera review documents that are publicly available with EMEA. We use Glybera as a proxy b/c similar to AVA-101, Glybera originally was manufactured using plasmids transfected into HEK293 cells, and during scale up the manufacture process was transitioned to a baculovirus production system. Comparability data from the two processes suggest product purity improved with baculovirus system.

The EMEA required the following parameters measured: 1) genomic integrity and size; 2) protein analysis and molecular mass; 3) stoichiometry of capsid proteins; 4) particle size; 5) glycosylation state of the virus particle; 6) sequence confirmation; 7) protein identification; 8) TEM and analytical ultracentrifugation to determine mass, density, and distribution profiles; and 9) biological activity as measured by infectious particle assay and ratio of full to infectious virus particles.

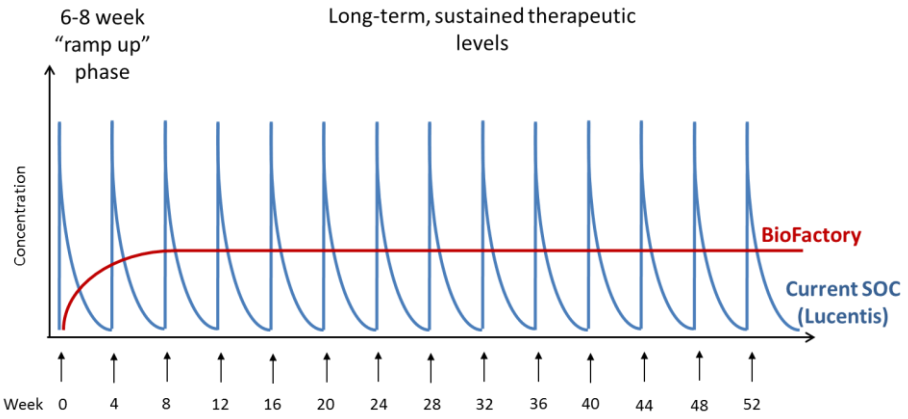
One of the key issues that EMEA focused on was the variability observed with residual baculovirus DNA and believed the assay developed by QURE may be underestimating but received data that suggested these would like not impact patient safety. QURE agreed to develop an additional release assay which would measure the ratio of baculovirus sequences proximal to the inverted terminal repeats (ITR) relative to that in the HR region. The EMEA also highlighted the level of impurities in the final product formulation but found the upper limits allowed for impurities may have been too high given the large amount of product administered and worried high level of impurities may lead to muscle damage as observed in preclinical animal models. Also, the agency focused on the levels of infectious baculovirus which were administered to the patient and required QURE to revise its manufacture process to inactivate or remove the recombinant baculovirus load used for production.

BioFactory Candidates Can Achieve Steady-state PK and Durable Responses. Current anti-VEGF therapy is based on "burst" pharmacokinetics, with peaks and troughs. AAVL's BioFactory candidates, like AVA-101, has a "ramp-up" phase (typically reaches

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

therapeutically beneficial level of continuous expression of sFlt-1 within 6-8 weeks of administration) and achieves sustained levels of the therapeutic protein, which could have implications on long-term safety. Furthermore, AVA-101 expression appears durable and has been shown to last up to 17 months in animal models. Other studies with AAV in the retina have shown gene expression to last ≥5 years.

Exhibit 7: BioFactory provides steady-state pharmacokinetics over long-term compared to standard-of-care



Source: Company presentation (adapted); Jefferies.

The Eye is Immune Privileged. Ophthalmic diseases represent a unique opportunity for gene therapeutic approaches because the eye is immune privileged. Thus, AVA-101 is not expected to cause expression of sFlt-1 outside of the eye, thereby limiting potential systemic safety issues. The Phase I trial showed no arterial thromboembolic events or anti-VEGF related AEs. Laboratory assessment showed no clinically significant changes. In preclinical models, no elevation of sFlt-1 was found outside the eye in monkey models. Measurements of sFlt-1 protein were taken in the serum following subretinal injections of AVA-101 and showed comparable levels to uninjected (control) monkeys at various timepoints post-injection out to 12 months. There was no evidence of virus outside of the eye. This feature could be viewed as particularly advantageous especially considering that Avastin has been shown to have significantly higher systemic safety risk than Lucentis (CATT), and Avastin occupies ~50% of treated wAMD.

Also, in the event of a safety issue, AAVL's Ocular BioFactory expression can be silenced following laser procedure, serving as a potential "kill-switch" for AAVL's gene therapy products. AAVL has demonstrated this feature in animal models, and remains to be corroborated in human subjects. This procedure is non-invasive.

Poor Compliance Leads to Progressive Vision Loss. While standard-of-care treatments are effective, patients must comply with the treatment regimen of every 4-8 weeks or they may face a decline in visual acuity. Given high treatment burden in the physician's office, oftentimes physicians will use alternative dosing regimens, including quarterly and as needed (PRN). Our own survey work conducted in November 2013 of retina specialists suggests that in the clinical setting the mean number of Lucentis/Avastin injections drops off to <5 starting the third year of treatment (v. 8 in the first year of treatment). However, studies have shown that receiving anti-VEGF therapy less frequently than recommended may have poorer outcomes. AVA-101's long and durable expression of sFlt-1 could therefore prove helpful in ensuring continuous anti-VEGF activity with

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

much lower treatment burden. AVA-101 expression has been shown to last up to 17 months in animal models, and other studies with AAV in the retina have shown gene expression to last ≥5 years.

FDA Guidance on Gene Therapy Products. In 2012, the EMA granted approval to QURE's Glybera for lipoprotein lipase deficiency (orphan disease), which uses an AAV-1 vector to deliver the lipoprotein lipase gene. Glybera is the first gene therapy product to be approved in the Western world. The FDA has not yet approved a gene therapy product in the U.S., therefore there may be some regulatory uncertainty associated with AAVL's gene therapy products. The FDA has provided guidance for the development of these products, and established the Office of Cellular, Tissue and Gene Therapies within the Center for Biologics Evaluation and Research (CBER). In 2011, the FDA published a briefing document that outlines the issues and concerns related specifically to gene therapy products for retinal disorders. The document highlights some of the efficacy endpoints that are typical for retinal disorders and discusses the challenges with these endpoints as they relate to gene therapy approaches. However, we believe that the FDA's concerns on efficacy endpoints do not impact AVA-101, as most of their concern lies with difficulties associated with inherited retinal disorders, and not wAMD (such as small sample sizes due to rarity of disease and children who are not old enough to provide reliable best corrected distance visual acuity scores). However, such issues may apply to AVA-311 in XLRS (see AVA-311 section). The FDA does raise important issues related to potential immune response and complications with subretinal injections:

- **Immune response**. The FDA raised concern for vector-mediated gene delivery where there is the potential for immune response against the vector or expressed transgene. Immune response can lead to inflammation, abrogation of in vivo gene expression, or destruction of transduced cells. The human is a natural host for AAV, and systemic infusion of AAV vectors has been shown to induce an increase in neutralizing antibodies and immune responses to the AAV capsid. Although the eye is an immune-privileged site, immune privilege can be compromised in high-risk eyes. Therefore, the immune privilege of the vitreous or subretinal space could be compromised or lost, and products injected into those sites could cause systemic exposure and trigger host immune responses.

- **Subretinal injections**. Subretinal injections also carry the potential to cause a break between the immune-privileged site and the vascular system, increasing the risk of sympathetic ophthalmia (SO), a rare bilateral granulomatous inflammation of the eye that usually follows accidental or surgical trauma to the eye. The FDA also raised potential safety concerns related to administration of the product to the contralateral eye or repeat administration to the first eye, considering that most diseases affect both eyes. Since immunization takes time to develop, the FDA recommends reducing the time between the first and subsequent injections and starting immunosuppressant therapy early and aggressively. Second exposure within 10 days of the first are generally not considered to induce SO. The FDA further suggests that although the vitreous cavity and subretinal space are both immune-privileged sites, the selection between these two sites of administration can influence the potential of immune response and subsequent response in the contralateral eye.

  The FDA noted that subretinal injection is more technically difficult than intravitreal injection. First, there were potential complications associated with victrectomy that is done prior to the subretinal injection, and these typically occur weeks to months following the procedure. Second, there were potential safety concerns associated with the subretinal injection such as the development of a retinal hole at the site of entry through the retina, reflux of the therapeutic

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

agent back into the vitreous cavity, potentially decreasing efficacy or scar formation from proliferation of cells on the retinal surface, and prolonged retinal detachment.

AVA-101

AAVL's lead candidate is AVA-101, a one-time subretinal injection which offers a potential cure (i.e. durable remission) for patients with wAMD. As a gene therapy product, AVA-101 induces the patient's own retinal cells to produce sFlt-1 (fms-like tyrosine kinase), a soluble isoform of VEGFR-1 and a naturally occurring endogenous VEGF inhibitor. sFlt-1 binds VEGF in the ~10 picomolar (pM) range (10^{-12} M), and is the same binding domain as REGN's Eylea. Given the experience of Eylea and Lucentis, VEGF is a clinically validated target for the treatment of wAMD, among other ophthalmic diseases as DME and CRVO. AVA-101 has shown impressive efficacy and safety results from eight patients from the Phase I study. The trial has enrolled 32 more patients, and topline data is expected in mid-2015. The IND filing for wAMD expected in H2 2015, and a Phase IIb study is planned in the U.S. for H2 2015.

Phase IIa for wAMD

Nuts & Bolts. AVA-101 is in a randomized, single-blind (outcomes assessor) Phase IIa study for treatment of wet age-related macular degeneration (wet AMD). The trial has enrolled 32 wAMD patients aged ≥55 at the Lions Eye Institute in Australia. For the Phase I portion of the trial (n=8), the patients were randomized to three groups investigating two dose levels of AVA-101 delivered by subretinal injection (single injection): 1 x 10^{10} vector genomes (vg) (low dose), 1 x 10^{11} vector genomes (vg) (high dose), and control (Lucentis alone, as needed). Patients were documented to have anti-VEGF dependence. All patients were given Lucentis on Day 0 and Week 4, and the patients were eligible for Lucentis re-treatment as needed every 4 weeks based on pre-specified criteria/masked graders (visual acuity, OCT, and fluorescein angiography). For the Phase IIa portion (n=32), patients will be randomized 2:1 to only two groups investigating one dose level of 1 x 10^{11} vg (high dose) (n=21) and control (n=11). Patients receive follow-up for a total of 3 years. The median age of the first 8 patients was 79 years.

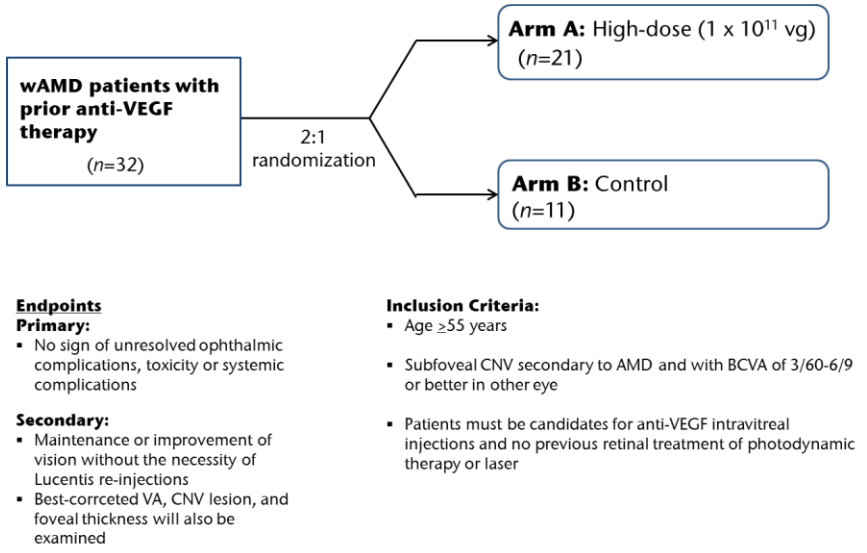
The primary endpoint is no sign of unresolved ophthalmic complications, toxicity or systemic complications as measured by laboratory tests from 1 month post-injection. Ocular examination will examine for ocular inflammation, intraocular pressure, visual acuity, and retinal bleeding. Abnormal laboratory data will be collected. There will be an extended follow-up for 3 years. Secondary endpoints include maintenance or improvement of vision without the necessity of Lucentis re-injections. Best-corrected VA, CNV lesion, and foveal thickness will also be examined.

Inclusion criteria include: age ≥55 years, subfoveal CNV secondary to AMD and with BCVA of 3/60-6/9 with 6/60 or better in other eye; patients must be candidates for anti-VEGF intravitreal injections and no previous retinal treatment of photodynamic therapy or laser. Exclusion criteria include: patients with liver enzymes >2x upper limit of normal; any prior treatment for AMD in the study/control eye, excluding anti-VEGF injections; extensive subfoveal scarring, extensive geographic atrophy, or thick subretinal blood in the study eye as determined by investigator. Patients with significant retinal disease other than sub-foveal CNV AMD are also excluded. The trial is fully enrolled as of April 2014, and topline data is expected in mid-2015.

AAVL also intends to initiate a Phase IIb trial (n=120) in the U.S. in H2 2015 for wAMD. The trial will be a randomized, controlled, multi-center, double-masked trial to assess efficacy and safety/tolerability of a single subretinal injection of AVA-101 compared to current anti-VEGF therapies. The trial is expected to have similar endpoints as the Phase IIa trial.

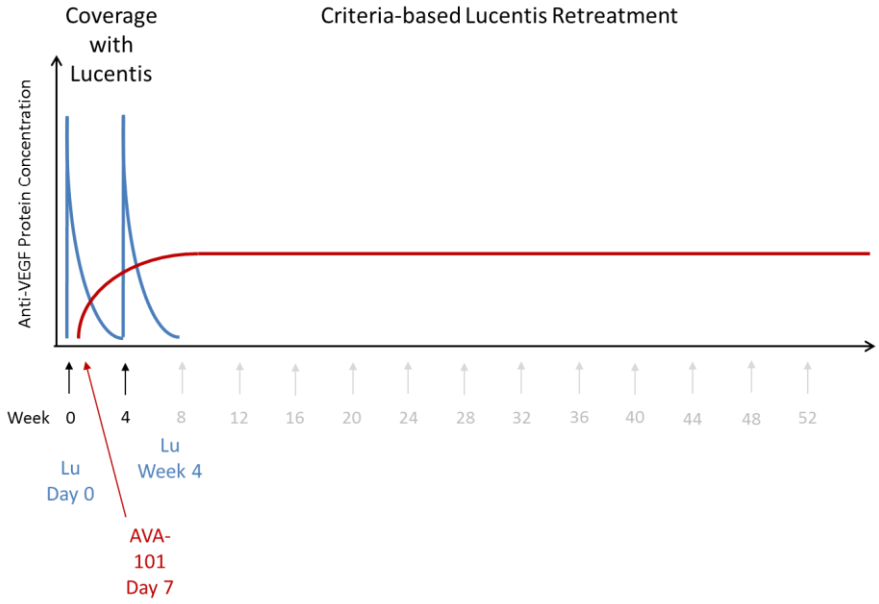
Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 8: Trial design of Phase IIa portion



Source: Company presentation (adapted); Jefferies.

Exhibit 9: Diagram representation of injections and anti-VEGF protein concentration in Phase IIa design



Source: Company presentation (adapted); Jefferies.

Highly Compelling Phase I Data Provides Glimpse of Potential Disruptive Technology. AVA-101 has demonstrated highly compelling proof-of-concept data in eight wAMD patients from its Phase I trial (inclusion and exclusion criteria details can be

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

seen under Nuts & Bolts). Patients were documented to have anti-VEGF dependence (median of 18 prior anti-VEGF injections). All patients received Lucentis at month 0 and 1 and received 100 µL of rAAV.sFlt-1 subretinally after undergoing a standard vitrectomy procedure (~30-60 minute procedure) on the 7th day.

The eight patients were randomized to 3 arms: low dose ($1x10^{10}$ vg), high dose ($1x10^{11}$ vg), and control (Lucentis as needed). Patients were eligible for Lucentis re-treatment every 4 weeks, and re-treatment criteria were based on visual acuity, OCT, and fluorescein angiography. Patients receive follow-up for a total of 3 years.

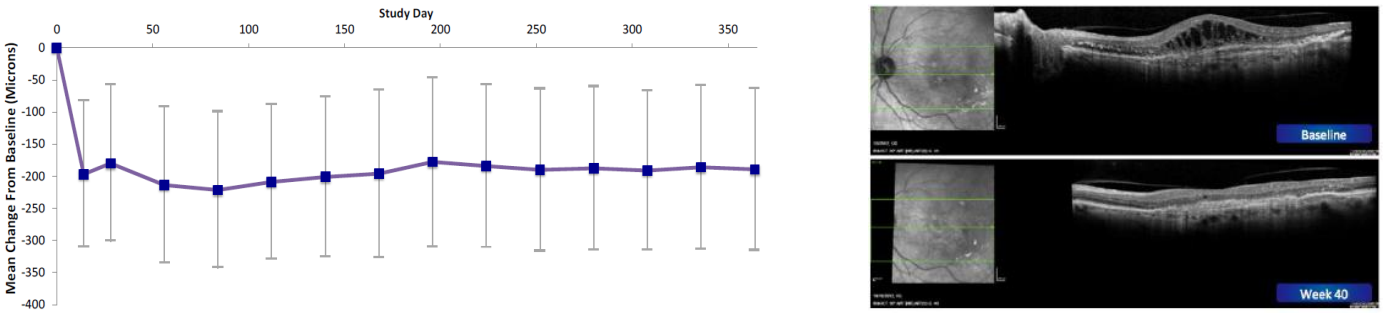
Mean VA improvement from baseline in the low-dose group was +8.7 letters at week 52 and +12.2 letters relative to the control. Mean VA improvement from baseline in the high-dose group was +6.3 letters at week 52 and +9.8 letters (Exhibit 10). Furthermore, the central retinal thickness was found to have improved and maintained through the 12 month period (Exhibit 11).

Exhibit 10: Phase I Data on Initial Eight Patients

Group	Subject	Baseline Visual Acuity (ETDRS letters)	Week 52 Visual Acuity (ETDRS letters)	Change from Baseline	Change from Baseline	Change from Control
Low dose	1	33	40	+7		
	2	28	41	+13	**+8.7**	**+12.2**
	3	46	52	+6		
High dose	4	56	50	-6		
	5	54	64	+10	**+6.3**	**+9.8**
	6	34	49	+15		
Control	7	28	21	-7		
	8	39	39	0	**-3.5**	

Source: Company presentation (adapted); Jefferies.

Exhibit 11: Central Retinal Thickness Improved and Maintained Through Month 12.



Source: Company presentation, Jefferies.

Comparison with GNVC's AdPEDF.11 Phase I Results Highlights the Strength of AVA-101's Efficacy. To provide reference for the mean VA gains achieved by AVA-101 in the Phase I trial, we highlight another recent Phase I trial for AdPEDF.11 by GenVec (GNVC, $2.08, NC) for comparison. AdPEDF.11 is another gene therapy product being

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

developed for wAMD that delivers a gene for the pigment epithelium-derived factor (PEDF) protein. The PEDF protein is known to have anti-angiogenic effects and therefore a gene delivery product that allows the human cells to express this protein may be useful for the treatment of wAMD. In its open-label, dose-escalation Phase I trial of 28 patients with wAMD, AdPEDF.11 showed no change from baseline in mean change in VA at the low dose, and a change of -4 letters at the high dose (worsening) at month 12.

AVA-101 Appears Safe and Well-tolerated. Long-term follow-up reported three cases of cataracts (increased risk with vitrectomy), four cases of minor hemorrhage at site of injection, and 2 mild cases of iritis. In addition, 50% of patients tested positive for AAV neutralizing antibodies but these did not affect the safety profile. Patients were followed through ELISA tests for presence of the AAV vector in tears, serum, urine, and saliva. Two patients reported presence of rAAV.sFLT1 particles in tears and this observation cleared in the next visit, and all patients did not experience variations in serum, urine, and saliva samples.

Interim drug safety surveillance data received in June 2014 from this ongoing study suggests that AVA-101 continues to be well tolerated. Most adverse events that have been observed to date are mild and not related to AVA-101 or the procedures used in the study. Adverse events related to study procedures include subconjunctival, vitreous and retinal hemorrhage, cataract progression and eye pain. Other infrequent adverse events may be related to study procedures, including retinal tears or holes and falls. A small number of adverse events may be possibly related to AVA-101, including inflammation and light chain analysis increase, but these were considered mild and transient and have not been associated with vision loss.

Fewer Lucentis Re-Treatment in AVA-101 v. Control. Only two patients on AVA-101 (one on low dose and other on high dose) required Lucentis re-treatment (one injection each), v. six patients in the control (one had five injections and the other had one). (p=0.035 for Mann-Whitney one-tailed and 0.07 for Mann-Whitney two-tailed). Thus, out of twelve opportunities, patients treated with AVA-101 needed only 0.33 injections whereas patients in the control group needed 3.0 injections. This result was statistically significant v. the control group and historical controls ($p<0.001$).

Can AVA-101 Be Administered In The Contralateral Eye. While AAVL has not investigated the administration of AVA-101 in the contralateral eye, a key question is whether it can be administered in the second eye without being impacted by pot'l safety issues. Patients with wet AMD may suffer from bilateral disease, and therefore, it may be critical to evaluate the pot'l administration of AVA-101 in the second eye. We highlight a published study (Bennett et al, Sci Transl Med, 2012) sponsored by Spark Therapeutics as supportive evidence that readministration into the second eye is safe. The trial evaluated the subretina administration of AAV2 carrying the RPE65 gene in 3 adult patients with Leber congential amaurosis (LCA). Two of the three patients received a higher dose in the second eye than the first. There were no obvious safety observations as measured through blood and tear samples nor any T cell responses to either vector or transgene product. Neutralizing antibody levels to AAV2 and RPE65 protein were near baseline levels. Visual acuity at day 180 improved in all pts in the second eye. Two of the three patients observed improvements in their navigation abilities using the second eye. Also, there were retina/vision function in the first eye improved after administration into the second eye.

Does Long-Term VEGF Suppression Cause Geographic Atrophy. A recent debate has arisen in the ophthalmology community that pot'l long-term use of anti-VEGF may lead to geographic atrophy in the eye. Geographic atrophy (GA) can occur in a third of all AMD patients and may lead to vision deterioration long-term. GA is characterized as

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

depigmentation of the retinal pigment epithelium (RPE) due to RPE dropout and these atrophic areas are at least 175 um in diameter. GA lesions that involve the fovea typically impact vision. The correlation btwn long-term VEGF inhibiton as a pot'l cause of GA came from the CATT trial (Grunwald, AAO Journal, 2014) which concluded increased dev't of GA at two years in 20% of patients treated in the study. The study authors, however, could not differentiate between de novo GA and lesions developed as a result of treatment of neovascularization. CATT reported 10.6% of patients (n = 1,024) developed GA by year 1 and 18.3% by year 2. At year 2, 83% of all GA was considered extrafoveal and the remainder impacted the fovea. Patients receiving monthly injections observed a 15% incidence at year 1, and 12.4% at year 2 whereas PRN patients observed a 8.3% incidence at year 1 and 8.8% at year 2. Patients that switched from monthly to PRN observed a 12.7% rate at year 1 and 7% in year 2. However, it's also possible that the greater rates of GA in the monthly arm is related also to the fact that the monthly arms of Lucentis and Avastin observed greater patients with no fluid on OCT vs the PRN arm.

In order to settle the debate, investigators from the HARBOR trial which evaluated ranibizumab 0.5 mg and ranibizumab 2.0 mg either monthly or as needed in 1,098 patients with wet AMD will analyse two-year data (to be presented at AAAO in Oct '14) to assess a correlation btwn anti-VEGF and the development of GA. Retina specialists that we've spoken to dismiss the relationship to long-term anti-VEGF use, and believe wet AMD is a more serious threat to vision than GA. Also, wet maculas may lead to an underdiagnosis of GA and an accurate diagnosis is made only after lack of fluid in the retina.

IP Estate

AAVL has 27 pending patent applications in the U.S. and corresponding foreign patent applications. At least 18 patent applications have been filed in the U.S. and corresponding foreign jurisdictions by or on behalf of universities which granted AAVL the exclusive license rights. To date, twelve patents have issued to AAVL or to their licensors.

What are the Treatment Dynamics for Wet AMD?

Currently Eylea and Lucentis are Stable at ~25% Market Share with Off-Label Avastin at ~50%. In November of 2013, we conducted a survey of retina specialists to determine the market dynamics of wAMD (and DME). Our survey suggests that Eylea's overall market share for wet AMD (including both treatment-naïve and treatment-experienced patients) remained at 22%. Lucentis 0.5 mg was slightly higher at 31%. Off-label Avastin was at 43%. Our results are largely consistent with REGN's own market research conducted over Q2 2014 which suggests Eylea and Lucentis are stable at ~25% market share, while off-label Avastin still occupies ~50% market share. REGN's results suggest their respective market shares continue to remain stable since we conducted our survey in November 2013. Our research suggests Eylea lags Lucentis slightly. The percentage of physicians not using any drug therapy for the wet AMD patients was at 4% overall. The evolution of the market shares of Eylea, Lucentis, and Avastin over three years (2011-2013) can be viewed in Exhibit 12.

Avastin remains the market leader in both treatment-naïve and experienced segments at 43% overall (46% for the -naïve and 42% for the -experienced segments). Eylea is at 20% for the treatment–naïve segment (v. 28% last year) and 22% for the treatment-experienced segment (v. 21% last year). Lucentis 0.5 mg is at 30% for the treatment-naïve segment (v. 23% last year) and 32% for the treatment-experienced segment (v. 31% last year). For the treatment-naïve segment, Lucentis 0.5 mg appears to have increased proportionately to Eylea's decrease over the past year.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 12: Overall market share in wet AMD (treatment-naïve and –experienced)

Overall

All respondents (n=48)	Nov'13 Survey	Dec '12 Survey	Dec '11 Survey
Lucentis 0.5 mg	**31%**	30%	32%
y/y growth	*5%*	*-5%*	
Avastin	**43%**	46%	60%
y/y growth	*-7%*	*-22%*	
Eylea	**22%**	22%	3%
y/y growth	*-1%*	*633%*	
No drug therapy	**4%**	1%	NA
y/y growth	*252%*		
Other	**0%**	NA	NA
y/y growth	*NA*	*NA*	

Source: Jefferies; MedPanel.

Exhibit 13: Wet AMD Treatment Dynamics (Treatment-naïve and -experienced).

Treatment-naïve

All respondents (n=48)	Nov'13 Survey	Dec '12 Survey	Dec '11 Survey
Lucentis 0.5 mg	**30%**	23%	30%
y/y growth	*28%*	*-22%*	
Avastin	**46%**	48%	62%
y/y growth	*-5%*	*-22%*	
Eylea	**20%**	28%	3%
y/y growth	*-28%*	*821%*	
No drug therapy	**4%**	1%	NA
y/y growth	*419%*	*NA*	
Other	**1%**	NA	NA
y/y growth	*NA*	*NA*	

Treatment-experienced

All respondents (n=48)	Nov'13 Survey	Dec '12 Survey	Dec '11 Survey
Lucentis 0.5 mg	**32%**	31%	32%
y/y growth	*3%*	*-4%*	
Avastin	**42%**	46%	59%
y/y growth	*-9%*	*-21%*	
Eylea	**22%**	21%	3%
y/y growth	*5%*	*607%*	
No drug therapy	**3%**	1%	NA
y/y growth	*154%*	*NA*	
Other	**0%**	NA	NA
y/y growth	*NA*	*NA*	

Source: Jefferies; MedPanel.

How Will the wAMD Landscape Change by 2020 When AVA-101 Potentially Enters Market? We expect AVA-101 to enter the U.S. wAMD market in 2020, and the wAMD landscape could change by that time. At least in the near-term, we expect the wAMD market dynamics to remain stable. We believe Eylea and Lucentis have largely matured in this indication and expect little change from the results in our November 2013 survey. Our survey work also suggests little impact on Avastin from the new compounding law. To reiterate, the U.S. Senate approved the bill known as the Drug Quality and Security Act (H.R. 3204) which was signed into law late November granted the FDA greater authority to regulate compounding pharmacies. In our survey, we asked our respondents on their predicted wet AMD drug use following the new compounding law. When asked whether they expected to have issues receiving Avastin from a compound pharmacy, 52% responded 'Yes' and 48% responded 'No.' The percentage of physicians responding 'Yes' is down considerably from our previous survey where 100% (49/49) of physicians responded 'Yes,' suggesting that the concern over receiving Avastin from a compounding pharmacy may be less widespread and subsiding. Avastin's continued stable market share would be consistent with our view that the compounding law has had little impact on the wAMD market dynamics.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Going forward, various competitive products for wAMD could alter the landscape before AVA-101 enters the market in 2020. However, most are still in early stages of clinical development with few differentiating features that exceed those of AVA-101 (see Competitive Landscape section for details and timelines on competitors). In particular, the most advanced gene therapy product for wAMD beyond AVA-101 is Genzyme's AAV2-sFlt01 (a Sanofi company, SAN FP, €79.43, Buy) is still in Phase I with data expected at AAO 2014 (October). Only two products are currently in Phase III development: Ophthotech's (OPHT, $37.16, NC) Fovista and Allergan's (AGN, $164.38, NC) DARPin. OPTH's Fovista is an anti-PDGF agent to be used in combination with an anti-VEGF therapy. Based on estimates for enrollment of the Phase III program, it expects to have topline data in 2016 with potential U.S./EU filing by YE 2016. If Fovista is approved potentially by YE 2017, because it is used in conjunction with an anti-VEGF, we do not expect Fovista to impact anti-VEGF use. Furthermore, OPTH's program plans to exclude wAMD patients with pure occult choroidal neovascularization which represents ~40% of cases, and potentially limiting the size of Fovista's market opportunity. AGN plans to begin Phase III studies for DARPin in Q2 2015 when new material from the new manufacturing process is available. However, DARPin has shown issues with ocular inflammation (~10%) in its Phase II studies and it remains to be seen whether AGN can resolve this issue. Other products such as Novartis' (NOVN VX, CHF81.35, Buy) ESBA-1008 have shown promising data in wAMD but it remains in Phase II and we have yet to see if the results will bear out in Phase III.

What are the Treatment Dynamics for DME?

DME Market Evenly Divided Between Lucentis, Avastin, and Laser/Steroids. In conjunction with our work in wAMD, we sought to understand the DME market dynamics on the heels of positive 1-year data from the Phase III VIVID and VISTA trials for REGN's Eylea in DME. Lucentis occupies 30% market share, and roughly ~2/3 of patients are treated with Lucentis at the approved 0.3 mg dose (21%) while ~1/3 are treated at the 0.5 mg dose (9%). For treatment-naïve patients, 20% are treated with Lucentis 0.3 mg and 12% are treated with Lucentis 0.5 mg. For treatment-experienced patients, 22% are treated with Lucentis 0.3 mg and 9% are treated with Lucentis 0.5 mg. Avastin is on par with Lucentis at 31% market share for both treatment-naïve and –experienced patients. About ~1/5 (19%) of patients are treated with laser photocoagulation, and ~1/10 (11%) are treated with steroids. There were no notable differences in the percentages between practices. Eylea currently has 3% market share off-label across both treatment-naïve and –experienced segments.

Exhibit 14: Overall market share in DME (treatment-naïve and –experienced)

	Nov'13 survey		
All respondents (n=48)	***Overall***	***Tx-naïve***	***Tx-exp***
Lucentis 0.5 mg	**9%**	12%	9%
Lucentis 0.3 mg	**21%**	20%	22%
Avastin	**31%**	31%	31%
Eylea	**3%**	3%	3%
Laser photocoagulation	**19%**	18%	19%
Steroids	**11%**	10%	11%
No drug therapy	**5%**	6%	5%
Other	**0%**	0%	0%

Source: Jefferies; MedPanel.
Note: Eylea was not yet approved for DME at time of survey

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Eylea Approved for DME on July 29; Launch Underway in H2 2014. Eylea was approved for DME on July 29, 2014, and REGN is currently marketing Eylea for DME leveraging its salesforce in wAMD. For 2014, REGN is guiding to $1.7-1.8 billion in U.S. Eylea sales driven by wAMD, DME, and potential approval in BRVO in October. If we assume a modest ~5% q/q growth in wAMD for the remainder of the year, we expect DME (and potentially some BRVO) to contribute ~$35-135 million to meet their $1.7-1.8 billion guidance. One of the critical drivers to Eylea's market share in DME will be driven by the DRCR Protocol T trial comparing Eylea to Avastin/Lucentis in 660 DME with a maximum of 25% with prior anti-VEGF treatment. We expect 1-year data will be presented at the AAO meeting in October.

Anti-VEGF Therapies May Suffer From Fewer-Than-Expected Injections Per Year, Limiting Their Total Market Opportunity. For DME, Lucentis 0.3 mg is to be administered by intravitreal injection once a month. According to the respondents in our survey, Lucentis 0.3 mg is given at slightly less than half that frequency (average of 6.9 injections in the first year). The frequency of injection is diminished in the second and third years, 5.5 and 4.2 injections, respectively. Lucentis 0.5 mg is administered less frequently at 5.3 injections in the first year, diminishing to 4.6 and 3.4 injections in the second and third years, respectively. Avastin is given at a similar frequency as Lucentis 0.3 mg with 6.4 injections in the first year, 5.1 in the second year, and 3.7 in the third year. Eylea is administered with 4.8 injections in the first year, 4.2 injections in the second year, and 3.1 in the third year. If following the VIVID/VISTA trials, Eylea is to be administered 2 mg every other month (after 5 initial monthly injections). Thus, like Lucentis, Eylea is being administered at much less frequency in the clinical setting v. Phase III trials.

Exhibit 15: Treatment injections for DME in first-, second-, and third-year.

	No. of inj		
All respondents (n=48)	First yr	Second yr	Third yr
Lucentis 0.5 mg	5.3	4.6	3.4
Lucentis 0.3 mg	6.9	5.5	4.2
Avastin	6.4	5.1	3.7
Eylea	4.8	4.2	3.1
Steroids	4.1	3.5	2.4
No drug therapy	0.5	0.7	0.7

Source: Jefferies; MedPanel.
Note: Eylea was not yet approved for DME at time of survey

Thus, anti-VEGF therapies may suffer from fewer-than-expected injections per year, limiting the total potential market opportunity for these agents. Currently, we model 237,000 eligible DME patients receiving treatment for 2014, which is in-line with this survey and with other market research (Roche disclosed in a presentation that the treated DME population is ~170,000 in 2012, not including bilateral disease). Of the 237,000 patients, 30,800 (13%) may receive Eylea translating to $331 million in sales. We estimate Eylea's market penetration to 20% in 2016 ($483 million) peaking at 29% by 2020 with sales of $852 million. Given the totality of our survey data, the DME market opportunity may not be as large as we expect for anti-VEGF therapies, driven largely by the reduced number of annual injections per DME patient.

We believe this limitation in anti-VEGF therapies represents an opportunity for AVA-101. As a single-shot injection that has very durable responses, AVA-101 sales would not be impacted by lower treatment injection frequency.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Assuming Positive PIII Data in DME, We Believe AVA-101 Can Win over SOC on Price and Treatment Frequency. In our survey, we wanted to determine which factors were most critical for swaying physicians into using Eylea for their DME patients. We presented the physicians with three pieces of information (in order): Eylea's 1-year VIVID/VISTA data, price information, and the differences in treatment frequency between therapies. Lucentis 0.3 mg is recommended to be administered by intravitreal injection once a month (~28 days), while Eylea may be administered 2 mg every other month (after 5 initial monthly injections) (fewer total injections per year for Eylea compared to Lucentis).

The positive VIVID/VISTA data had a favorable impact on Eylea's outlook. We asked our respondents to predict their DME drug use over the next few years after presenting them with the data. Overall, physicians appeared positive on Eylea's outlook for DME after viewing the data, expecting its market share to reach ~20% in 2014 (year of launch) and ~34% in 2016 for treatment-naïve patients. For treatment-experienced patients, physicians expected Eylea's market share to reach 31% in 2016. Avastin, Lucentis (0.5 and 0.3 mg doses), laser photocoagulation, and steroids are all expected to diminish in market share over the next few years in favor of Eylea.

However, Eylea expectations were tempered by price. After presenting the physicians with the VIVID/VISTA data, we wanted to determine the potential impact of the price differential between therapies. Lucentis 0.3 mg injection for DME is priced at $1,170, while Eylea 2 mg injection for DME is priced at $1,850. Physicians responded negatively to the higher price of Eylea, reducing their expectation of Eylea use for 2014-2016. For treatment-naïve patients, physicians expect Eylea use to be at ~14% in 2014, ~19% in 2015, and ~21% in 2016. For treatment-experienced patients, physicians expect Eylea use to be at ~14% in 2014, ~18% in 2015, and ~21% in 2016.

Expectations for Eylea modestly improved when presented with the treatment frequency information, raising their expectation for 2014-2016. For treatment-naïve patients, physicians expect Eylea use to be at ~16% in 2014, ~21% in 2015, and ~24% in 2016. For treatment-experienced patients, physicians expect Eylea use to be at ~20% in 2014, ~24% in 2015, and ~24% in 2016. While increased, it was not enough to offset the negative impact of price.

Exhibit 16: Expected DME Treatment Dynamics for 2014-2016 in Response to VIVID/VISTA Data, Price, and Treatment Frequency.

Treatment-naïve

	Nov' 13 Survey			
All respondents (n=48)	**Current**	**2014E**	**2015E**	**2016E**
Lucentis 0.5 mg	12%	**7%**	**8%**	**7%**
y/y growth		*-39%*	*13%*	*-12%*
Lucentis 0.3 mg	20%	**18%**	**17%**	**17%**
y/y growth		*-8%*	*-5%*	*-5%*
Avastin	31%	**29%**	**25%**	**24%**
y/y growth		*-5%*	*-15%*	*-5%*
Eylea	3%	**16%**	**21%**	**24%**
y/y growth		*358%*	*32%*	*16%*
Laser photocoagulation	18%	**16%**	**16%**	**17%**
y/y growth		*-16%*	*6%*	*1%*
Steroids	10%	**9%**	**7%**	**7%**
y/y growth		*-11%*	*-17%*	*-4%*
No drug therapy	6%	**5%**	**5%**	**5%**
y/y growth		*-10%*	*-2%*	*-2%*
Other	0%	**0%**	**0%**	**0%**
y/y growth		*NA*	*NA*	*NA*

Treatment-experienced

	Nov' 13 Survey			
All respondents (n=48)	**Current**	**2014E**	**2015E**	**2016E**
Lucentis 0.5 mg	9%	**5%**	**5%**	**5%**
y/y growth		*-37%*	*0%*	*-2%*
Lucentis 0.3 mg	22%	**20%**	**19%**	**19%**
y/y growth		*-7%*	*-9%*	*0%*
Avastin	31%	**27%**	**25%**	**25%**
y/y growth		*-13%*	*-6%*	*0%*
Eylea	3%	**20%**	**24%**	**24%**
y/y growth		*565%*	*20%*	*0%*
Laser photocoagulation	19%	**15%**	**14%**	**14%**
y/y growth		*-23%*	*-5%*	*0%*
Steroids	11%	**9%**	**9%**	**9%**
y/y growth		*-25%*	*7%*	*0%*
No drug therapy	5%	**4%**	**3%**	**3%**
y/y growth		*-25%*	*-7%*	*0%*
Other	0%	**0%**	**0%**	**0%**
y/y growth		*NA*	*NA*	*NA*

Source: Jefferies; MedPanel.
Note: Eylea was not yet approved for DME at time of survey

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Thus, assuming AVA-101's Phase III data can show similarly efficacious results as Eylea's VIVID/VISTA data, we believe AVA-101 can win over Eylea on two fronts: on price and on treatment-frequency. On price, our survey showed that physicians saw Eylea's cost of $1,850 per injection several times a year as a negative. We expect AVA-101 to be priced at ~$25k for the single injection, which we believe is justifiable given that AVA-101 can lead to very durable responses, potentially translating to significant costs savings over the long-haul. On treatment frequency, physicians saw Eylea as favorable over Lucentis given fewer treatment injections. The single injection of AVA-101 makes it a clear winner over Eylea and Lucentis' multi-injection regimens.

We do not model AVA-101 entry into DME until 2022. By that time, we expect the treatment dynamics to be similar to the results we observe in 2016 from our survey, depending on factors such as the outcome of DRCR Protocol T in October. Our survey shows that physicians expect all three anti-VEGF therapies to be used almost equally at ~24% for both treatment-naïve and treatment-experienced out to 2016 (if take Lucentis 0.5 mg and 0.3 mg together).

Competitive Landscape

We highlight some of the primary potential competitors to AAVL in wAMD:

Genzyme (AAV2-sFlt01): Genzyme, a Sanofi company, is developing an intravitreally-delivered AAV2-sFlt01 product for wAMD. Genzyme's product can be considered to the closest competition to AVA-101 given that it delivers the same therapeutic gene (for sFlt-1) utilizing the same viral vector (AAV), and the only differentiating feature is the fact that it can be delivered intravitreally, which could be an advantage. VEGF-A, one of the leading contributors to angiogenesis, binds to two tyrosine kinase receptors (VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1) to regulate vascular proliferation, migration, permeability, and secretion. Flt-1 has 10-fold greater affinity to VEGF-A than the VEGFR-2 receptor. GENZ's sFLT01 gene therapy is a domain 2 of Flt-1 coupled by a 9Gly linker to human IgG1 Fc. The company delivers via an AAV2 viral vector, and utilizes the chicken β-actin (CBA) promoter which is vital in expression of the transgene. Data from preclinical assays of human umbilical vein endothelial cells (HUVEC) observed similar VEGF inhibition as a FLT-1 with the first three domains (Pechan, Gene Ther 2009). Studies have observed the CH3 domain and the 9Gly peptide linker play a critical role to VEGF binding. In studies of a mouse model, AAV2.sFLT01 delivered through an intravitreal injection observed ~50% reduction in neovascularization compared to control animals, however, a closer examination of expression of the sFLT01 gene found that it was predominantly expressed in retinal ganglion cells and was infrequently found in a mouse retina however cells deeper in the retina such as the Muller cells observed lower quantities of the sFLT01 protein. Therefore, intravitreal delivery of sFLT01 may not be an optimal approach with current vector delivery technology.

Genzyme also has published data evaluating the long-term safety of sFLT01 (doses: 2.4 x 109 vg and 2.4 x1010 vg) in a 12-month primate study, and observed a dose-dependent expression of sFLT01 in the aqueous humor with expression of sFLT01 somewhat inconsistent across the two dose groups (MacLachlan, Molecular Ther 2011). The low dose group observed gene expression modestly decreased over the first 9 months then stabilized whereas the high dose group observed expression at 1 month but was reduced at month 3, and then stabilized thereafter. The study noted also a wide variation in gene expression across even animals treated in the same dose group, and suggests we could observe similar issues in human clinical studies with Genzyme's intravitreal delivery. Furthermore a safety examination observed signs of intraocular inflammation in 78% of

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

the eyes treated in the high dose group. For reference, we have not observed any intraocular inflammation with preclinical data generated with the Avalanche sFLT01. Recall, Genzyme previously partnered with AGTC (AGTC, $18.18, NC) regarding its rHSV production system, and evaluated in this study both rAAV2sFLT01 produced through AGTC's rHSV system, and also evaluated via production of an undisclosed transfection system. Animals dosed with sFLT01 produced from both systems exhibited vitreal inflammation. The study investigators conclude the viral vector capsid may be the leading cause of the inflammation. The study also investigated immunogenicity through AAV2 titers and found no relationship between pre-existing titers and intraocular inflammation.

The product is in a Phase I trial. The study enrolled 34 patients with wAMD and will investigate four different dose levels delivered intravitreally into a single eye using a fixed volume of 100 µL: 2 x 10^8, 2x 10^9, 2 x 10^{10}, and 2 x 10^{11}. Patients in this part of the study will not be randomized. In the second part of the study, the highest dose that was safe and well-tolerated will be studied in 10 more patients. Patients may have Lucentis injection 26 weeks after their AAV2-sFlt01 injection to verify their responsiveness to anti-VEGF therapy, if they have not yet demonstrated a response to the gene therapy. All patients in the trial will be asked to participate in the Extended Follow-Up (EFU) program for up to an additional 4 years. The primary endpoint will the maximum tolerated dose (MTD) of a single uniocular intravitreal injection of AAV2-sFlt01, and number of treatment emergent adverse events through to week 52 and 4 years. Secondary outcome measures include decreased retinal thickness out to week 52 and 4 years. It remains to be seen if Genzyme's intravitreal injection will lead to sufficient gene expression. Data is expected at AAO 2014 in October.

Novartis (ESBA-1008): At the most recent ASRS meeting, Dr. Pravin Dugel presented Phase I/II data from ESBA-1008 data which assessed the drug's potency and durability vs Lucentis in wet AMD patients. The data suggests the highest dose arm (6 mg) of ESBA-1008 could differentiate on efficacy after a single injection in treatment-naive wAMD patients. Novartis is currently pursuing a Phase II head-to-head study v. REGN's Eylea with the 6 mg dose.

Novartis evaluated four arms of ESBA-1008 (0.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg) v. Lucentis 0.5 mg in a trial where newly diagnosed wAMD patients were administered a single injection and followed for change in central subfield thickness at month 1 (1 EP), change in central subfield thickness to month 6 (2 EP), change in visual acuity to month 6 (2 EP), and time to standard-of-care (2 EP). The trial enrolled pts with baseline VA of 34 to 73 letters with predominantly classic, minimally classic, and occult wAMD disease. ESBA-1008 did not differentiate and was considered non-inferior to Lucentis on the 1EP of central subfield thickness (CSFT) change at month 1 when comparing to the 4.5 and 6.0 mg doses. The 6.0 mg dose observed only a 8.9 mm change in CSFT at month 1 vs Lucentis, however, beyond month 1, ESBA-1008 6.0 mg observed a numerically greater reduction of CSFT than Lucentis with a 24 mm difference at week 6 and 22 mm difference at week 8. It appears the greatest difference between ESBA-1008 6.0 mg and Lucentis was observed with the visual acuity endpoint. The 6.0 mg dose observed an 8.8 letter imp't over baseline at week 4 compared to 7.0 letters improvement with Lucentis. At week 6, the 6.0 mg dose observed a 10.4 letter improvement compared to 6.5 letters with Lucentis. By months 5 and 6, the 6.0 mg dose continued to observe a 2 letter improvement over Lucentis. Lastly, the median time to receiving std of care therapy was 30 days longer with ESBA-1008 6.0 mg compared to Lucentis. Clearly these preliminary data suggests ESBA-1008 could offer vision gains with potentially more infrequent delivery of treatment. SOC was administered by the study investigator if changes to retina thickness, vision acuity, or intraocular safety occurred. Safety appeared tolerable with no systemic adverse events, and further supported by 3-6 fold lower systemic exposure with ESBA-1008 compared to Lucentis in rabbit and monkey models.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Novartis is also conducting a head-to-head trial vs. Eylea in 173 patients in tx naïve wAMD. Interestingly, the design was changed mid-way in the trial with the current trial design stipulating a 7-injection tx regimen over 56 weeks with ESBA-1008 vs an 8-week tx regimen with Eylea. Previously, the trial design would have evaluated 4 inj over 24 weeks with both agents. Last pt enrolled was July 2013, therefore, we could expect ESBA-1008 data at AAO in October. We await these data as a one-injection difference with potentially better efficacy could differentiate to current std of care.

Allergan (DARPin): Allergan is developing DARPin (abicipar pegol) for wAMD, a long-acting anti-VEGF product which could potentially require fewer injections with better overall duration than Eylea or Lucentis. In late 2013, AGN presented data from the Phase II REACH study for wAMD and suggested that the product profile may not be differentiated on efficacy, and there was a greater rate of inflammation. The first two cohorts of the Phase II REACH trial evaluating DARPin in wet AMD were presented with the Stage I portion enrolling 3-9 pts in each of the four cohorts (1, 2, 3, and 4.2 mg) and suggests the median time to retreat was approximately at week 8 for 1-3 mg cohorts and 12 weeks with the 4.2 mg cohort. Stage II portion randomized pts to 3.0 (n = 58) and 4.2 mg (n = 67) of DARPin or Lucentis (n = 58) and pts received a second dose at wk 16 or earlier if re-tx criteria were met with the 1 EP as time to re-tx. Approximately 50% of the pts in the Lucentis and AGN 3mg arm and 40% of AGN 4.2mg pts requiring a second dose by day 65-70 and in our view suggesting a largely undifferentiated product profile for a treatment with supposedly longer half-life and better binding affinity. Interestingly, by wk 16 which is when all pts received a second dose, the visual acuity imp't was similar across all 3 arms (5.5-7 letters) with no evident dose-response btwn the 3.0 and 4.2 mg arms. DARPin advocates may point to the 3mg arm achieving a 10 letter gain at wk 8 vs 6 letters with Lucentis and 5 letters with AGN 4.2 mg, however, a close evaluation of the curves suggests 20% of AGN 3.0 mg pts received a second dose by day 40 vs only 10% in each of the other 2 arms, and with the second injection potentially driving this benefit. The safety profile continues to suggest safety remains an issue with 11.2% of patients reporting intraocular inflammation (anterior chamber inflammation, vitritis, AC cells, vitreal cells, endophthalmitis).

AGN provided an update on the Phase II data at the end of June for Stage 3 of the Phase II study. In the double-masked trial, a total of 64 patients were randomized to receive DARPin 1 mg (n=25), DARPin 2 mg (n=23), or Lucentis 0.5 mg (n=16) and were followed for 20 weeks. All patients received doses at the start of the trial and at weeks 4 and 8. Patients on Lucentis received additional doses at weeks 12 and 16 (patients on DARPin received sham on those weeks). The trial enrolled treatment-naïve patients and baseline visions of 20/32 to 20/320 v. the first two cohorts enrolling 20/40 to 20/800. So the trial is enrolling healthier patients v. the first two stages. The topline analysis showed that after 16 weeks, mean VA improvement from baseline was 8.2 letters for DARPin 2 mg, 6.3 letters for DARPin 1 mg, and 5.3 letters for Lucentis. After 20 weeks, mean VA improvement from baseline was 9.0 letters for DARPin 2 mg, 7.1 letters for DARPin 1 mg, and 4.7 letters for Lucentis. There were no serious adverse events in any study group. There were two patients on DARPin arm 2 mg and three patients on DARPin 1 mg who had ocular inflammation, implying about a 10% rate of inflammation, which is little improved from the other Phase II studies. AGN has been working to enhance the manufacturing process of DARPin. AGN plans to start Phase III studies in Q2 2015 when new material from the new manufacturing process is available.

Ophthotech (Fovista): Ophthotech is developing Fovista, an agent designed to target the platelet derived growth factor (anti-PDGF). Fovista is administered in combination with an anti-VEGF therapy for the treatment of wAMD. In mid-2013, OPHT began a Phase III program for Fovista, which consists of three separate trials for newly diagnosed wAMD conducted in ~1,866 patients in ~225 centers internationally. Two of the Phase III trials

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

will evaluate safety and efficacy of 1.5 mg Fovista + 0.5 mg Lucentis v. 0.5 mg Lucentis monotherapy randomized 1:1 with 311 patients in each arm. The third trial will evaluate 1.5 mg Fovista + 2.0 mg Eylea or 1.25 mg Avastin v. 2.0 mg Eylea or 1.25 mg Avastin monotherapy with 311 patients in each of the two arms. Based on estimates for enrollment, it expects to have topline data in 2016 with potential U.S./EU filing by YE 2016. Ophthotech believes that if two of the 3 trials demonstrate superior efficacy it will have a sufficient data package (including Phase I and Phase IIb results) to support marketing approval in the U.S. and EU. If, however, only one of those two trials includes Fovista + Lucentis, the company acknowledges the FDA/EMA may not grant regulatory approval.

The primary endpoint for the Phase III trials will be mean change in visual acuity (VA) from baseline of the combination therapy v. monotherapy at 12 mo. Secondary endpoints include: proportion of patients in each treatment group gaining >20 ETDRS letters, gaining >25 ETDRS letters, and losing >5 ETDRS letters from baseline all at month 12, and mean change in VA in ETDRS letters from baseline at month 6. Patients will be treated and assessed once a month for 12 months and continue for another 12 months thereafter. In the second 12 months, patients will continue to be assessed every month and treated every other month with final follow-up at 24 months. If at any alternate month visit during the second 12 months a patient's visual acuity has decreased by >5 ETDRS letters since previous visit, or the patient's VA decreased by any amount since the patient's previous visit and the physician makes certain negative findings by fluorescein angiography or OCT, the patient will be treated at that alternate month visit. The PIII program also provides a 30-min delay in the injection of Fovista after the anti-VEGF drug to minimize risk of unacceptable increases in intraocular pressure. Ophthotech may conduct a separate study to evaluate the safety of administering Fovista immediately after an anti-VEGF, or explore a potential co-formulation.

Ophthotech's program plans to exclude wAMD patients with pure occult choroidal neovascularization which represents ~40% of cases, potentially limiting the size of Fovista's market opportunity. Instead, it will likely conduct a separate study in such patients. Also, Ophthotech intends to investigate the Fovista/anti-VEGF combo in up to 50 VEGF-resistant patients.

The composition of matter (CoM) patent for Fovista will expire in 2017. Ophthotech also owns a method-of-use (MOU) patent covering Fovista + Avastin or Lucentis in wAMD to expire in 2024, and could be eligible for Hatch-Waxman extension. For Europe, the COM patents for Fovista are expected to expire in 2018. Ophthotech also owns European MOU patents expected to expire in 2024. The company has filed additional MOU patent applications for treating wAMD with Fovista + Eylea in the U.S. and Europe. These patents are still in early stages of prosecution, but if granted would be expected to expire in 2030.

Allegro (ALG-1001): Allegro Ophthalmics, LLC (private), is developing ALG-1001, an oligopeptide that binds to integrins ($\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha 5\beta 1$, and $\alpha 3\beta 1$) which have been reported to be expressed in ocular tissue of wAMD and diabetic retinopathy patients. The integrins are believed to play a role in cell signaling and regulating cellular shape, motility, and the cell cycle. ALG-1001 has anti-angiogenic properties and is believed to be able to shut down production, reduce leakage, and inhibit growth of aberrant blood vessels. ALG-1001 also targets key integrin receptor sites at the vitreoretinal interface to release cellular adhesion between the vitreous and retina. Allegro announced Phase I data last year at ARVO in patients with BCVA between 20/50 to 20/320. Fifteen patients (4 treatment-experienced) were dosed with ALG-1001 2.0 mg (n = 8) or 3.2 mg (n = 7) for 3 monthly injections. Data at day 120 (60-day post-treatment) report vision loss of 2.3 letters in the overall group driven by the lower 2.0 mg arm which observed a 10.6 letter decline vs the high dose 3.2 mg arm reporting a gain of 8.0 letters. In October 2013,

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Allegro announced that is beginning two Phase II clinical studies for wAMD and symptomatic vitreomacular traction (VMT).

Other Companies Developing Products for wAMD

Other companies are developing products for wAMD that may compete with AAVL. Many of these products aim at reducing the frequency of injections to relieve treatment burden. We summarize such companies in Exhibit 17:

Exhibit 17: Companies developing products for wAMD.

Company	Ticker/Parent	Product	Mechanism of Action	Stage in Clinical Development
Aerpio Therapeutics	Private	SKB-9778	Tie-2 Activator	Phase II
Allergan	AGN	DARPin	Pegylated abicipar for longer half-life	Phase III
Genzyme	A Sanofi company (SAN FP)	AAV2-sFlt01	wAMD	PI data at AAO (Genzyme)
Inconic Therapeutics	Private	hl-con1	Chimeric IgG-like homodimeric protein which targets Tissue Factor (TF)	Phase I
Lpath Therapeutics	LPTN	iSONEP	Anti-S1P mAb	Phase II, data in Q1 2015
Novartis	NOVN VX	ESBA-1008	Single-chain antibody fragment binding VEGF	Phase II (HTH with Eylea)
Ocular Therapeutix	OCUL	Anti-VEGF depot	Anti-VEGF, posterior segment sustained release injection	Preclinical
Ohr Pharmaceutical	OHRP	Squalamine Eye Drops	Anti-VEGF mAb	Phase II
Ophthotech Corporation	OPTH	Fovista	Anti-PDGF, in combination with anti-VEGF	Phase III
Regeneron Pharmaceuticals	REGN	REGN2176-3 Nesvacumab/REGN910	Anti-PDGF and Eylea Ang2 mAb + Eylea	Phase I Preclinical
Roche	ROG VX	Long-acting Lucentis	N/A	N/A
Neurotech Pharmaceuticals	Private	NT-503 NT-506	ECT implant capable of continuously secreting anti-VEGF agents ECT implant capable of continuously secreting anti-PDGF agents, may be used in conjunction with VEGF antagonists	Phase I/II Preclinical

Source: Company data; Jefferies.
Ticker(s): LPTN ($3.21, NC), OCUL ($15.45, NC), OHRP ($8.15, NC).
Abbreviations: ECT: Encapsulated Cell Technology

Other Companies Developing Gene Therapy Products for Opthalmic Diseases

Several other companies are developing gene therapy products for ophthalmic diseases, and many could potentially move into wAMD and compete with AAVL. We summarize such companies in Exhibit 18:

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 18: Companies developing gene therapy products for ophthalmic diseases.

Company	Ticker/Parent	Gene Therapy Product	Targeted Ophthalmic Disease	Stage in Clinical Development
Applied Genetic Technologies	AGTC	(no name)	X-linked juvenile retinoschisis (XLRS)	Initial clinical data mid-2015
			Achromatopsia	Initial clinical data mid-2015
			X-linked retinitis pigmentosa (XLRP)	Additional preclinical studies 2014-2015
			Additional eye indications	Initial preclinical studies 2015
Asklepios BioPharmaceuticals	Private	(no name)	Retinitis Pigmentosa	Preclinical
Eos Neuroscience	Private	(no name)	Retinitis Pigmentosa	Preclinical
			wAMD	Preclinical
GenSight	Private	GS010	Leber Hereditary Optic Neuropathy (LHON)	Phase I
			Retinitis Pigmentosa	Preclinical
Genzyme	A Sanofi company	AAV2-sFlt01	wAMD	PI data at AAO (Genzyme)
Hemera Biosciences	Private	HMR59	wAMD	Phase I
Nightstarx Biopharmaceuticals	Private	AAV-REP1	Choroideremia	Phase II
RetroSense Therapeutics	Private	RST-001	Retinitis Pigmentosa	Preclinical
			Dry AMD	Preclinical
ReGenX Biosciences	Private	rAAV2-NAV products	wAMD	Phase I
			X-linked Retinitis Pigmentosa	Preclinical
			Leber Congenital Amaurosis (LCA)	Preclinical
Spark Therapeutics	Private	AAV2-hRPE65v2	RPE65 Blindness	Phase III
		(no name)	X-linked Recessive Dystrophy	Entering clinic in 2014
		(no name)	GT038 for RHO-ADRP	Entering clinic in 2015
		(no name)	XLRS	Preclinical

Source: Company data; Jefferies.

Background on Wet AMD

Age-related macular degeneration affects the photoreceptors and the retinal pigment epithelium (RPE) in the eye. Photoreceptors are critical to converting light into signals that are converted into vision with two types of cells, rods and cones, which are responsible for transmission of light signals. Rods are narrower than cones but the chemical process in each that supports phototransduction is similar. The RPE are epithelial cells found at the base of the retina and are attached to the inner layer of the Bruch's membrane. The RPE plays a critical role in supplying nutrients and also transport water, ions, and metabolic end products from the subretinal space to the choroid and also provide a mechanism to eliminating waste products for the retina. Bruch's membrane is a thin connective tissue located btwn the RPE and choriocapillaris and serves to control the flow of material to/from choriocapillaris to the RPE. As Bruch's membrane's composition changes with age, RPE may be exposed to metabolic byproducts that diminish its function and as a result drusen (accumulated deposits of debris) may form. Drusen is believed to be metabolic byproduct material that cannot cross the Bruch's membrane for removal by the choroid capillaris. In dry AMD, drusen deposits form and are clustered around the macula with no abnormal vascularisation in the subretina and is generally asymptomatic. As RPE cells degenerate, geographic atrophy may develop and vision may be affected. In wet AMD, Bruch's membrane is compromised and ruptures and VEGF is released which leads to the formation of a CNV lesion(s). CNV lesions consist of leaky blood vessels that grow underneath the RPE and retina and can lead to edema in the retina. Disruption to the retina can cause progressive vision loss if untreated. CNV can be categorized to three types: occult, mixed, or classic. Occult CNV is restricted to the space beneath the RPE and vision loss is considered mild. Classic CNV is characterized by the CNV penetrating the pigment epithelium and grows into the subretina.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

AVA-201

A Potential Prophylactic Treatment of wAMD

AAVL is also developing AVA-201 for wAMD prevention. AVA-201 is designed to deliver same sFlt-1 expressing gene as AVA-101 but uses a different AAV vector delivery method optimized through AAVL's directed evolution platform. Also, AVA-201 is delivered by intravitreal injection rather by subretinal injection. AAVL owns exclusive rights for the development and commercialization of AVA-201 worldwide. AAVL expects to begin IND-enabling studies in 2015, and follow with a Phase I trial. AAVL estimates that there are ~73 million patients in the U.S. who are at high-risk for developing wAMD. If AVA-201 demonstrates efficacy in wAMD, AAVL may also consider expanding into DME and CRVO, which represent significant upside.

AAVL investigated AVA-201 in an initial study in non-human primates to establish proof-of-concept. In the non-human primate test subjects, AVA-201 was delivered in one eye, and a control vector was delivered in the other eye. At 16 months, choroidal neovascularization was induced by laser irradiation and assessed at 2 and 4 weeks. By week 4, none of the eyes treated with AVA-201 developed lesions while 46% of the control eyes did (Exhibit 19). Thus, a single dose of AVA-201 was able to prevent development of disease 17 months later.

Exhibit 19: Long-term prevention of choroidal neovascularization in non-human primates

	Lesions Graded on Fundus Fluorescein Angiogram	
Subject	**Right Eye (sFlt-1 treated)**	**Left Eye (inactive protein)**
1	0/8	6/8
2	0/8	3/8
3	0/8	2/8

Source: Company data (S-1); Jefferies.

AVA-311

Juvenile X-linked Retinoschisis (XLRS)

AAVL is also developing AVA-311 for juvenile X-linked retinoschisis (XLRS), an inherited retinal and genetic disease that occurs almost exclusively in males. XLRS is caused by mutations in the retinoschisis (RS1) gene on the X-chromosome. The RS1 protein binds to the surface of the photoreceptors and bipolar cells in the retina and helps maintain tissue integrety. If production of the RS1 protein is disrupted, schisis (splitting) may result and leakage of the blood vessels. Vision impairment and blindness can result in early childhood. The prevalence of XLRS is ~10,000 boys and men.

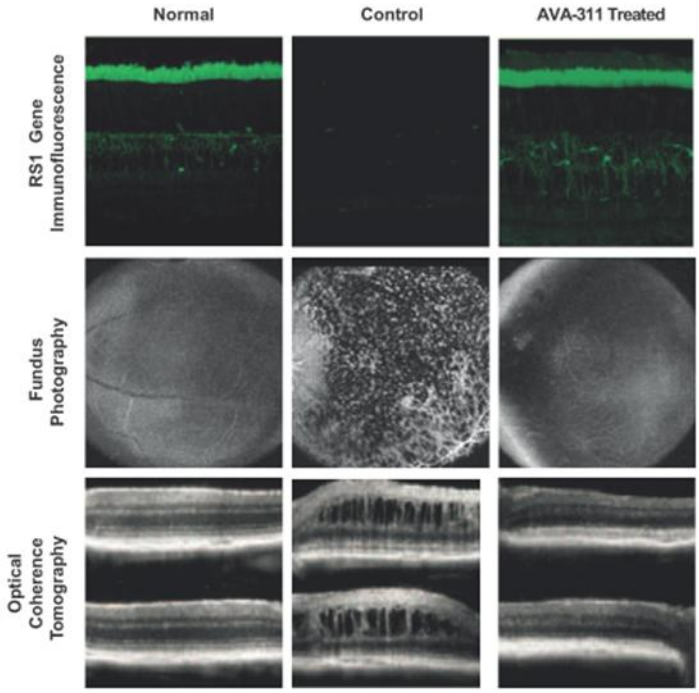
AAVL is working on AVA-311 under the Collaboration Agreement with REGN (see Collaborations), and REGN will be responsible for various preclinical studies. If REGN exercises its option it will be responsible for all preclinical studies and clinical trials for AVA-311 and will retain worldwide commercialization rights. AAVL has the option to share up to 35% of the development costs and profits from AVA-311.

AVA-311 is designed to deliver the retinoschisis (RS1) expressing gene, optimized by AAVL's directed evolution technology. AVA-311 is delivered intravitreally. As can be seen

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

from the immunofluorescence images of a mouse model in a preclinical study, a single intravitreal injection of AVA-311 into one eye showed noticeable improvement comparable to a normal eye v. the untreated eye (control). Fundus photographs and optical coherence tomography photographs also showed that AVA-311 restored the appearance of a normal retina. AAVL/REGN also evaluated retinal function through electroretinography (ERG), which measures electrical responses of various cell types in the retina. AAVL/REGN noted that treated eyes showed significant improvement in function in one month, and was maintained over 4 months. The untreated eyes showed continued decline over the same 4 month period.

Exhibit 20: RS1 gene immunofluorescence, fundus photography, and optical coherence tomography images of AVA-311 treated eyes (right) v. control (middle) and normal eyes (left).



Source: Company data (S-1); Jefferies.

Efficacy Endpoints for XLRS – Challenges and Considerations. As we have described earlier, the FDA published a briefing document that outlines the issues and concerns related specifically to gene therapy products for retinal disorders in 2011. We believe their discussion on efficacy endpoints may have relevance to AVA-311 for XLRS, considering that XLRS is an inherited retinal disease. Although AVA-311 has not moved to clinical trials yet, we believe it is useful to look at what efficacy endpoints may be appropriate.

In the briefing document, the FDA cites the following as useful efficacy endpoints: visual acuity (VA), visual field, color vision and area of non-seeing retina. The FDA cites that improvement in best corrected distance visual acuity is considered a clinically meaningful endpoint. On a standard ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity chart, the change is equivalent to a 15-letter improvement. The FDA raised some

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

concerns that pertain to inherited retinal disorders using VA as an endpoint. First, the FDA raised concern that the rarity of disease (~10,000 for XLRS), which would necessarily mean a trial with a small sample size. A clinically important effect may therefore be difficult to detect. Second, because XLRS is an inherited retinal disorder and its effects manifest themselves at an early age, young children who are not old enough may not be able to provide reliable best corrected distance visual acuity scores. Thus, endpoints used in adult populations may not be suitable for pediatric use.

Collaborations

REGN Collaboration. In May 2014, REGN and AAVL entered into a broad collaboration to jointly develop and commercialize novel gene therapy products based on AAVL's Ocular BioFactory platform for the treatment of ophthalmologic diseases. The collaboration covers up to eight distinct therapeutic targets including AVA-311. AAVL has received an initial payment of $8.0 million and is eligible for reimbursement of additional collaboration research costs. AAVL will also receive contingent payments of up to $640 million upon certain development and regulatory milestones, plus low-to-mid-single-digit royalties on worldwide net sales of collaboration product candidates. For any two targets, AAVL has the option to share up to 35% of the worldwide development costs and profits.

REGN has a time-limited right of first negotiation for certain rights to AVA-101 for wAMD upon completion of the ongoing Phase IIa trial.

Capital Structure

As of March 31, 2014, AAVL had cash and equivalents of $0.2 million. In April 2014, AAVL received gross proceeds of $52.9 million from the sale of 7,321,003 shares of Series B convertible preferred stock, including 7,025,88 shares to investors for cash at $7.53 per share, and 295,115 shares upon the conversion of the 2013 Notes. In connection with the closing of the Series B financing, AAVL also repurchased 531,208 shares of Series A convertible preferred stock from an investor for $4.0 million. AAVL also converted the outstanding balance under our related-party convertible notes of $2.0 million into 295,115 shares of Series B convertible preferred stock, and there was a related loss on extinguishment of related-party convertible notes of $2.2 million. Lastly, in May 2014, AAVL also received initial payments of $8.0 million in connection with its collaboration with REGN. REGN also agreed to purchase up to $10.0 million of AAVL's common stock in a separate private placement concurrent with the completion of the offering at a price per share equal to the public offering price.

AAVL believes it is sufficiently capitalized to operate through at least December 31, 2015.

Management Team

Thomas W. Chalberg, Jr., Ph.D. – Founder & Chief Executive Officer

Dr. Chalberg is a co-founder of Avalanche and has been a member of the board of directors since July 2006. He has served as President and Chief Executive Officer since October 2010. Prior to joining Avalanche, Dr. Chalberg worked at Genentech (December 2005 to October 2010), where he held a number of roles in ophthalmology and oncology, including Market Development Senior Manager for Lucentis and Avastin, Group Manager leading the Lucentis strategy team and Global Business Lead for Lucentis. From September 2001 to December 2005, Dr. Chalberg was a Howard Hughes Medical Institute Fellow at Stanford University, where his research focused on retinal diseases and new technologies for gene therapy. Dr. Chalberg is currently a member of the Board of Visionary Scientists for Hope for Vision, a non-profit charity supporting vision research. Dr. Chalberg holds an A.B. in Biochemical Sciences from Harvard University, a Ph.D. in Genetics from the Stanford University School of Medicine and an M.B.A. from the Haas

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

School of Business at the University of California, Berkeley. Dr. Chalberg has been chosen to serve on the board of directors due to his role as President and Chief Executive Officer, as well as his many years of experience in ophthalmology research and development and commercialization.

Linda C. Bain – Chief Financial Officer

Ms. Bain has served as Chief Financial Officer and Treasurer since April 2014. Linda has more than 20 years of finance, strategic business partner and audit experience in the biotech and pharmaceutical industries, in both large and small company settings. Prior to joining Avalanche, she served in a variety of senior finance management roles, most recently at bluebird bio where she helped lead the company through a successful IPO process. Preceding her tenure at bluebird bio, Ms. Bain was at Genzyme Corporation, Fidelity Investments and AstraZeneca Pharmaceuticals. Linda began her career as an auditor at Deloitte in Touche. She received her B.S. in Accounting and Business Administration and an Honors Degree in Accounting and Business Administration from the University of the Free State in South Africa. She is a Certified Public Accountant.

Samuel B. Barone, M.D. - Chief Scientific Officer

Dr. Barone has served as Chief Medical Officer since June 2014. Previously, he worked for the Food and Drug Administration (FDA) as a Medical Officer in the Office of Cellular, Tissue, and Gene Therapies from October 2009 to June 2014. Concurrent with his work at the FDA, Dr. Barone was active in clinical practice as an ophthalmologist and vitreoretinal surgeon at Retina Associates, P.C., from October 2010 to June 2014. Prior to that, Dr. Barone served on active duty as a Flight Surgeon for United States Air Force service members at Andrews Air Force Base and at bases in Korea, Afghanistan, and Iraq until 2004. He received his B.S. in Biology from Boston College and his M.D. from The Pennsylvania State University College of Medicine. Following his military service, Dr. Barone completed a residency in ophthalmology at The New York Eye and Ear Infirmary where he served as Chief Resident, as well as a medical and surgical retina fellowship at the University of California, San Diego.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 21: AAVL Income Statement

Avalanche Biotechnologies, Inc.

Quarterly Income Statement

(All values in $MM except EPS and average shares)

	2012A	2013E	2014E					2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
	FY	FY	1QA	2QA	3QE	4QE	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY	FY
Revenue:																			
AVA101- U.S.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	37.3	96.7	360.5	724.9	1129.3	1302.4	1318.3
AVA101- ROW royalty	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10.2	49.3	94.2	112.1	121.3	118.0
License and collaboration revenues	0.0	0.5	0.0	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total revenue, net	**0.0**	**0.5**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**2.0**	**0.0**	**0.0**	**0.0**	**0.0**	**37.3**	**106.9**	**409.8**	**819.0**	**1,241.4**	**1,423.7**	**1,436.2**
Costs and expenses:																			
Cost of goods sold	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9.3	26.7	102.5	204.8	297.9	327.4	316.0
Research & development	13	2.2	0.9	14	3.1	6.5	12.0	18.5	18.5	40.0	42.0	44.1	46.3	48.6	50.1	51.6	53.1	54.2	55.3
Selling, general & administrative	0.5	1.8	0.7	0.7	0.7	0.7	2.9	2.8	3.0	3.3	3.5	3.7	3.9	34.0	35.7	37.5	39.4	41.3	43.4
Total operating expenses	**1.8**	**3.9**	**1.6**	**2.1**	**3.8**	**7.2**	**14.9**	**21.3**	**21.5**	**43.3**	**45.5**	**47.8**	**59.5**	**109.4**	**188.2**	**293.8**	**390.4**	**423.0**	**414.6**
Income (loss) from operations	**(1.8)**	**(3.5)**	**(1.6)**	**(2.1)**	**(3.8)**	**(7.2)**	**(14.9)**	**(19.3)**	**(21.5)**	**(43.3)**	**(45.5)**	**(47.8)**	**(22.2)**	**(2.4)**	**221.6**	**525.2**	**851.0**	**1,000.7**	**1,021.6**
Other income (expense):																			
Miscellaneous (expense) income	(0.0)	(1.9)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Interest income	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Interest expense	0.0	0.0	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (loss) before income taxes	**(1.8)**	**(5.3)**	**(1.6)**	**(2.1)**	**(3.8)**	**(7.2)**	**(14.9)**	**(19.3)**	**(21.5)**	**(43.3)**	**(45.5)**	**(47.8)**	**(22.2)**	**(2.4)**	**221.6**	**525.2**	**851.0**	**1,000.7**	**1,021.6**
Income tax expense (benefit)										0.0	0.0	0.0	0.0	0.0	22.2	183.8	297.8	350.2	357.6
Income tax (%)										*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*10.0%*	*35.0%*	*35.0%*	*35.0%*	*35.0%*
Net Income (GAAP)	**(1.8)**	**(5.3)**	**(1.6)**	**(2.1)**	**(3.8)**	**(7.2)**	**(14.9)**	**(19.3)**	**(21.5)**	**(43.3)**	**(45.5)**	**(47.8)**	**(22.2)**	**(2.4)**	**15.0**	**341.4**	**553.1**	**650.5**	**664.0**
Adjusted Items (Non-GAAP)																			
Stock options	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	4.0	5.0	6.0	7.0	14.0	16.0	18.0	20.0	22.0	24.0	25.0
Depreciation and amortization expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Non-GAAP)	**(1.8)**	**(5.3)**	**(1.6)**	**(2.1)**	**(3.8)**	**(7.2)**	**(14.9)**	**(16.3)**	**(17.5)**	**(38.3)**	**(39.5)**	**(40.8)**	**(8.2)**	**13.6**	**33.0**	**361.4**	**575.1**	**674.5**	**689.0**
EPS, GAAP																			
Basic	(0.50)	(1.45)	(0.11)	(0.08)	(0.14)	(0.27)	(0.61)	(0.72)	(0.79)	(1.58)	(1.65)	(1.60)	(0.74)	(0.08)	0.49	10.96	17.59	20.48	20.70
Diluted	**$ (0.50)**	**$ (1.45)**	**$ (0.11)**	**$ (0.08)**	**$ (0.14)**	**$ (0.27)**	**$ (0.61)**	**$ (0.72)**	**$ (0.79)**	**$ (1.58)**	**$ (1.65)**	**$ (1.60)**	**$ (0.74)**	**$ (0.08)**	**$ 0.49**	**$ 10.96**	**$ 17.59**	**$ 20.48**	**$ 20.70**
Weighted average share- Basic	3.6	3.7	14.7	26.6	26.6	26.6	23.6	26.8	27.1	27.4	27.6	29.9	30.2	30.5	30.8	31.1	31.4	31.8	32.1
Weighted average share- Diluted	3.6	3.7	14.7	26.6	26.6	26.6	23.6	26.8	27.1	27.4	27.6	29.9	30.2	30.5	30.8	31.1	31.4	31.8	32.1

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 22: AAVL Balance Sheet

Avalanche Biotechnologies

Balance Sheet

(All values in $MM)

	2012A FY	2013A FY	2014E FY	2015E FY	2016E FY	2017E FY	2018E FY	2019E FY	2020E FY	2021E FY	2022E FY	2023E FY	2024E FY	2025E FY
Current assets:														
Cash and cash equivalents	0.4	0.6	159.9	145.8	130.8	92.2	55.9	91.8	85.6	101.3	136.4	499.9	1,076.1	1,751.6
Certificants of deposit	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cash and investments	**0.4**	**0.6**	**159.9**	**145.8**	**130.8**	**92.2**	**55.9**	**91.8**	**85.6**	**101.3**	**136.4**	**499.9**	**1,076.1**	**1,751.6**
Prepaid expenses/Acct receivable	0.0	0.3	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Total current assets	**0.4**	**0.8**	**160.5**	**146.4**	**131.4**	**92.8**	**56.5**	**92.3**	**86.2**	**101.9**	**137.0**	**500.5**	**1,076.7**	**1,752.2**
Other	0.0	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total assets	**0.4**	**1.1**	**160.8**	**146.7**	**131.7**	**93.2**	**56.9**	**92.7**	**86.6**	**102.2**	**137.4**	**500.9**	**1,077.0**	**1,752.5**
Current liabilities:														
Accounts payable	0.5	0.8	0.9	2.1	3.6	2.3	4.5	5.1	6.2	7.3	8.4	9.5	9.5	9.5
Accrued expenses	0.3	0.4	0.7	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Deferred rent	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Accrued bonuses	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Current portion of deferred revenue	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total current liabilities	**0.8**	**1.2**	**1.7**	**4.2**	**5.7**	**4.3**	**6.5**	**7.1**	**8.2**	**9.3**	**10.4**	**11.5**	**11.5**	**11.5**
Other	0.5	0.1	0.2	14	14	14	14	14	14	14	14	14	14	14
Total Liability	**1.4**	**1.3**	**1.9**	**5.6**	**7.1**	**5.7**	**7.9**	**8.5**	**9.6**	**10.7**	**11.8**	**12.9**	**12.9**	**12.9**
Stockholders' equity:														
Preferred stock	2.5	8.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Common stock	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Additional paid-in capital	0.1	0.6	63.1	122.1	123.1	124.6	126.6	129.1	252.6	405.2	576.4	240.5	666.7	1,167.2
(Deficit) accumulated during the development	(3.6)	(8.9)	(13.2)	(83.2)	(66.7)	(66.3)	27.2	156.2	156.2	15.6	15.6	236.0	386.0	561.0
Total stockholders' equity	**(1.0)**	**(0.2)**	**158.9**	**141.1**	**124.6**	**87.5**	**49.0**	**84.2**	**77.0**	**91.5**	**125.6**	**488.0**	**1,064.1**	**1,739.6**
Total liabilities and stockholders' equity	**0.4**	**1.1**	**160.8**	**146.7**	**131.7**	**93.2**	**56.9**	**92.7**	**86.6**	**102.2**	**137.4**	**500.9**	**1077.0**	**1752.5**

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 23: AAVL Cash Flow Statement

Avalanche Biotechnologies

Cash Flow Statement

(All values in $MM)

	2012A FY	2013A FY	2014E FY	2015E FY	2016E FY	2017E FY	2018E FY	2019E FY	2020E FY	2021E FY	2022E FY	2023E FY	2024E FY	2025E FY
Cash flows from operating activities:	(18)	(5.3)	(14.9)	(19.3)	(21.5)	(43.3)	(45.5)	(47.8)	(22.2)	(2.4)	15.0	341.4	553.1	650.5
Net income														
Adjustments to reconcile cash by operating activities:														
Depreciation and amortization expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Compensation expense	0.1	0.5	0.6	3.0	4.0	5.0	6.0	7.0	14.0	16.0	18.0	20.0	22.0	24.0
Other	0.0	2.6	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Changes in operating assets and liabilities:														
Prepaid expenses	(0.0)	(0.3)	(0.3)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Deferred rent	0.0	0.0	0.2	1.2	1.5	(1.3)	2.2	0.6	1.1	1.1	1.1	1.1	0.0	0.0
Deposit	0.0	(0.1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Accounts receivable	0.0	0.0	(0.2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Accounts payable	0.4	0.3	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Accrued expenses and deferred rent	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Net cash provided by operating activities	**(1.2)**	**(2.2)**	**(13.6)**	**(14.0)**	**(14.9)**	**(38.5)**	**(36.2)**	**(39.1)**	**(6.0)**	**15.8**	**35.2**	**363.6**	**576.3**	**675.6**
Cash flows from investing activities:														
Purchase of fixed assets	(0.0)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
Net cash (used in) provided by investing activities	**(0.0)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**	**(0.1)**
Cash flows from financing activities:														
Issuance of common stock, net of offering costs	0.0	0.0	119.1	0.0	0.0	0.0	0.0	75.0	0.0	0.0	0.0	0.0	0.0	0.0
Issuance of common stock from exercise of stock options	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds from preferred stock	0.0	1.0	52.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds from notes payable	0.5	1.5	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Principal payments on debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net cash (used in) provided by financing activities	**0.5**	**2.5**	**173.0**	**0.0**	**0.0**	**0.0**	**0.0**	**75.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Effect if exchange rate changes on cash/equivalents														
Increase (decrease) in cash and cash equivalents	(0.7)	0.2	159.3	(14.1)	(15.0)	(38.5)	(36.3)	35.8	(6.1)	15.7	35.1	363.5	576.2	675.5
Cash and cash equivalents at beginning of period	1.1	0.4	0.6	159.9	145.8	130.8	92.2	55.9	91.8	85.6	101.3	136.4	499.9	1,076.1
Cash and cash equivalents at end of period	**0.4**	**0.6**	**159.9**	**145.8**	**130.8**	**92.2**	**55.9**	**91.8**	**85.6**	**101.3**	**136.4**	**499.9**	**1,076.1**	**1,751.6**

Source: Jefferies estimates, company data.

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 24: AAVL DCF Analysis

Avalanche Biotechnologies

Discounted Cash Flow Analysis

(All values in $MM)	*2012A*	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
Sales	*0.0*	0.5	0.0	2.0	0.0	0.0	0.0	0.0	37.3	106.9	409.8	819.0	1,241.4	1,423.7	1,436.2
Operating Expenses	*1.8*	3.9	14.9	21.3	21.5	43.3	45.5	47.8	59.5	109.4	188.2	293.8	390.4	423.0	414.6
EBIT	*(1.8)*	(3.5)	(14.9)	(19.3)	(21.5)	(43.3)	(45.5)	(47.8)	(22.2)	(2.4)	221.6	525.2	851.0	1,000.7	1,021.6
(-): Taxes	*0.0*	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	22.2	183.8	297.8	350.2	357.6
EBIAT	*(1.8)*	(3.5)	(14.9)	(19.3)	(21.5)	(43.3)	(45.5)	(47.8)	(22.2)	(2.4)	199.4	341.4	553.1	650.5	664.0
(+):Depreciation	*0.0*	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
(+):FAS-123 Options	*0.0*	0.0	0.0	3.0	4.0	5.0	6.0	7.0	14.0	16.0	18.0	20.0	22.0	24.0	25.0
(-): Capital expenditures	*0.0*	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0
Unlevered free cash flow	***(1.8)***	***(3.5)***	***(15.0)***	***(16.4)***	***(17.6)***	***(38.3)***	***(39.6)***	***(40.9)***	***(8.3)***	***13.5***	***217.3***	***361.3***	***575.1***	***674.5***	***689.0***

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 25: AVA-101 Revenue Build for wAMD

Wet AMD

Wet AMD - U.S.	2020	2021		2022		2023		2024		2025		2026		2027		2028		2029		2030	
Total patients (000s)	2,659	2,792	5%	2,932	5%	3,078	5%	3,232	5%	3,394	5%	3,563	5%	3,741	5%	3,929	5%	4,125	5%	4,331	5%
No. of wet AMD pts receiving treatment (000s)	414	430	4%	439	2%	435	-1%	405	-7%	361	-11%	309	-14%	256	-17%	218	-15%	190	-13%	171	-10%
% of total AMD pts	*16%*	*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*	
No. of patients receive Avastin (000s)	166	172	4%	171	0%	165	-3%	150	-9%	130	-13%	108	-17%	87	-19%	72	-18%	63	-13%	56	-10%
% of treated pts	*40%*	*40%*		*39%*		*38%*		*37%*		*36%*		*35%*		*34%*		*33%*		*33%*		*33%*	
No. of patients receive other anti-VEGF (000s)	248	258	4%	268	4%	269	1%	255	-5%	231	-9%	201	-13%	169	-16%	146	-14%	127	-13%	115	-10%
No. of patients receiving AVA-101 (000s)	5.0	12.9	160%	26.8	108%	53.9	101%	68.8	28%	78.6	14%	80.3	2%	67.7	-16%	58.4	-14%	50.9	-13%	45.9	-10%
% of AVA101-treated pts (ex-Avastin)	*2%*	*5%*		*10%*		*20%*		*27%*		*34%*		*40%*		*40%*		*40%*		*40%*		*40%*	
% of entire AMD mkt	*1%*	*3%*		*6%*		*12%*		*17%*		*22%*		*26%*		*26%*		*27%*		*27%*		*27%*	
AVA-101 sales in wet AMD U.S. (000s)	**$124,200.0**	**$322,299.0**	160%	**$668,826.9**	108%	**$1,347,395.5**	101%	**$1,721,032.4**	28%	**$1,964,005.5**	14%	**$2,007,780.0**	2%	**$1,691,698.8**	-16%	**$1,459,106.1**	-14%	**$1,272,974.0**	-13%	**$1,146,970.7**	-10%
Assumptions																					
Total price	*$25,000*	*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*	
Wet AMD - ROW																					
Total patients (000s)	2,787.0	2,871	3%	2,957	3%	3,045	3%	3,137	3%	3,231	3%	3,328	3%	3,428	3%	3,530	3%	3,636	3%	3,745	3%
No. of patients diagnosed with wet AMD (000s)	1,393.5	1,435	3%	1,478	3%	1,523	3%	1,568	3%	1,615	3%	1,664	3%	1,714	3%	1,765	3%	1,818	3%	1,873	3%
% of patients diagnosed	*50%*	*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*	
No. of patients receive treatment (000s)	334	344	3%	343	0%	319	-7%	287	-10%	249	-13%	208	-16%	173	-17%	143	-17%	119	-17%	100	-16%
% of drug-treated pts	*12%*	*12%*		*12%*		*12%*		*12%*		*12%*		*12%*		*12%*		*12%*		*12%*		*12%*	
No. of patients receive Avastin (000s)	117	117	0%	113	-3%	102	-10%	89	-13%	75	-16%	60	-19%	48	-20%	39	-20%	31	-20%	25	-19%
% of Avastin-treated pts	*35%*	*34%*		*33%*		*32%*		*31%*		*30%*		*29%*		*28%*		*27%*		*26%*		*25%*	
No. of patients receive other anti-VEGF (000s)	217	227	5%	230	1%	217	-6%	198	-9%	174	-12%	148	-15%	124	-16%	104	-16%	88	-16%	75	-15%
No. of patients receiving AVA-101 (000s)	-	11.4		34.5	204%	43.4	26%	49.5	14%	52.2	6%	47.2	-9%	42.3	-11%	36.5	-14%	31.7	-13%	27.8	-12%
% of AVA101-treated pts (ex-Avastin)	*0%*	*5%*		*15%*		*20%*		*25%*		*30%*		*32%*		*34%*		*35%*		*36%*		*37%*	
% of entire AMD mkt	*0%*	*3%*		*10%*		*14%*		*17%*		*21%*		*23%*		*24%*		*26%*		*27%*		*28%*	
AVA-101 sales in wet AMD ROW (000s)		**$170,289.9**		**$517,054.3**	204%	**$651,061.7**	26%	**$741,817.8**	14%	**$782,825.3**	6%	**$708,671.6**	-9%	**$634,019.2**	-11%	**$546,968.9**	-14%	**$475,312.2**	-13%	**$417,637.6**	-12%
% royalty	*0%*	*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*	
AVA-101 royalty (000s)		**$34,058.0**		**$103,410.9**		**$130,212.3**	26%	**$148,363.6**	14%	**$156,565.1**	6%	**$141,734.3**	-9%	**$126,803.8**	-11%	**$109,393.8**	-14%	**$95,062.4**	-13%	**$83,527.5**	-12%
Assumptions																					
Total annual price	*$15,000*	*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*	
Total AVA-101 sales in wAMD U.S. (000s)	**$124,200**	**$322,299**	160%	**$668,827**	108%	**$1,347,396**	101%	**$1,721,032**	28%	**$1,964,005**	14%	**$2,007,780**	2%	**$1,691,699**	-16%	**$1,459,106**	-14%	**$1,272,974**	-13%	**$1,146,971**	-10%
Risk discount	*70%*	*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*	
Total AVA-101 sales in wAMD U.S. (risk-adjusted) (000s)	**$37,260**	**$96,690**	160%	**$200,648**	108%	**$404,219**	101%	**$516,310**	28%	**$589,202**	14%	**$602,334**	2%	**$507,510**	-16%	**$437,732**	-14%	**$381,892**	-13%	**$344,091**	-10%
Total AVA-101 sales in wAMD ROW (000s)		**$170,290**		**$517,054**	204%	**$651,062**	26%	**$741,818**	14%	**$782,825**	6%	**$708,672**	-9%	**$634,019**	-11%	**$546,969**	-14%	**$475,312**	-13%	**$417,638**	-12%
Royalty		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*	
Total AVA-101 royalty in wAMD (000s)		**$34,058**		**$103,411**	204%	**$130,212**	26%	**$148,364**	14%	**$156,565**	6%	**$141,734**	-9%	**$126,804**	-11%	**$109,394**	-14%	**$95,062**	-13%	**$83,528**	-12%
Risk discount		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*	
Total AVA-101 sales in wAMD ROW (risk-adjusted) (000s)	**$0**	**$10,217**		**$31,023**	204%	**$39,064**	26%	**$44,509**	14%	**$46,970**	6%	**$42,520**	-9%	**$38,041**	-11%	**$32,818**	-14%	**$28,519**	-13%	**$25,058**	-12%
Total AVA-101 sales in wAMD WW (000s)	**$124,200**	**$492,589**	297%	**$1,185,881**	141%	**$1,998,457**	69%	**$2,462,850**	23%	**$2,746,831**	12%	**$2,716,452**	-1%	**$2,325,718**	-14%	**$2,006,075**	-14%	**$1,748,286**	-13%	**$1,564,608**	-11%

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 26: AVA-101 Revenue Build for CRVO

CRVO

CRVO - U.S.	2020	2021		2022		2023		2024		2025		2026		2027		2028		2029		2030	
Total patients (000s)	860	886	3%	912	3%	940	3%	968	3%	997	3%	1,027	3%	1,058	3%	1,089	3%	1,122	3%	1,156	3%
No. of patients diagnosed with CRVO (000s)	645	664	3%	684	3%	701	2%	714	2%	721	1%	725	1%	728	0%	732	1%	741	1%	754	2%
% of patients diagnosed	*75%*	*75%*		*75%*		*75%*		*75%*		*75%*		*75%*		*75%*		*75%*		*75%*		*75%*	
No. of patients receive treatment (000s)	132	136	3%	140	3%	140	0%	135	-4%	121	-10%	103	-15%	84	-19%	65	-23%	51	-21%	41	-19%
% of drug-treated pts	*21%*	*21%*		*21%*		*21%*		*21%*		*21%*		*21%*		*21%*		*21%*		*21%*		*21%*	
No. of patients receive Avastin (000s)	63	64	1%	65	1%	63	-2%	59	-6%	52	-12%	43	-17%	34	-21%	26	-24%	20	-21%	17	-19%
% of Avastin-treated pts	*48%*	*47%*		*46%*		*45%*		*44%*		*43%*		*42%*		*41%*		*40%*		*40%*		*40%*	
No. of patients receive other anti-VEGF (000s)	69	72	5%	76	5%	77	2%	76	-2%	69	-9%	60	-13%	49	-18%	39	-21%	31	-21%	25	-19%
No. of patients receiving AVA101 (000s)	-	-		3.8		7.7	103%	15.1	96%	18.7	23%	20.4	9%	19.7	-3%	15.5	-21%	12.2	-21%	9.9	-19%
% of AVA101-treated pts (ex-Avastin)	*0%*	*0%*		*5%*		*10%*		*20%*		*27%*		*34%*		*40%*		*40%*		*40%*		*40%*	
% of entire CRVO mkt	*0%*	*0%*		*3%*		*6%*		*11%*		*15%*		*20%*		*24%*		*24%*		*24%*		*24%*	
AVA101 sales in CRVO U.S. (000s)				**$94,687.3**		**$192,392.6**	*103%*	**$377,952.8**	*96%*	**$466,434.1**	*23%*	**$509,500.0**	*9%*	**$492,800.3**	*-3%*	**$387,906.6**	*-21%*	**$305,873.8**	*-21%*	**$248,469.3**	*-19%*
Assumptions																					
Total annual price	*$25,000*	*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*	
CRVO - ROW																					
Total patients (000s)	1,013.0	1,043	3%	1,075	3%	1,107	3%	1,140	3%	1,174	3%	1,210	3%	1,246	3%	1,283	3%	1,322	3%	1,361	3%
No. of patients diagnosed with CRVO (000s)	507	522	0	537	0	553	0	570	0	587	0	605	0	623	0	642	0	661	0	681	0
% of patients diagnosed	*50%*	*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*		*50%*	
No. of patients receive treatment (000s)	81	83	3%	86	3%	89	3%	91	3%	94	3%	97	3%	100	3%	103	3%	106	3%	109	3%
% of drug-treated pts	*16%*	*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*		*16%*	
No. of patients receive Avastin (000s)	31	31	0	31	0	31	0	31	0	32	0	32	0	33	0	34	0	35	0	36	0
% of Avastin-treated pts	*38%*	*37%*		*36%*		*35%*		*34%*		*34%*		*33%*		*33%*		*33%*		*33%*		*33%*	
No. of patients receive other anti-VEGF (000s)	50	53	5%	55	5%	58	5%	60	5%	62	3%	65	5%	67	3%	69	3%	71	3%	73	3%
No. of patients receive Eylea (000s)	-	-		2.8		8.6	214%	12.0	39%	15.5	29%	19.4	25%	21.4	10%	23.4	9%	24.8	6%	26.3	6%
% ofAVA101-treated pts (ex-Avastin)	*0%*	*0%*		*5%*		*15%*		*20%*		*25%*		*30%*		*32%*		*34%*		*35%*		*36%*	
% of entire CRVO mkt	*0%*	*0%*		*3%*		*10%*		*13%*		*17%*		*20%*		*21%*		*23%*		*23%*		*24%*	
AVA101 sales in CRVO ROW (000s)				**$41,268.2**		**$129,511.1**	*214%*	**$180,598.2**	*39%*	**$232,520.2**	*29%*	**$291,749.5**	*25%*	**$320,535.4**	*10%*	**$350,786.0**	*9%*	**$371,936.3**	*6%*	**$394,039.9**	*6%*
% royalty				*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*	
AVA101 royalty (000s)				**$8,253.6**		**$25,902.2**	*214%*	**$36,119.6**	*39%*	**$46,504.0**	*29%*	**$58,349.9**	*25%*	**$64,107.1**	*10%*	**$70,157.2**	*9%*	**$74,387.3**	*6%*	**$78,808.0**	*6%*
Assumptions																					
Total annual price	*$15,000*	*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*	
Total AVA-101 sales in CRVO U.S. (000s)				**$94,687**		**$192,393**	*103%*	**$377,953**	*96%*	**$466,434**	*23%*	**$509,500**	*9%*	**$492,800**	*-3%*	**$387,907**	*-21%*	**$305,874**	*-21%*	**$248,469**	*-19%*
Risk discount				*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*	
Total AVA-101 sales in CRVO U.S. (risk-adjusted) (000s)				**$28,406**		**$57,718**	*103%*	**$113,386**	*96%*	**$139,930**	*23%*	**$152,850**	*9%*	**$147,840**	*-3%*	**$116,372**	*-21%*	**$91,762**	*-21%*	**$74,541**	*-19%*
Total AVA-101 sales in CRVO ROW (000s)				**$41,268**		**$129,511**	*214%*	**$180,598**	*39%*	**$232,520**	*29%*	**$291,749**	*25%*	**$320,535**	*10%*	**$350,786**	*9%*	**$371,936**	*6%*	**$394,040**	*6%*
Royalty				*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*	
Total AVA-101 royalty in CRVO (000s)				**$8,254**		**$25,902**	*214%*	**$36,120**	*39%*	**$46,504**	*29%*	**$58,350**	*25%*	**$64,107**	*10%*	**$70,157**	*9%*	**$74,387**	*6%*	**$78,808**	*6%*
Risk discount				*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*	
Total AVA-101 sales in CRVO ROW (risk-adjusted) (000s)				**$2,476**		**$7,771**	*214%*	**$10,836**	*39%*	**$13,951**	*29%*	**$17,505**	*25%*	**$19,232**	*10%*	**$21,047**	*9%*	**$22,316**	*6%*	**$23,642**	*6%*
Total AVA-101 sales in CRVO WW (000s)				**$135,955**		**$321,904**	*137%*	**$558,551**	*74%*	**$698,954**	*25%*	**$801,250**	*15%*	**$813,336**	*2%*	**$738,693**	*-9%*	**$677,810**	*-8%*	**$642,509**	*-5%*

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Exhibit 27: AVA-101 Revenue Build for DME

DME

DME - U.S.	2020	2021		2022		2023		2024		2025		2026		2027		2028		2029		2030	
No. of patients receive treatment (000s)	318	334	5%	351	5%	351	5%	333	5%	283	5%	221	5%	157	5%	102	5%	64	3%	40	3%
No. of patients receive AVA101 (000s)	-	-		17.5		35.1		66.6	90%	76.4	15%	75.1	-2%	62.7	-16%	40.8	-35%	25.7	-37%	16.2	-37%
% of AVA101-treated pts (ex-Avastin)	*0%*	*0%*		*5%*		*10%*		*20%*		*27%*		*34%*		*40%*		*40%*		*40%*		*40%*	
AVA101 sales in DME U.S. (000s)	**$0.0**	**$0.0**		**$438,243.8**		**$876,487.5**	*NM*	**$1,665,326.3**	*NM*	**$1,910,961.9**	*15%*	**$1,876,989.2**	*-2%*	**$1,567,838.1**	*-16%*	**$1,019,094.7**	*-35%*	**$642,029.7**	*-37%*	**$404,478.7**	*-37%*
Assumptions																					
Total annual price	*$25,000*	*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*		*$25,000*	

DME - RoW	2020	2021		2022		2023		2024		2025		2026		2027		2028		2029		2030	
No. of patients receive treatment (000s)	318	334	5%	351	5%	351	5%	316	5%	268	5%	215	5%	161	5%	117	5%	81	3%	55	3%
No. of patients receive AVA101 (000s)	-	-		17.5		52.6		63.1	20%	67.1	6%	64.4	-4%	51.5	-20%	39.9	-22%	28.4	-29%	19.8	-30%
% of AVA101-treated pts (ex-Avastin)	*0%*	*0%*		*5%*		*15%*		*20%*		*25%*		*30%*		*32%*		*34%*		*35%*		*36%*	
AVA101 sales in DME ROW (000s)	**$0.0**	**$0.0**		**$262,946.3**		**$788,838.8**	*NM*	**$946,606.5**	*NM*	**$1,005,769.4**	*6%*	**$965,538.6**	*-4%*	**$772,430.9**	*-20%*	**$599,116.7**	*-22%*	**$425,549.1**	*-29%*	**$297,641.2**	*-30%*
Assumptions																					
Total annual price	*$15,000*	*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*		*$15,000*	
% of royalty				*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*	
AVA101 royalty (000s)				**$52,589.3**		**$157,767.8**	*200%*	**$189,321.3**	*20%*	**$201,153.9**	*6%*	**$193,107.7**	*-4%*	**$154,486.2**	*-20%*	**$119,823.3**	*-22%*	**$85,109.8**	*-29%*	**$59,528.2**	*-30%*

Total AVA-101 sales in DME U.S. (000s)				**$438,244**		**$876,488**	*100%*	**$1,665,326**	*90%*	**$1,910,962**	*15%*	**$1,876,989**	*-2%*	**$1,567,838**	*-16%*	**$1,019,095**	*-35%*	**$642,030**	*-37%*	**$404,479**	*-37%*
Risk discount				*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*	
Total AVA-101 sales in DME U.S. (risk-adjusted) (000s)				**$131,473**		**$262,946**	*100%*	**$499,598**	*90%*	**$573,289**	*15%*	**$563,097**	*-2%*	**$470,351**	*-16%*	**$305,728**	*-35%*	**$192,609**	*-37%*	**$121,344**	*-37%*
Total AVA-101 sales in DME ROW (000s)				**$262,946**		**$788,839**	*200%*	**$946,607**	*20%*	**$1,005,769**	*6%*	**$965,539**	*-4%*	**$772,431**	*-20%*	**$599,117**	*-22%*	**$425,549**	*-29%*	**$297,641**	*-30%*
Royalty				*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*		*20%*	
Total AVA-101 royalty in DME (000s)				**$52,589**		**$157,768**	*200%*	**$189,321**	*20%*	**$201,154**	*6%*	**$193,108**	*-4%*	**$154,486**	*-20%*	**$119,823**	*-22%*	**$85,110**	*-29%*	**$59,528**	*-30%*
Risk discount				*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*		*70%*	
Total AVA-101 sales in DME ROW (risk-adjusted) (000s)				**$15,777**		**$47,330**	*200%*	**$56,796**	*20%*	**$60,346**	*6%*	**$57,932**	*-4%*	**$46,346**	*-20%*	**$35,947**	*-22%*	**$25,533**	*-29%*	**$17,858**	*-30%*
Total AVA-101 sales in DME WW (000s)				**$701,190**		**$1,665,326**	*138%*	**$2,611,933**	*57%*	**$2,916,731**	*12%*	**$2,842,528**	*-3%*	**$2,340,269**	*-18%*	**$1,618,211**	*-31%*	**$1,067,579**	*-34%*	**$702,120**	*-34%*

Source: Jefferies estimates, company data

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Company Description

Avalanche Biotechnologies, Inc., a clinical-stage biotechnology company, focuses on discovering and developing novel gene therapies for the treatment of ophthalmic diseases based on its Ocular BioFactory platform. Its lead product candidate includes AVA-101, which is in a Phase I/IIa trial for the treatment of wet age-related macular degeneration (AMD). The company is also developing AVA-201, an anti-vascular endothelial growth factor gene therapy product candidate for the prevention of wet AMD; and AVA-311 that is in preclinical studies for the treatment of juvenile X-linked retinoschisis, a rare genetic disease of the retina with no approved therapy. Avalanche Biotechnologies, Inc. has a collaboration agreement with Regeneron Pharmaceuticals, Inc. research, develop, and commercialize gene therapy products. The company was founded in 2006 and is headquartered in Menlo Park, California.

Analyst Certification

I, Biren Amin, certify that all of the views expressed in this research report accurately reflect my personal views about the subject security(ies) and subject company(ies). I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed in this research report.

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Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

Risk which may impede the achievement of our Price Target

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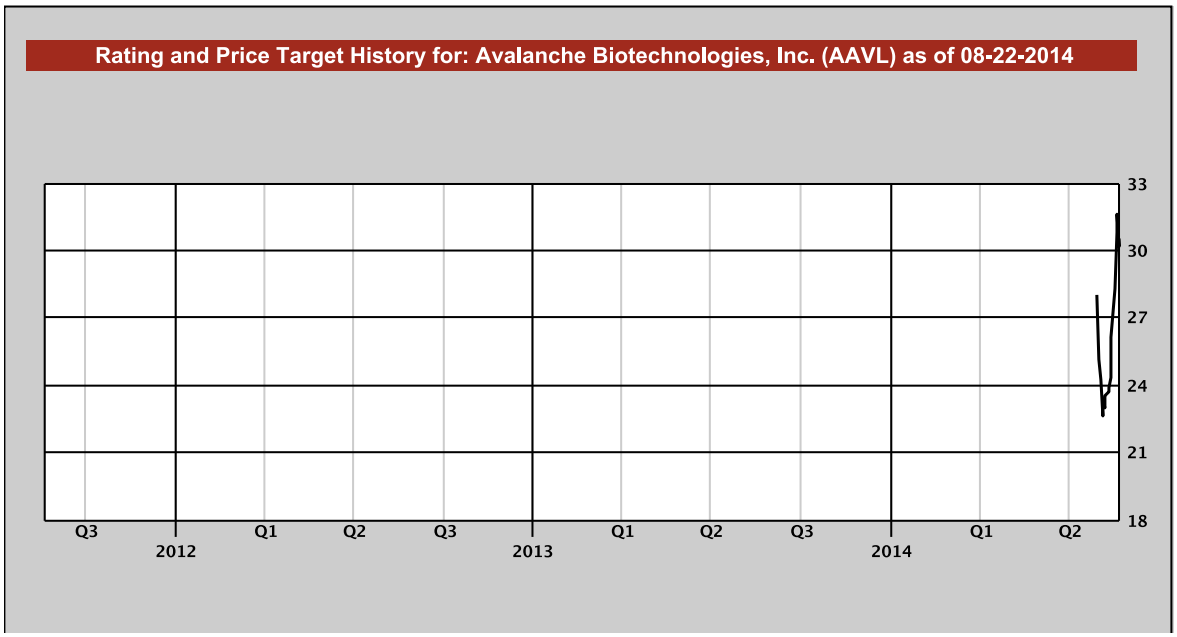
Other Companies Mentioned in This Report

- Bayer AG (BAYN GR: €99.05, BUY)
- Celldex Therapeutics, Inc. (CLDX: $14.55, BUY)
- Kite Pharma (KITE: $21.82, BUY)
- Lonza Group AG (LONN VX: CHF101.40, HOLD)
- Newlink Genetics Corp. (NLNK: $25.06, BUY)
- Novartis AG (NOVN VX: CHF81.35, BUY)
- Regeneron Pharmaceuticals, Inc. (REGN: $340.79, HOLD)
- Roche (ROG VX: CHF265.90, BUY)
- Sanofi (SAN FP: €79.43, BUY)
- uniQure BV (QURE: $11.51, BUY)
- XOMA Ltd. (XOMA: $4.24, BUY)



Distribution of Ratings

Rating	Count	Percent	IB Serv./Past 12 Mos. Count	IB Serv./Past 12 Mos. Percent
BUY	968	51.27%	257	26.55%
HOLD	774	41.00%	128	16.54%
UNDERPERFORM	146	7.73%	6	4.11%

Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

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Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com

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Biren Amin, Equity Analyst, (212) 284-8162, bamin@jefferies.com