Aerie Pharmaceuticals

AERI : NASDAQ : US$10.61

BUY

Target: US$19.00

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COMPANY STATISTICS:

Forecast Return:	79%
Shares Out (M):	20.5
Market Cap (M):	US$217.5
52-week Range:	US$10.25 - 12.08

EARNINGS SUMMARY:

FYE Dec		2013E	2014E	2015E
Revenue:		0.0	0.0	0.0
EPS:		(1.06)	(1.38)	(1.47)
Revenue:	Q1	-	0.0	-
	Q2	-	0.0	-
	Q3	0.0A	0.0	-
	Q4	0.0	0.0	-
Total		0.0	0.0	0.0
EPS:	Q1	-	(0.31)	-
	Q2	-	(0.33)	-
	Q3	(0.28)A	(0.36)	-
	Q4	(0.28)	(0.38)	-
Total		(1.06)	(1.38)	(1.47)

SHARE PRICE PERFORMANCE:

Source: Interactive Data Corporation

COMPANY DESCRIPTION:

AERI is a clinical-stage pharmaceutical company focused on the treatment of glaucoma (one of the largest segments in the global ophthalmic market) and other eye diseases. Its product candidates are the dual-action AR-13324 and triple-action PG324.

All amounts in unless otherwise noted.

Life Sciences -- Biotechnology

EAGLE EYE FOR VALUE; INITIATING WITH BUY, $19 PRICE TARGET

Investment recommendation

Initiating coverage with BUY rating, $19 target on AR-13324's potential in open-angle glaucoma as a monotherapy and as part of PG324 combotherapy. We believe AR-13324, a novel ROCK/NET inhibitor, may become one of the most versatile drugs for open-angle glaucoma. We think Ph3 AR-13324 data and Ph2 PG324 data expected in 2015 will be positive, showing good efficacy and safety. We estimate $600M peak sales across both drugs. Our $19 target is based on a pNPV analysis.

Investment highlights

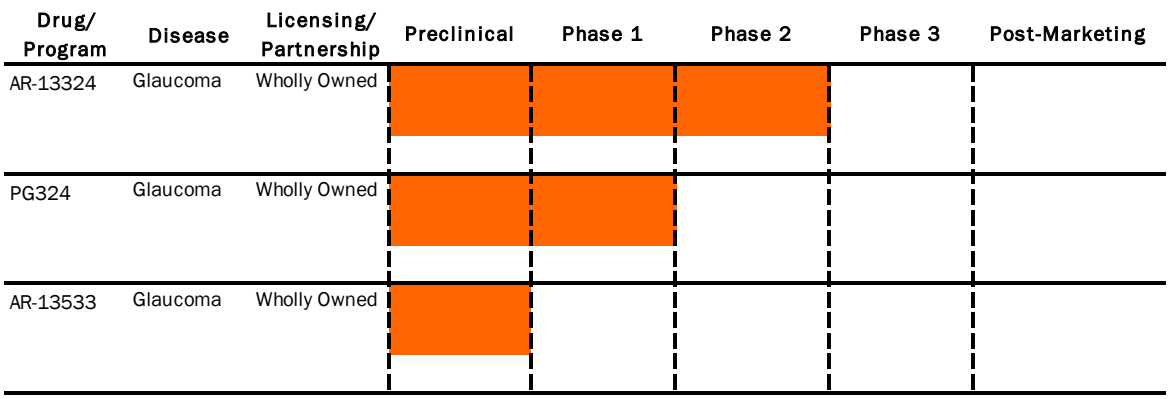
- **AR-13324 may become the most versatile, widely used open-angle glaucoma drug.** Open-angle glaucoma (OAG) is optical nerve damage and vision loss caused by high intra-ocular pressure (IOP), the result of inadequate fluid drainage through the trabecular meshwork (TM), the eye's primary drain. AR-13324 is the most advanced ROCK/NET inhibitor in development, the only class that targets the TM. It also reduces fluid inflow. AR-13324 Ph3 trials are to start in mid-2014 (data H2/15). Ph2 data from combo product PG324 is due in H1/15.
- **Ph2 AR-13324 data: potential for once-daily dosing, excellent safety.** Ph2 data suggest AR-13324 can lower IOP by 5-6mm Hg with good safety. Ph3 data may show similar efficacy, especially in patients with low IOP (~26 mm Hg) where current glaucoma drugs are weak. Unlike popular current drugs like beta-blockers, AR-13324 does not have systemic side effects. Once-daily dosing of AR-13324 may allow for less eye redness as opposed to most drugs.
- **ComboTx PG324 represents another Tx option for OAG.** Prostaglandin analogues (PGAs) are another popular glaucoma drug class, the only drugs that are also once-daily. Their mechanism is complementary to AR-13324, supporting combination therapy. Most patients continue to deteriorate despite a cocktail of current drugs, indicating a need for new drug options.

Figure 1: AERI upcoming catalysts

Expected date	Drug/Program	Item	Impact
Q1/14	PG324 for open angle glaucoma	Inidiation of Ph2b trial	+
Q2/14	AR-13324 for open angle glaucoma	Initiation of Ph3 pivotal trial	+
Q3/14	PG324 for open angle glaucoma	Data from Ph2b trial	++
Q2/15	AR-13324 for open angle glaucoma	Data from Ph3 pivotal trial	+++
H1/16	AR-13324 for open angle glaucoma	NDA submission	++

Source: Company reports and Canaccord Genuity estimates

Figure 2: AERI pipeline



Source: Company reports

INVESTMENT THESIS

We see Aerie's AR-13324 and PG324 and highly innovative, first-in-class drugs for glaucoma with potentially broad usefulness. Aerie's AR-13324 is a highly innovate ROCK/NET (rho-kinase/norepinephrine transporter inhibitor) set to enter Phase 3 development for the treatment of glaucoma. The drug is positioned to be the first-in-class ROCK inhibitor, potentially the first approved mechanism for glaucoma treatment in decades. Clinical data to date suggests the drug could be at least as effective, if not more, than current drugs, and effective for a larger percentage of the glaucoma patient population.

AR-13324's ROCK-NET dual mechanism may be uniquely targeted to best improve the underlying pathology of glaucoma, especially for "low IOP" patients who are not well treated by current drugs. AR-13324's mechanism is thought to facilitate fluid flow through the trabecular meshwork, the main tissue drain of the vitreous humor of the eye. No other currently approved drug targets the trabecular meshwork; rather they target the secondary uveoscleral drain. AR-13324 also reduced fluid inflow into the eye through its NET inhibition (like some other current glaucoma drug), making it one of the few dual action glaucoma drug candidates (other than alpha agonists). This may result in stronger lowering of intra-ocular pressure (IOP) than other drugs, as well as effective IOP lowering in a broader range of glaucoma patients (since it targets the disease's primary pathology).

We believe AR-13324 also represents a significantly safer and more patient-friendly treatment than currently available products. AR-13324 has demonstrated very low levels of systemic exposure and has no systemic tox or side effects in clinical trials to date. AR-13324 has the potential to be dosed once daily, unlike almost all other glaucoma drugs save for prostaglandin analogues (which are thought to be synergistic with AR-13324). Once-daily dosing allows for better compliance as patients on once-daily drugs are generally 90% compliant whereas patients on twice-daily drugs are only 80% compliant. Further, the once-daily dosing allows for mitigation of AR-13324's main side effect, post-dosing eye redness (hyperemia). Nighttime dosing will likely allow patients a much lower level of any redness than twice-daily drops, most of which also have hyperemia side effects. Overall, we think this will give AR-13324 a better safety and tolerability than most glaucoma drugs, particularly in the non-PGA class.

Phase 2 data to date strongly supports Phase 3 success (H2/15) and US regulatory approval, likely in late 2017 – We give AR-13324 a 65% chance of success. Ph2 clinical data from AR-13324 has been very positive to date, indicating the drug can lower IOP by 5-6 mmHg in glaucoma patients. Most non-PGA drugs are able to lower IOP by 4-5mm HG. We think the threshold for approval of new glaucoma drugs is only ~3-4mm Hg, a hurdle that AR-13324 could easily clear to secure approval for first-line use. However, due to premium pricing, we expect payors to restrict its use to second-line treatment and beyond. We expect PG324 will need to prove incrementally more IOP lowering than PG alone in its pivotal trial in order to secure approval in the US. AERI is starting its discussion with EU and Japanese regulators to determine requirements for approval in those regions.

In our opinion, PG324 combination product may also be a clinically successful product, with a profile distinct from AR-13324 monotherapy – we give PG324 a 45% chance of success. Most glaucoma patients are on combination therapy with two or more drugs from

the four different classes approved for glaucoma treatment (PGAs, beta-blockers, alpha-agonist and carbonic anhydrase inhibitors). Most patients are initially put on a single therapy (most often BBs) but quickly progress to combotherapy at about six months as their IOP starts steadily rising again. PGAs (prostaglandin analogues) are most often added in second-line, and this is where we think PG324 would best fit in. While AR-13324 would make an ideal front-line treatment, it will likely be second line due to pricing. PG324 as a second-line treatment would very likely be safer, more convenient and likely more efficacious than a BB+PGA regimen.

Glaucoma itself represents a large and growing market with many drawbacks to current treatment options. There are currently an estimated 2.2M glaucoma patients in the US, only about half of whom are diagnosed. We believe with expanded healthcare access, diagnosis rates will increase as well. Further, with the aging of the general population, we think the prevalence of glaucoma will also rise. Current therapies delay progression of the disease by a small margin, and additional add-on treatments with complementary mechanisms are in demand by clinicians to delay loss of sight. AR-13324 may be even able to treat a portion of currently untreated patients who have IOPs in the lower range of glaucoma (22-26mm Hg), and are likely not currently treated due to lack of efficacy of existing drugs in this IOP range. As such, our market model includes increasing rates of prevalence, diagnosis and treatment.

We strongly believe the ultimate AR-13324 and PG324 drug profile will support a strong launch and very healthy peak sales of ~$600m in aggregate. We think, based on Phase 2 precedent, AR-13324 and PG324 will prove to have a compelling therapeutic profile that would support first-line approval and use. We think due to the fact that most glaucoma medications are now cheap generics, coverage restrictions will limit its use in mostly second-line setting. Despite this, we think there will be excellent uptake as the vast majority of glaucoma patients progress rapidly to second-line treatment. We expect AR-13324 to reach peak share of 39% of the non-PGA market and 19% market share of the overall market. We think PG324 will ultimately reach peak share of 30% of the current PGA market and 15% share of the overall US market.

AERI management is already constructing a potential commercial plan for AR-13324 and PG324 based on their previous successful experience with promotion of novel ophthalmology products. AERI management has already outlined a commercial strategy to potentially promote AR-13324. The company believes that they can target the majority of high prescribing ophthalmologists with a sales force of 100 representatives. The senior management team has a positive track record of launching previous ophthalmology products as a team at ISTA pharmaceuticals, which promoted 5 different ophthalmology products. ISTA was sold in 2012 to Bausch and Lomb for $500M.

AERI may also be able to strike rich partnerships for AR-13324 and PG324 in other geographies. Should AR-13324 and/or PG324 have positive data in Phase 2 and 3 trials, as we predict, we think a number of large pharmaceutical companies may be interested in development/commercial partnerships for geographies in which AERI does not intend to promote its products on its own. We think strong partnership with meaningful upfront payments and royalties could be struck for Europe and Japan. We do not yet include these royalties in our model as the timelines for sales in these geographies is uncertain.

We also believe AERI itself may represent a compelling acquisition target after additional clinical progress, given the company's ophthalmology focus and clean corporate structure.

We believe that given the consolidation in the ophthalmology space and the lack of innovation within the bigger specialty pharmaceutical players (e.g., Allergan, Bausch and Lomb, Alcon/Novartis), there may be significant business development interest in AERI after additional clinical data from the AR-13324 and/or PG324 programs are generated. We believe any acquisition would likely be in excess of the average biotech acquisition premium of ~40%.

INVESTMENT RISKS

Clinical risk – AR-13324's planned Phase 3 program and or PG324's Phase 2 and 3 programs may not be successful. While we believe there is strong positive precedent data for AR-13324 from Phase 2 studies, there is a chance the planned Phase 3 trial will not be successful. The planned Phase 3 will measure efficacy at three months and safety at 12 months. The Phase 2 trials only measured efficacy and safety at one month. In addition, a previous AERI drug candidate showed roll-off of effect between month 1 and 3. However, we believe this older drug was more highly specific to ROCK inhibition than AR-13324, which also has low-level PKC inhibition activity as well. The PKC pathway may compensate for ROCK-mediated IOP lowering; therefore inhibiting both may result in sustained benefit. Given almost no systemic exposure with 13324 drops, we expect continued clean safety, even with longer treatment duration in the upcoming Phase 3 trials versus the Phase 2.

Regulatory risk – FDA may not approve AR-13324 or PG234. There is no guarantee that FDA will approve AR-13324 or PG324 even if they showed expected levels of IOP lowering. Should FDA's understanding of the relationship between IOP lowering and loss of visual acuity change, the agency may want additional measures of benefit to grant approval. Further, clinical trials could yield some new safety signal that could be of concern to the agency.

Competitive risk – There are a number of other current, well-established classes of glaucoma therapy on the market that clinicians have significant experience with. As we have previously described, there are a number of other glaucoma drugs approved that utilize different mechanisms to treat the disease. All of these drugs have been approved for years, if not decades; ophthalmologists have had significant experience treating patients with these medications, and have significant comfort with their efficacy and side effect profiles. As a result, ophthalmologists may continue to preferentially prescribe these drugs despite any potentially superior therapeutic profile of AR-13324 or PG324.

Commercialization/reimbursement risk – Most current glaucoma therapies are generics, and are available relatively cheaply compared to AERI's intended pricing for AR-13324 and PG324; therefore, there is no guarantee AERI will be able to secure reimbursement for these drugs. Most (but not all) glaucoma medications are available in generic form in the US for <$1 per day in treatment cost. Branded glaucoma therapies that cost between $2 and $3/day (the commercial plan for AR-13324 and PG324) are still able to secure reimbursement and meaningful market share, although many are restricted to second-line use with step-edits. We think this will also be the case of the AERI drug despite a significant premium to the existing generics, especially given our predicted superior therapeutic profile.

Financial risk – AERI's current cash position will not extend through commercialization of AR-13324. AERI has current pro forma assets of **$70M**, which we estimate will cover operating expenses through NDA filing of AR-13324, expected in H1/16. This includes the $35M estimated cost of the Phase 3 and estimated $7-8M for the planned Phase 2b trial of PG324. However, unless AERI secures a significant amount of non-dilutive financing through establishment of commercial partnerships (likely for Europe and/or Japan), it will not have cash to cover operating expenses through the AR-13324 launch or for additional Phase 3 development of PG324. Aerie may raise money through the issuance of additional equity.

VALUATION

We have built our valuation of AERI using a probability-weighted NPV model of peak sales of AR-13324 and PG324.

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Stronger-than-expected efficacy in lowering of IOP in the general open-angle glaucoma population.** There is a chance AR-13324 and PG324 could show >6mm Hg lowering of IOP with extended duration of treatment in Phase 3 studies. Stronger efficacy with the same clean safety as the Phase 2 data could drive even higher peak market share and a more rapid launch than what we are modeling.
- **Stronger-than-expected efficacy in low-pressure OA glaucoma.** Should AR-13324 generate data showing compelling evidence of meaningful IOP lowering in glaucoma patients with IOP in the low range for the disease (22-26, Hg), it could see even greater use. The ability to treat this lower IOP range of disease could enhance diagnosis and increase willingness to treat, growing the market size that AR-13324 could address.
- **Revenues generated in the EU, Japan, ROW markets could boost peak sales past our estimates.** The glaucoma patient population in Europe is estimated to be at least as large as the US population, and the number of glaucoma patients in Japan is thought to be significant. Should AR-13324 and PG324 data be as positive as anticipated, and should AERI or a potential partner identify a regulatory path forward, AERI could strike a partnership that would generate meaningful royalties off of substantial EU and Japanese sales of the drugs.

Potential downside to valuation

As with all companies in commercial and clinical development, there always exists the risk of failed or inconclusive clinical trials, slower-than-expected commercial launches, or lower-than-expected peak sales, which could lead to downward pressure on the stock. For more detailed risks, see our "Investment risks" section.

Figure 3: AERI valuation

Product Development

Drug name	Indication	Status	Launch	Years to Launch	Years to Peak	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
AR-13324	Open angle glaucoma	Phase 3	2017.5	4	9	65%	297.6	193.4	95%	85%	156.18	7.05	13.37
PG324	Open angle glaucoma	Phase 2	2018.5	5	11	45%	290.8	130.9	95%	85%	105.69	11.01	5.79
										Total			**19.16**

Source: Company reports and Canaccord Genuity estimates

REVENUE MODEL AND FINANCIALS

Our forecast financial model is built on the assumption that AR-13324 will launch in the US in the second half of 2017 for first-line treatment of open-angle glaucoma. We assume, however, that due to reimbursement the vast majority of its use will be in second line treatment. Our AR-13324 market model assumes peak market share of 39% of the non-PGA market and 19% market share of the overall market in 2023, about six years after launch. We also model for a H2/18 launch for PG324 and think PG324 will ultimately reach peak share of 30% of the current PGA market and 15% share of the overall US market by 2024, also about six years after launch.

We assume that AERI and potential partner, if any, will price AR-13324 at $1,000 annually in the US. Our discussion with AERI management indicates its market research supports a branded drug pricing, $2-3/day, if it proves to be able to reduce IOP in moderately severe open-angle glaucoma (OAG) patients and show sustained treatment efficacy with minimal side effects. Management also indicates PG324 would be priced at a 20%-30% premium to AR-13324. We assume market research would support an even larger margin on improved efficacy and/or safety, but are currently modeling at a much more conservative price point.

Overall, we forecast peak market share for AR-13324 in 2023 with corresponding sales of $300M and PG324 in 2024 with $290M. We have not modeled potential revenue streams from EU or ROW, or from patients with low IOP who are traditionally not treated but may be seen to benefit based on potentially positive Phase 3 results, which could increase the peak sales figure significantly.

AERI reported current assets of $3.6M on June 30, 2013; we estimate it has ~$70M pro forma cash on balance sheet, which we think will cover operating expenses through NDA filing of AR-13324, expected in H1/16, but not enough cash to cover operating expenses through the AR-13324 launch or for additional Phase 3 development of PG324. We believe AERI could secure non-dilutive financing on positive data readout in the form of development/commercial collaboration or additional equity raise from the capital markets.

Figure 4: AR-13324 and PG324 revenue projections

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
Glaucoma market model														
	growth rates													
US population	1.0%	321.2	324.4	327.6	330.9	334.2	337.6	340.9	344.3	347.8	351.3	354.8	358.3	361.9
Patients with glaucoma		2,350,903	2,410,028	2,470,640	2,532,777	2,596,476	2,661,778	2,728,721	2,797,349	2,867,702	2,939,825	3,013,761	3,089,558	3,167,260
Glaucoma incidence	1.5%	*0.73%*	*0.74%*	*0.75%*	*0.77%*	*0.78%*	*0.79%*	*0.80%*	*0.81%*	*0.82%*	*0.84%*	*0.85%*	*0.86%*	*0.88%*
Diagnosed patients with glaucoma		1,245,979	1,301,415	1,358,852	1,418,355	1,479,992	1,543,831	1,609,946	1,678,409	1,749,298	1,822,691	1,898,670	1,977,317	2,058,719
Diagnosis rate	1.0%	*53.00%*	*54.00%*	*55.00%*	*56.00%*	*57.00%*	*58.00%*	*59.00%*	*60.00%*	*61.00%*	*62.00%*	*63.00%*	*64.00%*	*65.00%*
Dx Glaucoma patients on Tx		1,065,498	1,124,034	1,185,379	1,249,658	1,317,004	1,387,551	1,461,442	1,538,827	1,619,858	1,704,699	1,793,516	1,886,486	1,983,790
Glaucoma treatment rate	1.0%	*85.51%*	*86.37%*	*87.23%*	*88.11%*	*88.99%*	*89.88%*	*90.78%*	*91.68%*	*92.60%*	*93.53%*	*94.46%*	*95.41%*	*96.36%*
Patients on non-PGA Tx		**532,749**	**562,017**	**592,689**	**624,829**	**658,502**	**693,775**	**730,721**	**769,413**	**809,929**	**852,350**	**896,758**	**943,243**	**991,895**
% of pts on non-PGA Tx		*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*
Timolol intolerant pts		79,912	84,303	88,903	93,724	98,775	104,066	109,608	115,412	121,489	127,852	134,514	141,486	148,784
Intolerance incidence		*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*	*15.00%*
AR-13324 penetration rate		*0.00%*	*0.00%*	*0.00%*	*10.00%*	*25.00%*	*50.00%*	*70.00%*	*80.00%*	*80.00%*	*80.00%*	*80.00%*	*80.00%*	*80.00%*
Pts converting to AR-13324		-	-	-	9,372	24,694	52,033	76,726	92,330	97,192	102,282	107,611	113,189	119,027
Pts with low IOP		53,275	56,202	59,269	62,483	65,850	69,378	73,072	76,941	80,993	85,235	89,676	94,324	99,190
Low IOP incidence		*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*	*10.00%*
AR-13324 penetration rate		*0.00%*	*0.00%*	*0.00%*	*10.00%*	*25.00%*	*50.00%*	*70.00%*	*80.00%*	*80.00%*	*80.00%*	*80.00%*	*80.00%*	*80.00%*
Pts converting to AR-13324		-	-	-	6,248	16,463	34,689	51,150	61,553	64,794	68,188	71,741	75,459	79,352
Outstanding pts on non-PGA Tx		399,562	421,513	444,517	468,622	493,876	520,332	548,041	577,060	607,447	639,262	672,569	707,432	743,921
Percentage of outstanding pts		*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*	*75.00%*
AR-13324 penetration rate		*0.00%*	*0.00%*	*0.00%*	*3.00%*	*10.00%*	*15.00%*	*20.00%*	*22.50%*	*25.00%*	*25.00%*	*25.00%*	*25.00%*	*25.00%*
Pts converting to AR-13324		-	-	-	14,059	49,388	78,050	109,608	129,838	151,862	159,816	168,142	176,858	185,980
Total addressable pts - AR-13324		-	-	-	29,679	90,544	164,772	237,484	283,721	313,848	330,285	347,494	365,507	384,359
Number of pts on AR-13324					29,679	90,544	164,772	237,484	283,721	313,848	330,285	347,494	365,507	384,359
Gross price	2.0%				1,000.00	1,020.00	1,040.40	1,061.21	1,082.43	1,104.08	1,126.16	1,148.69	1,171.66	1,195.09
Net revenue	20.0%				850.00	816.00	832.32	848.97	865.95	883.26	900.93	918.95	937.33	956.07
AR-13324 Revenue					12.61	73.88	137.14	201.62	245.69	277.21	297.56	319.33	342.60	367.48
Patients onOAG PGA Tx		**532,749**	**562,017**	**592,689**	**624,829**	**658,502**	**693,775**	**730,721**	**769,413**	**809,929**	**852,350**	**896,758**	**943,243**	**991,895**
% of pts on PGA Tx		*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*	*50.00%*
PG324 penetration rate	0.0%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*1.00%*	*5.00%*	*10.00%*	*15.00%*	*20.00%*	*25.00%*	*30.00%*	*30.00%*	*30.00%*
Pts converting to PG324		-	-	-	-	6,585	34,689	73,072	115,412	161,986	213,087	269,027	282,973	297,569
Total addressable pts - PG324		-	-	-	-	6,585	34,689	73,072	115,412	161,986	213,087	269,027	282,973	297,569
Number of pts on PG324						6,585	34,689	73,072	115,412	161,986	213,087	269,027	282,973	297,569
Gross price	2.0%					1,200.00	1,224.00	1,248.48	1,273.45	1,298.92	1,324.90	1,351.39	1,378.42	1,405.99
Net revenue	10.0%					1,020.00	979.20	998.78	1,018.76	1,039.13	1,059.92	1,081.12	1,102.74	1,124.79
PG324 Revenue						3.36	33.97	72.98	117.58	168.33	225.86	290.85	312.05	334.70
Market share														
AR-13324 of non-PGA market					*4.75%*	*13.75%*	*23.75%*	*32.50%*	*36.88%*	*38.75%*	*38.75%*	*38.75%*	*38.75%*	*38.75%*
AR-13324 of overall OAG market					*2.38%*	*6.88%*	*11.88%*	*16.25%*	*18.44%*	*19.38%*	*19.38%*	*19.38%*	*19.38%*	*19.38%*
PG324 of PG market						*1.00%*	*5.00%*	*10.00%*	*15.00%*	*20.00%*	*25.00%*	*30.00%*	*30.00%*	*30.00%*
PG324 of overall OAG market						*0.50%*	*2.50%*	*5.00%*	*7.50%*	*10.00%*	*12.50%*	*15.00%*	*15.00%*	*15.00%*
Molecule market share of '324 in overall market						7.38%	14.38%	21.25%	25.94%	29.38%	31.88%	34.38%	34.38%	34.38%

Source: Company reports and Canaccord Genuity estimates

RECOMMENDATION

We would be buyers of AERI stock in the 12- to 18-month timeframe based on expectation of progression of the clinical development of both Phase 3 AR-13324 and Phase 2 PG324. We expect positive Phase 2 PG324 data to come in this 18-month timeframe.

We ultimately expect AR-13324 and PG324 to become very important therapeutic options in the treatment of open-angle glaucoma. In our opinion, AERI will be starting two well-designed Phase 3 trials for AR-13324 that we think have a very good chance of success. We think data from the trials (expected H2/15) will show a mean >5mm Hg decline in IOP among study subjects, which clinicians have indicated to us is clinically meaningful. We

also think the 12-month safety will prove to be very clean, as all data to date suggest the drug to be very safe and well tolerated.

We expect NDA of AR-13324 to be filed in H1/16, to obtain US approval in H1/17 and to be launched shortly thereafter with its own 100-person specialty sales force targeting ophthalmologist. We believe that AR-13324 may take a peak share of 39% of the non-PGA market four to five years after initial launch, representing 19% share of the overall glaucoma market. Overall peak sales in our model are expected to be ~$300M. AERI may strike development/commercialization partnerships for AR-13324 sometime after the pivotal data is released.

We also believe that the planned Phase 2b trial for combination product PG324 will be successful, showing at least incremental IOP lowering over the PG analog and AR-13324 alone. We also this benefit in IOP reduction will be >5mm Hg. We then expect that this drug will go through Phase 3 development successfully, showing good safety and efficacy, and that AERI will file the NDA for this drug in H1/17 with US approval in H2/18. PG324 should drop very easily into the promotional effort of AERI's newly formed sales force at this point, and may even be part of a previously struck geographical partnership. We believe that PG324 will achieve peak market share of 30% of the original PGA market, translating to about 15% of the overall glaucoma market. This also translates into about $300M in peak sales, we estimate, 5-6 years after the drug is launched.

Total peaks sales for both drugs is about $600M in our estimates, which means the total molecule market share of AR-13324 would be around 34%.

COMPANY OVERVIEW

AERI is a clinical-stage pharmaceutical company focused on the discovery, development and commercialization of first-in-class therapies for the treatment of glaucoma and other eye diseases. Glaucoma is one of the largest segments in the global ophthalmic market. In 2012, branded and generic glaucoma product sales exceeded $4.5 billion in the United States, Europe and Japan in aggregate, according to IMS, and prescription volume is expected to grow, driven in large part by an aging population.

AERI is advancing its product candidates, namely the dual-action AR-13324 and triple-action PG324, to secure regulatory approval and commercialize these products on its own in the United States. AERI is planning on building a commercial team of approximately 100 sales reps to target approximately 10,000 high-prescribing eye-care professionals throughout the United States. For key markets outside the United States, including Europe, Japan and emerging markets, AERI intends to explore collaboration opportunities through licensing arrangements with a partner with strong international presence, who has the distribution expertise in ophthalmology products.

AERI's product candidates are once-daily eye drops that, if approved, could be the first novel intraocular pressure-lowering mechanisms of action, or MOA, to treat glaucoma in nearly 20 years. AR-13324, AERI's lead dual-action product candidate, recently completed a Phase 2b clinical trial. AERI is currently planning two Phase 3 registration trials for AR-13324 and we think the trial in on track to start in mid-2014. In addition, we anticipate a Ph2b trial to start in early 2014 for triple-action PG324, which contains a fixed-dose combination of AR-13324 and the prostaglandin analogue (PGA) latanoprost, the most commonly prescribed drug for the treatment of patients with glaucoma.

GLAUCOMA

BACKGROUND

Glaucoma is a condition primary characterized by optical nerve damage resulting in sight loss that is likely mediated in some form by increased intraocular pressure. Open-angle (OAG) and angle-closure (ACG) glaucoma are the leading cause of irreversible blindness worldwide and the second most common cause of blindness after cataracts.

Prevalence

The two conditions afflict almost 70 million people, of whom 10% are believed to be bilaterally blind. With the aging of the general population, the number of individuals with glaucoma is expected to rise, posing a substantial public health challenge in the US and worldwide.

Several population-based studies have contributed to the understanding of OAG incidence and prevalence within defined populations in the United States. The NIH estimated in 2010 there were 2.7M patients with glaucoma in the US alone. However, only 50% of patients are diagnosed due to poor rates of comprehensive eye exams, even in the elderly.

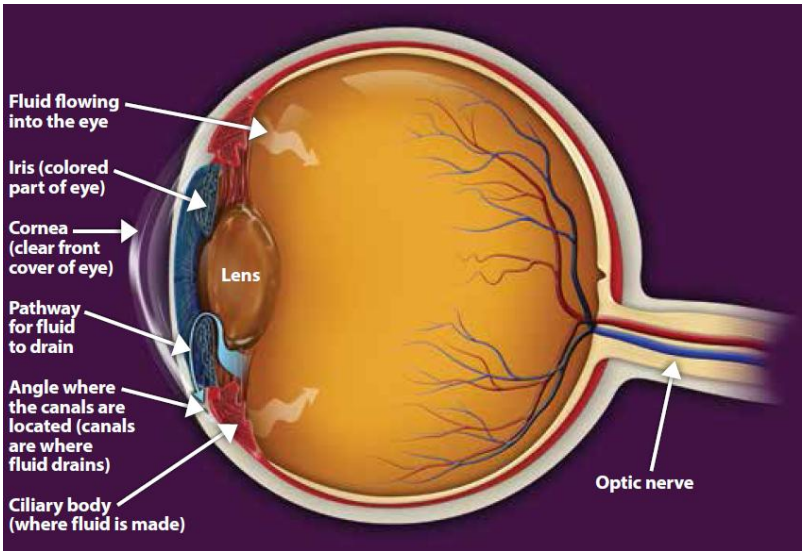
In the Baltimore Eye Survey, the prevalence of OAG was significantly higher in African Americans (4.7%) than in Caucasians (1.3%). The Los Angeles Latino Eye Study found that Hispanics in the United States have a prevalence of OAG of 4.7%. The prevalence of OAG in Asians varies widely, perhaps in part because the term Asian encompasses broad racial and ethnic categories. Rudnicka *et al.* documented OAG rates in Asia to range from 1 to 4%, whereas Ramakrishnan *et al.* found the prevalence of OAG in India to be 1.7%.

Pathology

The manifestations of glaucoma range from mechanical angle closure of outflow structures in patients with angle-closure glaucoma (ACG), who typically present with ocular pain and acute visual loss, to increased resistance of outflow in patients with open-angle glaucoma (OAG), who are often asymptomatic. OAG is the most common form of glaucoma, accounting for at least 90% of cases in the United States and is caused by the slow clogging of the drainage canals resulting in increased eye pressure (Figure 5). There is a wide and open angle between the iris and cornea, hence the namesake disease. Although glaucoma embodies a diverse group of diseases, all these diseases share common characteristics, the hallmarks of which include progressive irreversible damage to the optic nerve head and the retinal ganglion cells with corresponding visual field loss.

Primary OAG is defined as a chronic optic neuropathy with characteristic changes in the optic disc and visual field. Risk factors for OAG include older age, African American ethnicity, family history (first-degree relative), thinner central corneal thickness, myopia and elevated intraocular pressure (IOP). ACG is characterized by the opposition of the iris to the trabecular meshwork, resulting in blockage of the aqueous outflow. Risk factors for developing angle-closure glaucoma include Asian ethnicity, female gender and advanced age. Anatomic features predisposing to ACG are hyperopia, anterior iris insertion and shallow anterior chamber.

Figure 5: Flow of fluids in open angle glaucoma



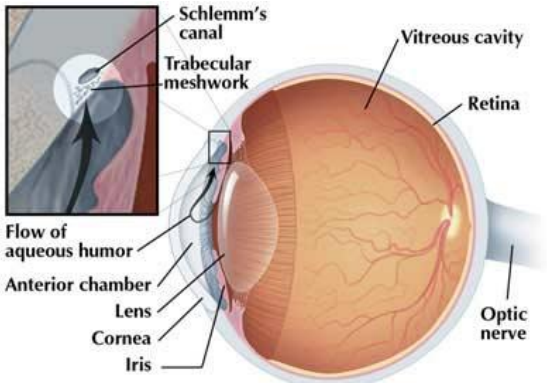
Source: Department of Health and Human Services

It is important to note that glaucoma is a progressive and highly individualized disease, in which elevated levels of intraocular pressure are associated with damage to the optic nerve, which results in irreversible vision loss and potentially blindness. The definition of glaucoma has evolved from a disease of eye pressure to a disease of optic neuropathy as patients may suffer the adverse effects of glaucoma across a wide range of IOP levels. The level of IOP in healthy individuals is generally accepted to be 10 to 21 millimeters of mercury, or mmHg. The majority of glaucoma patients have IOP of 26 mmHg or below at the time of diagnosis, which is commonly referred to as "low to moderately elevated" IOP. An elevated IOP in the affected eye is now seen as a risk factor for glaucoma rather than its cause. However, at present IOP is the only modifiable risk factor that can be used to prevent progressive optic neuropathy as the reduction of IOP has been shown to slow the progression of vision loss. The US Food and Drug Administration, or FDA, recognizes sustained lowering of IOP as the primary clinical endpoint for regulatory approval. Once glaucoma develops, it is a chronic condition that requires life-long treatment.

Pathology of elevated intra-ocular pressure

In the normal eye, aqueous humor forms in ciliary processes of the ciliary body, passes through the pupil to the anterior chamber, and exits through the trabecular meshwork (TM). From the TM, aqueous humor exits through one of two routes. The trabecular route, often referred to as the conventional outflow pathway, accounts for 40–96% of outflow in the human eye. This percentage depends on the age of the patient. This outflow of aqueous humor involves aqueous transport through the TM, into Schlemm's canal (SC), then out into the episcleral and conjunctival venous system (Figure 6).

Figure 6: Movement of fluid in the eye

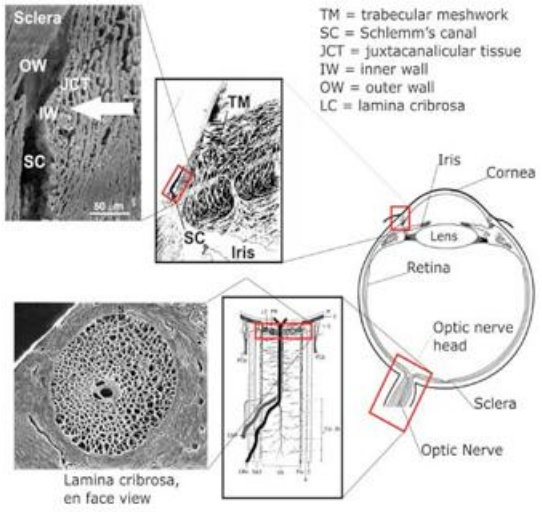


Source: Mayo Foundation for Medical Education and Research

Certain cellular properties of the TM are critical for conventional outflow. High levels of RhoA (Ras homolog gene member A, a small GTPase protein that regulates the actin cytoskeleton in the formation of stress fibers) have an important function. These high levels of RhoA in TM cells induce a contractile morphology, increased actin stress fibers, increased focal cell–cell adhesions, increased levels of phosphorylated myosin light chain (MLC), and increased extracellular matrix protein production. These changes lead to decreased aqueous humor drainage due to cellular and morphological changes in the TM cells. The ciliary muscle (CM) contraction leads to increased TM pore size and subsequent increased aqueous drainage (Figure 7). In contrast, the second route, known as the

uveoscleral route, accounts for 4–60% of outflow in the human eye and it involves the passage of aqueous humor from CM fibers into the suprachoroidal space. From there, aqueous humor drains into the venous system of the ciliary body, choroid and sclera.

Figure 7: Tissues involved in glaucoma



Source: Ethier Lab Website, Georgia Tech/Emory

Glaucoma morphology of the optic nerve with disease progression

Glaucoma damages the ganglion cell and its respective axons, which comprise the retinal nerve fiber layer (rNFL). This results in progressive and asymmetric changes in the optic cup, with corresponding visual field loss (Figure 8). Typically, structural changes occur before functional loss. Up to 40% of the retinal nerve fibers (rNF) may be destroyed before detectable changes in visual field. The morphology of these rNF loss (rNFL) defects follows the normal structural pattern of the rNFL in the retina. Normally, rNFL has a striated appearance, radiating from the optic disk, and is thickest in the superior and inferior poles, compared with the nasal and the temporal poles. Glaucomatous rNFL changes can present as focal wedge-shaped defects of varying width radiating from the optic nerve head or as diffuse loss of the striations in rNFL. Because glaucoma tends to afflict the superior and inferior nerve fibers preferentially, focal loss is often detected in these areas.

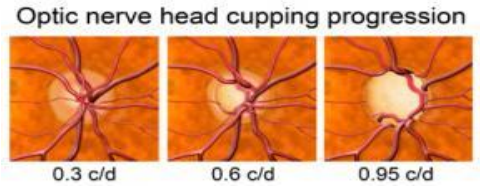
Figure 8: Glaucoma is often associated with decrease in field of vision

Source: Department of Health and Human Services

Disc changes present with a variety of characteristic patterns. As ganglion cells and their axons are destroyed, the neural rim begins to thin. Typically, localized thinning in early glaucoma can lead to focal atrophy of the neural rim, known as focal notching. This tends to occur in the inferotemporal region of the optic nerve head because of preferential loss of the inferior nerve fibers. This is followed, to a lesser extent, by focal neural loss and atrophy in the superotemporal region. As a result, the optic cup usually enlarges in a vertical or oblique fashion. As the glaucomatous process progresses, the temporal rim becomes involved. The nasal quadrant is the last to be affected.

Early glaucomatous damage can also lead to progressive, generalized and concentric expansion of the nerve cup. In some cases, early glaucomatous optic atrophy presents with deepening of the cup, exposing the underlying lamina cribrosa. In other cases, early glaucoma can be evidenced by saucerization of the disc, in which shallow sloping and cupping extend to the margins of the disk. Progressive glaucoma results in axonal loss and backward bowing of the lamina cribrosa, leading to enlargement and/or excavation of the cup. Loss of all neural rim tissue with exposure of the laminar pores can be seen in advanced glaucoma. Complete cupping with undermining of the neural rim produces a bean pot appearance, with a pale disc and vessels that bend at the margins of the disc (Figure 9)

Figure 9: Nerve damage with disease progression in glaucoma



Source: NIH

Vascular signs of glaucomatous optic atrophy include splinter hemorrhages that result due to loss of axons at the optic nerve head and reflect progressive rNFL damage. They occur more commonly in patients with normal-tension glaucoma (NTG) than those with primary OAG, with a cumulative incidence of 35.3% and 10.3%, respectively. The most common

location for these hemorrhages is the temporal rim, followed by the inferior and superior rim. Rarely, splinter hemorrhages occur nasally. They are most often seen in the early to middle stages of glaucoma and are a prognostic sign of progressive disease. The hemorrhages leave behind a focal area of rNFL defect, focal notching and a corresponding visual field defect. The disappearance of neural rim can lead to overpassing vessels. The bending of the retinal vessels along the edge of a disappearing rim is termed bayoneting. Circumlinear vessels may be also barred from the margin of the cup. In advanced glaucoma, the central vessels can be nasally displaced.

Visual field pathology progression

Early glaucoma can create mild, diffuse depression in the visual fields and/or localized visual field defects. In these earlier stages, peripheral changes in visual fields may be the only detectable abnormality. Increasing scatter and fluctuation is often noted. Isolated defects tend to occur in the superior half of the visual field because of the susceptibility of the inferior poles of the optic nerve in early glaucomatous damage. Although central vision is preserved during the early course of glaucoma, defects can involve the fixation point. Isolated paracentral defects can appear as the initial glaucoma defect in 41% of the patients.

Progression in visual fields can occur in a variety of ways. There can be gradual but steady decrease in retinal sensitivity affecting the field uniformly. Initial defects that were shallow can coalesce, extend, deepen and enlarge into nasal steps, arcuate scotomas or complete altitudinal defect. New defects can also appear with further progression. For example, in advanced glaucoma, arcuate scotomas can manifest superiorly and inferiorly, forming a double arcuate scotoma. This double arcuate scotoma comes together nasally at the horizontal meridian, creating the central and temporal islands seen in advanced glaucoma. With the destruction of the remaining areas of the macular fibers and the nasal retina, these islands continue to disappear until they are extinguished. Temporal islands may be more resistant and may persist after central islands are lost. However, these too can be destroyed, leaving patients with complete visual loss.

Natural history of open-angle glaucoma

The lack of symptoms in OAG plays a large role in delaying its detection and diagnosis. Typically, OAG is slowly progressive, remaining asymptomatic until late. By the time OAG becomes symptomatic, severe and irreversible damage has usually occurred to the visual field in one or both eyes.

The rate of progression of the visual field defect varies in patients, and treatment of the glaucoma may not completely halt the visual field loss. Some patients progress despite aggressive therapy. The incidence of blindness 20 years after the initial diagnosis of OAG has been estimated at 27% for one eye and 9% for both eyes in a primarily white population. Data from population-based, cross-sectional studies revealed that for patients with OAG, the mean change in visual field testing for European-derived, Hispanic, African-derived and Chinese was –1.12, –1.26, –1.33 and –1.56 dB/year, respectively. The differences in the mean deviation (MD) were not statistically significant by ethnicity. Because some participants were treated, the data cannot be used to represent the natural history of OAG.

The Ocular Hypertension Treatment Study elucidated the natural history of OAG by identifying the rate of conversion from ocular hypertension to primary OAG and the impact

of treating IOP (decreasing IOP more than 20% from baseline) on the development of OAG. After 60 months of follow-up, conversion to OAG from ocular hypertension was 4.4% in the treated group as compared with 9.5% in the untreated group. Thus, a protective effect of 54% was seen with treatment. However, over 90% of the untreated subjects did not develop visual field or disc changes consistent with OAG during this time. To prevent one patient with ocular hypertension from developing glaucoma, 19 would need to be treated unnecessarily if the risk factors were ignored. Baseline factors associated with the conversion to OAG included advanced age, elevated IOP, central corneal thickness thinner than the study mean, increased cup-to-disc ratio and increased pattern standard deviation on the visual field.

Data from individuals in the Early Manifest Glaucoma Trial (EMGT) randomized to the no-treatment group shed light on the natural course of newly detected OAG and can be used to predict the likelihood of visual loss from glaucoma. After 4 years of follow-up, 49% of the individuals without treatment progressed compared with 30% with treatment (an average IOP lowering of 25%). After 6 years of follow-up, 68% of the untreated patients showed definite visual field progression, with an overall median time to progression of 42.8 months.

The study also revealed a very large variation in time to progression among the subjects. Some progress quickly, with a deterioration in the MD index of greater than 10 dB per year; others did not progress at all, even after lengthy follow-up. Of those individuals in the high-tension glaucoma (HTG) group (with elevated IOP ≥21 mm Hg), 74% had progressed, with a median time to progression of 44.8 months, while 56% of those individuals with NTG progressed, with a median time to progression of 61.1 months. Of the pseudoexfoliation patients (PXEG), 93% progressed, with a median time to progression of 19.5 months. Thus, the visual field loss progressed for most of these patients; the majority progressed slowly, but a minority progressed rapidly. Specifically, in the PXEG group, the MD on automated visual field testing was –3.13 dB/year. The perimetric MD for the NTG group and the HTG group was –0.36 dB/year and –1.31 dB/year, respectively. Large variations existed between the rates of progression in visual field for HTG, NTG and PXEG as well as among subjects within each group.

This variability in clinical course was also found by the Collaborative Normal Tension Glaucoma Study (CNTGS). Similar to the EMGT, the CNTGS documented the natural course of untreated NTG. The study specifically focused on patients with glaucomatous optic nerve damage and visual field loss accompanied by IOP in the normal range. While some believe that NTG represents a distinct variety of glaucoma from primary OAG, the two most likely represent a continuum of glaucoma. After 5–7 years of follow-up, progression of the visual field defect was noted in 60% of those individuals with untreated glaucoma with optic nerve damage, visual loss and IOP under 21 mmHg. Treatment targeting IOP lowering of >30% decreased the progression rate to 20%. Most cases progressed slowly, requiring several years to demonstrate progression; in other cases, deterioration manifested within 1 year. The mean estimated slope of the MD index deterioration for all untreated subjects was –0.41 dB/year. However, the MD index ranged from –0.2 dB/year to –2 dB or more/year. This 10-fold range reflects the broad range in the rates of deterioration.

Because the course of glaucomatous progression is highly variable, identifying factors that predict progression can help guide clinical practice and patient treatment and monitoring. In the EMGT, faster and greater progression was noted in older patients (≥68 years of age)

when compared with younger patients. Frequent disc hemorrhages predict faster progression, as did bilateral disease and greater visual field loss at initial diagnosis, as measured by perimetric MD. PXEG glaucoma, when compared with NTG and HTG, was also noted to be a more aggressive disease, with a mean progression rate corresponding to full-field blindness within 10 years. In addition, glaucoma patients with higher IOP are more likely to progress rapidly than those with IOP <21. NTG patients progressed more slowly and had a lower risk of rapid evolution to blindness. Investigators on multiple clinical trials have found that the immediate aggressive therapy for these patients may be less than that for patients with HTG and PXEG, but given the high intra-group variability, treatment should be guided by individual presentation.

The EMGT and the CNTG are the only two prospective studies that studied large groups of people with glaucoma without treatment. These two studies have provided important data on the natural course of OAG and on its risk factors for progression. Investigators of the trials suggested careful monitoring after glaucoma diagnosis to determine the rapidity of the disease's progression.

TREATMENT LANDSCAPE FOR OAG

There are no treatments that can reverse damages to the optic nerves, and clinicians can only treat OAG by lowering the pressure in the eyes. There are three categories of treatment for OAG. Though none will cure glaucoma, they can help slow and stop damages to the optic nerve. Medicine is often the first treatment for OAG and works by either reducing fluid production in the eyes or increasing the outflow of fluid from inside the eyes. The initial treatment for glaucoma patients is typically the use of a prescription eye drop (Figure 10). PGAs have become the most widely prescribed glaucoma drug class, although until recently, beta-blockers were the preferred first line treatment. .

The last two types of therapeutic intervention are laser surgery and traditional surgery to increase fluid outflow. These procedures are discussed more in depth later this report.

Drug therapies for Glaucoma

The four most commonly approved classes of eye drops to lower IOP in glaucoma are: PGAs, beta blockers, carbonic anhydrase inhibitors, and alpha agonist.

The most frequently prescribed PGA is once-daily latanoprost (brand name Xalatan, Pfizer). The most commonly prescribed non-PGA drugs belong to the beta-blocker class and the most prescribed beta blocker is twice-daily timolol. Other non-PGA drug classes include the alpha agonists and carbonic anhydrase inhibitors. When PGA monotherapy is insufficient to control IOP, non-PGA products are used either as add-on therapy to the PGA or as an alternative monotherapy. Progression to combination therapy usually occurs within the first year or two of diagnosis as IOP starts creeping up with existing treatments. Due to the multiple daily dosings, side effects and contraindications of non-PGA products, we believe there is a significant unmet need in the non-PGA market segment, which represents approximately half of the US and European glaucoma market based on prescription volumes.

Figure 10: Currently available eye drop treatments for open-angle glaucoma

Type of Medicine	Brand Name	How Taken	Taken How Often	Generic Available?	Drug Name
Prostaglandin Analogs	Lumigan®	Eye drops	Once a day	No	Bimatoprost
	Travatan Z®			No	Travoprost
	Xalatan®			Yes	Latanoprost
	Zioptan®*			No	Tafluprost*
Beta-Adrenergic Antagonists	Betagan®	Eye drops	Twice a day	Yes	Levobunolol
	Betoptic S®			Yes	Betaxolol
	Ocupress®			Yes	Carteolol
	Timoptic®			Yes	Timolol
Carbonic Anhydrase Inhibitors	Azopt®	Eye drops	Three times a day	No	Brinzolamide
	Trusopt®			Yes	Dorzolamide
	Diamox®	Pills	Twice a day	Yes	Acetazolamide
	Neptazane®*			Yes	Methazolamide*
Alpha-Adrenergic Agonists	Alphagan® P	Eye drops	Three times a day	Yes	Brimonidine
Miotics	Isopto® Carpine*	Eye drops	Up to 4 times a day	Yes	Pilocarpine*
Combination Medicines	Combigan®	Eye drops	Twice a day	No	Brimonidine and timolol
	Cosopt®			Yes	Dorzolamide and timolol

*These medicines were not studied in the research for this summary.

Source: Department of Health and Human Services

Common side effects of open-angle glaucoma eye drops include redness in and around the eyes, blurred vision, burning and stinging, itching, increased tears, photosensitivity, dry eye, and general eye discomfort. Prostaglandin analog drugs can cause darkened color of the iris, the eyelid, and eyelash changes. The most prevalent side effect of glaucoma eye drop medicines is redness in the eyes and out of all the prostaglandin analogs latanoprost seems to cause the least eye redness than its peers in the same class.

On effects on optic nerve damage and visual field loss, Vass and colleagues reported that any topical medical treatment (including beta-blockers and unspecified topical medications) had a protective effect on incident worsening of visual field defect when compared with placebo or no treatment (odds ratio [OR], 0.6 [CI, 0.5 to 0.8]). Beta-blockers were also protective when compared with placebo (OR, 0.7 [CI, 0.5 to 1.00]), as was timolol when compared with carteolol. Participants receiving timolol, however, experienced two-fold higher odds of visual field defects than participants receiving levobunolol (CI, 1.2- to 4.1-fold).

Maier and colleagues summarized the evidence from five RCTs that randomly assigned ocular hypertensive participants to medical or surgical treatment, or to no treatment. Participants receiving topical medications were 44% less likely to experience progression of visual field loss and optic disc damage than participants receiving no treatment (hazard ratio, 0.6 [CI, 0.4 to 0.8]). Medically or surgically treated patients with primary OAG were 35% less likely to experience progression of field loss and optic disc damage than those receiving no treatment. Burr and associates reviewed the evidence from three RCTs of initial medical treatment versus initial trabeculectomy for preventing the progression of visual field loss and optic nerve damage. One trial found that trabeculectomy resulted in less visual field progression than medical treatment (OR, 2.56 [CI, 1.12 to 5.83]), whereas

the other two trials found no clear difference in the risk for progression (trial 1: OR, 0.69 [CI, 0.29 to 1.67]; trial 2: change in visual field mean deviation, -0.28 [CI, -0.59 to 0.03]). Two trials included in Rolim de Moura and colleagues' review compared argon laser trabeculoplasty with medications in patients with newly diagnosed glaucoma.

The three systematic reviews provide high strength of evidence that decreasing IOP by medical therapies or laser or incisional surgery reduces optic nerve damage as assessed by functional (visual field) or structural measures.

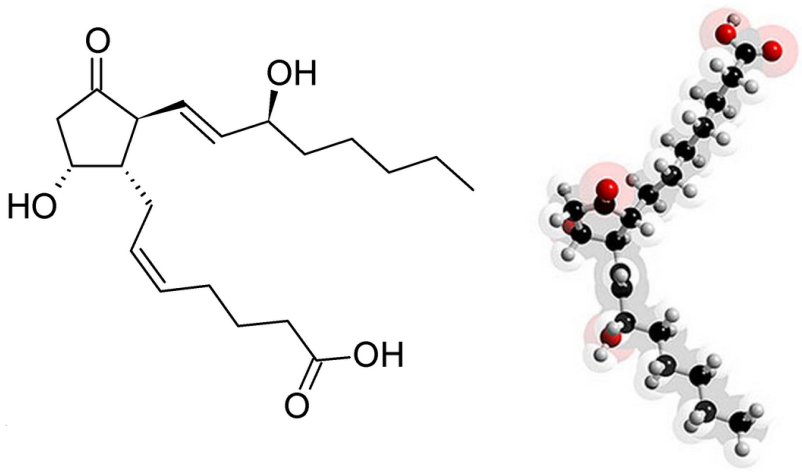
PROSTAGLANDIN (PG) & PROSTAGLANDIN ANALOGS (PGA)

Most PGAs (prostaglandin analogues) are once-daily dosed eye drops generally prescribed as the initial drug to reduce IOP by increasing fluid outflow through the eye's secondary drain. PGAs represent about half of the US and European prescription volume for the treatment of glaucoma. Xalatan (latanoprost), the best-selling PGA, and Xalacom, its fixed-combination with a beta blocker, which is not available in the US, had worldwide peak sales of $1.7 billion before their patent expired in 2012.

Prostaglandins (PGs) are a group of lipid compounds derived enzymatically from fatty acids. PGs are bioactive lipids that exert an autocrine or paracrine function by binding to specific G-protein-coupled receptors (GPCRs) to activate intracellular signaling and gene transcription. With thromboxanes and prostacyclins, PGs form the prostanoid class of fatty acid derivatives.

Prostaglandins are unsaturated carboxylic acids made up of 20 carbon atoms, including a 5-carbon ring (Figure 11). They are synthesized from the fatty acid arachidonic acid. PGs exhibit differences in their chemical structures on various side-chain substitutions, and their classification is based on these subtle structural differences.

Figure 11: Skeletal structure and 3D model of prostaglandin molecule

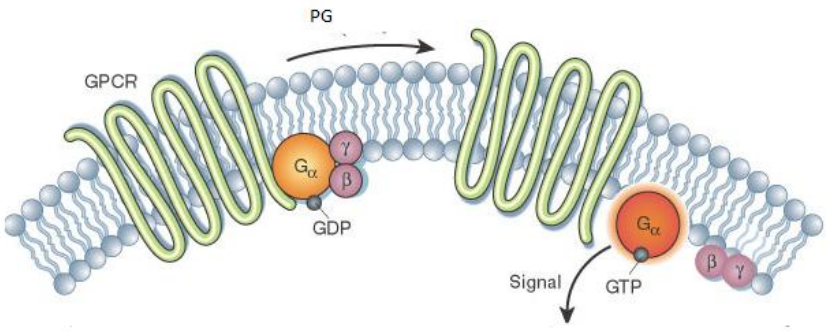


Source: National Institutes of Health

Prostaglandins serve a similar function as hormones, but differ in that they are not produced in one unique location, but in many sites throughout the body. The target cells of

prostaglandins are located in the immediate vicinity of the secretion of the prostaglandin. Figure 12 illustrates that PGs work by activating rhodopsin-like seven transmembrane spanning G protein-coupled receptors (GPCRs). GPCRs are integral membrane proteins that are coupled to the intracellular side of the membrane. They are activated by a wide variety of ligands and are the target of approximately half of all modern medicinal drugs. Because they are expressed on cell surfaces, GPCRs are easily accessible to hydrophilic drugs and because they are non-uniformly expressed, it is possible to selectively activate or block physiological events.

Figure 12: Activation of GPCR by PG



Source: Nature, 2010

Prostaglandin analogues (PGA) are molecules manufactured to bind to a prostaglandin receptor. Prostanoid receptors couple to a range of intracellular signaling pathways that mediate the effects of receptor activation on cell function. They are synthesized and released upon cell stimulation and act on cells located near their synthesis to exert their actions. Common agents include latanoprost, travoprost, bimatoprost, and unoprostone isopropyl.

PGA efficacy in glaucoma. Systematic reviews comparing timolol with travoprost and latanoprost showed prostaglandin analogues to be more effective at decreasing IOP. Two systematic reviews concluded that bimatoprost 0.03% decreased IOP more effectively than did latanoprost at 3 months (risk difference [RD], 12 [95% CI, 4 to 21]), although this difference was not present at 1 and 6 months. Both Li and Eyawo and their respective colleagues concluded that mean IOP reduction was similar with travoprost and latanoprost. For the comparison of bimatoprost with travoprost, Eyawo and colleagues reported a significant difference in favor of bimatoprost at three or more months of follow-up (weighted mean difference, 0.88 [CI, 0.13 to 1.63]), whereas Li and colleagues concluded that bimatoprost and travoprost were similarly effective (weighted mean difference, 0.08 [CI, -0.62 to 0.79]). Two studies examined brand and generic latanoprost and found that both decreased IOP equivalently, by 6 to 7 mm Hg. A single study also showed that latanoprost (7.5 mm Hg) and the combination of brimonidine–timolol (7.0 mm Hg) both decreased IOP by the same amount. We think the conclusion that topical glaucoma medications decrease IOP is well-supported, as is the conclusion that prostaglandin agents are superior to other monotherapies with regard to decreasing IOP.

PGA side effects. Prostaglandin analogs have an excellent safety profile with regard to systemic side effects, but often induce ocular side effects. Some of these side effects are common and do not have serious consequences, for example conjunctival hyperemia, elongation and darkening of eyelashes, iris darkening, and periocular skin pigmentation. More serious side effects include iris cysts, cystoid macular edema, and reactivation of herpes simplex keratitis.

Aptel and colleagues noted that the risk for conjunctival hyperemia (redness) was 1.7 times higher with use of bimatoprost than with latanoprost (CI, 1.4 to 2.0). Cheng and Wei, Eyawo and colleagues, and Honrubia et al reported similar results for the same comparison. Cheng and Wei further noted no differences in eye irritation (RD, 1 [CI, -3 to 4]), ocular inflammation (RD, -1 [CI, -2 to 1]), cystoidmacular edema (RD, 0 [CI, -2 to 2]), and iris pigmentation (RD, 0 [CI, -1 to 2]) with use of bimatoprost versus latanoprost. Participants randomly assigned to latanoprost experienced less redness than did those receiving travoprost. Eyawo and colleagues reported 49% lower odds of redness with latanoprost compared with travoprost. Li and associates further noted that travoprost 0.004% increased the odds of redness compared with travoprost 0.0015% (OR, 1.6 [95% CI, 1.3 to 2.0]). Redness, dry eye, and increased pigmentation did not differ between latanoprost, brimonidine, or dorzolamide. Participants using brimonidine had an increased risk for fatigue.

Li, Vass, Zhang, and Loon compared timolol with brimonidine, prostaglandin analogues (travoprost, latanoprost), other beta-blockers, and placebo. Although the odds of participant dropout due to drug-related adverse events was increased two-fold with timolol versus betaxolol (OR, 2.4 [CI, 1.0 to 5.5]), the odds of dropping out were lower among participants receiving timolol than those receiving brimonidine (OR, 0.21 [CI, 0.14 to 0.31]). Participants receiving travoprost or latanoprost had 6 times the odds and twice the odds, respectively, of dropping out of the study because of redness than patients receiving timolol. Both drugs increased iris pigmentation. Redness and iris pigmentation also were related to use of latanoprost when compared with fixed and concomitant administration of timolol and dorzolamide. Figure 13 summarizes the publications that address the adverse effects of medical therapy for glaucoma. Collectively, they identified primarily localized AEs, such as eye irritation, redness, and iris color change. As the most commonly used medical therapy, the prostaglandin agents do not have systemic adverse effects or known interactions with other systemic medications

Figure 13: Summary AEs associated with OAG therapy

Studies Included, *n*	Comparators	Main Results	Strength of Evidence
Systematic reviews			
Medical: 11	Latanoprost vs. bimatoprost Latanoprost vs. bimatoprost vs. travoprost Latanoprost vs. dorzolamide–timolol Latanoprost vs. brimonidine Latanoprost vs. travoprost vs. bimatoprost Travoprost vs. latanoprost vs. bimatoprost vs. timolol Timolol vs. brimonidine Timolol vs. latanoprost	Participants receiving timolol were less likely to drop out of studies because of adverse effects than those receiving brimonidine, latanoprost, travoprost, or betaxolol	
Surgical: 10	Efficacy and safety of viscocanalostomy Nonpenetrating filtering surgery β-radiation during trabeculectomy 1-site phacotrabulectomy vs. 2-site phacotrabulectomy Intraoperative mitomycin C vs. placebo during trabeculectomy Posttrabeculectomy injections of 5-fluorouracil	Adverse effects occurred more often in participants randomly assigned to trabeculectomy than to those assigned to other nonpenetrating surgeries Harms were reported for the addition of antimetabolites to primary trabeculectomy Addition of β-radiation to trabeculectomy resulted in significantly higher risk for cataract when compared with trabeculectomy alone Harms associated with glaucoma drainage devices have not been adequately compared with harms of other procedures in OAG treatment	
Medical–surgical: 2	Medical vs. surgical treatment	Trabeculectomy is associated with cataract worsening and increased need for cataract surgery over time compared with medical treatments for glaucoma Intraocular surgery rarely results in severe vision loss due to infection and or bleeding; these risks are not associated with medical or laser treatments Laser trabeculoplasty can produce peripheral anterior synechiae, whereas medical treatment does not	
Primary studies			
Medical: 21 RCTs, 16 observational	Timolol vs. brimonidine vs. travoprost Timolol vs. carteolol Timolol vs. latanoprost Timolol vs. betaxolol Latanoprost vs. bimatoprost Latanoprost vs. travoprost vs. dorzolamide–timolol Topical medication vs. observation Latanoprost vs. bimatoprost latanoprost vs. timolol vs. brimonidine Latanoprost vs. dorzolamide–timolol	Prostaglandins produce more ocular redness than does timolol Among the prostaglandins, latanoprost is less likely to cause redness than is bimatoprost or travoprost	Unable to assess because of heterogeneity in outcomes and comparisons across studies
Surgical: 26 RCTs, 8 observational	Trabeculectomy with adjuvants (mitomycin C, 5-fluorouracil, Ologen implant [Aeon Astron Corp., Taipei, Taiwan], polytetrafluoroethylene membrane, amniotic graft) Trabeculectomy techniques and variations Combined cataract–glaucoma surgery Laser trabeculoplasty Deep sclerectomy with or without mitomycin C Deep sclerectomy with or without collagen implant	Profile of harms does not differ between 1- and 2-site combined cataract and glaucoma surgery Reports of adverse effects across studies that addressed questions related to combined surgery for coexisting cataract and glaucoma varied by intervention under consideration	Unable to assess because of heterogeneity in outcomes and comparisons across studies
Medical–surgical: 2 RCTs, 0 observational	Trabeculectomy vs. medical treatment Medical or surgical vs. no treatment	Primary studies did not systematically address harms	Unable to assess because of heterogeneity in outcomes and comparisons across studies

Source: Annals of Internal Medicine, 2013.

Beta-blockers

Beta blockers inhibit aqueous production and they are one of the oldest approved drugs for the lowering of IOP. The most commonly used drug in this class is timolol. Beta blockers are less effective than PGAs in terms of IOP lowering and are typically used twice daily. Beta blockers are the most commonly used non-PGA drug. They are used as an initially prescribe monotherapy and as an adjunct therapy to PGAs when the efficacy of PGAs is insufficient. Systemic exposure from topical application of beta-blocker eye drops may lead to cardio-pulmonary events such as bronchospasm, arrhythmia and heart failure.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors are designed to inhibit aqueous production. CA inhibitors are less effective than PGAs and are required to be dosed three times daily in order to

obtain the desired IOP lowering. Most frequently reported adverse events were blurred vision and bitter, sour or unusual taste. Carbonic anhydrase inhibitors are sulfonamides and extended exposure may increase risk of adverse responses such as Stevens-Johnson syndrome and blood dyscrasias.

Alpha agonists

Alpha agonists decrease aqueous production and elevate uveoscleral outflow. This class of eye drop is less effective than PGAs. For example, brimonidine ophthalmic solution, a commonly prescribed alpha agonist, needs to be dosed three times daily in order to obtain the desired IOP reduction. Common adverse events include allergic conjunctivitis, conjunctival hyperemia, eye pruritus, burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness and visual disturbance.

Figure 14 summarizes the competitive dynamics between different classes of OAG eye drops.

Figure 14: Summary AEs associated with OAG therapy

	Mechanism	Efficacy	First approved	Peak sales (include generics)	Market share
Alpha agonist	Decreases aqueous production and elevates uveoscleral outflow	+	1996	Over $400M	11%
Beta blocker	Inhibits aqueous production	+/++	1980	Over $500M	15%
CAI	Inhibits aqueous production	+	1982	Over $500M	10%
PGA	Increases uveoscleral outflow	++	1996	$1.7B	50%

Source: IMS, FDA, Bloomberg and Canaccord Genuity estimates.

Surgical treatment options

OAG surgery involves either laser treatment or making an incision in the eye to reduce the intraocular pressure. The type of surgery one's physician recommends will depend on the type and severity of glaucoma disease progression and the general health of the eyes. Surgery may be able to help lower pressure when medication is not sufficient; however, it cannot reverse vision loss.

Physicians often recommend laser surgery before filtering microsurgery, unless the eye pressure is very high or the optic nerve is severely damaged. During laser surgery, a focused beam of light is used to treat the eye's trabecular meshwork thereby increases the flow of fluid out of the eye. In contrast, conventional surgery (filtering microsurgery) involves creating a drainage hole with the use of a small surgical tool. This new opening allows the intraocular fluid to bypass the clogged drainage canals and flow out of this new, artificial drainage canal. When laser surgery does not successfully lower eye pressure, or the pressure begins to rise again, the doctor may recommend conventional surgery. If necessary, glaucoma surgery can be done several times without substantial risk.

Figure 15 summarizes the comparative advantages of different treatment options.

Figure 15: Currently available treatments for open-angle glaucoma

	Medicines	Laser Surgery	Traditional Surgery
Description	Eye drops that are used or pills that are taken one or more times a day	Surgery with a laser that is done in an outpatient surgery center that only takes a few minutes □ The effects of this surgery may wear off after several years.	Surgery done in an operating room □ The effects of this surgery may wear off after several years.
Possible Benefits	■ Lowers eye pressure □ Prostaglandin analogs (Lumigan®, Travatan Z®, Xalatan®) and a combination of the medicines dorzolamide and timolol (Cosopt®) seem to lower eye pressure better than the other medicines. ■ Helps prevent optic nerve damage and loss of side vision	■ Lowers eye pressure ■ Helps prevent optic nerve damage and loss of side vision ■ May reduce the need for medicines to treat glaucoma, but there is not enough research to know this for certain □ Some people who have laser surgery may still need to use medicine to treat their glaucoma.	■ Trabeculectomy lowers eye pressure ■ Trabeculectomy helps prevent optic nerve damage and loss of side vision □ Some people who have traditional surgery may still need to use medicine to treat their glaucoma.
Possible Side Effects	■ Eye drops can cause eye redness, blurred vision, stinging, and itching. ■ Pills can cause nausea, vomiting, diarrhea, and drowsiness. ■ The pills may cause more severe side effects or allergic reactions than the eye drop medicines.	■ Temporary eye redness, blurred vision, increased eye pressure, and swelling in the eye (all of these usually go away within 24 hours after surgery)	■ Increased risk of bleeding, infection, and vision loss, although these are rare ■ Increased risk of developing cataracts

Source: Department of Health and Human Services

After examining data collected through 86 primary studies, we note there are three trials, discussed below, that compared patient-reported outcomes between different treatment groups.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) randomly assigned 607 patients with glaucoma to topical medications or trabeculectomy. No differences in the Visual Activities Questionnaire Total or Peripheral Vision subscale scores were reported; however, for the Acuity subscale, the surgically treated group reported more dysfunction at 2-, 6-, and 30-month follow-up. Surgical patients reported approximately 22% more bothersome symptoms on the Symptom Impact Glaucoma Total score than those in the topical treatment group. The CIGTS also reported a decrease in the fear of blindness in both the pharmacologic and surgical groups.

The Early Manifest Glaucoma Trial randomly assigned 255 patients with early glaucoma to no treatment or to a combination of topical betaxolol 0.5% and laser trabeculoplasty. No difference in quality of life measured with a visual function questionnaire was noted between groups. Javitt and colleagues treated 219 patients with brimonidine 0.2% or

timolol 0.5% for 4 months and assessed quality of life with the Short-Form 36 instrument. The change in Short-Form 36 scores varied from only 1 to 3 units (on a scale of 0 to 100), and no group differences were identified.

Though we see the overall strength of evidence for glaucoma treatments preventing visual impairment and the evidence linking glaucoma treatments to patient-reported outcomes as inconclusive, we think patients may opt for the less-invasive eye drop as their treatment course.

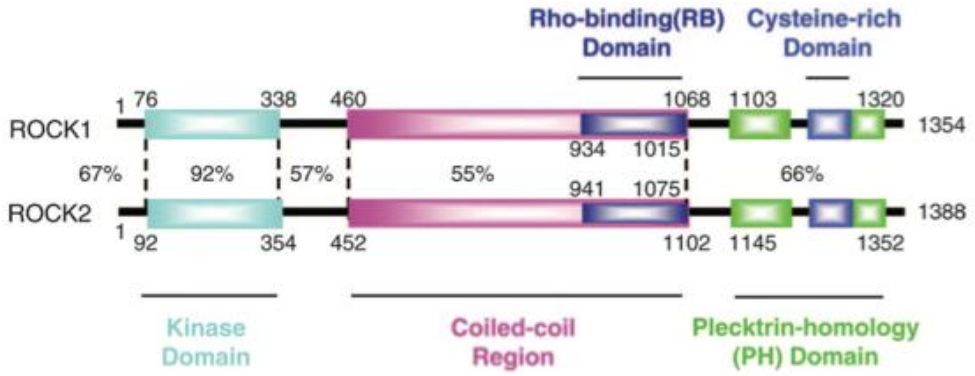
ROCK SIGNALING PATHWAY & IOP REDUCTION

The small GTP-binding proteins that make up the Rho family regulate various aspects of cell shape, motility, proliferation, and apoptosis. Rho kinases (ROCKs) were the first downstream effectors of Rho discovered. These kinases were found to mediate RhoA-induced actin cytoskeletal changes through effects on myosin light chain phosphorylation. The Rho kinases ROCK1 and ROCK2, are Rho kinase isoforms that were initially discovered as downstream targets of the small GTP-binding protein, Rho.

ROCKs consist of an amino-terminal kinase domain, followed by a mid coiled-coil-forming region containing a Rho-binding domain (RBD), and carboxy-terminal cysteine-rich domain (CRD) located within the pleckstrin homology (PH) motif. These carboxy-terminal regions of ROCKs serve as autoregulatory inhibitors of the amino-terminal kinase domain (Figure 16).

ROCK activity is increased through the derepression of the carboxyl-terminal RBD-PH domain on the amino-terminal kinase domain, leading to an active ‘‘open’’ kinase domain. The open conformation could also be caused by the binding of arachidonic acid to the PH domain10 or cleavage of the carboxyl-terminus in ROCK1 by caspase-311,12, and in ROCK2 by granzyme B or caspase-2. ROCKs can also be activated independently of Rho by way of amino-terminal transphosphorylation or when inhibited by other small GTP-binding proteins such as Gem and Rad.

Figure 16: ROCK isoforms



Source: Nature, 2010

ROCK inhibitors act by increasing facility of fluid outflow from the eye, thereby reducing intraocular pressure. These inhibitors have a vasodilatory effect on conjunctival vessels, which can lead to eye redness, which is a less-than-desirable cosmetic side effect for patients who would use this medication.

In the normal eye, aqueous humor forms in ciliary processes of the ciliary body, passes through the pupil to the anterior chamber, and exits through the trabecular meshwork (TM). From the TM, aqueous humor exits through one of two routes. The trabecular route, often referred to as the conventional outflow pathway, accounts for 40–96% of outflow in the human eye. This percentage depends on the age of the patient. This outflow of aqueous humor involves aqueous transport through the TM, into Schlemm's canal (SC), then out into the episcleral and conjunctival venous system.

Certain cellular properties of the TM are critical for conventional outflow. High levels of RhoA (Ras homolog gene member A, a small GTPase protein that regulates the actin cytoskeleton in the formation of stress fibers) have an important function. These high levels of RhoA in TM cells induce a contractile morphology, increased actin stress fibers, increased focal cell–cell adhesions, increased levels of phosphorylated myosin light chain (MLC), and increased extracellular matrix protein production. These changes lead to decreased aqueous humor drainage due to cellular and morphological changes in the TM cells. The ciliary muscle (CM) contraction leads to increased TM pore size and subsequent increased aqueous drainage. In contrast, the second route, known as the uveoscleral route, accounts for 4–60% of outflow in the human eye and it involves the passage of aqueous humor from CM fibers into the suprachoroidal space. From there, aqueous humor drains into the venous system of the ciliary body, choroid and sclera.

The Rho GTPase signal transduction pathway is made up of a complex series of interactions between extracellular ligands, trans-membrane receptors, intracellular enzymes, and cytoskeletal effector proteins. Activation of the Rho GTPase pathway in the eye causes cellular and molecular changes within cells in the TM leading to the contraction of smooth muscle-like cells and diminished aqueous humor drainage.

Several studies support this molecular understanding of conventional outflow. In vitro studies using human and porcine TM cells infected with adenovirus containing a dominant-negative Rho-binding domain of ROCK have shown that ROCK inhibition induces cell rounding, and cell–cell detachment, and decreases actin stress fibers and focal adhesion staining. In these studies, in addition to alterations consistent with TM relaxation and morphological changes, ROCK inhibition increased outflow in human anterior segments. Increased outflow has been shown to decrease IOP, making Rho GTPase signaling a promising target for the treatment of glaucoma.

The Rho proteins (RhoA, RhoB, and RhoC) belong to the Ras superfamily of GTPases. Rho GTPases receive inputs from one of four transmembrane receptor classes, including G-protein-coupled receptors, receptor tyrosine kinases, cytokine receptors and adhesion receptors. These receptors collectively respond to signals from growth factors, cytokines and extracellular matrix proteins. ROCKs are intracellular serine/threonine kinases located downstream of Rho in the signal transduction pathway. These ROCKs represent an important target in glaucoma therapy.

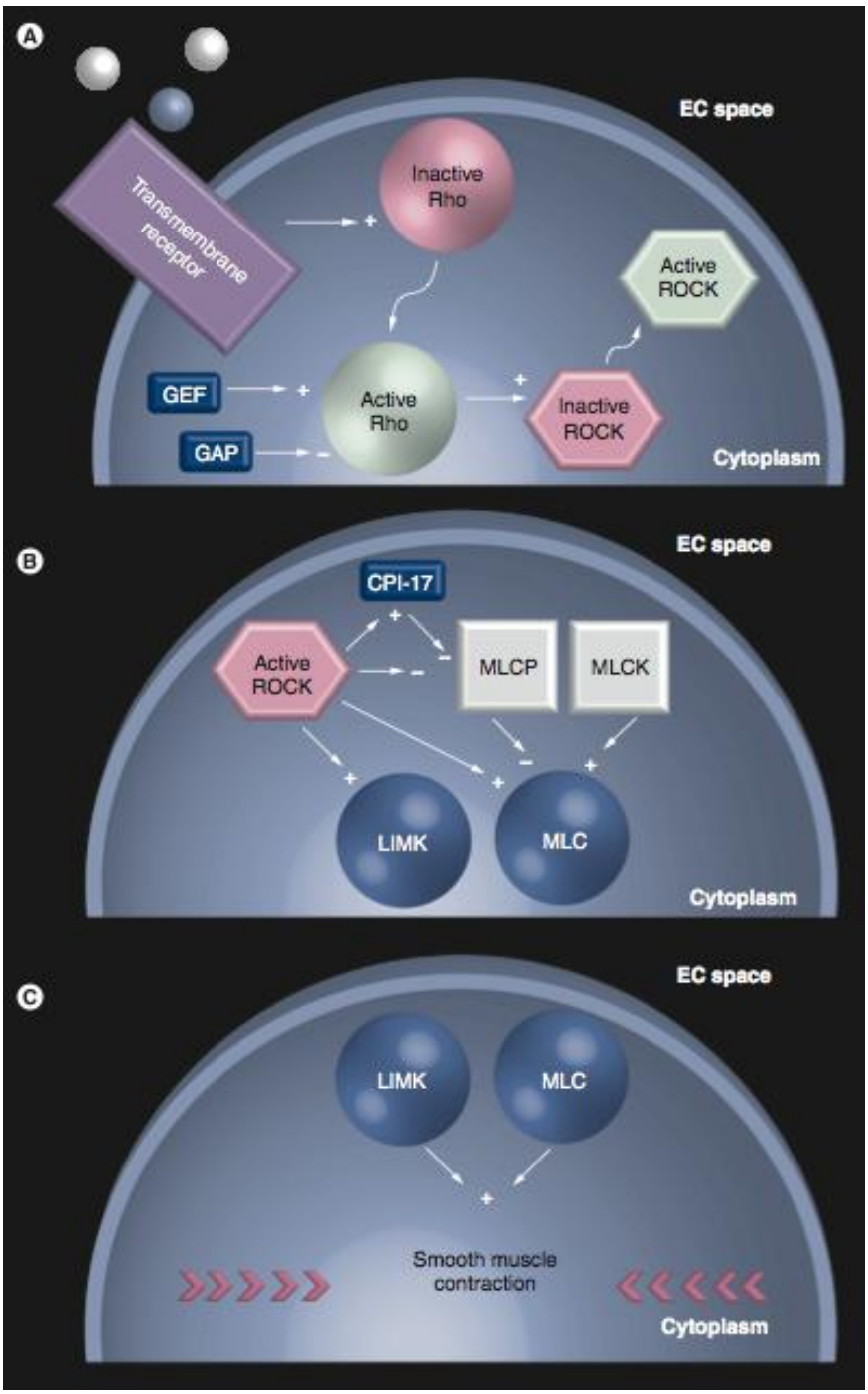
ROCKs consist of three domains: an N-terminal kinase domain, a C-terminal pleckstrin homology domain, and a coiled-coil domain. These domains interact with Rho–GTP to

regulate ROCK activity. When present, Rho–GTP binds the coiled-coil domain and enhances ROCK activity. When absent, N-terminal kinase activity diminishes through an autoinhibitory intramolecular fold of the pleckstrin homology domain. As with Rho, ROCK localization is important. ROCKs are primarily distributed in the cytoplasm; however, upon activation by Rho, ROCKs partially translocate to the membrane.

Although both ROCK-I and ROCK-II are expressed in the CM and TM of humans and monkeys, the TM exhibits greater expression levels of both kinases. These differences are consistent with the proposed mechanism of action of ROCK inhibitors, through which inhibition of ROCKs cause increased aqueous outflow, leading to a decrease in IOP. ROCK activation induces contraction of smooth muscle-like cells in the eye. Therefore, protein levels have been used to predict that ROCK inhibition would lead to greater relaxation of the TM than of the CM. Since CM contraction increases outflow while TM contraction reduces it, greater relaxation of the TM would cause increased outflow.

In addition to Rho GTPases and ROCKs, other downstream targets in this pathway are believed to play an important role in IOP regulation. An example of these downstream targets is noted as ROCKs regulate MLC phosphatase (MLCP), MLC, LIM domain kinase (LIMK) and CPI-17. During activation, ROCKs phosphorylate and inhibit MLCP, causing an increase in myosin regulatory light chain phosphorylation at serine 19, facilitating myosin–actin binding and contraction of smooth muscle-like cells. ROCK can also directly phosphorylate MLC; however the physiologic importance of this direct phosphorylation remains unknown. Figure 17 illustrates the Rho GTPase signaling pathway.

Figure 17: Rho GTPase signaling pathway

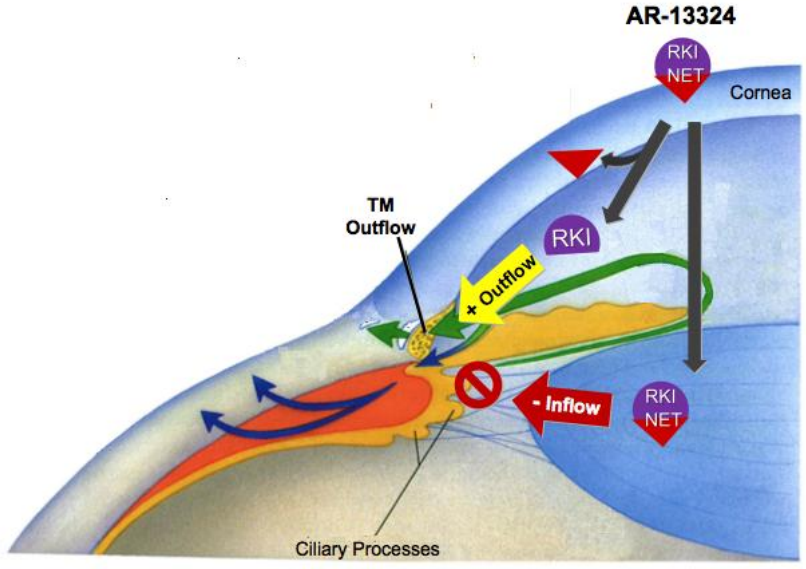


Source: PNAS, 2006

AERI'S ROCK/NET INHIBITORS – AR-13324 AND PG324

AERI's primary product candidates, once-daily dual-action AR-13324 and once-daily triple-action PG324, lower IOP through novel MOAs. Both formulations lower intraocular pressure (IOP) through novel mechanisms of action. AR-13324 and PG324 both inhibit Rho kinase (ROCK) and the norepinephrine transporter (NET). By inhibiting ROCK, these formulations reduce IOP by increasing the outflow through the trabecular meshwork (TM), which is responsible for elevated IOP in glaucoma and is the eye's primary drain. Through NET inhibition, these products also lower IOP by reducing the production of eye fluid. AR-13324 is a once-daily dual-action formulation. ROCK/NET inhibition mechanism is illustrated in Figure 18.

Figure 18: ROCK/NET inhibition pathway



Source: Company presentation

AR-13324 PHASE 2 DATA

Phase 2b data. AERI completed a 28-day, 224-patient AR-13324 Phase 2b clinical trial comparing AR-13324 0.01% and 0.02% against latanoprost in May 2013. Trial design is summarized in Figure 19. Although AR-13324 is expected to compete primarily against other non-PGA drugs, latanoprost was used as the comparator as it is the most widely-prescribed drug of all currently marketed glaucoma products.

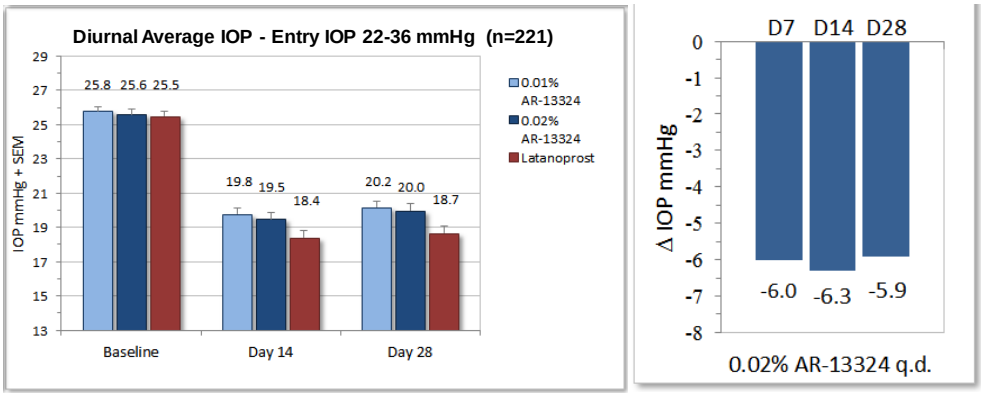
Figure 19: Summary of AR-13324 Ph2 trials

	A Phase 2, Double-masked, Randomized, Multi-center, Active-controlled, Dose-response Parallel-group Study Comparing the Safety and Ocular Hypotensive Efficacy of AR-13324 to Latanoprost in Patients With Elevated Intraocular Pressure
NCT ID	NCT01731002
Design	Randomized, placebo controlled, double blind
Enrollment	224
Dosing	AR-13324 Ophthalmic Solution 0.01%/0.02% and latanoprost ophthalmic solution
Key inclusion criteria	• Diagnosis of open angle glaucoma (OAG) or ocular hypertension (OHT). • Unmedicated (post-washout, p.r.n.) IOP ≥ 24 mm Hg in one or both eyes at 08:00 hours, ≥ 21 mm Hg at 10:00, 12:00 and 16:00 hours on post-washout measurement (Visit 1). • Corrected visual acuity in each eye +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200).
Key exclusion criteria	• Glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure or narrow angles. Note: Previous laser peripheral iridotomy is NOT acceptable. • Intraocular pressure > 36 mm Hg • Previous glaucoma intraocular surgery or glaucoma laser procedures in study eye(s, e.g., laser trabeculoplasty). • Ocular medication of any kind within 30 days of Visit 0, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after Visit 0) or c) lubricating drops for dry eye (which may be used throughout the study). • Clinically significant ocular disease (e.g. uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for one month is not judged safe (i.e., cup-disc ratio > 0.8). • Central corneal thickness greater than 600 µm. • Due to the current status of the preclinical safety program, women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study
Primary endpoint	Mean IOP across subjects within treatment group on each day at each post-treatment time point
Secondary endpoint	None
Powering	80% power to conclude non-inferiority in the mean diurnal IOP at Day 28 compared to latanoprost assuming a non-inferiority limit of 1.5 mm Hg
Data expected	H2/14

Source: Clinicaltrials.gov

Baseline IOP was measured prior to treatment, and IOP was measured on day seven at 8 a.m. and on days 14 and 28 at 8 a.m., 10 a.m. and 4 p.m. On day 14, mean diurnal IOP decreased to 19.8, 19.5 and 18.4 mmHg in the AR-13324 0.01%, AR-13324 0.02% and latanoprost groups, respectively, representing a decrease from untreated baseline of 5.9, 6.2 and 7.1 mmHg. On day 28, mean diurnal IOP was 20.1, 20.0 and 18.7 mmHg, respectively, representing a decrease from untreated baseline of 5.5, 5.7 and 6.8 mmHg (Figure 20).

Figure 20: AR-13324 demonstrated strong IOP lowering in Ph2b



Source: Company filings

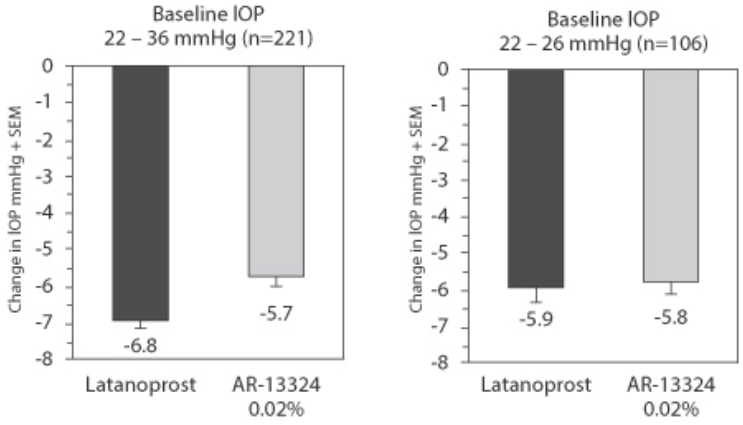
AR-13324 maintained consistent efficacy from day seven through day 28. For AR-13324 0.02%, the concentration AERI intends to use in the planned Phase 3 trials, at the 8 a.m.

time point, the time of highest baseline IOP, the IOP reductions achieved on day seven and day 28 were 6.0 and 5.9 mmHg, respectively. The level of IOP reduction achieved by AR-13324 0.02% in the Phase 2b study was clinically significant, since previously published long-term studies have demonstrated that a sustained 5 mmHg reduction in IOP reduces the risk of disease progression by approximately 50%. In the full Phase 2b trial population, which consisted of patients with baseline IOPs ranging from 22 to 36 mmHg, the IOP-lowering effect of our once-daily AR-13324 0.02% was 1.2 mmHg less than that of latanoprost on day 28 and did not show non-inferiority. However, AR-13324 0.02% efficacy relative to latanoprost was in line with published historical data for twice-daily timolol relative to latanoprost. Timolol is the most commonly prescribed non-PGA drug and the comparator for the planned Phase 3 non-inferiority registration trial.

A study by Hedman and Alm, which reports on the pooled data from three registration trials of latanoprost versus timolol, showed the IOP-lowering effect of timolol to be 1.2 mmHg less than that of latanoprost, as reflected in the graph on the following page under the heading "Comparison of latanoprost and timolol from pooled data of three registration trials." We note the AR-13324 Phase 2b clinical trials similarly showed AR-13324 to have an IOP-lowering effect of 1.2 mmHg less than that of latanoprost.

An additional protocol-specified analysis that compared the results for the patients who entered the trial with moderately elevated baseline IOPs (22 to 26 mmHg) to patients with highly elevated baseline IOPs (greater than 26 mmHg) revealed a differentiated efficacy profile of AR-13324 compared to latanoprost. Consistent with previous scientific literature, latanoprost produced smaller IOP reductions in patients with moderately elevated IOPs than in patients with highly elevated IOPs. In contrast, AR-13324 maintained by and large the same IOP-lowering effect in patients with moderately elevated IOPs as in patients with highly elevated IOPs (p>0.30) (Figure 21). As a result, the IOP-lowering effect of AR-13324 was equivalent to latanoprost in patients with moderately elevated baseline IOPs and AR-13324 thereby demonstrated statistical non-inferiority to latanoprost in this sub-group.

Figure 21: AR-13324 shows superior IOP-lowering effect to latanoprost

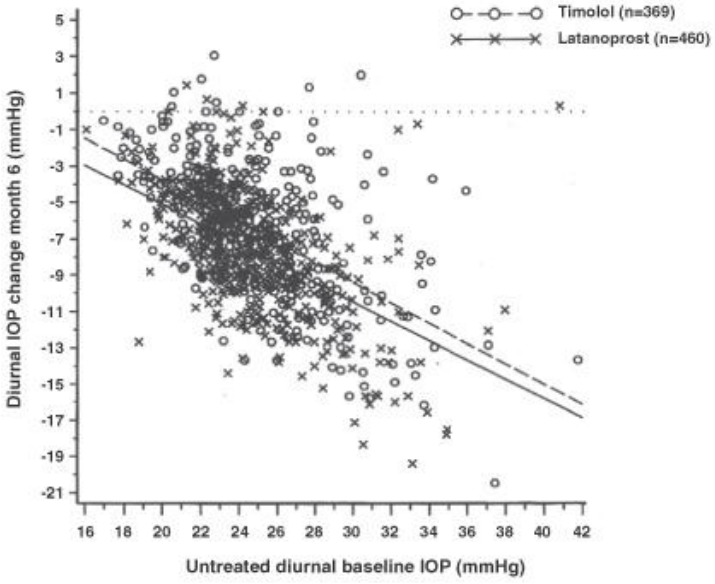


Source: Company filings

A study published in 2000, which pooled data from three latanoprost registration trials, demonstrated that both latanoprost and timolol lose approximately 0.5 mmHg in efficacy for every 1 mmHg lower baseline IOP, as illustrated in Figure 22. Additional publications

have indicated similar declining efficacy results for other currently marketed non-PGA glaucoma drugs, including the alpha agonist brimonidine and the carbonic anhydrase inhibitor dorzolamide.

Figure 22: Latanoprost and timolol have reduced efficacy in patients with low baseline IOP



Source: Eur J Ophthalmol, 2000.

We think the ability of AR-13324 to maintain a consistent IOP-lowering effect on baseline IOP will place AR-13324 in a favorable competitive position relative to current non-PGA drugs because a significant majority of glaucoma patients have baseline IOPs of 26 mmHg or less. Results from a large epidemiological survey published in 1991, the Baltimore Eye Survey, demonstrated that greater than 78% of patients have unmedicated baseline IOPs of 26 mmHg or below when first diagnosed with glaucoma (Figure 23).

Figure 23: Prevalence of glaucoma by baseline IOP at the time of diagnosis

Baseline IOP (mmHg)	Percentage of OAG Patients	Cumulative Percentage
≤ 15	13%	13%
16-18	24%	37%
19-21	22%	59%
22-24	19%	78%
25-29	10%	88%
30-34	9%	97%
≥ 35	3%	100%

Source: Baltimore Eye Survey

AR-13324 Phase 2a efficacy and safety results

In August 2012, AERI completed a seven-day AR-13324 Phase 2a clinical trial with 85 patients who were treated once-daily with AR-13324 0.01%, AR-13324 0.02%, AR-13324 0.04% or AR-13324's vehicle.. There was observed statistically significant decreases in mean diurnal IOP in all AR-13324 treatment groups following seven days of dosing compared to unmedicated baseline.

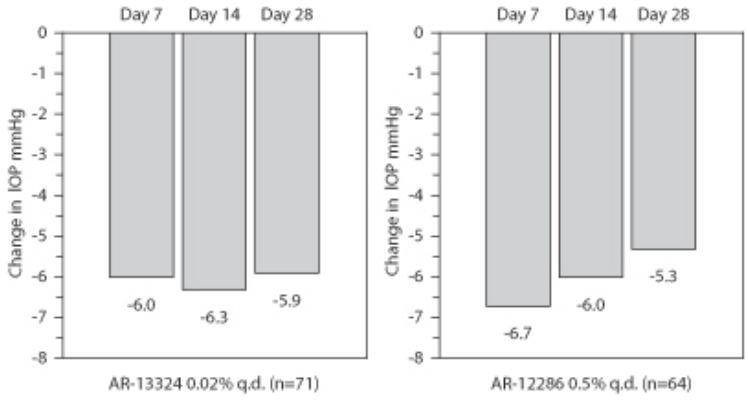
The main adverse event seen in clinical studies thus far include transient hyperemia, or asymptomatic redness of the eye, with all hyperemia scored as mild or moderate. We think the ROCK/NET MOA of the drug, which induces a transient dilation of small blood vessels located over the sclera, may have contributed to the cosmetic tolerability finding.

The biomicroscopy results from the Phase 2b trial for the vast majority of patients who experienced ocular hyperemia were mild and transient, and there were no observations of severe ocular hyperemia. On Day 28, mild and moderate conjunctival hyperemia was observed in 18% and 24% of patients in the AR-13324 0.01% and 0.02% treatment groups, respectively, and in 11% of patients in the latanoprost group. The incidence of conjunctival hyperemia decreased throughout the study for AR-13324 and increased for latanoprost.

Note published data indicate that latanoprost generates the lowest rate of hyperemia among the commonly prescribed PGAs. In a study that compared the relative frequency of hyperemia for bimatoprost, travaprost and latanoprost after 12 weeks of treatment, the largest proportion of patients reporting redness was found in the bimatoprost group with 35%, followed by the travoprost and latanoprost groups with 27% and 16%, respectively.

AERI has analyzed clinical and preclinical data for AR-13324, dual-action ROCK/NET inhibitor, relative to its clinical and preclinical data for AR-12286, single-action ROCK-selective compound. Similarly designed 28-day Phase 2 clinical trials for each of AR-13324 and AR-12286 were conducted, and the comparative results of which are presented in Figure 24. AR-13324 0.02% maintained stable efficacy on day 28 relative to day 7 in its 28-day Phase 2 clinical trial. In contrast, AR-12286 0.5% lost 1.4 mmHg of IOP-lowering efficacy from day 7 to day 28 in its 28-day Phase 2 clinical trial.

Figure 24: IOP-lowering effect of AR-13324 and '286 at Day 7, 14, and 28



Source: Company filings.

Prior AERI ROCK-NET Candidates. AERI also completed a three-month Phase 2 clinical trial for AR-12286 that confirmed the trend observed in the 28-day trial discussed above. In the three-month trial, the efficacy of AR-12286 continued to decline over the trial period such that it failed to meet its primary efficacy endpoint, non-inferiority to timolol.

AR-13324 has a number of characteristics that distinguish it from AR-12286. AR-13324 lowers IOP through a dual mechanism of action by inhibiting both ROCK and NET, whereas AR-12286 has a single mechanism of action inhibiting only ROCK. In addition, AR-13324 has a unique chemical composition that was specifically designed to allow maximal efficacy of the drug in the eye. Enzymatic conversion of AR-13324 produces two separate molecules, one of which is approximately ten times more potent at inhibiting ROCK than AR-12286. AR-13324's more potent ROCK inhibition, as well as its ability to inhibit NET, contributes to its greater efficacy and longer duration of effect relative to AR-12286. In addition, the analyses of Phase 2 data suggest that there is a secondary signaling pathway that is activated by a protein called PKC that also leads to contraction of the TM. Preclinical analyses show that AR-13324 is a potent inhibitor of both ROCK and PKC, whereas AR-12286 is a potent inhibitor of ROCK but not of PKC. We think that the ability of AR-13324 to inhibit both the primary ROCK and the secondary PKC signaling pathways also contributes to AR-13324's ability to maintain its efficacy over time.

Furthermore, in a six-month toxicology study with exaggerated dosing of AR-12286, cataracts were observed in rabbit eyes beginning at three months. In a similar six-month toxicology study with exaggerated dosing of AR-13324, no adverse lens effects were observed. As a result of these observations, in June 2013, AERI selected dual-action AR-13324 for advancement to Phase 3 clinical development and discontinued development of AR-12286 and its related fixed-dose combination product PG286.

FUTURE CLINICAL DEVELOPMENT OF AR-13324: PHASE 3

We expect registration trials for AR-13324 to begin mid-2014 upon completion of three-month interim study reports from the ongoing six-month and nine-month Phase 3-enabling ocular toxicology studies. The AR-13324 doses and dosing frequencies being tested in these studies have previously been shown to be well tolerated in 28-day and six-month ocular toxicology studies.

AERI plans to run two pivotal trials that will include at least 1,200 patients in total. The entry criteria for the Phase 3 trials are planned to include a minimum IOP of 21 mmHg and a likely maximum of 26 to 30 mmHg. Based on discussions with the FDA, AERI believes the planned entry criteria for the Phase 3 trials is acceptable to the FDA and will not impact the product label. The entry criteria for the completed Phase 2 trials were 22 to 36 mmHg. Lowering the IOP entry criteria for Phase 3 trials will increase the representation of patients with moderately elevated IOPs in the trials and thereby provide a more representative cross-section of the glaucoma patient population. Figure 25 depicts what we would expect to see as the design of the registrational trials.

Figure 25: Pivotal Phase 3 design - Canaccord Genuity projection

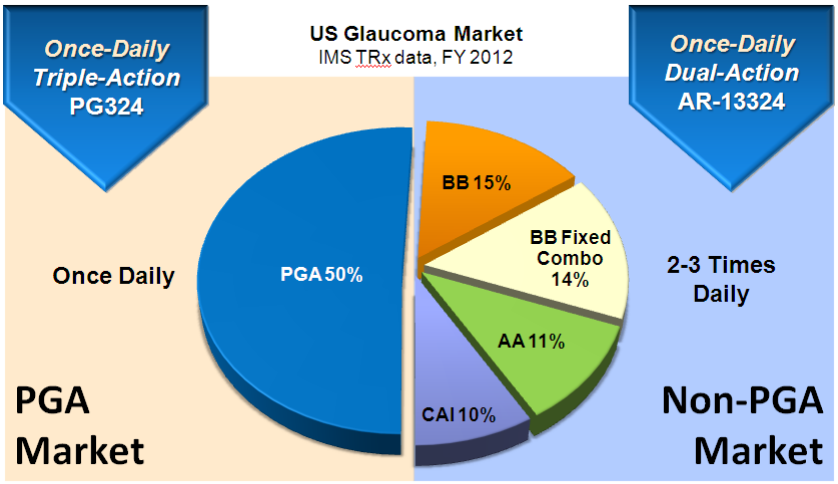
	Pivotal Phase 3 – Canaccord Genuity projection
NCT ID	TBA
Design	Randomized, placebo controlled, double blind
Enrollment	At least 1200 subjects
Dosing	AR-13324 Ophthalmic Solution 0.01% and 0.02% and latanoprost ophthalmic solution
Key inclusion criteria	• Diagnosis of open angle glaucoma (OAG) or ocular hypertension (OHT). • Unmedicated (post-washout, p.r.n.) IOP ≥ 24 mm Hg in one or both eyes at 08:00 hours, ≥ 21 mm Hg at 10:00, 12:00 and 16:00 hours on post-washout measurement (Visit 1). • Corrected visual acuity in each eye +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200).
Key exclusion criteria	• Glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure or narrow angles. Note: Previous laser peripheral iridotomy is NOT acceptable. • Intraocular pressure > 36 mm Hg • Previous glaucoma intraocular surgery or glaucoma laser procedures in study eye(s, e.g., laser trabeculoplasty). • Ocular medication of any kind within 30 days of Visit 0, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after Visit 0) or c) lubricating drops for dry eye (which may be used throughout the study). • Clinically significant ocular disease (e.g. uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for one month is not judged safe (i.e., cup-disc ratio > 0.8). • Central corneal thickness greater than 600 µm.
Primary endpoint	Intraocular pressure at 3 months
Secondary endpoint	Safety at 12 months and visual acuity
Powering	TBA

Source: Clinicaltrials.gov

The registration trials will be non-inferiority trials comparing AR-13324 0.02% taken once daily in the evening to twice-daily timolol, the standard comparator for glaucoma registration trials. Phase 3 efficacy results will be determined after three months of treatment and safety results will be analyzed and submitted following 12 months of treatment. Assuming a mid-2014 Phase 3 start with anticipated enrollment rate, AERI expects efficacy data from the two trials in mid-2015 and if the results of the Phase 3 trials are positive, AERI would submit NDA by mid-2016. AERI intends to seek priority review with the FDA and we think the probability of success here is high.

If approved, we expect AR-13324 to compete against non-PGA products, the significant majority of which have been in the market for at least 20 years. The non-PGA market segment represents approximately half of the total prescription volume of the glaucoma market, for which 2012 branded and generic product sales exceeded $4.5 billion in the United States, Europe and Japan in aggregate according to IMS. Due to the multiple daily doses, side effects and contraindications of the currently marketed non-PGA products, we believe there is a significant unmet need in this market segment. We believe that AR-13324 has several significant differentiating characteristics that would make it a strong competitor in the non-PGA market segment (Figure 26).

Figure 26: Currently prescribed glaucoma therapies

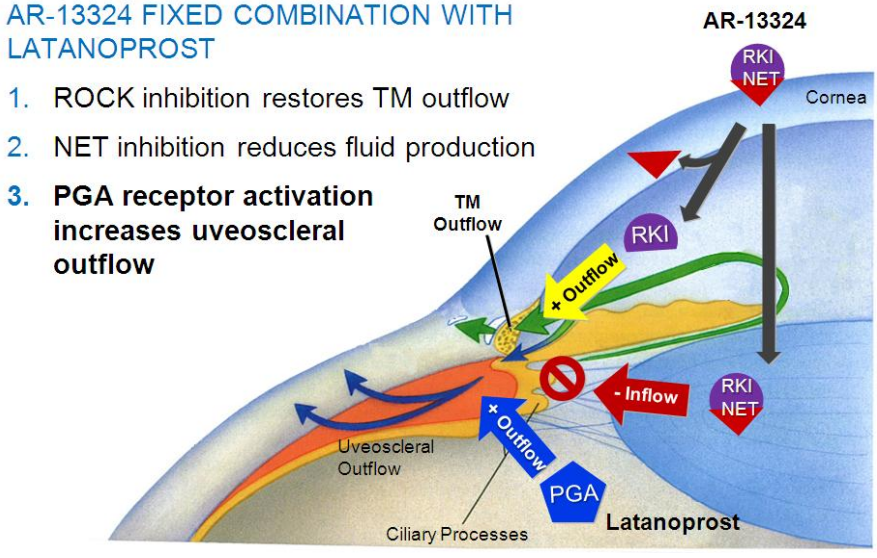


Source: IMS data, company filings

Triple-action PG324

AERI's once-daily, triple-action product candidate PG324 is a combination of the dual-action compound AR-13324 formulated with latanoprost in a single eye drop. If approved, the company believes that PG324 would be the first glaucoma product to lower IOP through all three MOAs: increasing fluid outflow through the TM and uveoscleral and reducing fluid production (Figure 27).

Figure 27: PG324 combines AR-13324 and latanoprost to lower IOP through 3 MOAs

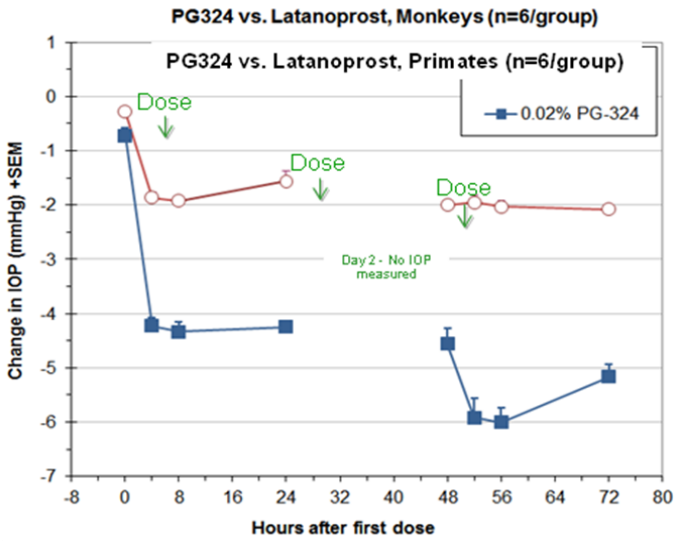


Source: Company filings

Triple-action PG324 has been tested in a preclinical primate model to assess its effectiveness at lowering IOP. Figure 28 shows the data from dosing PG324 and

latanoprost once daily for three days (at hours 0, 24 and 48). At all time points measured, PG324 reduced IOP substantially more than latanoprost alone. No IOP measurements were taken on day two of the study between hours 24 and 48. We note that in prior ROCK inhibitor/PGA combination trials, AERI's discontinued PG286 product demonstrated significant IOP lowering beyond the PGA alone at 28 days.

Figure 28: Inclusion-exclusion criteria and patient demographics



Source: Company filings

We think PG324, if approved, has the potential to be the only glaucoma product that covers the full spectrum of IOP-lowering mechanisms, giving it the potential to provide a greater IOP-lowering effect than any currently approved glaucoma product. As such, we think PG324 could be competitive against both PGA and non-PGA therapies.

In light of AERI's clinical experience with AR-13324 to date and the extensive clinical track record of latanoprost, we think AERI's plan to advance PG324 directly into a Phase 2b clinical trial is feasible. PG324 is currently covered by AERI's IND for AR-13324 and there is 28-day toxicology data to support a 28-day clinical trial. We expect AERI to initiate the Ph2b trial in early 2014. The trial is planned to be a randomized, controlled 28-day trial in approximately 300 patients. The trial will be designed to measure the efficacy of two concentrations of PG324 (with 0.01% and 0.02% concentrations) compared to latanoprost and AR-13324 0.02%, all with qd dosing. The efficacy endpoint will be superiority of PG324 to each of its components. The Phase 3 registration trial for PG324 is expected to mirror the planned Phase 2b trial but with three-month efficacy and a 12-month safety trial, and will only test one concentration of PG324. We expect data readout in mid-2014.

Second-generation, dual-action AR-13533

In addition to its primary product candidates, AERI is currently developing AR-13533, a second-generation dual-action ROCK/NET inhibitor. AR-13533 does not require enzymatic conversion in the eye to deliver maximal ROCK inhibitor activity, and therefore AR-13533 may provide additional IOP-lowering effect in patients beyond that obtained with AR-

13324. We expect updates from AERI in the coming month regarding this program and expect an IND to be filed based on strong data.

COMPETITION

AERI faces competition from established branded and generic pharmaceutical companies, such as Bausch + Lomb (recently acquired by Valeant Pharmaceuticals), Merck & Co, Novartis International AG, Allergan and Santen, as well as other biopharmaceutical companies. The key competitive factors affecting the success of AERI's product candidates, if approved, are likely to be efficacy, safety, convenience, price, tolerability and the availability of reimbursement from government and other third-party payors.

In addition, many of the older glaucoma drugs are associated with compliance issues. Non-compliance results from the difficulty of administering multiple eye drops in a single day. Challenges such as this are magnified in the elderly, who constitute the largest and fastest growing proportion of the glaucoma population. Administration of multiple eye drops daily not only increases intrinsic side effects of the active ingredients, but also elevates exposure of patients to the preservatives in eye drops. Over time, the extended exposure may lead to damage to the surface of the cornea resulting in discomfort and symptoms of dry eye disease.

Despite their modest efficacy, safety and tolerability profiles, and the requirement for two to three doses per day, the beta blocker, carbonic anhydrase inhibitor and alpha agonist products account for up to half of the total prescription volume for the treatment of glaucoma based on historical prescription patterns, with beta blocker timolol being the most widely prescribed non-PGA drug. This is driven by the PGA products not being sufficiently effective as monotherapy for up to half of all glaucoma patients. Among the non-PGA drug classes, brands such as Allergan's Alphagan / Combigan franchise generated combined global revenues in 2012 of over $420 million, and prior to the introduction of generics, the branded beta blockers and carbonic anhydrase inhibitors generated peak annual product revenues of over $400 million. Fixed-combination glaucoma products currently marketed in the United States include Cosopt, the combination of a beta blocker with a carbonic anhydrase inhibitor, and Combigan, the combination of a beta blocker with an alpha agonist. There are no fixed-combinations of PGAs with other glaucoma drugs currently available in the United States, which PG324 could address.

Bausch + Lomb/NicOx currently have a once-daily NO-donating latanoprost formulation in Phase 3 development. The Ph3 trials are ongoing, and we expect data to read out in the next 12 to 24 months. We note this formulation may have limited efficacy in low IOP patients given latanoprost mechanism as seen in previous trials.

Amongst non-PGA product candidates there are two ROCK-only inhibitors in development: K-115 (Kowa, Ph3 Japan) and AMA0076 (Amakem, Ph2a). We note Kowa is a large Japanese-based multinational conglomerate with a differentiated revenue base and big-name pharmaceutical partners like Eli Lilly and Merck, whereas Amakem is a VC-backed, clinical stage biotechnology firm developing therapeutics options for glaucoma patients. Both of their product candidates require twice-a-day dosing, and from the data we saw in AR-12286 (ROCK-only inhibitor) we believe the efficacy of these molecules may pale in comparison with AR-13324's dual mechanistic approach, let alone the added strength of

latanoprost in PG324. Both candidates are in late stage development, and we expect registrational data to become available in the 18 to 24 months time frame.

We note Synlentis, a subsidiary of Spanish-based pharmaceutical company Zeltia, is currently conducting Ph2 trials for SYL012, a RNAi beta blocke. We believe the once daily dosing of AR-13324 will be preferable to SYL012's BID schedule, and we note the beta blocker class has demonstrated CV risk through prolonged systemic exposure may pose concerns for physicians.

Figure 29 outlines current development programs for the treatment of open angle glaucoma from various competitors.

Figure 29: Competitive landscape of drug candidate pipeline for OAG treatment

Brand	New PGA*	Trial Stage
BOL-303259 (Bausch + Lomb)	NO-donating latanoprost (qd)	Phase 3
DE-117 (Santen)	EP2 agonist (qd)	Phase 2a
ONO-9054 (Ono)	FP/EP3 agonist (qd)	Phase 1

Brand	New non-PGA*	Trial Stage
AR-13324 (Aerie)	ROCK/NET inhibitor (qd)	Phase 2b
K-115 (Kowa)	ROCK inhibitor (bid)	Phase 3 (Japan)
AMA0076 (Amakem)	ROCK inhibitor (bid)	Phase 2a
INO-8875 (Inotek)	Adenosine-A1 agonist (bid)	Phase 2
LX7101 (Lexicon)	LIMK2 inhibitor (bid)	Phase 1/2
SYL040012 (Sylentis)	RNAi beta blocker (bid)	Phase 2

* References to "qd" are to once daily-dosed products, and "bid" are to twice-daily products.

Source: Company presentation

MANUFACTURING

AR-13324 is can be manufactured in a reliable and reproducible seven-step synthesis from readily available starting chemical ingredients. We think the chemistry used to manufacture AR-13324 is amenable to scale up and does not require special equipment in the production process. AERI currently relies on third-party manufacturers to produce the active pharmaceutical ingredient and the final drug product for clinical development purposes and manages such production with all vendors on a purchase order basis in accordance with applicable master service and supply agreements. AERI does not currently operate manufacturing facilities for clinical or commercial production of its product candidates and plans to outsource the production of the active pharmaceutical ingredients and final drug product once they are approved for marketing by respective regulatory authorities. Latanoprost, an ingredient of PG324, is available in commercial quantities from various reliable third-party manufacturers and AERI intends to procure quantities on a purchase order basis. AERI does not have any current contractual relationships for the manufacture of commercial supplies of its product candidates. We think there are a number of potential replacements in AERI's supply chain, but there may be a delay in shipment fulfillment as AERI seeks alternative suppliers.

INTELLECTUAL PROPERTY

Aerie's exclusively-owned product candidates and technology are protected by patents lasting through at least 2030.

Aerie has obtained patent protection for its two primary product candidate, AR-13324 and PG324, in the United States. Patent protection for PG324 stems from the patent protection the company has secured for AR-13324. The company is seeking patent protection in various foreign jurisdictions for these product candidates.

As of June 30, 2013, Aerie has nine US or foreign patents issued, covering previously discontinued product candidates, and 33 US patent applications of foreign national patent applications, that if patents were to issue based on existing claims, would cover aspects of Aerie's current and previously discontinued product candidates.

Aerie's Board of Directors authorized the divestiture of non-core intellectual property for implantable ophthalmic devices, such that it could be used by Novaer Holding, an independent company. As part of this transaction, Aerie also licensed non-ophthalmic rights to its intellectual property portfolio to Novaer. This agreement to exclusively license intellectual property for non-ophthalmic indications to Novaer was terminated on September 6, 2013. As of that date, Aerie owns all of the worldwide rights to the company's current product candidates for all indications.

Figure 30: Summary of key AR-13324 patents

Patent #	Name	IP Covered	Status	Expiration Date
8,450,344	Beta- and gamma-amino-isoquinoline aminde compounds and substituted benzamide compounds	Compounds that affect the function of kinases in a cell that are usesful as therapeutic agents or with therapeutic agents	Issued	2026
8,394,826	Dual mechanism inhibitors for the treatment of disease	Compounds that are inhibitors of both rho kinase and of monoamine transporter (MAT) that act to improve the disease state or condition	Issued	2030
8,455,513	6-aminoisoquinoline compounds	6-Amino isoquinoline compounds that influence, inhibit or reduce the action of a kinase	Issued	2027
8,455,514	6-and 7-amino isoquinoline compounds and methods for making and using the same	6- and 7-amino isoquinoline compounds that influence, inhibit or reduce the action of a kinase	Issued	2028

Source: Company reports and Canaccord Genuity estimates

MANAGEMENT TEAM

The Aerie management team has a strong history of research, development and commercialization in the Biotechnology space.

Vicente Anido, Jr., Ph.D., Aerie's chief executive officer since July 2013, joined Aerie in April 2013 as a chairman and member of the company's Board of Directors. Before Aerie, Dr. Anido served as president, chief executive officer and director of ISTA Pharmaceuticals, which was acquired by Bausch + Lomb in 2012. Prior to his work at ISTA Pharmaceuticals, Dr. Anido served as general partner of Windamere Venture Partners. Before his work at Windamere Venture Partners, he served as president and chief executive officer of a drug discovery company called CombiChem Inc. From 1993 to 1996, Dr. Anido was the president of the Americas Region of Allergan, and was responsible for Allergan's commercial operations in North and South America. Before serving as president of Allergan, Dr. Anido worked at Marion Laboratories and Marion Merrell Dow for 17 years, where he held positions including vice president-business management of the company's Prescription Products Division. Dr. Anido currently serves as a member of the Board of Directors of QLT and Depomed. He previously served as a member of the Board of Directors of Apria Healthcare. He received his BS and MS from West Virginia University and a PhD from the University of Missouri, Kansas City.

Casey C. Kopczynski, Ph.D., co-founded Aerie in 2005 and has since served as the company's chief scientific officer. Before cofounding Aerie, he was the managing partner at Biotech Imitative, LLC, a consulting practice for emerging biotech companies. Before his work at Biotech Initiative, Dr. Kopczynski was the vice president of research at Ercole Biotech, a company developing drugs for the treatment of cancer, inflammation, and orphan genetic diseases. Before his work at Ercole Biotech, he was director of research and a founding member of the scientific staff at Exelixis. Dr. Kopczynski received his Ph.D. in molecular, cellular, and developmental biology from Indiana University and was a Jane Coffin Childs Research Fellow at the University of California, Berkeley.

Brian Levy, O.D., M.Sc. joined Aerie in January 2012 as chief medical officer. Before joining Aerie, Dr. Levy was the chief scientific officer of Nexis Vision, a small venture-backed company developing products in ophthalmology. Before Nexis Vision, Dr. Levy served as chief operating officer of Danube Pharmaceuticals. Prior to his work at Danube Pharmaceuticals, Dr. Levy worked at Bausch + Lomb, serving in various roles including vice president of research & development, corporate vice president of research & development, and chief medical officer. Before Bausch + Lomb, Dr. Levy worked in a private clinical practice in Toronto, Ontario, after which time he served as an associate professor in the Department of Ophthalmology at California Pacific Medical Center in San Francisco. He currently holds an appointment as clinical professor in the Department of Ophthalmology at the University of Rochester's School of Medicine. Dr. Levy received his doctor of optometry degree from the University of California at Berkeley and received his MS from the University of Waterloo in Ontario, Canada.

Thomas A. Mitro, president and chief operating officer of Aerie, joined the company in August 2013. Prior to joining Aerie, Mr. Mitro served as vice president, sales and marketing at Omeros Corporation, a publicly traded clinical-stage biopharmaceutical company. Before Omeros, Mr. Mitro served as vice president, sales and marketing at ISTA

Pharmaceuticals, where he played a key role in building commercial operations for products including Bromday and Bepreve. Earlier in his career, Mr. Mitro served in various positions at Allergan, including vice president, skin care; vice president, business development; and vice president, e-business. He received his B.S. degree from Miami University.

Richard J. Rubino, Aerie's chief financial officer, joined the company in October 2012. Before joining Aerie, Mr. Rubino served as senior vice president, finance and chief financial officer of Medco Health Solutions. Earlier roles at Medco include controller and vice president of planning for the company. Prior to his work at Medco, Mr. Rubino held various positions at International Business Machines Corporation and PricewaterhouseCoopers LLP. He is a Certified Public Accountant and member of the American Institute of Certified Public Accountants. He received his B.S. in accounting from Manhattan College. Mr. Rubino currently serves as a director and the treasurer of the Northside Center for Child Development in addition to serving as a member of the organization's Finance Committee.

Figure 31: Aerie key management members

Name	Title	Industry experience prior to Aerie	Joined Aerie in:
Vicente Anido, Jr., Ph.D.	Chief Executive Officer	ISTA Pharmaceuticals, Inc. Windamere Venture Partners ComiChem, Inc. Allergan, Inc. Marion Laboratories and Marion Merrell Dow Inc.	2013
Casey C. Kopczynski, Ph.D.	Chief Scientific Officer	Biotech Initiative, LLC Ercole Biotech, Inc. Exelixis, Inc.	2005
Brian Levy, O.D., M.Sc.	Chief Medical Officer	Bausch + Lomb, Inc. Danube Pharmaceuticals Nexis Vision	2012
Thomas A. Mitro	President and COO	Omeros Corporation ISTA Pharmaceuticals, Inc. Allergan, Inc.	2013
Richard J. Rubino	Chief Financial Officer	Medco Health Solutions, Inc. International Business Machines Corporation Pricewaterhouse Coopers LLP	2012

Source: Company reports and Canaccord Genuity estimates

Figure 32: AERI P&L

	2012A	H1/13A	Q3/13A	Q4/13E	2013E	Q1/14E	Q2/14E	Q3/14E	Q4/14E	2014E	2015E	2016E
AR-13324	-	-	-	-	-	-	-	-	-	-	-	-
PG324												
Product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Grant revenue	-	-	-	-	-	-	-	-	-	-	-	-
Total revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Cost of goods sold	-	-	-	-	-	-	-	-	-			
Gross Profit	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
R&D expense	9.3	6.3	3.5	3.5	13.3	4.0	4.5	5.0	5.5	19.0	20.0	25.0
SG&A expense	5.0	3.4	3.0	3.0	9.4	3.3	3.3	3.5	3.5	13.6	15.0	17.0
Other operating expense	0.7	0.4			0.4	-	-	-	-	-	-	-
Total operating expense	**15.0**	**10.1**	**6.5**	**6.5**	**23.1**	**7.3**	**7.8**	**8.5**	**9.0**	**32.6**	**35.0**	**42.0**
Operating income	**(15.0)**	**(10.1)**	**(6.5)**	**(6.5)**	**(23.1)**	**(7.3)**	**(7.8)**	**(8.5)**	**(9.0)**	**(32.6)**	**(35.0)**	**(42.0)**
Net Interest/Investment income	-				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	0.1	0.1
Other non-operating income (expense)	(0.7)	(0.3)			-					-	-	-
Interest and other, Net	-	-	-	-	-	-	-	-	-	-	-	-
Pre-tax income	**(15.7)**	**(10.4)**	**(6.5)**	**(6.5)**	**(23.1)**	**(7.3)**	**(7.8)**	**(8.5)**	**(9.0)**	**(32.5)**	**(34.9)**	**(41.9)**
Income tax expense (benefit)	-	-	-	-	-					-	-	-
Net income (loss)	**(15.7)**	**(10.4)**	**(6.5)**	**(6.5)**	**(23.1)**	**(7.3)**	**(7.8)**	**(8.5)**	**(9.0)**	**(32.5)**	**(34.9)**	**(41.9)**
Basic EPS	**(0.93)**	**(0.55)**	**(0.28)**	**(0.28)**	**(1.06)**	**(0.31)**	**(0.33)**	**(0.36)**	**(0.38)**	**(1.38)**	**(1.47)**	**(1.76)**
Diluted EPS	**(0.93)**	**(0.55)**	**(0.32)**	**(0.32)**	**(1.06)**	**(0.31)**	**(0.33)**	**(0.36)**	**(0.38)**	**(1.38)**	**(1.47)**	**(1.76)**
Basic shares outstanding	16.8	18.9	23.2	23.3	21.8	23.4	23.6	23.7	23.8	23.6	23.7	23.9

Source: Company reports and Canaccord Genuity estimates

APPENDIX: IMPORTANT DISCLOSURES

Analyst Certification: Each authoring analyst of Canaccord Genuity whose name appears on the front page of this research hereby certifies that (i) the recommendations and opinions expressed in this research accurately reflect the authoring analyst's personal, independent and objective views about any and all of the designated investments or relevant issuers discussed herein that are within such authoring analyst's coverage universe and (ii) no part of the authoring analyst's compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed by the authoring analyst in the research.

Site Visit: An analyst has visited Aerie Pharmaceuticals' material operations in Bedminster, NJ. No payment or reimbursement was received from the issuer for the related travel costs.

Distribution of Ratings:
Global Stock Ratings
(as of 30 September 2013)

	Coverage Universe		IB Clients
Rating	#	%	%
Buy	562	57.9%	37.7%
Speculative Buy	47	4.8%	57.4%
Hold	313	32.2%	11.2%
Sell	47	4.8%	6.4%
	971*	100.0%	

*Total includes stocks that are Under Review

Canaccord Genuity Ratings System:

BUY: The stock is expected to generate risk-adjusted returns of over 10% during the next 12 months.
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SELL: The stock is expected to generate negative risk-adjusted returns during the next 12 months.
NOT RATED: Canaccord Genuity does not provide research coverage of the relevant issuer.

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Risk Qualifier: **SPECULATIVE:** Stocks bear significantly higher risk that typically cannot be valued by normal fundamental criteria. Investments in the stock may result in material loss.

Canaccord Genuity Research Disclosures as of 19 November 2013

Company	Disclosure
Aerie Pharmaceuticals	1A, 2, 3, 5, 7

1	The relevant issuer currently is, or in the past 12 months was, a client of Canaccord Genuity or its affiliated companies. During this period, Canaccord Genuity or its affiliated companies provided the following services to the relevant issuer: A. investment banking services. B. non-investment banking securities-related services. C. non-securities related services.
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3	In the past 12 months, Canaccord Genuity or any of its affiliated companies have been lead manager, co-lead manager or co-manager of a public offering of securities of the relevant issuer or any publicly disclosed offer of securities of the relevant issuer or in any related derivatives.
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5	Canaccord Genuity or one or more of its affiliated companies is a market maker or liquidity provider in the securities of the relevant issuer or in any related derivatives.
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