

October 11, 2010

Market Outperform / Aggressive Risk

Illuvien could present a nice adjunctive therapy in Diabetic Macular Edema

MARKET DATA 10/8/2010

Price	\$10.89
Exchange	NASDAQ
Target Price	\$13.00
52 Wk Hi - Low	\$11.30 - \$6.30
Market Cap(MM)	\$339.1
EV(MM)	\$278.9
Shares Out (MM)	31.1
Public Mkt Float (MM)	7.1
Avg. Daily Vol (000)	37,652.0
Short Interest(000)	507,180.00

BALANCE SHEET METRICS

Cash (MM)	\$4.9
Debt/Capital	NA
Cash/Share	NA
Book Value(MM)	NA
Book Value/Share	\$1.81

EARNINGS DATA (\$)

FY - Dec	2011E	2012E	2013E
Q1 (Mar)	--	(0.06)	0.04
Q2 (Jun)	(0.11)	(0.04)	0.13
Q3 (Sep)	(0.10)	(0.01)	0.19
Q4 (Dec)	(0.14)	(0.02)	0.28
Full Year EPS	(0.56)	(0.09)	0.64
Revenue (MM)	16.4	47.8	81.0

VALUATION METRICS

Price/Earnings	NM	NM	17.0x
EV/Revenue	17.0x	5.8x	3.4x

INDICES

DJIA	11,006.5
SP-500	1,165.2
NASDAQ	2,027.0
NBI	910.7



Initiating Coverage with Market OutPerform & \$13 PT

We are initiating coverage of Alimera Sciences with a Market OutPerform rating and a 12-month PT of \$13. Our valuation methodology employs a traditional DCF using projected Illuvien sales growing to \$250 million by 2016, discounted back at 14%.

The Crux of the Story

- Diabetic macular edema (DME) represents a serious long-term ocular complication of diabetes and laser photocoagulation is the only approved therapy. An NIH study evaluating lasers in DME showed mean visual acuity improvement of 1 letter at 24-months and 5.5 letters at 36-months. Research is under way on sustained intravitreal delivery of corticosteroids & other VEGF antagonists.
- ALIM recently announced Ph III results in DME for its 24-month sustained release fluocinolone acetonide intravitreal implant called Illuvien. Per protocol specified endpoint of "proportion of patients with best corrected visual acuity of #15 letters at 24-months", *the trial did not meet statistical significance*. However, 29% of the control arm and about 12% of low-dose Illuvien arm patients were given off-label treatments. This tells us that the prescribing physician was more uncomfortable with the progress in the control arm. Secondly, 78% of phakic patients in the low-dose arm developed cataracts between 6-18 months, causing mean acuity scores to go down. It is certainly possible that the physician (being masked) allowed low-dose patients to get an off-label anti-VAGF injection to reduce the edema. We suspect that it is possible that once the cataract was discovered, surgery ensued and this resulted in scores bouncing right back up. Net-net mean acuity scores improved by 6.6 letters at 24-months, which is a significant improvement over lasers. Retinal thickness decreased consistently, which points to clinical efficacy of Illuvien; however functionality seems to have gotten blurred with cataracts and protocol violations.
- FDA has given priority review for Illuvien and PDUFA date is Dec 30, 2010. We try to bolster our case for Illuvien approval by highlighting that Allergan (AGN – Not Rated) got approval for Ozurdex in retinal vein occlusion even though the trial failed and there was no efficacy signal at 6-months. Illuvien, relatively, is showing a much better signal than laser therapy at 24-months. It is certainly possible that novel VEGF antagonists could present a better safety-efficacy profile in the future. However, balancing efficacy and systemic side-effects remains a tricky task.
- Illuvien, assuming usage as 2nd line therapy to lasers can generate peak sales of at least \$250 million by 2016. Ultimately, we can envision ALIM as a potential takeout target. While it is too early to hypothesize on takeout multiples, it nonetheless points to the scarcity value in the sustained drug-delivery ophthalmology space.

Risks Regulatory Risk. Market Risk. Competitive Risk.

INVESTMENT THESIS

Diabetic Macular Edema (DME) – a strong growth opportunity given sub-optimal currently approved treatments

DME is an ocular complication arising due to capillaries in the eyes of diabetics (Type I & Type II) leaking fluid into retinal tissue of the macula. The end result of untreated DME is usually retinopathy and blindness. A growing prevalence of diabetes worldwide, with approximately 325 million people expected to be suffering from diabetes by 2030, and prevalence estimates of anywhere between 2 – 12% (depending on the age of the patient and years since onset of diabetes) makes this a daunting healthcare challenge indeed. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), a prospective, population-based cohort study on the prevalence of diabetes and associated complications showed a direct correlation between prevalence of DME and onset since diagnosis. Overall prevalence of DME was 11.1% for the younger (≤ 30 years of age) and 8.4% for patients > 30 years. Interestingly, prevalence was 0% for onset time < 5 years and almost 30% with onset time 20 years or greater. In older patients, the respective numbers were 3% and 12%, respectively. DME has also been shown to be prevalent in about 20% of insulin users and 12% of non-users. While DME is a significant threat, a greater amount of focus has been shed on clinically significant DME (CSDME) that requires immediate intervention. Per industry estimates, CSDME has a prevalence rate of approximately 11.5% in Type I diabetics, 4.1% in Type II's not requiring insulin and 9.1% in Type II's requiring insulin. The cost of treating DME (medical care costs, prescription drug costs, indirect costs, etc) with retinopathy runs approximately \$30,000 / year. As far as we know, there is no "drug" therapy approved for treating DME. Laser photocoagulation is the only treatment officially approved for treatment of CSDME. In a 2004 study, it was shown that 60% of DME patients received one or more fluorescein angiography in the year after diagnosis, 30% underwent laser photocoagulation, 18% were evaluated using optical coherence tomography; and 14% got laser photocoagulation. The burden of DME continues to take a heavy toll in terms of direct and indirect costs to society. Despite the widespread use of lasers in DME, a recent NIH study has shown only a 1.1 letter improvement in mean visual acuity score at 24-months. Specifically, at 24-months in the DRCR study, the laser group had a mean change in BCVA of +1 letter, while the triamcinolone acetonide (TA) groups mean visual acuity actually reduced. At 36-months, the laser group mean visual acuity change was +5, while the TA groups were essentially 0.

Not Many options exist for treating CSDME; Extensive amount of research is under way with novel agents

Utopia in ophthalmology treatment would be good efficacy with minimal side-effects (systemic or local). We know that there is significant amount of research being done in researching not only novel VEGF antagonists, but also novel mechanisms of delivering these agents (whether in form factor, microspheres, etc). Corticosteroids are probably the most widely used off-label therapeutic agent in DME. Novel VEGF antagonists such as ranibizumab and bevacizumab are being actively explored in this indication. In a few studies, Lucentis has shown good efficacy up to 24-months, with mean visual acuity improvements over baseline of approximately 7-10 letters at 24-months. However, systemic side-effects include about 4-5% thromboembolic events, and about 6% reporting systemic hypertension. Interestingly enough, the only randomized study evaluating Lucentis and Avastin is the CATT study in AMD, results of which are expected in late 2012. As far as we know, there are no studies being conducted using these agents for DME specifically, and it almost seems to be that Genentech / Roche are aggressively trying to protect their \$1 billion Lucentis franchise from cannibalization by the lower cost Avastin. A newer type of antagonist, the VEGF-Trap is being actively explored by Regeneron Pharmaceuticals and has shown some interesting signals in Phase II studies. However, it should be noted that the demands on the "optimal" product currently seem to be an insurmountable task. Reason being, some of the standard VEGF antagonists, while good in efficacy long-term, have shown systemic side-effects. Plasma levels of these VEGF antagonists have been picked up in various studies, which could present an interesting conundrum for treatment of diabetic patients with compromised cardiovascular function. In a meta-analysis conducted on the use of Lucentis in wet-AMD indication, the risk of stroke was noted to be around 2.2%. VEGF-Traps have also shown good clinical efficacy to 6-months, however, a systemic side-effect of hypertension has been reported in some presentations. While the work on the ideal therapeutic agent is being conducted, there is also active work on the delivery mechanism for these therapeutic agents. For example, while intravitreal injections have been the standard delivery mechanism so far, companies are actively pouring in the resources to evaluate use of sustained drug-delivery mechanisms while reducing drug-payload. The thought process here being that if drug loading is reduced, the potential side-effects can be reduced. Moreover, with localized delivery, systemic side-effects can be reduced and / or eliminated. The localized delivery is being evaluated in the form of intravitreal biodegradable implants, polymeric microspheres laden with drug, laser activated reservoir depletion, etc. The ideal scenario would be reducing the frequency of injections given to the eye and having a sustained response over months or years with manageable side-effects and minimal patient relapse. Alimera and its partner, pSivida's long-duration corticosteroid implant Illuvien is the first one to go through Phase III trials in DME and seems to have generated a good amount of attention in the space, especially given that other novel treatments have not even started Phase III trials.

Illuvien is the first sustained release therapy for DME to complete clinical trials

Alimera's lead product Illuvien has been the subject of a randomized, double-blinded Phase III study called FAME. The study was a 2:2:1 randomized three arm study of high-dose fluocinolone acetonide delivered via Illuvien (0.45 ug/day); low-dose (0.23 ug/day); and control arm. FAME included DME patients who had undergone at least one prior photocoagulation treatment. Since the physicians were masked by protocol, laser treatments were allowed after week 6. However, off-label treatments such as intravitreal triamcinolone acetonide and Lucentis were not allowed. The protocol defined endpoint was "proportion of patients with BCVA ≥ 15 letters @ 24-months". This endpoint excluded patients with off-label treatment, and data imputation was allowed per ICH E9 guidelines from the point that they were dropped off. There were 2 kinds of analysis that were performed: first, the full-analysis set which included BCVA change comparisons between the various arms. In the full-analysis set, the trial reached statistical significance. However, in the modified-analysis (wherein off-label treatments patient data was removed and data was imputed to 24-months where they were dropped off), the trial did not meet statistical significance. The debate over the FAME study is really about what data set the FDA will look to in terms of granting (or denying) regulatory approval. We try to analyze as best as we can on the various confounders in the trial.

- *Different bogeys used by different players*

We note that throughout our work on different ophthalmology players in the space, trials are tweaked in a variety of ways. For example, some trials use mean visual acuity scores as endpoints. Some use intraocular pressure > 22 mm Hg as the threshold for safety event calculations; some using time to first response of BCVA ≥ 15 letters. However, the FDA considers BCVA ≥ 15 letters as the sacrosanct standard for determining clinical efficacy of ocular therapies. By some of the well-known metrics used by the FDA, we believe ALIM's trial is rigorous and relatively well-designed.

- *The modified-ART data set for Trial A did not reach statistical significance*

Per protocol, the m-ART data was defined as all randomized and treated patients included, but excluding data subsequent to out-of-protocol treatments such as Lucentis, vitrectomy, triamcinolone injections, etc. The data for these patients was imputed to the 24-month point using ICH E9 guidelines from the last follow-up period. Our understanding is that $> 50\%$ of data was imputed in the control arms of Trial A & Trial B combined and about 26% data was imputed in the low-dose arm of the combined study. While data imputation is to be expected and is usually factored in during trial design, it is unclear to us how the overall data would have fared had this level of imputation not been employed. Granted the study size would have increased substantially, but it is not known how the FDA would look at this. More number of patients in the control arm (ex off-label treatments) dropped out in the study which tells us that their progress was not going well. However, it is interesting to see that more number of patients in the control arm opted for treatments outside of protocol, which tells us that the prescribing physician was uncomfortable with the progress in these patients and hence chose a Lucentis or some other off-protocol therapy (remember the physicians were double-blinded in the trial). Theoretically these patients would be worse off at the 24-month time frame; we can guesstimate that the analysis should be in favor of Illuvien. Interestingly, one of the points of contention on this study is the % of patients who underwent off-label treatment such as Lucentis or triamcinolone acetonide in the arms. Our understanding is that 12% of patients in the low-dose arm and 29% of patients in the control arms of the combined studies underwent some sort of off-label treatment. Based on existing data, about 3 ½ times the number of off-label treatments were given per subject in the control arm as compared to the low-dose Illuvien arm. We also know that Illuvien accelerated cataract formation in phakic eyes. It is a well-known fact that cataract formation is a function of a long-term exposure to corticosteroids rather than the form factor of Illuvien itself. Between 6 – 18 months, about 78% of patients in the low-dose arm developed cataracts. An early clinical manifestation of cataracts is edema in the back of eye. Did the prescribing physician miss the onset of cataract formation and noticing the edema give an off-label injection of TA or Lucentis?? We don't know. It is certainly possible though. Majority of the cataract formation occurred between 6 – 18 months, which implies that during the onset of cataract formation to the time of surgery, visual acuity scores were going down. As seen in the available data, visual acuity scores bounced right back up after surgery. Did the weighted average time of surgery of phakic eyes affect the final visual acuity score calculation? It is certainly possible. Interestingly enough, when we look at the pseudophakic eye subset, visual acuity improves by about 8 letters and remains steady over 24-months. There was also a distinct difference in the off-label treatments given to the control arm vs. the low-dose arm, which tells us that Illuvien did have a significant clinical response vs. the control arm. The combination of all of the above, in our opinion, most likely explains why the m-ART analysis did not meet statistical significance. Despite all of this, the clinical response of Illuvien is evident in two data subsets (albeit not powered appropriately), which are the pseudophakic eye subset and the retinal thickness change data.

- *Relapse rates / Durability of efficacy*

Another possible missing data point in the trial is "potential relapse rates. Remember in Allergan's trial, about 40 - 50% of patients in the treatment arm had relapsed 4-6 weeks into the 6-month study. In the case of Illuvien, while we

do not have the specific relapse numbers, it seems that response rates were significantly better and held up over time. While ALIM and its partner pSivida point to the 30-month results (follow-up) which showed the low-dose arm of 123 treated patients and 63 control arm patients with BCVA ≥ 15 letters proportion of patients at 39.8% vs. 17.5%, respectively. However, we note that while this is directionally encouraging, we should take it within context. Presumably the low-dose patients, or for that matter control arm patients could have included patients with off-label treatments. We cannot make any statistical conclusions from the 30-month data set. Also, when we look at the foveal thickness numbers, the low-dose group at 24-months showed a foveal thickness reduction of about 150 um as compared to the control arm which saw a 100 um decrease. While it is well known that reduction in foveal thickness is indicative of a reduction in retinal leakage (and hence edema), we are not sure if the exact correlation between foveal thickness and change in BCVA is known. In other words, while clinically the reduction in foveal thickness was consistently seen over 24-months, the functional improvements in BCVA were not exactly correlated due to development of cataracts.

- *Phakic vs. pseudophakic patients*

When we look closer at the mean BCVA score of patients relative to baseline, we see that the low-dose group had a mean BCVA improve by 4.4 letters as compared to control of 1.7 letters @ 24-months ($p=0.02$). Also, it can be seen that about 80% of patients in the low-dose group developed cataracts y month 18, which lowered their BCVA scores. As can be seen in the statistical review of Allergan's Ozurdex, "High intra-ocular pressure and cataract formation are directly expected with use of corticosteroids." The logical question in our mind is...if cataract surgery was performed sooner than 18-months, the mean BCVA scores would certainly have been higher for the aggregate treatment arm. This is certainly manifested in the pseudophakic eye subset.

- *Safety concerns*

As seen from the adverse event profile, the key thing to note is that there were no glaucoma's reported and the % of intra-ocular pressure lowering surgeries were about 4% in the control arm. However, cataract formation in the low-dose arm was around 78%, which is lower than what Retisert showed (98% at 24-months). The high intraocular pressure adverse events (trabeculoplasty = 1.3%; trabeculotomy = 2.1% in the low-dose group; intraocular pressure >30 mm Hg = 16% in low-dose arm)) could present some concern for the clinical community.

- *How does it stack up relative to Allergan's Ozurdex*

As is well known, AGN in its pivotal Phase III trial for Ozurdex in CRVO changed the primary endpoint 5.5 months into the trial (probably after getting a glimpse of the data). While this trial was not designed to get a DME indication, the trendline of results + the overall clinical efficacy demonstrated + the trial modifications + eventual FDA approval are interesting benchmarks against which the chances of Illuvien getting approved should be measured. The endpoint in AGN's study was changed from proportion of patients with improvement in BCVA ≥ 15 letters to time to first response of BCVA ≥ 15 letters. While the trial met statistical significance on the modified endpoint, it did not meet statistical significance on the original hypothesis, thereby raising serious credibility issues with the study. Interestingly enough, about 50% of the patients in the treatment arms had relapsed in terms of visual acuity improvements and this was seen as early on as 4 – 6 weeks. A variety of regression analysis could not causatively determine the cause for the relapses. In study 008, the difference in patients with BCVA ≥ 15 letters improvement from baseline was 1.1% (CI = 95%; $p = 0.78$). In the low-dose arm the difference between the treatment arm and sham was -2.0% (95% CI; $p = 0.60$). Neither comparison was statistically significant. There were no differences between the 2 doses of dexamethasone. For study 009, the proportion of patients with BCVA ≥ 15 letters improvement from baseline was 6.5% (CI = 95%; $p = 0.087$) for the high-dose group and 5.1% (CI = 95%; $p = 0.180$) for the high-dose group. Neither comparison was statistically significant. Ozurdex did get FDA regulatory approval with a labeling for CRVO even though the statistical review by the medical examiner highlighted that the trial did not meet its endpoints, that the change in endpoints was suspicious, and that the efficacy is not maintained over 6-months. Our point through this exercise is....if Ozurdex got approved without an FDA panel, in Illuvien's case the device has shown sustained clinical efficacy in a sicker patient population and apparently with fewer relapses. Hence, its chances at getting approval seem to be better.

Valuation

We have performed a standard DCF model on ALIM using a 14% discount rate, which leads us to our 12-month PT of \$13. Our models assume an implied penetration rate of approximately 5% by 2016. We are assuming ASP for Illuvien at \$5,000 in 38,000 patients by 2016. The operational leverage in the story is contingent on Illuvien gaining a solid audience and that 30 – 40 reps being able to effectively penetrate and manage the 500 retina centers across the U.S. We have not factored the NADPH oxidase inhibitor program in our valuation analysis. Our rationale being, if we can showcase the elements of this

story with just the Illuvien piece, any other development on ongoing R&D programs represents a nice additive to the story. Our PT of \$13 represents an approximately \$380 million market cap company with good potential for margin expansion.

Risks

Regulatory Risk, Execution Risk, Market Risk.

Company Description

Alimera Sciences, based in Alpharetta, GA, is a biopharmaceutical company presently focused on diseases affecting the back of the eye. Its most advanced product, Illuvien, is an intravitreal insert containing fluocinolone acetonide. Alimera has licensed the product through pSivida Corp (PSDV – Market OutPerform; \$7 PT) and hopes to market the product for up to 36 months in the treatment of DME. Along with DME, the company is engaged in R&D work for assessing the effectiveness of Illuvien in other retinal diseases such as dry AMD, wet-AMD and retinal venous occlusion (RVO). The company has acquired worldwide rights to two classes of NADPH oxidase inhibitors from Emory University in the treatment of dry-AMD. Assuming its Illuvien product gets approved sometime in calendar Q1-11, the company plans on going direct in the U.S. and using distributors in Europe and Canada. Expectations are high on regulatory approval of Illuvien and the company is anticipating hiring 25 or so reps to meet the demand for Illuvien in DME.

Product Portfolio

Illuvien is Alimera's trademark in DME for the Medidur technology licensed from pSivida Corp. It is inserted via a 25-gauge, transconjunctival delivery system to the back of the eye in an in-office procedure, is designed to deliver fluocinolone acetonide on a sustained basis for up to 36 months. This is the key focus of the story. Alimera is in Phase II trials for evaluating Illuvien in dry and wet-AMD applications and RVO. *These products are probably 2015 and beyond products, due to which we do not spend time on them in this report*

Figure 1. Illuvien



Source: Company reports

Alimera is also investigating the use of NADPH (nicotinamide adenine dinucleotide phosphate oxidase) inhibitors in dry AMD applications. NADPH oxidase is most well known for its role in atherosclerosis where it releases reactive oxygen species that make macrophages adhere to the artery wall. Some of the NADPH oxidase inhibitors include agents like apocynin and diphenyleneiodonium. Researchers have pointed out hypothesized that glucose-induced mitochondrial production of reactive oxygen species stimulates several of the biochemical mechanisms thought to be involved in hyperglycemia-mediated complications of diabetes, including retinopathy. The causal link between glucose and vascular damage in diabetes has been thought to be due to increased production of superoxide by the mitochondrial electron transport chain. However, increasing evidence suggests that NADPH oxidase probably is the most important source of cellular reactive oxygen species (free radicals) in blood vessels. NADPH oxidase complex in neutrophils and, most probably, endothelial cells and other cell types, involves four essential subunits. The subunits gp91phox and p22phox reside in the plasma membrane. These subunits bind the components of the electron transport chain heme and FAD, forming cytochrome b558. The cytosolic NADPH oxidase subunits p47phox and p67phox are involved in the activation of the enzyme complex. Unlike the phagocytic type, the NADPH oxidases present in blood vessels are constitutively active, producing relatively low levels of reactive oxygen under basal conditions, and generating higher levels of oxidants in response to cytokines. Among the non-phagocytic cells examined so far, endothelial NADPH oxidase has been investigated more extensively. Alimera has licensed worldwide rights to NADPH oxidase inhibitor technology from Emory University and is engaged in pre-clinical work on assessing activity in dry AMD, especially the late stage known as geographic atrophy. *While theoretically interesting, we do not believe this is the core focus of the Alimera story and hence we do not delve into it any more.*

Diabetic Macular Edema – Market Size & Primer

Diabetic Macular Edema (DME)

According to the latest American Diabetes Association stats, approximately 24 million Americans have some form of diabetes, with approximately 50% having undiagnosed diabetes. Moreover, with approximately 2 million diabetics being of Type I kind, the implications for long-term complications and associated costs remain a serious concern to practitioners and payors alike. The complications of diabetes range from dysfunction of the kidneys to vascular inflammation to blindness. Diabetic macular edema is one such ophthalmic complication of diabetes, resulting in approximately 12,000 – 24,000 cases of new blindness in the U.S. per year. All patients with diabetes are at risk of developing DME. The onset is usually insidious and painless, and manifests with blurring of central visual acuity. The severity may range from mild and asymptomatic to profound loss of vision. After 20 years, about 60% of Type II diabetics and almost 100% of Type I diabetics will have some form of diabetic retinopathy. Industry sources estimate that at least 30% of the Type I diabetics will have clinically significant diabetic retinopathy. We estimate that in the U.S., of the 2 million Type I diabetics, 50% are undiagnosed, and of the remaining 50%, 30% have clinically significant DME. In Type II diabetes, approximately 7-10% of patients are thought to be at risk of developing clinically significant DME. Thus, the numbers of patients in the U.S. who have clinically significant DME (who, without intervention, will eventually develop proliferative retinopathy, resulting in profound visual loss (<5/200; acuity worse than that used to define legal blindness)), we estimate, number around 1,000,000 or so with an annual incidence of about 200,000.

Etiology & Pathophysiology

DME is a swelling of the retina in diabetes due to leaking of fluid from blood vessels within the macula, the central portion of the retina rich in cones upon which daytime vision depends. As macular edema develops, blurring occurs in the middle or just to the side of the central visual field. Visual loss from diabetic macular edema can progress over a period of months and make it impossible to focus clearly. Clinically, DME is defined as retinal thickening within 2 disc diameters of the foveal center, whether it is diffuse or focal in nature. Focal edema is often associated with circinate rings of protein deposits resulting from leakage from microaneurysms. Diffuse edema represents a more extensive breakdown of the blood-retinal barrier, with leakage both from microaneurysms and retinal capillaries. Clinically significant edema exists when any of the following are present: Any retinal thickening within 500um of the foveal center; protein deposits within 500um of the foveal center that are associated with adjacent retinal thickening; an area of retinal thickening at least 1 disc area in size.

Figure 2. Clinical Stages of Diabetic Retinopathy

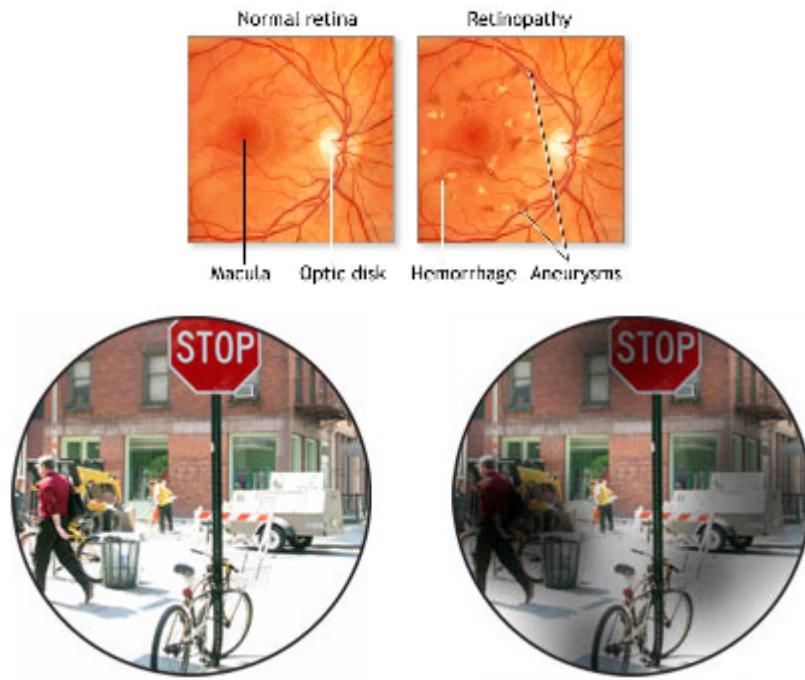
	Preclinical	Nonproliferative Diabetic Retinopathy	Proliferative Diabetic Retinopathy	Diabetic Macular Edema
Symptoms	None	None, or blurred vision and glare	None, or reduced vision or floaters	None, or blurred vision
Clinical signs indicating need for referral	<ul style="list-style-type: none"> • Normal appearing retina 	<ul style="list-style-type: none"> • Retinal vasodilation • Microaneurysms • Nerve fiber layer infarcts • Intraretinal hemorrhages • IRMAs • Venous bleeding 	<ul style="list-style-type: none"> • Retinal vasodilation • Beading • IRMAs • Neovascularization of optic disc, retina, and/or iris 	<ul style="list-style-type: none"> • Swelling of retina due to leaky capillaries • Increased capillary leakage • Fluid accumulation in retinal layers

Source: Medical Literature

Diabetes, manifested by either insulin resistance or inadequate insulin production, is a complex cascade of pro-inflammatory processes. The hallmark of diabetes is chronic hyperglycemia, and this hyperglycemia has been implicated as the root cause of the detrimental effects on blood vessels, vascular dysfunction, and eventual vascular occlusion. Diabetes' effects as a chronic pro-inflammatory disease and the effects on vascular dysfunction and occlusion are also being actively investigated through various research projects. Vascular dysfunction causes hypoxia, and local hypoxia in the eye triggers affected tissues in the retina to upregulate production of vascular endothelial growth factors (VEGF). VEGF not only helps in angiogenesis (formation of new blood vessels), but also increases permeability in tissue. It is the increased permeability in retinal tissue due to upregulation of VEGF that causes a decoupling of the tight junctions between retinal vessels. Once retinal junctions are loosened, cellular interactions get impaired, resulting in breakdown of the blood-retina barriers and the

accumulation of extracellular fluid. On a cellular level, hypoxia results in thickening of the basement membrane of the vascular endothelium, and also in a reduction of the supportive pericytes lining blood vessels. These changes also promote incompetence of the retinal vasculature and leakage of extracellular fluid and manifestation of macular edema. Figure 7 shows a cross-section of a human eye with a presence of diabetic retinopathy, and below that, an image that is distorted due to the presence of retinopathy.

Figure 3. Diabetic Macular Edema



Source: Medical Literature

Treatment for DME

- *Primary Prevention*

Primary prevention for DME consists of aggressive glucose monitoring and control. The goal of glycemic control is primarily to reduce the chronic hyperglycemia that patients normally find themselves in, thereby dampening the cascade of pro-inflammatory processes that accompany diabetes. The lack of large-scale randomized trials, as well as lack of optimal safety-efficacy profile with current treatments, has resulted in primary prevention being the main therapy adopted, or at least recommended for patients at risk for developing DME.

- *Laser Photocoagulation*

Laser photocoagulation is the current standard of care for treating DME. It uses heat from a laser to seal or destroy abnormal, leaking blood vessels in the retina. Focal treatment is used to seal specific leaking blood vessels in a small area of the retina, usually near the macula. Scatter treatment is used to slow the growth of new abnormal blood vessels that have developed over a wide area of the retina. The ophthalmologist may make hundreds of laser burns on the retina to stop the blood vessels from growing. The person may need two or more treatment sessions.

- *Anti-VEGF therapy*

In the pathophysiologic cascade leading to DME, chronic hyperglycemia leads to oxidative damage to endothelial cells as well as to an inflammatory response. The ensuing ischemia results in overexpression of a number of growth factors, including not only VEGF but also insulin-like growth factor-1, angiopoietin-1 and -2, stromal-derived factor-1, fibroblast growth factor-2, and tumor necrosis factor. Synergistically, these growth factors mediate angiogenesis, protease production, endothelial cell proliferation, migration, and tube formation. Tumor necrosis

factor-alpha (TNF-alpha) and VEGF play a role in the early stages of angiogenesis, with TNF-alpha promoting leukocyte adhesion and VEGF promoting leukostasis, resulting in ischemia. Blockade of all involved growth factors will likely be necessary to completely suppress the detrimental effects of ischemia, but even isolated blockade of VEGF may have beneficial effects on DME. VEGF increases vascular permeability by relaxing endothelial cell junctions, which increases permeability and leakage. Inhibition of VEGF blocks this effect to some extent, as demonstrated in several recent clinical trials and case series involving the anti-VEGF molecules pegaptanib, ranibizumab, and bevacizumab.

Bevacizumab (Avastin) is a recombinant, humanized antibody that binds all isoforms of VEGF-A. Bevacizumab is approved by the FDA for systemic use in the treatment of various malignancies. In small randomized trials, intravitreal bevacizumab was associated with short-term improvement in patients with DME. The DRCR Network studied 121 patients for up to 24 weeks in a Phase II RCT. As measured by optical coherence tomography, central subfield thickness decreased by over 11% in 43% of patients receiving bevacizumab and 28% of patients receiving photocoagulation at 3 weeks. When compared directly, bevacizumab appears relatively less effective than IVTA against DME. Ranibizumab (Lucentis) is a recombinant, humanized antibody fragment against all isoforms of VEGF-A. Ranibizumab is approved by the FDA for intravitreal use in the treatment of exudative age-related macular degeneration. Ranibizumab has shown short-term efficacy against DME in two pilot studies. The DRCR Network recently completed enrollment into protocol I, in which patients were randomized to receive photocoagulation, intra-vitreous triamcinolone acetone (IVTA) injections plus laser photocoagulation, ranibizumab plus photocoagulation or ranibizumab plus deferred photocoagulation. Ranibizumab for Edema of the Macula in Diabetes (READ)-2, a Phase II RCT, studied 126 patients. Patients were randomized to receive ranibizumab for 6 months, photocoagulation alone or ranibizumab for 6 months plus photocoagulation. At 6 months, the mean change in visual acuity score was +7 letters in eyes treated with ranibizumab, -1 letter in eyes treated with photocoagulation and +4 letters in eyes treated with photocoagulation and ranibizumab. Two additional Phase III RCTs, the Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE) and Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RIDE), are currently recruiting patients.

Pegaptanib (Macugen) is a pegylated aptamer against the VEGF-A 165 isoform. Pegaptanib is approved by the FDA for intravitreal use in the treatment of exudative age-related macular degeneration. In a Phase II RCT, 172 patients were studied for 36 weeks. At 36 weeks, median visual acuity was 20/50 in eyes treated with pegaptanib and 20/63 in eyes treated with sham injections. Unlike IVTA, risks of glaucoma and cataract have not generally been associated with the anti-VEGF agents. Large RCTs of pegaptanib and ranibizumab reported rates of endophthalmitis in the range of 1% per eye over a 12-24 month period of continuous treatment. However, because most eyes underwent a series of injections, the risk of endophthalmitis per injection is much lower than 1%. Several other VEGF antagonists are being investigated as potential treatments for DME. Aflibercept, or VEGF Trap-Eye (Regeneron Pharma) is a recombinant fusion protein against all VEGF-A isoforms, as well as placental growth factor. In a Phase I trial, five patients were treated with a single injection and followed for 6 weeks. At 6 weeks, four out of the five patients showed improved vision, with a median improvement of 3 letters.

- *Corticosteroid Therapy*

Macrophages are inflammatory cells that play a significant role during angiogenesis by secreting angiogenic cytokines and growth factors. Recently, they have also been found to produce INF-gamma, which is involved in angiogenic inhibition, and it has therefore been proposed that the role of macrophages during the process of neovascularization might be that of angiogenic on/off switch. Glucocorticoid steroids possess the ability of regulating macrophage activity via a glucocorticoid receptor (GR), which inhibits inflammatory programs of gene expression. Macrophages activated by glucocorticoids exhibit a different growth factor expression pattern than classically activated cells, with considerable differences in expression of angiogenic proteins like Tumor Necrosis Factor-alpha, Insulin-like Growth Factor-1, Platelet-derived Growth Factor-A and M-Kinase. It is therefore possible that a corticosteroid environment results in a change of macrophage behavior affecting not only the inflammatory response, but also the neovascular process. In the retina, activation of the complement system leads to the secretion of angiogenic factors by recruited inflammatory cells and to the buildup of cells and extracellular deposits resulting in local ischemia and subsequent release of angiogenic stimuli by the retinal pigment epithelium. Oxidative stress has been shown to induce expression of Vascular Endothelial Growth Factor and Transforming Growth Factor-beta, as well as of the fibrosis-promoting Connective Tissue Growth Factor by RPE cells. Treatment of cells with TA, a corticosteroid with known anti-angiogenic effect, affects the expression of all three cytokines.

The observed upregulation of VEGF and TGF-beta is reduced by treatment with TA in a concentration-dependent manner, while upregulation of CTGF is accelerated. The potent anti-angiogenic effect observed after treatment of retinal cells with TA probably occurs due to the fact that this corticosteroid affects multiple pathways, increasing the probability of effectively disrupting the neovascular process. In addition to down-regulating the initial angiogenic stimulus by modifying expression of VEGF and TGF-beta, TA can also inhibit the degradation of capillary basal membrane. This degradation process constitutes a critical component of choroidal angiogenesis in vivo and it is carried out by matrix metalloproteinases that become activated in choroidal endothelial cells. Treatment of these cells with TA has been described as resulting in metalloproteinase downregulation and subsequent inhibition of endothelial cell migration and tube formation. In addition to degradation of endothelial basal membrane, a breakdown of extracellular matrix also occurs during the invasive phase of angiogenesis, allowing endothelial cells to proliferate and migrate. This process is mediated by the urokinase-type plasminogen activator (uPA), which can be regulated by corticosteroids via activation of the PA inhibitor (PAI). This corticosteroid-induced suppression of PA function leads to a halt in endothelial cell proliferation and migration, and consequently to their inability to participate in new blood vessel formation.

Since a report described the use of intravitreal triamcinolone acetonide (TA) for the treatment of diabetic macular edema in 2001, retinal physicians have used corticosteroids for DME with considerable frequency. In the ETDRS study, laser photocoagulation reduced the three-year incidence of moderate vision loss by 50 percent. With the use of intravitreal TA, multiple reports have described transient improvement to both the retinal thickness and visual acuity, although significant side effects, including cataract and secondary open-angle glaucoma, were also reported. Therefore, the Diabetic Retinopathy Clinical Research Network (drcr.net), a consortium of more than 150 clinical centers and 500 physicians across the United States, developed a well-powered randomized controlled trial to compare these two treatment modalities directly. In the trial of 840 eyes, intravitreal TA (1 mg or 4 mg) was compared with focal/grid photocoagulation in patients with DME. After a two-year period, photocoagulation produced superior visual acuity and retinal thickness measurements and had fewer side-effects than TA. This was regarded as strong support for focal/grid photocoagulation as the benchmark against which other therapies for DME should be measured. The results of this trial raised an important question: Is therapy with intravitreal corticosteroids now ever justified for treating DME given the inferior efficacy to photocoagulation and significant side-effect profile? Corticosteroids administered intravitreally bypass the blood-ocular barrier, achieving therapeutic levels in the eye while avoiding systemic side effects. However, in view of the chronic nature of most of the neovascular diseases and the relatively rapid clearance of corticosteroids from the posterior segment, multiple injections are frequently necessary, increasing the risk of infection, hemorrhage and retinal detachment. Some corticosteroid compounds, such as triamcinolone acetonide and fluocinolone acetonide have been found to have a longer intravitreal half-life than the originally studied dexamethasone, but multiple injections are still usually required to achieve disease remission. In addition, some of the most common and serious complications of intravitreal corticosteroid administration are not related to the injection procedure per se, but rather the individual sensitivity to prolonged presence of corticosteroids in the vitreous. One of the most common adverse effects is ocular hypertension, which occurs in 40 – 50% of eyes treated between one and two months following the procedure. Most of the episodes of intraocular pressure elevation respond favorably to topical medical treatment, but approximately 1% of patients eventually require filtering surgery. Another ocular side effect that occurs with frequency during treatment is rapid cataract progression. A meta-analysis revealed a nearly 10% rate of significant cataract formation over one year and 25% at two years. The exact molecular mechanisms behind these complications are not known, but they are thought to be related to the sustained effects on cell metabolism. This has prompted an intense search for a new generation of corticosteroid compounds, which are specifically angiostatic yet free of hormonal activity.

The DRCR results apply to monotherapy for DME, but it is likely that combinations of therapies will be the best options in the future, especially in refractory cases. Combination therapies may be important for minimizing repeated administration and the risk of side effects in chronic disorders such as DME—i.e., cataract or glaucoma in the case of steroids, laser-related field defects and scotoma in the case of laser treatment, and intravitreal injection in general. The Laser-Ranibizumab-Triamcinolone for Diabetic Macular Edema (LRT for DME) study is a National Eye Institute-sponsored Phase III clinical trial of nearly 700 patients that began enrollment in 2007 and will directly compare laser alone with laser combined with triamcinolone, laser combined with ranibizumab, and ranibizumab alone. Similarly, as mentioned, Allergan is studying laser versus a combined dexamethasone implant and laser. It will be some time before quality studies answer whether corticosteroids hold promise as combination therapies, but the initial transient improvement in visual acuity and macular thickness reported in monotherapy provides hope for

future applications involving this class of therapeutics. In current clinical practice, most retinal specialists would treat focal DME with laser initially. In cases refractory to laser, intravitreal TA (4 mg/0.1cc) is often employed. Many retina specialists will consider intravitreal TA after the patient fails to respond to the first laser treatment, but others attempt a second or third session of macular laser photocoagulation before considering intravitreal TA. Generally, after three to four sessions of macular laser photocoagulation (i.e., after 300 to 400 spots), most retina specialists would not continue to offer laser photocoagulation, but would seek alternative treatments such as intravitreal TA, intravitreal bevacizumab or, as a last resort, vitrectomy with or without stripping of the internal limiting membrane. In cases that are refractory to both laser and TA, some retina specialists retreat with bevacizumab with or without half-dose 2 mg TA (to limit the risk of ocular hypertension and limit the amount of volume injected concurrently), as there may be mechanistic rationale for combining a target-specific anti-VEGF agent with a mechanistically "broad-spectrum" angiostatic corticosteroid. Medicare and most insurers reimburse for intravitreal TA used for DME, but do not reimburse for bevacizumab for this indication, although the out-of-pocket costs for bevacizumab are not unreasonable. Patients who present initially with severe diffuse DME are sometimes initially treated with combination intravitreal TA plus laser treatment, either on the same visit or on consecutive visits. Given these increasingly complex choices, the entire ophthalmic community eagerly awaits the results of DME clinical trials involving TA, bevacizumab, ranibizumab and other agents in order to provide more definitive guidance for this very common and potentially devastating disorder

While there are many other retinal indications on which products like Illuvien can be used, we specifically focus our report on DME as that is the core thesis on ALIM. Any further indications on Illuvien can be considered to be call options with a long time-value.

Competition

Laser photocoagulation

Laser photocoagulation is the only approved treatment for DME. The 2008 Preferences and Trends Survey showed that 84% of patients treated with laser photocoagulation required an off-label drug therapy or a combination of both additional laser photocoagulation and an off-label drug therapy to treat the disease. The DRCR.net study is by far the most comprehensive evaluation of laser therapy and corticosteroid therapy in diabetic retinopathy. This study was a multicenter one, randomized into three groups - Focal/grid laser; 1 mg intravitreal triamcinolone, and 4mg triamcinolone to compare the efficacy and safety of preservative free intravitreal triamcinolone acetonide compared to focal / grid laser. Follow-up visits and re-treatment were allowed as often as every 4 months. Duration of follow-up was 3 years. The primary outcome measure was mean change in BCVA ≥ 15 letters at 2 years, with a secondary outcome measure on retinal thickening as measured by OCT. Patient inclusion criteria centered on being at least 18 years of age, confirmed DME on optical coherence tomography and finally, baseline Snellen equivalents of 20/40 to 20/320. In this study, 840 eyes (693 subjects) were enrolled at 88 clinical sites. The randomization protocol allowed for the three groups as follows: laser (n = 330), 1 mg TA (n = 256), and 4 mg (n = 254). The 2-year visit completion rate was 88% excluding deaths. We highlight here only the 24-month readouts for the purposes of comparison. As can be seen in figure below, at 24-months, the mean change in BCVA was +1 letter relative to baseline, while the triamcinolone acetonide groups reduced in mean BCVA levels.

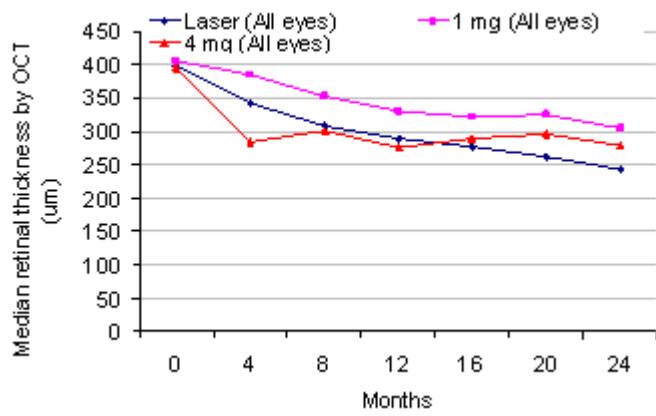
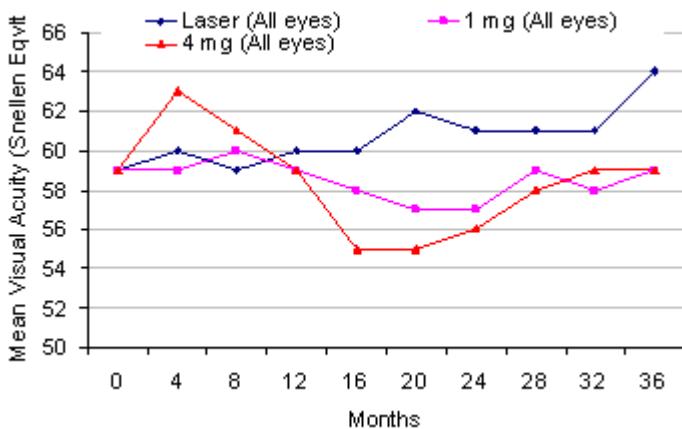
Figure 4. In order: Mean Change in Visual Acuity at 2 years; Pairwise Comparisons

			Mean Δ	p-value
Laser n = 330	1mg TA n = 256	4mg TA n = 254		
+1	-2	-3		
Laser vs. 1mg	+3.5 letters	0.02		
Laser vs. 4 mg	+4.6 letters	0.002		
1 mg vs. 4 mg	+1.1 letters	0.49		

Source: drcr.net

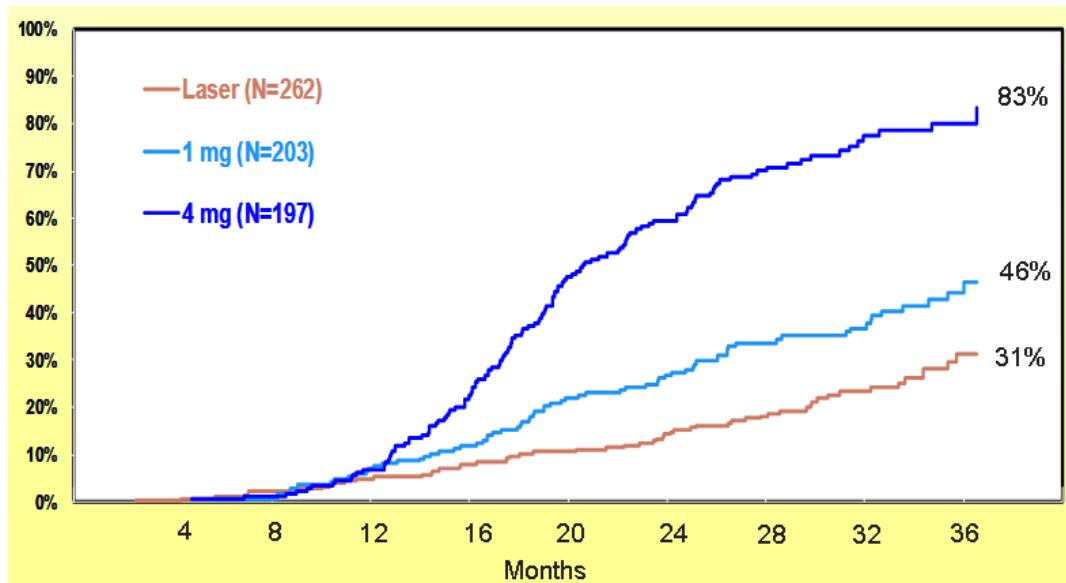
At 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in either the laser group ($P < 0.001$) or the 1-mg triamcinolone group ($P = 0.001$). By 1 year, there were no significant differences among groups in mean visual acuity. At the 16-month visit and extending through the primary outcome visit at 2 years, mean visual acuity was better in the laser group than in the other 2 groups (at 2 years, $P = 0.02$ comparing the laser and 1-mg groups, $P = 0.002$ comparing the laser and 4-mg groups, and $P = 0.49$ comparing the 1-mg and 4-mg groups). Treatment group differences in the visual acuity outcome could not be attributed solely to cataract formation. Optical coherence tomography results generally paralleled the visual acuity results. Intraocular pressure increased from baseline by 10 mmHg or more at any visit in 4%, 16%, and 33% of eyes in the 3 treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the 3 treatment groups, respectively.

Figure 5. In order: Mean Visual Acuity over 3 years; Median retinal thickness by OCT



Source: drcr.net

Figure 6. Cumulative probability of cataract surgery over 3 years



Source: drcr.net

The DRCR study, based on published 2-year results concluded that there was no difference in visual acuity improvements between triamcinolone acetonide and laser groups at 1 year, but by year 2 there was a greater visual acuity benefit with the laser group as compared to TA group, along with fewer side effects and cataracts. Based on the 2-year results, the authors concluded that the laser should essentially be first line of defense in DME treatment and other DME treatments should be measured against laser therapy. Interestingly enough, the 3-year results of the study were similar to the 2-year results. Among the eyes with three-year follow up, the mean number of treatments with the assigned treatment regimen during the three years of follow up were 3.1 in the laser group, 4.2 in the 1 mg triamcinolone group, and 4.1 in the 4 mg triamcinolone group. There were no cases of endophthalmitis following any of the 1898 injections during the entire study. During the third year of follow up, 20 (17%), 22 (24%), and 28 (29%) of eyes in the three treatment groups, respectively, were treated once with the assigned treatment regimen, 8 (7%), 9 (10%), and 21 (21%) were treated twice, and 1 (1%), 8 (9%), and 4 (4%) were treated three times. Among the 3-year completers, 7 (6%) in the laser group received the 4 mg triamcinolone study drug at some point during the 3 years of follow up, 21 (23%) in the 1 mg triamcinolone group received focal/grid photocoagulation, and 20 (20%) in the 4 mg triamcinolone group received focal/grid photocoagulation. Other treatments for DME (primarily vitrectomy, non-study triamcinolone [Kenalog], and bevacizumab) were received by 15 (13%), 16 (17%), and 11 (11%) of eyes in the three treatment groups, respectively.

Between two years and three years of follow up, visual acuity improved more often than it worsened in all three treatment groups. Among eyes with visual acuity at two years that was worse than 20/32, about twice as many in each treatment group improved 10 or more letters than worsened 10 or more letters from 2 to 3 years. At 3 years, visual acuity outcomes slightly favored the laser group compared with the two triamcinolone groups (Table 3), with the differences between groups at 3 years being of similar magnitude to the differences at 2 years. The mean change in the visual acuity letter score from baseline to 3 years was +5 in the laser group and 0 in the two triamcinolone groups (for the 3 2-group comparisons, mean difference adjusted for baseline visual acuity and prior macular photocoagulation: laser-1mg = +5.6 [95% confidence interval +0.8 to +10.4], laser-4mg = +4.7 [95% confidence interval 0.0 to +9.5] 1mg-4mg = -0.8 [95% confidence interval -6.0 to +4.3]). Using multiple imputation to handle missing data for eyes without 3-year follow up, mean change in the letter score was +2, 0, and -1, respectively and using the last observation carried forward method, mean change in the letter score was +1, -1, and -2, respectively. For the subjects with two study eyes, the mean paired difference in the change in the visual acuity letter score at 3 years was +9.3 (95% confidence interval +2.1 to +16.4) for the laser-1 mg subjects (N=29) and +4.6 (95% confidence interval -6.2 to +15.5) for the laser-4 mg triamcinolone subjects (N=27), in each case favoring the laser group. Among the completers of the 3-year visit, 51 (44%) in the laser group, 23 (25%) in the 1 mg group, and 37 (38%) in the 4 mg group had improvement in the visual acuity letter score of 10 or more from baseline to 3 years and 14 (12%), 24 (26%), and 22 (22%), respectively had worsening of 10 or more letters. For comparison, from baseline to 2 years among the

completers of the 3-year visit, the percentages were 33%, 18%, and 32%, respectively improving and 12%, 29%, and 27%, respectively, worsening. Results of treatment group comparisons were similar when limited to eyes that were either pseudophakic or had minimal lens changes by clinician assessment at 3 years. The mean change in the visual acuity letter score from baseline to 3 years was +5 in the laser group (N=79), +2 in the 1 mg triamcinolone group (N=61), and 0 in the 4 mg triamcinolone group (N=90).

Similar to the visual acuity results, more eyes in all three treatment groups had a decrease in OCT central subfield thickness from year two to year three than had an increase. At three years, central subfield thickness was <250 microns in 75 (67%) eyes in the laser group, 37 (43%) in the 1 mg triamcinolone group, and 45 (51%) in the 4 mg triamcinolone group. Four eyes in the 4 mg triamcinolone group had a procedure for glaucoma prior to the 2-year visit (1 had laser trabeculoplasty and 3 had glaucoma surgery), but there were no additional cases of glaucoma surgery in any treatment group during the third year of follow up. At 3 years, mean intraocular pressure was 16 ± 3 mm Hg in the laser group, 17 ± 3 mm Hg in the 1 mg triamcinolone group, and 16 ± 4 mm Hg in the 4 mg triamcinolone group, with 6 (5%), 14 (15%), and 10 (10%) having an intraocular pressure ≥ 21 mm Hg. Intraocular pressure lowering medications were being used in 3 (3%), 2 (2%), and 12 (12%) eyes, respectively. Among completers of the 3-year visit, an intraocular pressure increase of ≥ 10 mm Hg occurred at any visit between baseline and 2 years in 4 (3%) eyes in the laser group, 16 (17%) in the 1 mg triamcinolone group, and 30 (31%) in the 4 mg triamcinolone group, and occurred at any visit between baseline and 3 years in 4%, 18%, and 33%, respectively. Among phakic eyes at baseline, the three-year cumulative probability of cataract surgery was 31% in the laser group, 46% in the 1 mg group, and 83% in the 4 mg group ($P < 0.001$ for all pairwise comparisons). Excluding eyes in the laser group that received triamcinolone, the cumulative probability was 27%. Finally, using purely a BCVA of ≥ 15 letters improvement over baseline, 26% of patients in the laser arm showed improvement at 3-yr as compared to 20% for the 1-mg TA group and 21% for the 4-mg TA group.

Figure 7. In order: Adverse events at 2 years; IOP change up to 3 years over baseline

	Laser n = 330	1mg TA n = 256	4mg TA n = 254
Endophthalmitis	0	0	0
Psuedoendopthalmitis	0	0	0
Retinal detachment	2	2	3
Retinal vein occlusion	3	1	2
Retinal artery occlusion	1	0	0
Glaucoma procedure	0	0	4
Vitrectomy	31	26	19

	Laser n = 115	1mg TA n = 93	4mg TA n = 98
Increase 10 mm Hg any time	3%	17%	31%
Mean IOP at 3-yr visit (mm Hg)	16	17	16
IOP ≥ 21 mm Hg at 3-yr visit	5%	15%	10%
On IOP-lowering meds at 3-yr	8%	12%	30%

Source: drcr.net

Other Intravitreal Devices**Allergan**

This device is being developed by Allergan, and is currently in Phase III trials. Posudex is a polymer pellet that releases drug as it biodegrades. The pellet completely dissolves in about 37 days, although initial studies suggest that the effect of the drug may persist for 2 or more months after dissolution. Although Posudex was surgically implanted initially, the phase 3 studies evaluating delivery of dexamethasone in patients with DME are being conducted with a 22-g applicator that permits treatment as an office procedure. In a phase 2 dexamethasone study with Posudex, 306 patients were randomized to receive a 350- μ g implant, a 700- μ g implant, or observation. Although the majority of patients in this study had DME, 102 had RVO, 25 had Irvine-Glass syndrome, and 14 had uveitis. When evaluated at 6 months, 36% of those randomized to 700- μ g group and 27% of those randomized to 350- μ g group vs. only 19% of the observation patients had at least a 2-line improvement in best-corrected visual acuity. A 3-line or better improvement was achieved in 19% of those on the highest dose of dexamethasone vs. 8% of the observation group. The most common adverse event was an increase in intraocular pressure. A 10 mm Hg or greater pressure increase was observed in 17% of the 700- μ g group, 12% of the 350- μ g group, and 3% of the observation group. Phase III results from the Posudex study are estimated sometime in 2013.

Figure 8. Allergan's Posudex device



Source: Company reports

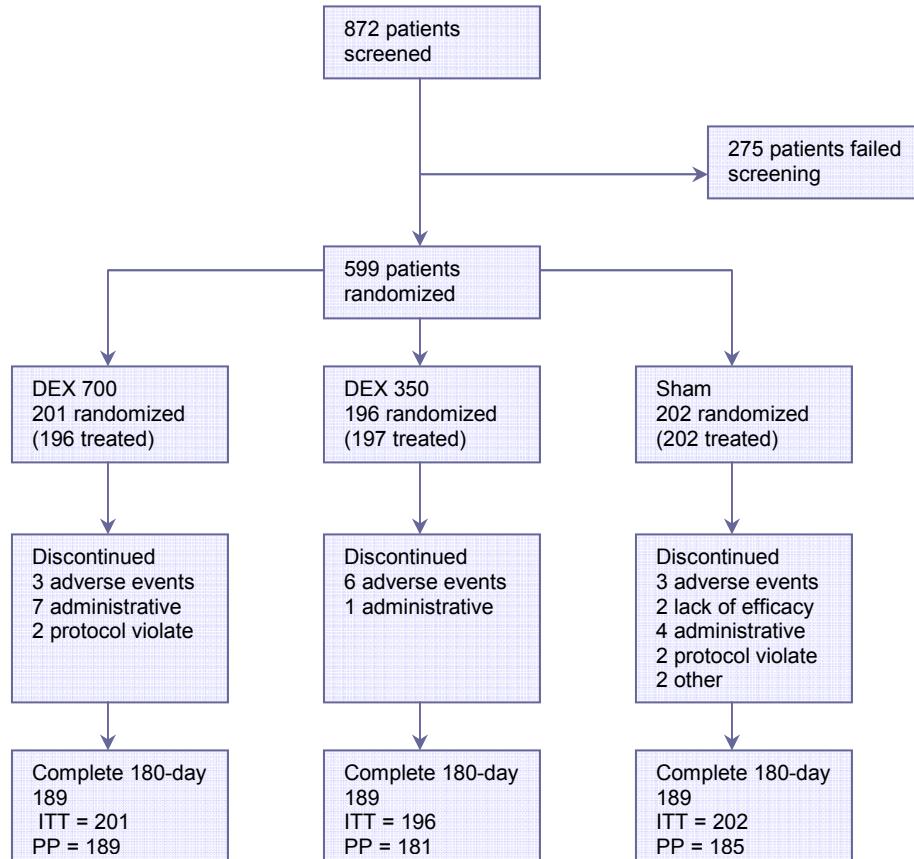
Allergan is currently conducting a Phase III trial for Posudex in DME. This is a randomized, double-blinded, dose comparison, parallel assignment, safety/efficacy study on 860 patients; with primary outcomes measures of BCVA @ 24 months; and secondary outcomes measure of macular thickness @ 36 months. The study is expected to have 3 arms: dexamethasone 350 μ g; injectable implant into intravitreal cavity every 6 months for 36 months / dexamethasone 700 μ g; injectable implant into intravitreal cavity every 6 months for 36 months / sham comparator

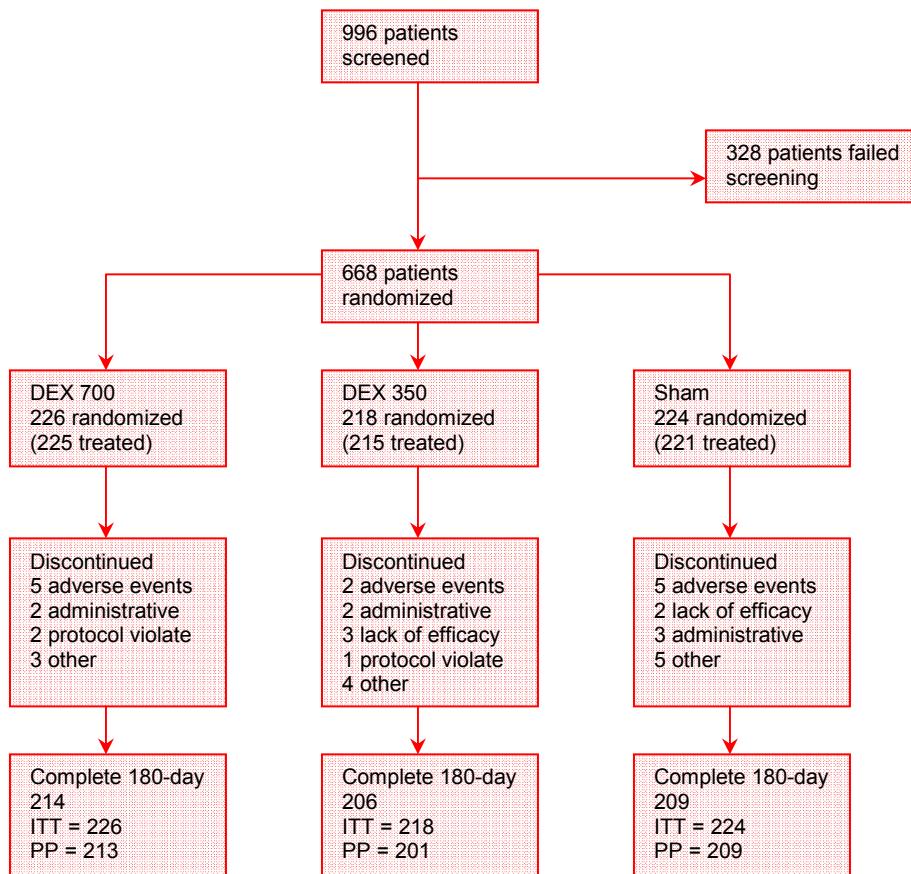
Allergan recently received regulatory approval for its Ozurdex intravitreal implant using dexamethasone for branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Ozurdex contains 0.7 mg of dexamethasone in the NOVADUR solid polymer drug delivery system. We highlight here results from the two pivotal studies that Allergan conducted on Ozurdex. However, pls note that these studies were for a different indication than DME. Our goal in identifying these studies is mainly to highlight the process of how Ozurdex gained regulatory approval.

Allergan Studies 206207-009 & 206207-008

Both studies 206207-008 and 206207-009 were Ph III trials with primary objective of evaluating safety & efficacy of DEX 700 and DEX 350 (dexamethasone 700 ug and 350 ug loading in Ozurdex) compared with sham in patients with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Each trial was a 6-month, multicenter, randomized, masked, sham-controlled study followed by a 6-month open label extension. Patients were randomized 1:1:1 ratio to DEX 700: DEX 350: Sham for the first 6-months. All patients received an assigned treatment on randomization (day 0) and could receive an open-label dose of DEX 700 at initial treatment day 180. There were 12 scheduled visits (14 visits if re-treatment occurred) consisting of qualification, randomization, and days 1, 7, 30, 60, 90 and 180. Study 206207-008 enrolled 599 patients in 85 centers in 13 countries. Study 206207-009 enrolled 668 patients in 82 centers in 13 countries. The originally planned sample size for each study was 195 patients per group with a 10% dropout. The sample size was later reduced to 165 patients by changing $\alpha = 0.05$ from the original 0.025. Key inclusion criteria were male or female, at least 18 years of age, macular edema due to CRVO at least 6 weeks to 9 months prior to study entry; and macular edema due to BRVO at least 6 weeks to 12 months prior to study entry, best-corrected visual acuity (BCVA) score between 34 and 68 letters by ETDRS, retinal thickness of $\geq 300 \mu\text{m}$ by optical coherence tomography (OCT). If both eyes were eligible for the study, the eligible eye with the shorter duration of disease was used as the study eye. Key exclusion criteria were ocular condition that would prevent a 15-letter improvement in VA, epiretinal membrane, ocular hypertension, aphakia or anterior chamber intraocular lens, diabetic retinopathy, retinal or disc or choroidal neovascularization, rubeosis iridis, active ocular infection, toxoplasmosis, visible scleral thinning or ectasia, media opacity, intraocular surgery, need for ocular surgery or laser, hemodilution, periocular depot or systemic steroids, carbonic anhydrase inhibitors, immunosuppressants/modulators, antimetabolites, alkylating agents, topical ophthalmic steroids or topical non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, heparin, enoxaparin, history of intraocular pressure (IOP) elevation in response to steroids. Dosages were to remain constant throughout the course of the trial for those concurrent medications that may have affected the study outcomes (e.g. treatment of elevated IOP, if systemic NSAIDs were regularly used prior to enrolment, these medications may have continued during the study, carbonic anhydrase inhibitors were not prohibited if they needed to be used to treat elevated IOP that developed during the course of the study. A trial design synopsis is shown in figure below.

Figure 9. In order: Study 206207-008 design; Study 206207-009 design; Patient Baseline characteristics 206207-008 & 206207-009





	Study 008			Study 009		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Mean Age (years)	65.8	65.9	64.8	63.7	64	63.1
Male (%)	52.7	53.1	57.9	49.1	53.2	54.9
CRVO (%)	30.3	36.7	35.6	33.2	37.6	33.5
Duration of macular edema ≥90 days (%)	86.1	79.6	88.1	81.4	83.5	88.7

Source: Company reports

The primary efficacy endpoint in these studies was the proportion of patients with BCVA ≥ 15 letters at 6-months. In Study 008 however, 5.5 months into the study, Allergan changed the primary endpoint to "time to achieve a treatment response of ≥ 15 letters from baseline." The secondary efficacy analysis included comparisons between the DEX 700 and DEX 350 arms vs. Sham for BCVA variables. Three analysis groups of interest were defined for the initial treatment period:

- Intent-to-Treat (ITT): All randomized patients
- Per protocol (PP)population: All patients who had no major protocol violations determined prior to database lock
- Safety population : All randomized and treated patients

The ITT and PP populations were used in all efficacy analyses. The safety population was used in all safety analysis. While Allergan changed the primary endpoint of Study 008 to "time to achieve ≥ 15 letters improvement in BCVA", we do not highlight that analysis. Reason being, it is inconsistent with original trial design and some of the patients relapsed after seeing initial improvement.

Figure 10. Proportion of patients with BCVA ≥ 15 letters from baseline (ITT population)

			Study 008			
	DEX 700 n = 201	DEX 350 n = 196	Sham n = 202		p-values	
				DEX 700 vs. Sham	DEX 350 vs. Sham	DEX 700 vs. DEX 350
Day 30	19.9%	14.8%	7.4%	<0.001	0.019	0.18
Day 60	28.9%	25.5%	10.4%	<0.001	<0.001	0.454
Day 90	22.4%	20.9%	12.4%	0.008	0.022	0.722
Day 180	19.4%	16.3%	18.3%	0.78	0.6	0.424

			Study 009			
	DEX 700 n = 226	DEX 350 n = 218	Sham n = 224		p-values	
				DEX 700 vs. Sham	DEX 350 vs. Sham	DEX 700 vs. DEX 350
Day 30	22.6%	20.6%	7.6%	<0.001	<0.001	0.622
Day 60	29.6%	31.2%	12.1%	<0.001	<0.001	0.723
Day 90	21.2%	25.7%	13.8%	0.039	0.002	0.268
Day 180	23.5%	22.0%	17.0%	0.087	0.18	0.719

Source: Company reports

For Study 008, the proportion of patients with ≥ 15 letters improvement from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90. At the primary time point initial treatment day 180, the difference (95% CI) between DEX 700 and Sham was 1.1%, $p = 0.78$. The difference (95% CI) between DEX 350 and Sham was -2.0%, $p = 0.60$. Neither comparison was statistically significant. There were no differences between the 2 doses of DEX. The results for BCVA ≥ 15 letters improvement in PP population were similar to the ITT population. For Study 009, the proportion of patients with ≥ 15 letters improvement from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90. At the primary time point initial treatment day 180, the difference (95% CI) between DEX 700 and Sham was 6.5% (-0.9% to 13.9%), $p = 0.087$. The difference (95% CI) between DEX 350 and Sham was 5.1% (-2.3% to 12.4%), $p = 0.180$. Neither comparison was statistically significant. There were no differences between the 2 doses of DEX.

For the secondary endpoint analysis of study 008, the following were observed:

- The proportion of BRVO patients in the ITT population with a BCVA improvement of ≥ 15 letters from baseline in the study eye was similar to the overall ITT population. The proportion of patients with BCVA improvement of ≥ 15 letters from baseline was significantly higher with DEX 700 compared to Sham at days 30, 60, and 90 ($p \leq 0.021$) and with DEX 350 compared to Sham at day 60 ($p = 0.014$). The response rates in the DEX 700 group were consistently higher than that in the DEX 350 group, with a statistically significant difference at day 60 ($p = 0.038$). The results were not significant on day 180. Findings for BRVO patients in the PP population were similar to the ITT population.
- The proportion of CRVO patients in the ITT population with a BCVA improvement of ≥ 15 letters from baseline in the study eye was lower than the overall population for the DEX 700 group but generally higher than the overall ITT population for the DEX 350 group. The proportion of patients with BCVA improvement of ≥ 15 letters from baseline was significantly higher with DEX 350 compared to Sham at day 60 ($p = 0.002$) and day 90 ($p = 0.025$). There were no differences between the 2 doses of DEX. Findings for CRVO patients in the PP population were similar to the ITT population.
- BCVA ≥ 15 letters improvement in patients with longer duration of macular edema. The analysis was repeated excluding patients with duration of macular edema less than 90 days in order to assess the impact on the results of spontaneous improvement in BCVA. The proportion of patients with longer duration of macular edema had similar BCVA improvement of ≥ 15 letters from baseline in the study eye as the ITT population. The proportion of patients with BCVA improvement of ≥ 15 letters from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90. The proportion was not significant for any of the groups at day 180. There were no differences between the 2 doses of DEX. Overall, the results after excluding patients with shorter disease duration (<90 days), which represent less than 20% of patients, showed consistent results to those seen in the overall study population.

- Time to ≥ 15 letters improvement in BCVA. The last amendment of the protocol established this as the primary endpoint for the FDA submission. Cumulative response rate curves were significantly different for the DEX 700 and DEX 350 groups compared to the Sham group ($p \leq 0.007$). The response rates were consistently higher with DEX 700 and DEX 350 than with Sham, starting at initial treatment day 30. Rates were somewhat lower with DEX 350 compared to DEX 700, although the difference between the 2 doses was not statistically significant.
- The categorical change from baseline showed statistically significant better visual acuity in the study eye with DEX 700 and DEX 350 compared to Sham at days 30, 60 and 90.
- At day 90 in the ITT population, the mean decrease in retinal thickness was significantly greater with DEX 700 (-199.3 microns) and DEX 350 (-144.1 microns) compared to Sham (-78.2 microns), $p < 0.001$, and with DEX 700 compared to DEX 350 ($p = 0.002$). There were no between-group differences at day 180. For BRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham at day 90, though not at day 180. There were no differences between the 2 doses of DEX. For CRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham ($p \leq 0.020$), and with DEX 700 compared to DEX 350 ($p = 0.004$) at day 90. There were no between-group differences at day 180.

For study 009, the following were noted in terms of secondary endpoint analysis:

- The proportion of BRVO patients in the ITT population with a BCVA improvement of ≥ 15 letters from baseline in the study eye was similar to the overall ITT population. The proportion of patients with BCVA improvement of ≥ 15 letters from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at the early visits but not at initial treatment day 180. There were no differences between the 2 doses of DEX.
- The proportion of CRVO patients in the ITT population with a BCVA improvement of ≥ 15 letters from baseline in the study eye was similar to the overall ITT population for the DEX patients, but lower than the overall population for the Sham patients. The proportion of patients with BCVA improvement of ≥ 15 letters from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at the early visits, and with DEX 700 compared to Sham at initial treatment day 180. There were no differences between the 2 doses of DEX.
- The analysis was repeated excluding patients with duration of macular edema less than 90 days in order to assess the impact on the results of spontaneous improvement in BCVA. This subgroup was defined a posteriori and should therefore be read with caution. The proportion of patients with longer duration of macular edema had similar BCVA improvement of 15 or more letters from baseline in the study eye as the ITT population. Excluding patients with acute macular edema (<90days), the rate of responders in the sham groups decreased leading to statistical, although not clinical, significant differences between DX700 and sham.
- Treatment response was defined a posteriori as 15 or more letters improvement from baseline BCVA in the study eye at any time during the initial treatment period. Time to response was analyzed using a Kaplan-Meier survival analysis with the log-rank test for treatment differences. Overall, the cumulative response rate curves were significantly different for the DEX 700 and DEX 350 groups compared to the Sham group ($p < 0.001$). Cumulative response rates were consistently higher with DEX 700 and DEX 350 than with Sham from day 30 to the end of the initial treatment period. There was a separation of curves as early as day 30 which was consistent over time without any crossover at any visit. There were no differences between the 2 doses of DEX.
- The categorical change from baseline showed statistically significant better visual acuity in the study eye with DEX 700 and DEX 350 compared to Sham at each follow-up visit. From initial treatment day 30 onward, the beneficial effects of DEX 700 and DEX 350 compared to Sham were shown, not only in terms of ≥ 15 letters improvement but also in the prevention of ≥ 15 letters worsening. There were no differences between the 2 doses of DEX.
- Retinal thickness was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p < 0.001$), though not at day 180. There were no differences between the 2 doses of DEX. For BRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p < 0.001$), though not at day 180. There were no differences between the 2 doses of DEX. For CRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p \leq 0.003$), though not at day 180. There were no differences between the 2 doses of DEX at day 90; however the mean thickness was significantly less with DEX 350 compared to DEX 700 at day 180.

An interesting analysis included classification patients with BCVA ≥ 15 letters in the ITT population. Figure 11 highlights the stratification by days, and by responders. As can be seen, in study 008, 50.6% of the 79 patients who ever

Figure 11. Classification of patients with BCVA ≥15 letters improvement in ITT population

	Study 008			Study 009		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Patients who never improved (%)	60.7	64.3	74.8	55.3	56	77.7
Patients who improved but relapsed (%)	20	19.4	7	21.2	22	5.4
Patients with improvements and no relapse (%)						
<i>Improved on day 30 + no relapse</i>	8.5	5.1	2.5	9.7	10.1	5.4
<i>Improved on day 60 + no relapse</i>	2	3.1	2.5	1.3	3.7	2.7
<i>Improved on day 90 + no relapse</i>	2	1	4	2.7	1.4	3.6
<i>Improved on day 180 (no follow-up)+ no relapse</i>	7	7.1	9.4	9.7	6.9	5.4

Source: Company reports

BCVA ≥15 letter improvement relapsed and their BCVA's were not above baseline on day 180. Out of the 101 patients considered responders in study 009, 47.5% had relapsed. Relapse rates were similar in both studies. Overall, relapse rates were 50% in the DEX groups and about 26% in the sham groups ($p<0.05$). Figure below highlights the number of patients whose BCVA's were missing and data was imputed by the LOCF method. In the final analysis, the missing data was not found to materially change the final outcomes.

Figure 12. Number of patients with BCVA missing and imputed using LOCF

	Study 008			Study 009		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Day 30	4.5%	1.5%	2.5%	1.3%	1.8%	2.7%
Day 60	6.0%	7.1%	3.0%	2.7%	3.7%	8.5%
Day 90	3.5%	2.6%	3.5%	2.7%	3.2%	6.7%
Day 180	6.0%	5.1%	8.4%	5.8%	5.5%	6.7%
Overall	5.0%	4.1%	4.3%	3.1%	3.6%	6.1%

	Study 008			Study 009		
	DEX 700	DEX 350	Sham	DEX 700	DEX 350	Sham
Missing data imputed using LOCF						
% of patients with ≥15 letters improvement	19.4%	16.3%	18.3%	23.5%	22.0%	17.0%
Missing data counted as having no improvement						
% of patients with ≥15 letters improvement	18.4%	15.8%	17.8%	22.6%	21.1%	17.0%
Missing data counted as having improvement						
% of patients with ≥15 letters improvement	24.4%	20.9%	26.2%	28.3%	26.6%	23.7%
Missing data excluded						
% of patients with ≥15 letters improvement	19.6%	16.7%	19.5%	23.9%	22.3%	18.2%

Source: Company reports

The overall incidence of serious adverse events in the initial treatment period for the pooled phase 3 studies was 5.0% (21/421) in the DEX 700 group, 6.6% (27/412) in the DEX 350 group, and 5.9% (25/423) in the Sham group. One additional Sham patient developed a recurrence of melanoma in the right axilla which met the criteria for a serious event but was reported as non serious. The rates of ocular serious events and non-ocular serious events were similar among the 3 treatment groups. None of the serious adverse events was related to treatment with the following exceptions: ocular hypertension in the study eye (1 DEX 700) and intraocular pressure increased in the study eye (1 DEX 700 and 3 DEX 350). The overall cumulative incidence of serious adverse events during the 12-month treatment period for the pooled phase 3 studies (re-treated population) was 9.4% in the DEX 700/700 group, 8.2% in the DEX 350/700 group, and 10.7% in the

Sham/DEX 700 group. The serious adverse event profile was similar between the 3 treatment groups. Four of the serious events in the re-treated population were considered by the investigator to be related to the study treatments. Three were intraocular pressure increased (one in each group) and one was retinal detachment (in DEX 700/700). The cumulative incidence of serious adverse events during the 12-month treatment period for the pooled phase 3 studies (single treated population) was 10.0% in the DEX 700 group, 10.8% in the DEX 350 group, and 10.4% in the Sham group. Five of the serious events in the single treatment population were considered by the investigator to be related to the study treatments. Ocular hypertension and IOP in DEX 700 group, two cases of IOP in the DEX 350 group and one corneal disorder in the Sham group. The overall incidence of adverse events during the initial treatment period was 72.4% for the patients receiving DEX 700. For the retreated patients the incidence of adverse events was between 80.1% and 87.2% depending on the initial treatment. The most common non-ocular events reported were influenza 9 (2.1%) DEX 700 vs. 2 (0.5%) Sham, headache 14 (3.3%) DEX 700 vs. 7 (1.7%) Sham and hypertension 17 (4.0%) DEX 700 vs. 15 (3.5%) Sham. For systemic adverse reactions, no specific pattern indicating safety risks with the active treatment was revealed. The overall incidence of ocular adverse events in the study eye during the initial treatment was; 62.9% for DEX 700, 61.9% for DEX 350 and 42.8% for Sham treatment respectively. The most frequently reported events in patients who received DEX 700 were increased IOP (25.2 %) and conjunctival hemorrhage (20.2 %). Ocular adverse events related to the insertion procedure included conjunctival hemorrhage, conjunctival hyperemia, eye pain, vitreous hemorrhage and conjunctival edema, which are reported generally occurring soon after the injection procedure.

Figure 13. Adverse event profile for pooled studies

Pooled Analysis			
	DEX 700 n = 421	DEX 350 n = 412	Sham n = 423
All adverse events	72.4%	71.8%	57.0%
Treatment-related adverse events	47.3%	46.6%	17.5%
Non-ocular adverse events	29.9%	28.9%	31.0%
Ocular adverse events in study eye	62.9%	61.9%	42.8%
Adverse events >5% incidence in any treatment group			
Intraocular pressure increased	25.2%	24.8%	1.2%
Conjunctival hemorrhage	20.2%	17.5%	14.9%
eye pain	7.4%	4.4%	4.7%
maculopathy	4.5%	5.3%	5.4%
Serious adverse events	5.0%	6.6%	5.9%
discontinuation due to adverse events	1.7%	1.9%	1.9%

Source: Company reports

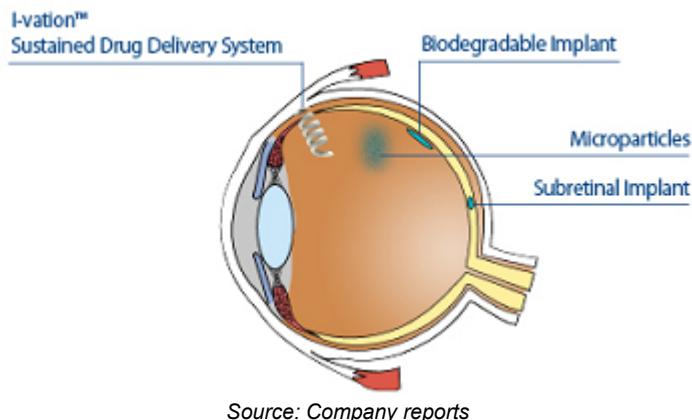
SurModics

SurModics, via its acquisition of InnoRx, Brookwood Pharma, BioFx, and assets of PR Pharma, entered the field of ophthalmology in the 2007 – 2008 timeframe. These acquisitions were designed to supplement organic R&D programs while allowing SurModics access to new technologies both with back of the eye and front of the eye applications. Some of these companies potentially provided an easy access to new customers, thereby helping SurModics diversify its shrinking revenue base. SurModics has for the last 3 years or so expressed high enthusiasm for its long-lasting drug delivery technologies for ophthalmology applications, with the goal being site-specific drug delivery for conditions such as diabetic macular edema, wet age-related macular degeneration, retinitis uveitis, etc. There is a growing interest in mimicking the long-lasting site-specific drug delivery solutions such as drug-eluting stents on the cardiovascular side, and apply the lessons learned on the ophthalmology front.

- I-vation

The InnoRx acquisition for about \$60+ million added the I-vation implant to the SurModics portfolio. The I-vation Sustained Drug Delivery System is an implantable drug-coated helical coil used for the sustained release of drugs into the anterior chamber of the eye. SurModics, amongst much fanfare, signed a deal with Merck licensing the I-vation implant for diabetic macular edema and other conditions using the I-vation implant. Although initial clinical data on I-vation was lukewarm at best, Merck did sign an agreement only to cancel the agreement in 2008; exactly one year after the deal was signed. SurModics generated roughly about \$44 million in revenues from this agreement, mostly through upfront payments and through R&D work. SurModics has finished a Phase I study evaluating the use of its I-vation platform using TA in 31 diabetic patients. Study design was as follows:

Figure 14. SurModics ophthalmology suite of products



Source: Company reports

Study Population:

31 diabetic patients (31 study eyes) with macular edema associated with diabetic retinopathy
 Preoperative best corrected visual acuity (BCVA) of 20/40 or worse; Angiographic evidence of leakage involving the perifoveal capillary net; Retinal thickening in the fovea; Failure of macular edema to improve with prior photo-coagulation, or benefit from photocoagulation unlikely; Randomized to: Slow-release (SR), 1 µg/day (n=14); Fast-release, 3 µg/day (n=17); Stratified by preoperative BCVA, and presence or absence of prior laser treatment; Average age: 63.6 years (range 46 to 79)

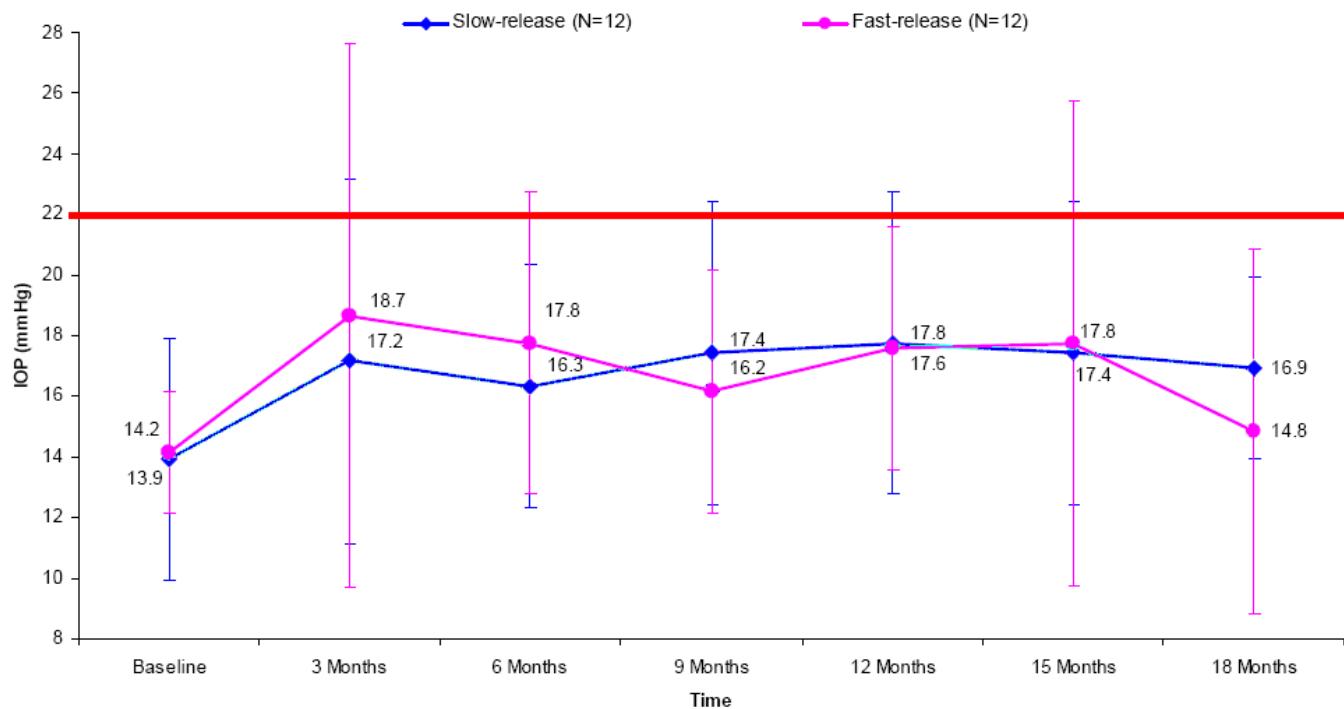
Outcome Measures:

Study duration: 36 months; BCVA (Early Treatment Diabetic Retinopathy Study - ETDRS) – Snellen equivalent and # of letters; Retinal thickness by optical coherence tomography (OCT); Fundus exam and fundus photography (FP); Fluorescein angiography (FA); Slit lamp exam; Intraocular pressure (IOP); Complications and adverse events (AEs); Blood pressure and Hemoglobin A1c

Retreatments:

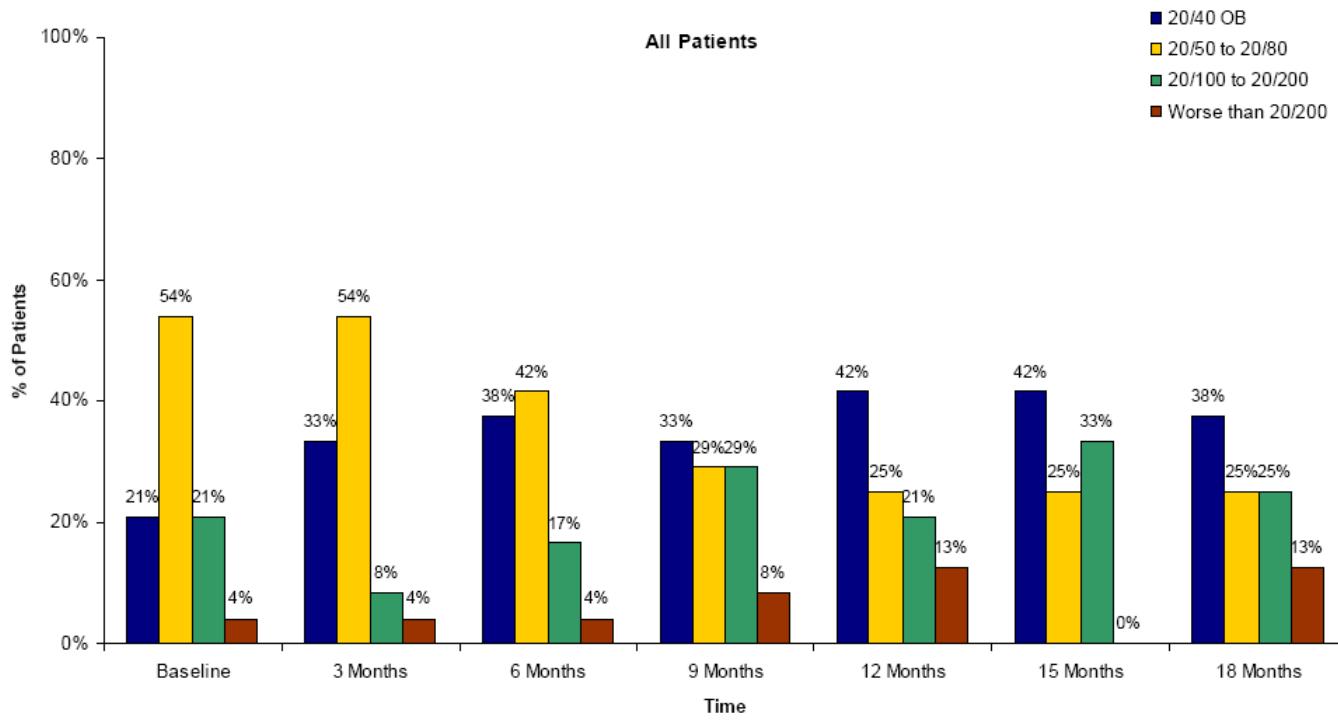
Implant exchange allowance: maximum of 4 per patient based on clinical outcomes per the study protocol

Figure 15. Change in Mean Intra-Ocular Pressure over Baseline (including those on pressure-relieving eye drops)



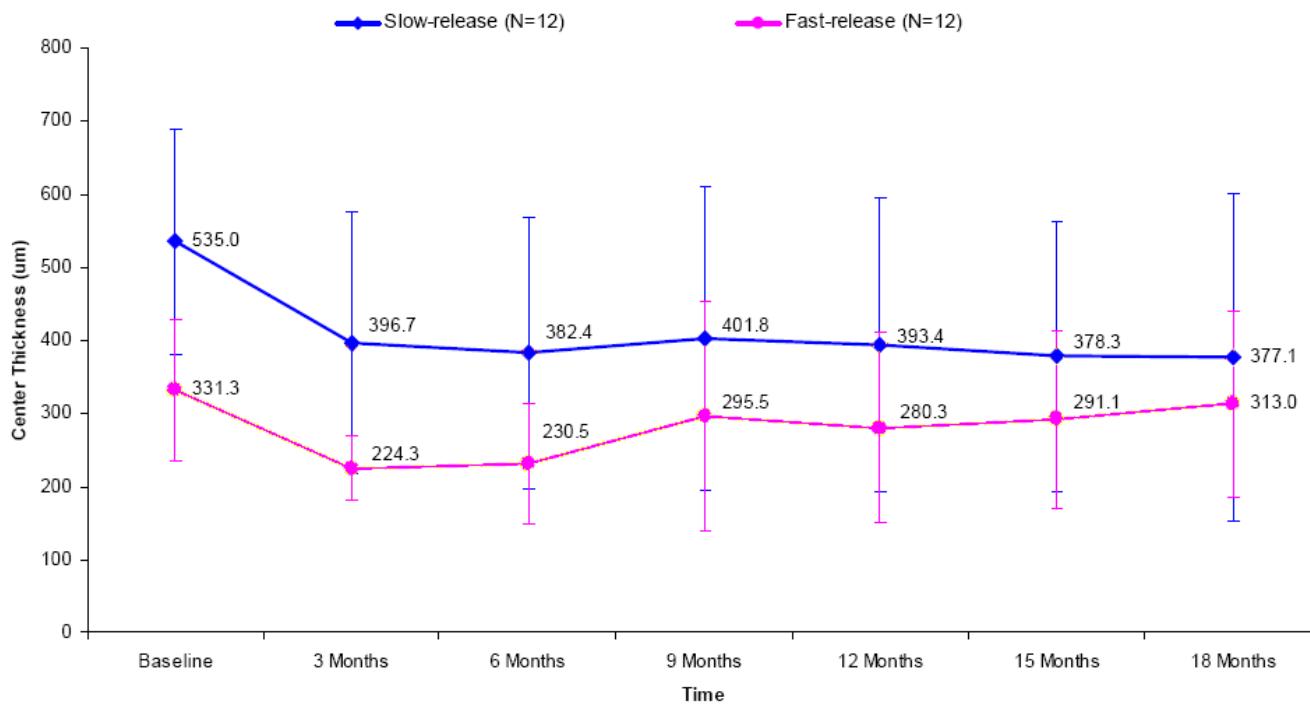
Source: SurModics

Figure 16 . Change in Best Corrected Visual Acuity Over Baseline



Source: SurModics

Figure 17. Change in Center Foveal Thickness over Baseline



Source: SurModics

Other data that was reported in the poster included:

Patients achieving 20/40 or better BCVA at 18 months	= 38% vs. 21% at baseline
Mean number of letters achieved in SR group	= 52.2 ± 16.2 vs. 59.9 ± 11.2 at baseline
Mean number of letters achieved in FR group	= 63.8 ± 16.2 vs. 59.6 ± 7.7 at baseline
Phakic patients with cataracts in SR group at 18 months	= 4 (25%)
Phakic patients with cataracts in FR group at 18 months	= 1 (6%)
Mean center thickness at 18 months for all patients	= 345um ± 181.9um
Change in mean center thickness at 18 months	= -88.1um
Change in mean center thickness for patients in SR arm	= -157.9um
Change in mean center thickness for patients in FR arm	= -18.3um
Retreatments after 18 months	= 14
Dropout rate 18 months	= 20% (3 deaths; 2 explants; 1 alternative therapy; 1 patient missed 9-month visit)
Serious event	= 1 case of endophthalmitis in retreatment procedure 15 months after implantation
Most common procedural adverse event	= conjunctival hemorrhage
Most common medication adverse event	= lenticular opacity
Glaucoma surgery at 18 months	= 0
Uncontrollable IOP requiring filter surgery	= 0

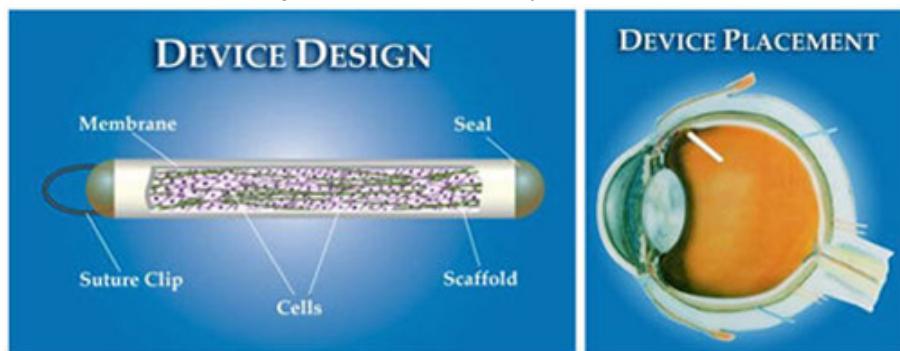
- Sub retinal Cannula / Biodegradable biospheres

The company also has a RetinaInject Subretinal Cannula device, which utilizes a needle to transconjunctivally enter the vitreous, and then a flexible cannula is advanced to create the retinotomy. The procedure can be performed without sutures and minimizes the risk of infection. The device is in pre-clinical trials. Also, through its acquisition of PR Pharma's drug delivery assets, SRDX has acquired PGLA based microspheres which potentially can elute drugs over long periods of time. The company has recently signed a licensing agreement with Genentech for use of Lucentis and other agents, probably for smaller delivery periods in wet-AMD. Further details are not known.

Neurotech

Neurotech, based in CA, is developing its proprietary Encapsulated Cell Technology (ECT), which enables the controlled, continuous delivery of biologics directly to the back of the eye. ECT implants consist of cells that have been genetically modified to produce a desired therapeutic factor that are encapsulated in a section of semi-permeable hollow fiber membrane with a suture loop at one end to anchor the implant to the sclera in the vitreo-retinal body inside the eye. The current product is 6 mm in length. In contrast to gene therapy, ECT does not modify the host genome. The implant is surgically placed in the vitreous body of the eye as an out-patient procedure. The implant is sutured in a manner that allows for its retrieval when desired, providing an added level of safety as well as the ability to reverse or adjust therapy, if needed.

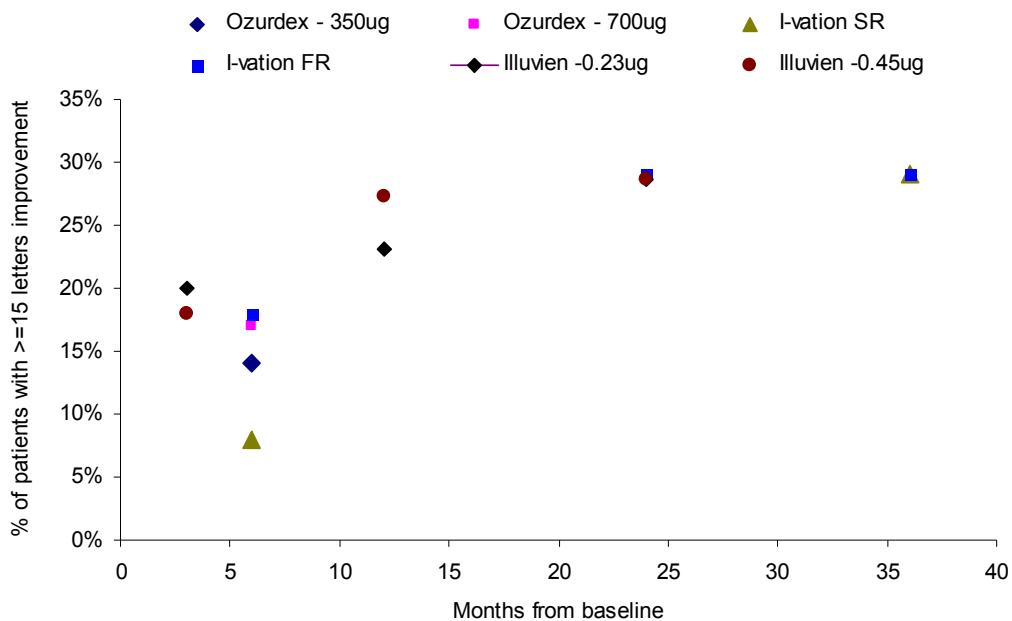
Figure 18. Neurotech's ECT product



Source: Company reports

Overall, the development in the field is exciting, albeit early. The graph below highlights the available data sets we have for the various implants used for DME. PIs note that the trial sizes are different, how the final data set is calculated might not be comparable across different products. However, we find it interesting to see the trendlines, especially out to 24 & 36-months. We note that no conclusions can be made from this graph and we highlight it for informational purposes only.

Figure 19. In order: Allergan's Posudex; pSivida's Illuvien; Available 15 letter improvement from various clinical trials



Source: Company reports

Other companies actively working on intravitreal implants include:

Glaukos

Glaukos, based in CA, is developing the iStent, the first ab interno micro-bypass implant for the treatment of glaucoma. Future therapeutic areas to be targeted are not known.

Icon Biosciences

Icon BioSciences is developing its Verisome sustained release drug delivery system that injects a liquid into the vitreous that coalesces into a single spherule. The drug can then be delivered for up to 1 year for the treatment of edema associated with retinal vein occlusion

On Demand Therapeutics

ODT is developing the ODTx biocompatible, non-resorbable injectable rod that can hold multiple cells of a drug. Each reservoir can safely store small or large molecule drugs in the eye until release is initiated using a standard ophthalmic laser during a simple, routine office-based procedure. Administering a laser pulse creates an opening in the device that releases the drug into the eye. Unactivated reservoirs remain intact until those doses are indicated. There is no need for monthly injections and the patient is maintained through regular follow-up visits and subsequent laser activation procedures.

Figure 20. On Demand Therapeutics Device



Source: ivaronsjournal.blogspot.com

OctoPlus N.V.

OctoPlus, based in the Netherlands is working on its OctoDex, PolyActive and SynBiosys drug delivery technologies for large molecule proteins and lipophilic drugs. Our checks suggest that the company has some partner sponsored development programs ongoing. Further details are not known at this stage.

The pursuit of the optimal intravitreal implant continues, complicated by the following unknowns:

- *What is the ideal time for delivery of a therapeutic agent in the eye? Is it 6-months, 12-months, 2-years?*
- *How do you titrate the dosing schedule for a patient of a particular etiology, especially given that there is no way to know if the pharmacokinetic profiles are of first-order kinetics?*
- *What is the balance between optimal efficacy and safety? How do you titrate the right amount of agent loading without causing side effects, and causing any systemic issues?*
- *What is the best mode of delivery? Is it biodegradable microspheres, is it subretinal cannula, is it rod like structures? How do you modulate the elution characteristics given changing in-vivo pH in the vitreous humor and the fact that by nature, some of the biodegradable polymers can clump together over time cause vision obstruction?*
- *Is it better to inhibit an isoform of VEGF, or inhibit all forms of VEGF? How do you stabilize large molecule proteins in a polymeric matrix, and make sure that shelf life and potency remain intact in-vivo?*
- *What is the economic benefit from an intravitreal implant vs. injection therapy? How do you address the lost revenue for vitro-retinal specialists who make \$50 - \$190 per injection delivered for eye diseases? What pricing is the market really able to tolerate?*
- *What is really motivating the players in the field: is it patient concern and the need to alleviate repeat office visits—is it a desire to penetrate a vast market segment and offer a differentiating product; is it a desire to protect an existing drug franchise by using a different delivery mechanism; or is it all of the above?*
- *Who are the patients that are really going to benefit by use of these devices?*

Pharmacotherapy Agents

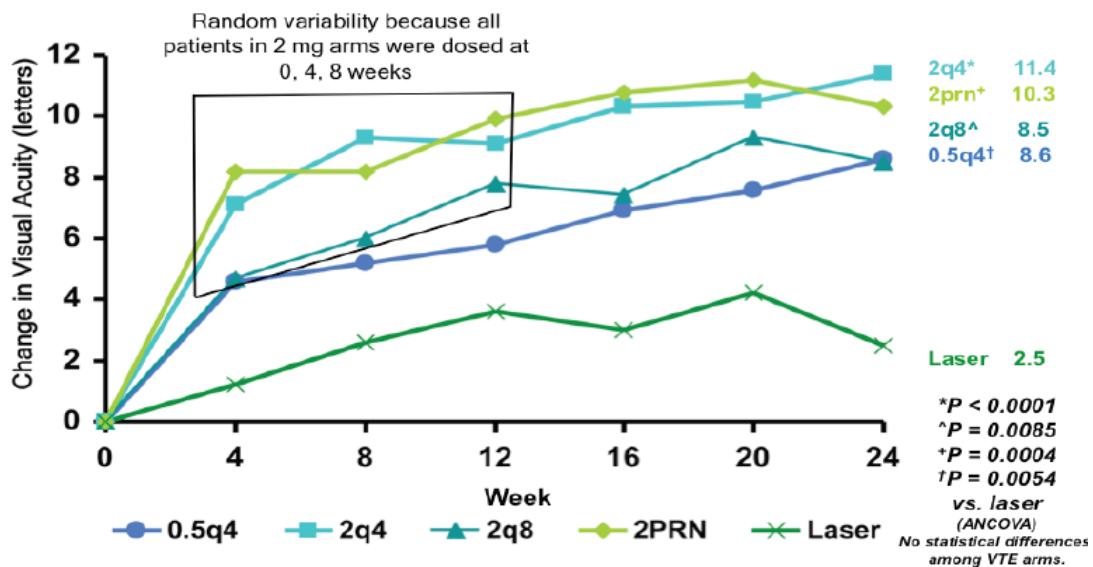
Regeneron Pharma

While many companies are working on the intravitreal implants, there is significant activity on the pharmacotherapy front also. We highlight one key player in the space, at least from a timeline and a preliminary efficacy perspective. Regeneron Pharmaceuticals is conducting a Phase III trial for evaluating a VEGF Trap, a protein which blocks VEGF-A, VEGF-B and PI GF (placental growth factor) for DME. Results of the Phase II trial have indicated positive results. In this double-masked, prospective, randomized, multi-center Phase 2 trial, entitled DA VINCI (DME And VEGF Trap-Eye: INvestigation of Clinical Impact), 219 patients with clinically significant DME with central macular involvement were randomized to five groups. The control group received macular laser therapy at week one, and patients were eligible for repeat laser treatments, but no more frequently than at 16 week intervals. Two groups received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye throughout the 6-month dosing period. Two groups received three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by either every 8-week dosing or as-needed (PRN) dosing with specific repeat dosing criteria. The following summarizes the mean gain in visual acuity at week 24 by dosing arm and the mean number of treatments received by patients over the first six monthly visits:

- Standard-of-care macular laser therapy (n=44; 1.7 treatments): +2.5 letters gained
- VEGF Trap Eye 0.5 mg monthly (n=44; 5.6 injections): +8.6 letters gained
- VEGF Trap-Eye 2 mg monthly (n=44; 5.5 injections): +11.4 letters gained
- VEGF Trap-Eye 2 mg every other month, following 3 monthly injections (n=42: 3.8 injections): +8.5 letters gained
- VEGF Trap-Eye 2 mg as-needed, following 3 monthly injections (n=45; 4.4 injections): +10.3 letters gained

The study was not designed to evaluate statistical differences among the results achieved in each of the VEGF Trap-Eye groups, and no significant differences were observed. Over 90% of the VEGF Trap-Eye patients and the laser patients remained in the study at the 6-month primary endpoint evaluation. VEGF Trap-Eye was generally well-tolerated, and there were no ocular or non-ocular drug-related serious adverse events reported in the study. The adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent adverse events reported among patients receiving VEGF Trap-Eye included conjunctival hemorrhage, eye pain, floaters (myodesopsia), ocular redness (hyperemia), and increased intraocular pressure. There were three deaths among the 175 patients treated with VEGF Trap-Eye and none in the 44 patients treated with laser over 6 months. All three patients had underlying risk factors for their cause of death, and the cases were not reported to be drug-related. Following the initial 24 weeks of treatment, patients continued to be treated for another 24 weeks on the same dosing regimens.

Figure 21. DA VINCI Phase II results in DME



Source: Regeneron company reports

VEGF Trap-Eye is currently in Phase 3 development in wet (age-related) macular degeneration (AMD). The VIEW 1 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study is being conducted in the United States and Canada by Regeneron and the VIEW 2 study is being conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. The primary endpoint of these non-inferiority studies is the proportion of patients treated with VEGF Trap-Eye who maintain vision at the end of one year, compared to ranibizumab patients. Patient enrollment has been completed in both studies with initial year-one primary endpoint data expected in the second half of 2010. VEGF Trap-Eye is also in Phase 3 development for the treatment of central retinal vein occlusion (CRVO), another major cause of blindness. The COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study is being led by Regeneron, and the GALILEO (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. Initial data from the CRVO program are anticipated in early 2011. Interestingly enough, it is unclear at this stage if VEGF-Trap will have a role in DME. There has not been much news coming out of Regeneron on VEGF-Trap, and some anecdotal evidence suggests that there might be systemic reactions with VEGF-Trap's such as hypertension.

Genentech

Genentech, one of the bellwethers in the oncology and ophthalmology space, currently manufactures two of the most potent VEGF antagonists in use, ranibizumab (Lucentis) and bevacizumab (Avastin). Ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF-A. Bevacizumab is a full length recombinant humanized antibody active against all isoforms of VEGF-A. Several studies have reported the use of the off-label intravitreal bevacizumab (IVB) to treat DME, complications of PDR, and iris neovascularization. To date, all studies regarding IVB (1.25 mg) for DME therapy, have demonstrated transient beneficial effects with a requirement for repeated injections. Increased visual acuity with decrease in macular edema with a single injection of IVB lasts for 4 to 6 weeks with deterioration of visual acuity and recurrence of macular edema 8 to 12 weeks later necessitating another injection. Moreover, some studies have also suggested that IVB treatment has better outcomes on DME eyes that have previously not been treated, which included focal or grid laser photocoagulation. Two recent studies have shown a signal response of bevacizumab activity in clinically significant DME. In one study, the results of IVB injection alone or in combination with intravitreal triamcinolone acetonide (IVT) versus macular laser photocoagulation (MPC) as a primary treatment of DME were compared. This study was a randomized 3-arm clinical trial, with a total of 150 eyes of 129 patients with clinically significant DME and no previous treatment. The eyes were randomly assigned to 1 of the 3 study arms: the IVB group, patients who received 1.25 mg IVB (50 eyes); the IVB/IVT group, patients who received 1.25 mg of IVB and 2 mg of IVT (50 eyes); and the MPC group, patients who underwent focal or modified grid laser (50 eyes). Retreatment was performed at 12-week intervals whenever indicated. The main outcome measure was change in BCVA at week 24. Overall, visual acuity changes among the groups were statistically significant at 6 ($P<0.001$) and 24 ($P = 0.012$) weeks. The significant treatment effect was demonstrated in the IVB group at all follow-up visits and in the IVB/IVT group at 6 and 12 weeks. Visual acuity changes +/- standard deviation at 36 weeks were -0.28 ± -0.25 , -0.04 ± -0.33 , and $+0.01\pm-0.27$. Significant central macular thickness (CMT) reduction was observed in all groups only up to 6 weeks; however, CMT changes were not significant among the groups in all visits. Overall, retreatment was required for 27 eyes up to 36 weeks (14 in the IVB group, 10 in the IVB/IVT group, and 3 in the MPC group). In the IVB group, in which a greater visual acuity improvement was observed, only 1 injection was required in 72% of the cases. Acuity improvement >2 Snellen lines at 36 weeks was detected in 37%, 25%, and 14.8% of patients in the IVB, IVB/IVT, and MPC groups, respectively.

The DRCR Study evaluating Lucentis

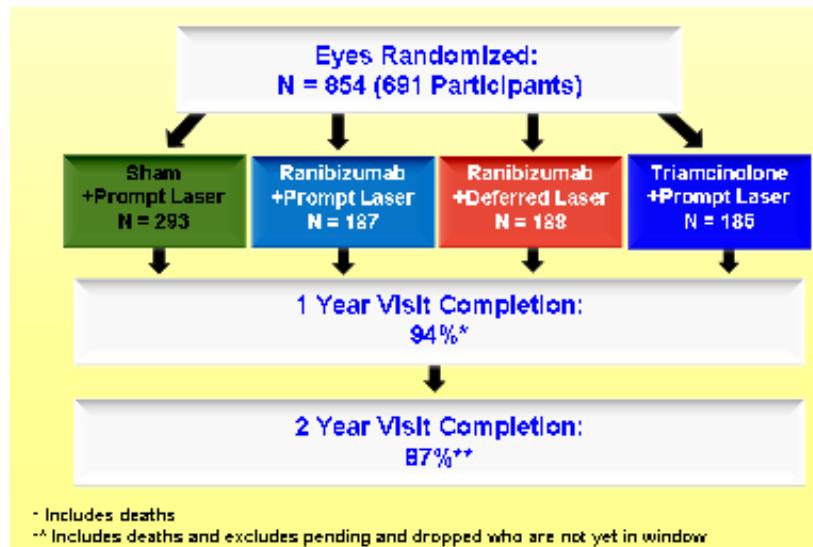
In another NIH funded study, the efficacy and safety of 0.5-mg intravitreal ranibizumab plus prompt (within 1 week) or deferred laser (≥ 24 weeks), or 4-mg intravitreal triamcinolone plus prompt (within 1 week) laser, in comparison with sham plus prompt laser for treatment of DME was evaluated. This was a multi-center, randomized trial with inclusion criteria calling for at least one eye meeting all of the following criteria:

- Electronic-ETDRS© best corrected visual acuity letter score of 78 to 24 (~20/32 to 20/320)
- Definite retinal thickening due to diabetic macular edema involving the center of the macula on clinical examination
- Central subfield (Stratus OCT) $\geq 250 \mu\text{m}$

Primary endpoint was defined as change in mean visual acuity from baseline at 24-months. Every subject has a follow-up visit at 1 year, with follow-up every 4 weeks. All groups except ranibizumab plus deferred laser group: Additional follow-up visit occurred 3 to 10 days after injection if focal/grid laser also was to be given

The randomized study enrolled 691 participants (854 study eyes); some patients had DME in one eye and others with two eyes. The eyes were assigned randomly and equally to the following treatment groups: placebo plus a laser treatment called focal/grid photocoagulation, intravitreal ranibizumab (Lucentis) plus laser treatment, or intravitreal triamcinolone (steroid) plus laser treatment. The Lucentis plus laser treatment was further broken up into 2 subgroups; one group received laser soon after Lucentis was administered, and the other group received a delayed laser treatment 16 weeks following Lucentis. Lucentis injections were given as often as every four weeks, and steroid (triamcinolone) injections or laser treatments were given as often as every 16 weeks. Treatment was continued until a participant's vision reached 20/20, retinal thickness returned to normal, or additional treatment did not improve vision or retinal swelling. Patient baseline characteristics are shown in figure 23 below.

Figure 22. DRCR Study on Lucentis plus laser in DME



Source: drcr.net

Figure 23. Patient baseline characteristics in DRCR study for Lucentis

	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
Median age	63	62	64	62
Diabetes type				
Type I	9%	6%	8%	8%
Type II	89%	92%	90%	89%
Uncertain	3%	2%	2%	3%
Median E-ETDRS® visual acuity letter score (Snellen equivalent)	65 (20/50)	66 (20/50)	66 (20/50)	66 (20/50)
Median OCT CSF thickness (µm)	407	371	382	374

Source: drcr.net

Figure 24. In order: Injections / Sham prior to 1-year; Laser Treatments prior to 1-year; Alternative treatments prior to 1-year

	Sham +Prompt Laser N = 274	Ranibizumab +Prompt Laser N = 171	Ranibizumab +Deferred Laser N = 178	Triamcinolone +Prompt Laser N = 176
Maximal possible # of sham/injections	13 sham*	13 drug	13 drug	9 sham/4 drug
Median number of sham/study drug injections to 1 year	11*	8	9	5 sham/3 drug
AE Precluding Study Drug Injection†	NA	2%	2%	15%
Compliance with sham/drug injection when required by protocol	96%	95%	97%	97%
Masked participant with 1 study eye identified correct assignment at 1 year	10%	88%	90%	44%

	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser* (permitted starting at 24-week visit)	Triamcinolone +Prompt Laser
Median number of laser treatments including baseline	3	2	0	2
Proportion of eyes receiving laser at 48-week visit	26%	16%	8%	21%
No, only 1, only 2 or 3 more lasers after baseline	13%, 27%, 40%, 20%	31%, 32%, 27%, 11%	70%, 20%, 10%, 1%	26%, 30%, 28%, 15%

	Sham +Prompt Laser N = 293	Ranibizumab +Prompt Laser N = 187	Ranibizumab +Deferred Laser N = 188	Triamcinolone +Prompt Laser N = 186
Eyes with alternative treatments (number of treatments)	14 (25)	1 (1)	0	1 (1)
Per protocol (failure‡ criteria met)	5	1	0	1
Deviations from protocol - clinical care	9	0	0	0

Source: drcr.net

Based on the data published by the DRCR, approximately 50% of eyes treated with intravitreal ranibizumab improved by at least 2 lines on a standard eye chart, while fewer than 5% of eyes lost sight of 2 or more lines through at least the first year. In contrast, laser treatment alone resulted in only 28% of eyes improving by 2 lines and 13% losing vision of 2 or more lines at first year. In contrast to the Lucentis combination therapy, the steroid plus laser treatment showed an improvement in vision at 12 months, and declined thereafter. The Lucentis + prompt laser group demonstrated statistically significant improvement in mean BCVA at 1-year of 30% over baseline, and this went down to 26% at 2-years (Mean VA improvement = 9 letters; p<0.001 at 1-year; Mean VA improvement = 7 letters; p=0.01 at 2-years). The Lucentis + deferred laser group showed BCVA ≥15 letter improvement over baseline of 28% (Mean VA improvement = 9 letters; p<0.001), and this was held up at the 2-year point of 29% (Mean VA improvement = 10 letters; p<0.001).

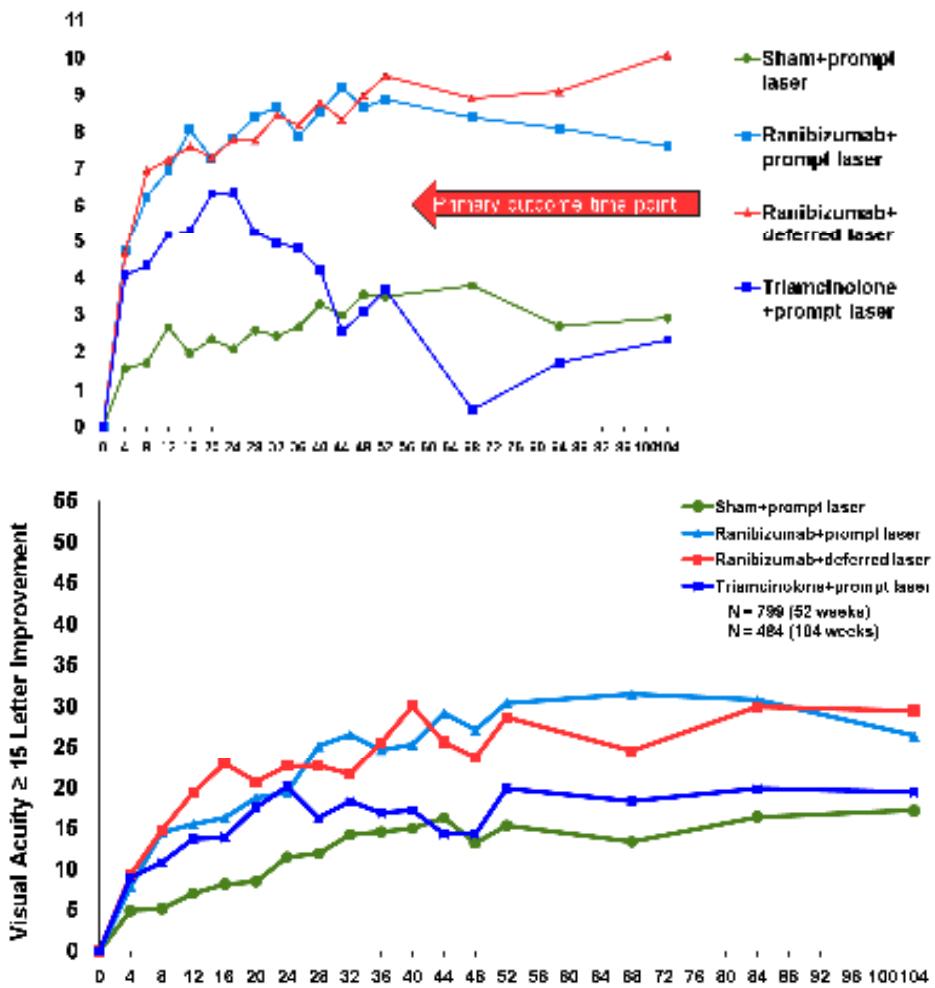
In the ranibizumab group, only a few eyes lost more than 10 letters of vision from the time the study started, whereas eyes losing vision of more than 10 letters in the steroid group and laser-alone group gradually increased throughout the study. Subgroup analysis for visual acuity is shown in the next few figures.

Figure 25. In order; Change in visual acuity scores at 1-year; Change in visual acuity scores at 2-year

Change in Visual Acuity (letters)	Sham +Prompt Laser N = 293	Ranibizumab +Prompt Laser N = 187	Ranibizumab +Deferred Laser N = 188	Triamcinolone +Prompt Laser N = 186	Change in Visual Acuity (letters)	Sham +Prompt Laser N = 163	Ranibizumab +Prompt Laser N = 106	Ranibizumab +Deferred Laser N = 112	Triamcinolone +Prompt Laser N = 103
Mean	+3	+9	+9	+4	Mean	+2	+7	+10	0
Difference in mean change from Sham +Prompt Laser [P Value]**		+5.8 [P<0.001]	+6.0 [P<0.001]	+1.1 [P = 0.31]	Difference in mean change from Sham +Prompt Laser [P Value]**		+5.0 [P = 0.01]	+7.2 [P<0.001]	-1.6 [P = 0.43]

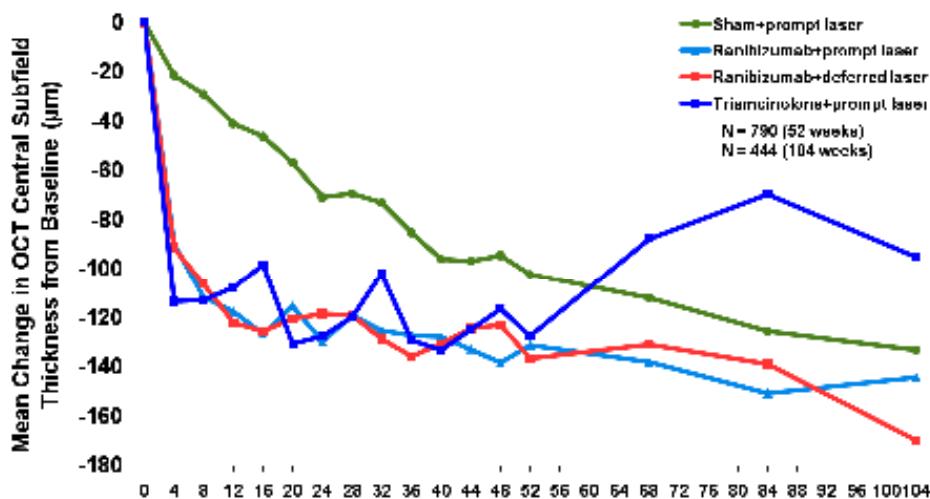
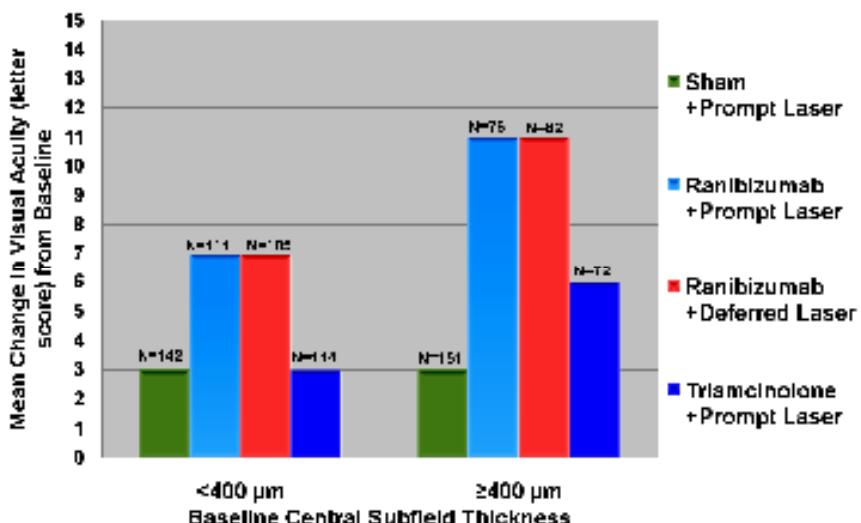
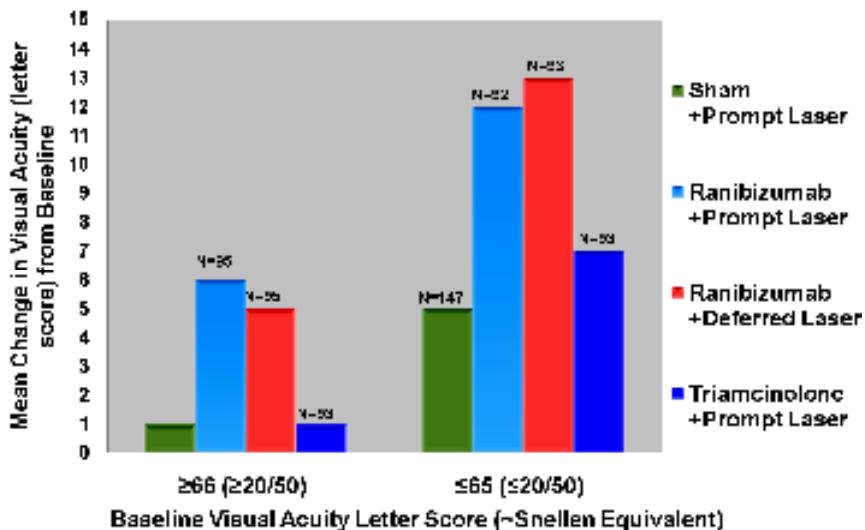
Source: drcr.net

Figure 26. In order; Mean visual acuity scores; BCVA ≥15 letters (X-axis = weeks)



Source: drcr.net

Figure 27. In order; Change in VA at 1-Year Stratified by Baseline VA; Change in VA at 1 Year Stratified by Baseline CSF; Retinal thickness change by OCT



Source: drcr.net

A closer look at the safety profile of the Lucentis and TA arm highlights that about 25% of the corticosteroid group patients had IOP >30 mm Hg, while only about 3% of the Lucentis arm patients had high IOP's. In terms of cataract surgeries, more than 50% of the TA patients had undergone surgery at 24-months, compared to 13% with Lucentis. Retinal thickness as measured by OCT saw a mean change of approximately 160 um decrease over 2-years, thereby demonstrating clinical activity with Lucentis.

Figure 28. In order: Major ocular adverse events at 2 years; Elevated IOP during 2-yr f/u; Cataract surgery at 2 yrs;

	Sham +Prompt Laser N = 293	Ranibizumab +Prompt Laser N = 187	Ranibizumab +Deferred Laser N = 188	Triamcinolone +Prompt Laser N = 186
Number of injections		1833	2140	685
Endophthalmitis*	1 (<1%)	2 (1%)	2 (1%)	0
Pseudoendophthalmitis†	1 (<1%)	0	0	1 (1%)
Ocular vascular event‡	1 (<1%)	1 (1%)	1 (1%)	3 (2%)
Retinal detachment§	0	0	1 (1%)	0
Vitrectomy	15 (5%)	4 (2%)	7 (4%)	2 (1%)
Vitreous Hemorrhage	27 (9%)	6 (3%)	8 (4%)	7 (4%)

Elevated Intraocular Pressure/Glaucoma	Sham +Prompt Laser N = 293	Ranibizumab +Prompt Laser N = 187	Ranibizumab +Deferred Laser N = 188	Triamcinolone +Prompt Laser N = 186
Increase ≥10 mmHg from baseline	8%	9%	6%	42%
IOP ≥30 mmHg	3%	2%	3%	27%
Initiation of IOP-lowering meds at any visit*	5%	5%	3%	28%
<i>Number of eyes meeting ≥1 of the above</i>	11%	11%	7%	50%
Glaucoma surgery**	<1%	1%	0	1%

	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
Phakic at baseline	N = 192	N = 131	N = 134	N = 124
Eyes that had cataract surgery	12%	12%	13%	55%

Source: drcr.net

The authors concluded that :

- *Intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser had superior VA and OCT outcomes compared with focal/grid laser treatment alone.*
- *~50% of eyes had substantial improvement (≥10 letters) while ~30% gained ≥15 letters*
- *Substantial visual acuity loss (≥10 letters) was uncommon*
- *Results were similar whether focal/grid laser was given starting with the first injection or it was deferred >24 weeks*
- *If ranibizumab is to be given as it was in this study, the data indicate a need to follow eyes continuously undergoing this treatment*

- *Additional ranibizumab and/or laser were needed in most eyes through ≥2 years, even if ‘success’ criteria were met early in the course of treatment.*
- *Intravitreal triamcinolone combined with focal/grid laser did not result in superior VA outcomes compared with laser alone.*
- *Intravitreal triamcinolone did result in a greater reduction in retinal thickening at 1 year but not 2 years compared with laser alone.*
- *In an analysis limited to pseudophakic eyes, the triamcinolone group’s outcome for VA appeared to be of similar magnitude to that of the 2 ranibizumab groups.*

In other Lucentis studies such as READ-2 which compared Lucentis to laser therapy, Lucentis was shown to be efficacious at 6-months with 46% of patients experiencing ≥2 lines of VA improvement and 22% improving ≥3 lines ($p=0.0003$ with mean change in VA of 7.24 letters). At 12-months the visual acuity improvement dropped down to 6.7 letters. Data from another study evaluating Lucentis alone (0.5 mg) or in conjunction with laser showed mean BCVA change of 6.1 and 5.9 letters, respectively at 12-months. The safety profile also appeared manageable, with 6% reporting hypertension and about 4% thromboembolic events.

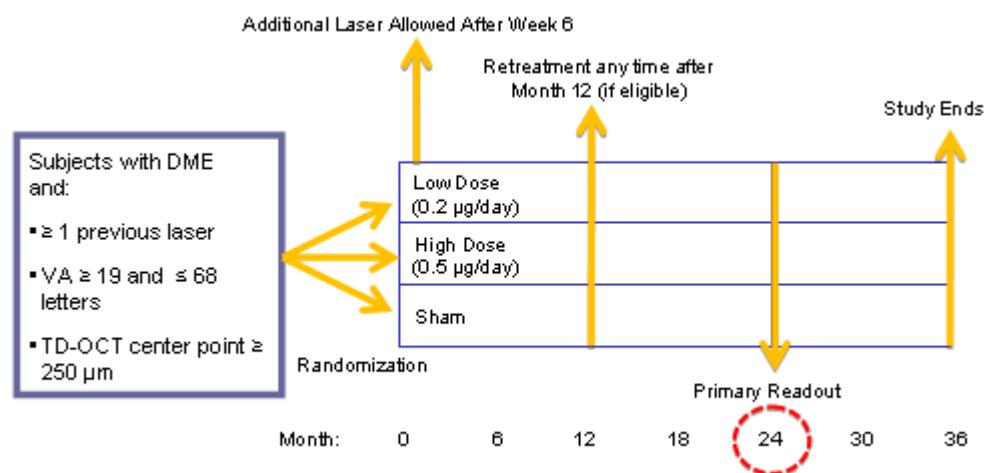
The question with this class of VEGF antagonists is really about systemic side effects and cost. Repeat monthly injections of Lucentis for example cause pulsations in the retina, and this can have serious long-term effects. Some limitations of the combination approach is that Lucentis currently is not reimbursed by insurance. Since ranibizumab costs over \$2000 per injection, this treatment regime will only go into effect once it is reimbursable. Physicians will likely substitute Avastin (\$50) but there are still many injections required which is problematic. Finally, the interesting question regarding this study is why was ranibizumab (>\$2000) chosen as the anti-VEGF therapy when its much cheaper counterpart (Avastin, \$50) was available? Genentech (Roche) supplied the Lucentis for the study and over \$9 Million to run the study. Interesting, when the National Eye Institute chose to study Avastin versus Lucentis in macular degeneration (CATT Trial), Genentech did not choose to participate by neither providing medication nor funding. Genentech is clearly trying to protect its \$1.1 Billion Lucentis franchise. In the February 2009 issue of Ophthalmology, a meta-analysis was reported in a letter to the editor pointing out some risks associated with intravitreal injection of ranibizumab. The letter looked at pooled data from the MARINA, ANCHOR and FOCUS studies which were done to determine effectiveness and adverse effects of Lucentis. The authors of the letter pointed out that when pooling all the data, the ranibizumab group had a 2.2% incidence of stroke, whereas the control group had a 0.7% incidence of stroke. They concluded that the risk of stroke rises as a result of ranibizumab treatment. Since the letter was published, there has been some discussion regarding the implications of the meta-analysis for use of Avastin. There is currently an NIH sponsored head-to-head clinical trial comparing Lucentis and Avastin underway. The results are due in 2012.

CLINICAL EVIDENCE (*Iluvien*)

Phase III – FAME trial

Alimera & its partner pSivida recently announced results for its double-blinded Phase III study called FAME. This study was designed to assess the safety and efficacy of Iluvien in patients with DME involving the center of the macula, and who had at least one prior macular laser treatment 12 weeks or more before study entry. The inclusion criteria for the study were DME patients with BCVA between 20/50 (68 letters on the ETDRS eye chart) and 20/400 (19 letters on the ETDRS eye chart) in the study eye and no worse than 20/400 in the non-study eye. Patients who had received steroid drug treatments for DME within three months of screening or anti-VEGF injections within two months of screening, and patients with glaucoma, ocular hypertension, IOP greater than 21mmHg or concurrent therapy with IOP-lowering agents in the study eye at screening were not eligible to participate in this trial. Overall, 956 patients were treated across 101 academic and private practice centers. Patients were assigned to one of three groups at a ratio of 2:2:1. The first two of these groups were assigned to an active drug formulation and the third group served as the control group, undergoing a sham insertion procedure designed to mimic an intravitreal insertion. The treatment groups consist of one group receiving a low dose of Iluvien (0.02 ug/day) and the high dose of Iluvien (0.05 ug/day). In order to simulate an insertion and help to maintain proper patient masking, the sham insertion procedure includes all steps involved in the insertion procedure, except that a blunt inserter without a needle is used to apply pressure to the anesthetized eye. Trial A drew patients from sites located in the northern regions of the United States, Europe and India and all sites in Canada, while sites in the southern regions of the United States, India and Europe comprised Trial B. Patient characteristics, such as age, gender and baseline BCVA, were balanced across the treatment and control groups. As part of randomization, the patients were divided into two separate groups, those with a baseline BCVA score greater than or equal to 49 letters on the ETDRS eye chart and those with a baseline BCVA score of less than 49 letters on the ETDRS eye chart. Investigators were able to re-treat each patient with Iluvien following their month 12 follow-up visit. Through month 24, 24.5% of patients had been treated with more than one Iluvien insert and 2.5% of patients had been treated with three or more Iluvien inserts.

Figure 29. In order: FAME Study Design; Patient baseline characteristics



	Trial A			Trial B		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Patients	95	190	196	90	186	199
Mean Age (years)	62.7	64	62.3	61.1	61.8	62.2
Mean Baseline Vision (letters)	54.8	53.4	52.5	54.7	53.3	53.3
Male/Female (percent)	50.5/49.5	57.9/42.1	60.2/39.8	66.7/33.3	56.5/43.5	63.8/36.2
Mean Time Since Diagnosis (years)	16.5	17.4	16.5	16.3	16.8	15.9
Diabetes	4.4	3.9	3.9	3.5	3.3	3.3
DME						

Source: Dr. Pearson presentation; Company reports

The primary efficacy endpoint for the study was the difference in the % of patients with improved BCVA from baseline of ≥ 15 letters on the ETDRS eye chart at month 24 between the treatment and control groups. Based upon the H-B procedure, if either dose of Iluvien in a trial did not meet statistical significance, the alternate dose was required to achieve a p-value of 0.02455 or lower in that trial to demonstrate statistical significance. In the Full Analysis Set, the primary efficacy endpoint was met with statistical significance for both the low dose and the high dose of Iluvien in Trial A and Trial B, as well as on a combined basis. Additionally, as required by the FDA, a numerical comparison of the responder rates at month 18 and month 24 in the full analysis set demonstrated that the responder rates for both the low dose and high dose of Iluvien at month 24 were numerically greater than the month 18 responder rates in both Trial A and Trial B. This study protocol also included analyses of additional data sets. The all-randomized and treated (ART) data set includes 953 patients randomized in the study and treated, with data imputation employed, using the LOCF method, for data missing because of patients who discontinued the trial or were unavailable for follow-up. Three patients who were randomized, but not treated, were included in the full data set and excluded from the ART Data Set. In the ART Data Set, the primary efficacy endpoint was met with statistical significance for both doses of Iluvien in both Trial A and Trial B. The % of patients in the ART data set achieving improved BCVA of ≥ 15 letters at month 24 for Trial A was 14.7% for the control group, 26.8% for the low dose (p-value 0.029) and 26.2% for the high dose (p-value 0.032). The percentage of patients in the ART data set achieving improved BCVA of ≥ 15 letters at month 24 for Trial B was 17.8% for the control group, 30.8% for the low dose (p-value 0.028) and 31.3% for the high dose (p-value 0.026).

The modified ART data set included all 953 patients included in the ART data set, but excluded data collected subsequent to the use of treatments prohibited by the protocol, such as Avastin, Lucentis, triamcinolone acetonide or vitrectomy (the Modified ART data set). In instances when a treatment prohibited by the study protocol was used, the last observation prior to the protocol violation was imputed forward to month 24 using the LOCF method. The % of patients in the modified ART data set achieving improved BCVA of ≥ 15 letters for Trial A was 12.6% for the control group, 22.6% for the low dose (p-value 0.057) and 24.1% for the high dose (p-value 0.026). Neither dose of Iluvien for Trial A was statistically significant based on the H-B procedure. The percentage of patients in the modified ART data set achieving improved BCVA of ≥ 15 letters at month 24 for Trial B was 13.3% for the control group, 29.7% for the low dose (p-value 0.004) and 29.3% for the high dose (p-value 0.005). Both doses of Iluvien for Trial B were statistically significant.

Figure 30. In order: Patients gaining ≥ 15 letters at month 24 – FULL DATA SET; ART DATA SET; Modified – ART DATA SET

Study Group (956 patients)	Trial A		Trial B	
	%	p-value	%	p-value
Control	14.7	—	17.8	—
Low Dose	26.8	0.029	30.6	0.03
High Dose	26	0.034	31.2	0.027

Study Group (953 patients)	Trial A		Trial B	
	%	p-value	%	p-value
Control	14.7	—	17.8	—
Low Dose	26.8	0.03	30.8	0.03
High Dose	26.2	0.03	31.3	0.03

Study Group	Trial A		Trial B	
	%	p-value	%	p-value
Control	12.6	—	13.3	—
Low Dose	22.6	0.06	29.7	0.004
High Dose	24.1	0.03	29.3	0.005

Source: Company reports

As indicated earlier, the key point of contention in the FAME study is the use of off-label treatments, specifically IVTA (intravitreal triamcinolone acetonide injections) and anti-VEGF injections. As seen in figure 24 on the next page, based on reported data, approximately 47 low-dose Iluvien and 53 sham patients received off-label treatments during the study. This translated into 12.5% of low-dose Iluvien and 28.6% of sham patients undergoing off-label treatments. Per the strict definition of modified-ART, these patients when excluded from the final analysis led to the FAME study failing its pre-defined endpoint.

Based on our due diligence, the level of data imputed either due to a patient not completing follow-up or getting off-label treatments and using the LOCF method was approximately 26% for the low-dose group and >50% in the control arm. As seen in figure 23 on the previous page, it is in the m-ART analysis that the low-dose arm did not reach statistical significance and the high-dose arm did not reach the threshold of p<0.0245, due to which the combined trial failed.

Figure 31. In order: Laser treatments after week 6 (physician masked); Off-label intravitreal TA and anti-VEGF injections

	Sham (N = 185)	Iluvien (N = 376)		Sham (N = 185)	Iluvien (N = 376)
<i>Administered</i>					
Number of treatments	248	277		134	70
% (n) of subjects	58.9% (109)	36.7% (138)		28.6% (53)	12.5% (47)
p< 0.001				P<0.001	
Number of treatments per subject	1.34	0.74		0.72	0.19

Source: Dr. Pearson presentation

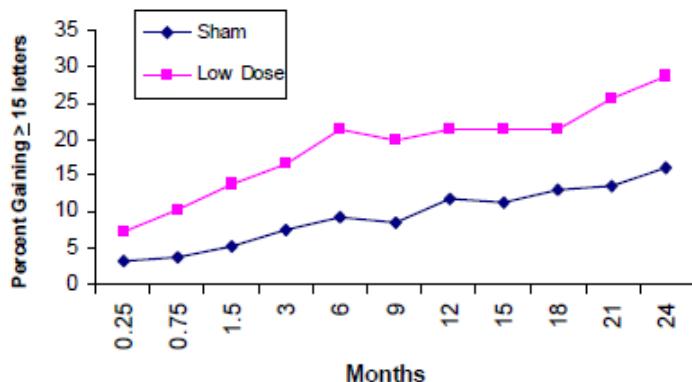
A few things come to mind:

- While use of the laser after week 6 was specified per protocol and the inclusion criteria called out for patients who had at least one laser photocoagulation treatment done prior to randomization, it is unclear as to what the sole effect of Iluvien would have been (albeit a moot point since it was specified by protocol). Also, more # of laser treatments per subject was given in the control arm vs. the low-dose arm. Could this have an effect on the mean visual acuity scores? Don't know.
- Our understanding is that about 8% of the patients died during the trial.
- The number of off-label IVTA and anti-VEGF treatments per subject in the control arm were almost 3.5x that of the low-dose arm. This tells us that the physician was uncomfortable with the progress in the sham arm and hence chose to use additional off-label combo therapies. When the off-label treatments are removed, and the data is imputed using LOCF, we believe it presents an interesting conundrum. First, more than twice the percent of patients were imputed in the control arm. It should be noted that these patients theoretically would have gotten worse or not fared very well and we guesstimate that that was the reason why an off-label treatment was chosen. Hence, the LOCF is probably using a higher mean visual acuity level and imputing it to 24-months, which in our opinion is skewing the data. Second, it is entirely possible that a phakic patient in the low-dose arm was developing cataracts and this cataract could be causing edema in the retinal macula. The physician being masked to the treatment could have used an intravitreal triamcinolone acetonide injection to reduce the edema not knowing that the patient had an Iluvien put in. It is also interesting to note that in the full-analysis data set, more # of treatments per subject in the control arm were given as compared to the low-dose arm. This implies that the control arm should have theoretically performed better than the m-ART analysis. However, both Trials A&B as well as the combined trial showed statistical significance, which tells us that even a minor off-label treatment combined with Iluvien had a much better outcome in responders.

In addition to the primary efficacy variable, a number of other clinically relevant results in the month 24 clinical data from the study were observed. Using the Full Analysis Set observations for Trial A and Trial B on a combined basis for patients who received the low dose of Iluvien in comparison to the control group, the following observations were made (*statements regarding statistical significance do not reflect any adjustments to the p-values calculated for multiple comparisons and analyses*):

- *Patients with Improved BCVA of 15 Letters or More at Each Follow up Visit.*
Through month 24, the low dose of Iluvien provided an improvement in BCVA as early as three weeks after insertion. The low dose of Iluvien was statistically significantly better than the control group in the study by week 3 of patient follow-up, and maintained a statistically significant advantage over the control through month 24.
- *Patients with Improved BCVA of 15 or More Letters at Any Time Point.*
Through month 24, a significantly greater % of patients receiving the low dose of Iluvien vs. the control group had an improvement in BCVA of ≥15 letters when assessed at any follow up visit. During the first 24 months, 165 out of 376 patients randomized to receive the low dose of Iluvien, or 43.9%, demonstrated improved BCVA of ≥15 letters at any time point compared to 47 out of 185 patients, or 25.4%, randomized to the control group.

Figure 32. Onset of activity in low-dose



Source: Company reports

- **Other Levels of BCVA Improvement at Month 24.**

While the FDA's requirement for the registration and approval of drugs being developed for DME is that the primary efficacy variable be based on an improvement in BCVA of ≥ 15 letters, lesser degrees of improvement in BCVA are considered clinically significant by retinal physicians. The low dose of Iluvien's statistically significant improvements in BCVA versus the control group at month 24 are shown below:

Figure 33. Other BCVA improvements at 24-months

BCVA Improvement	Combined		
	Control	Low Dose	p-value
Greater than 1 letter	54.1%	66.8%	0.005
Greater than 5 letters	40.0%	52.1%	0.01
Greater than 10 letters	26.5%	38.3%	0.009

Source: Company reports

- **BCVA Improvement of 15 or More Letters Relative to Baseline BCVA.**

At month 24, Iluvien had a statistically significant advantage over the control group irrespective of the severity of a patient's baseline BCVA. The table below demonstrates the statistically significant treatment effect of Iluvien versus the control group in patients with baseline BCVA of more than 49 letters on the EDTRS eye chart, and patients with BCVA of 49 letters or less on the EDTRS eye chart at baseline.

Figure 34. BCVA improvements of ≥ 15 letters relative to baseline

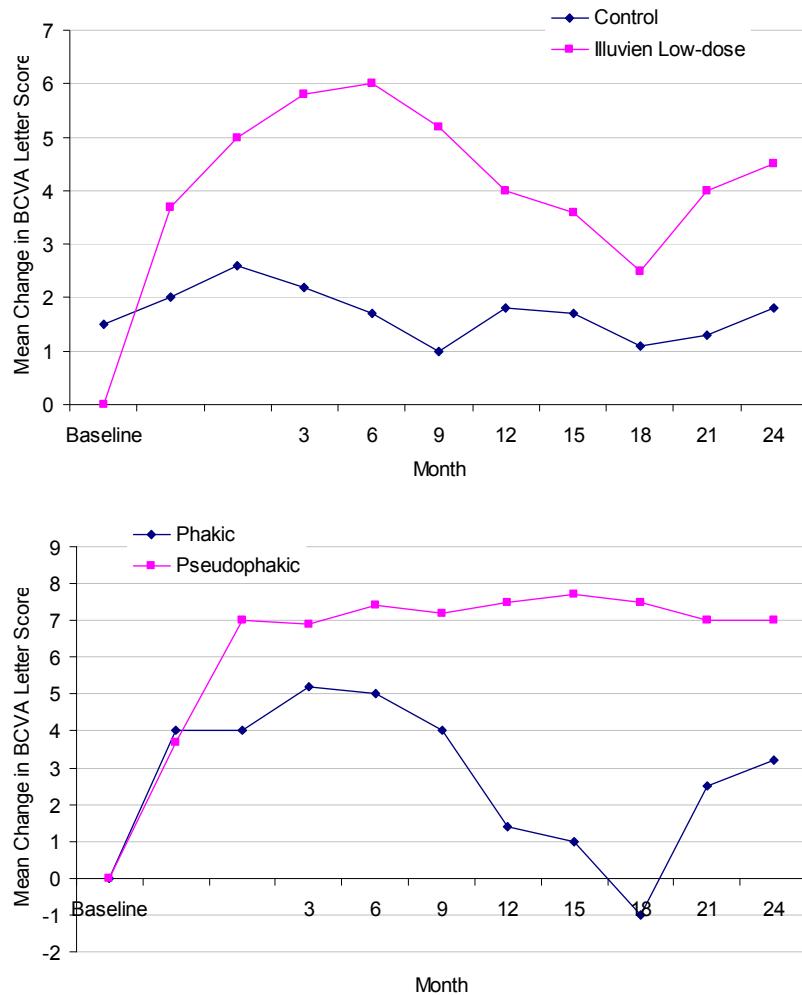
Baseline BCVA	Trial A & Trial B Combined		
	Control	Low Dose	p-value
Greater than 49 Letters	11.8%	21.1%	0.027
49 Letters or Less	28.6%	46.1%	0.039

Source: Company reports

- **Mean Change in BCVA Letter Score.**

Through month 24, the low dose of Iluvien provided a more beneficial improvement in visual acuity than the control group as analyzed by the mean change in the BCVA letter score from baseline. As demonstrated in the graph below, the mean change in BCVA for the patients receiving the low dose of Iluvien was an increase of 4.4 letters at month 24, peaking at an increase of 6.0 letters at month 6, compared to an increase of 1.7 letters in the control group, peaking at an increase of 2.6 letters at week 6. The low dose of Iluvien was statistically significantly better than the control group at month 24 (p-value 0.020).

Figure 35. In order; Mean Change in BCVA Score; Mean Change in BCVA by type of lens at baseline



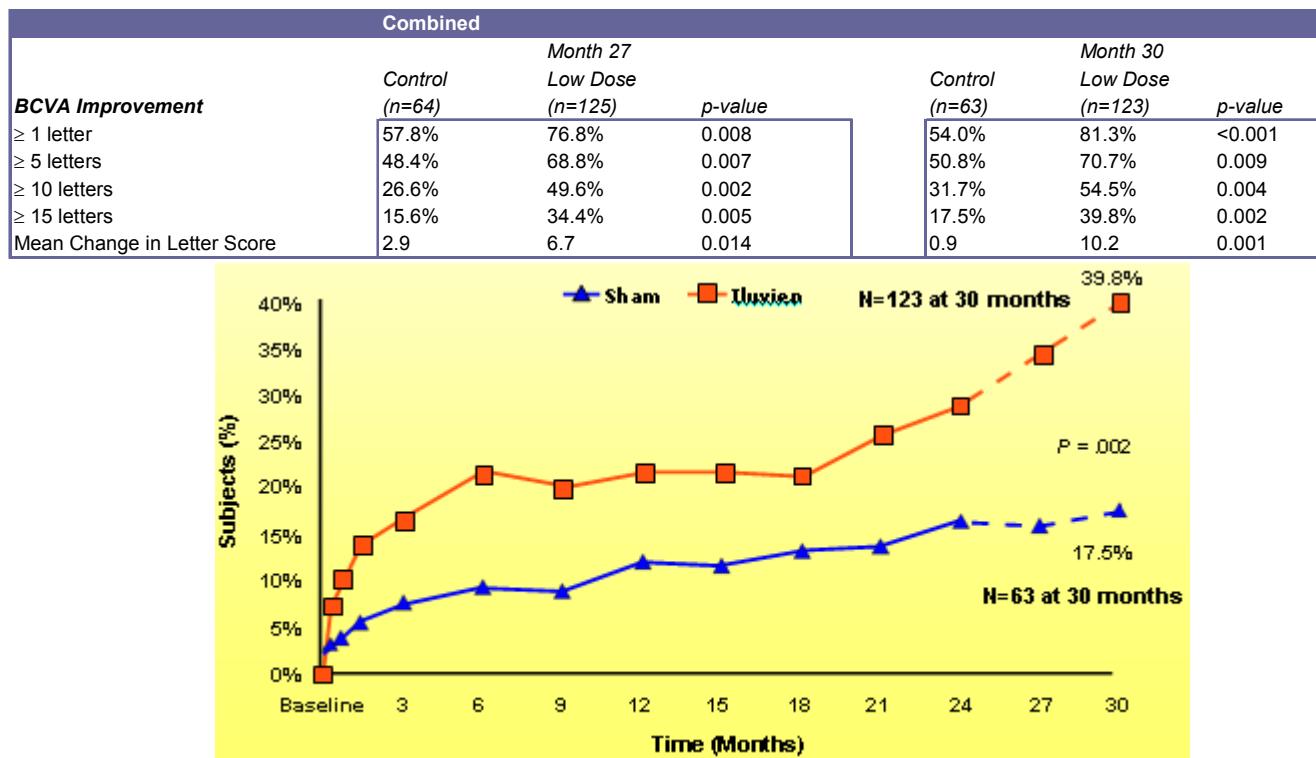
Source: Company reports

During the first 24 months of follow-up, patients that were phakic (had a natural lens and no prior cataract surgery) at baseline; 50 of 121, or 41.3% of the control group and 182 of 235, or 77.4% of the low dose had cataract formation reported as an adverse event through month 24. For these same phakic patients, 19.8% of the control group and 66.0% of the low dose group underwent cataract surgery through month 24. For the patients in the low dose group the median time to reporting cataract formation as an adverse event was approximately 12 months from randomization into the study. The median time to cataract surgery was approximately 18 months. This interval between the report of cataract formation as an adverse event and cataract surgery accounts for the decrease in the mean change in BCVA in patients receiving the low dose of Iluvien from the month 6 follow up visit to the month 18 follow up visit. The temporary effect of cataracts is further illustrated by comparing the mean change in BCVA of the 140 low dose patients that were pseudophakic (had an artificial lens) to the 235 that were phakic (natural lens and no prior cataract surgery) at baseline. The chart below shows the pseudophakic subset (those who would not have vision affected by a cataract) achieved a mean change in BCVA of more than 7 letters by month 6 and maintained this mean change through month 24 while the phakic subset experienced a decrease in the mean change in BCVA from the month 6 follow up visit to the month 18 follow up visit. The temporary decrease in mean change in BCVA in the phakic population is consistent with the total low dose population.

- **BCVA Improvements beyond Month 24.**

Analyses of available data from patients that had completed month 27 and month 30 follow up visits show incremental improvements in efficacy relative to the control group. We do not know the extent of the off-label treatments in the patients followed-up to 30-months and the number of treatments per subject.

Figure 36. In order: Mean BCVA scores and Improvements over baseline; BCVA ≥15 letters over 30-months

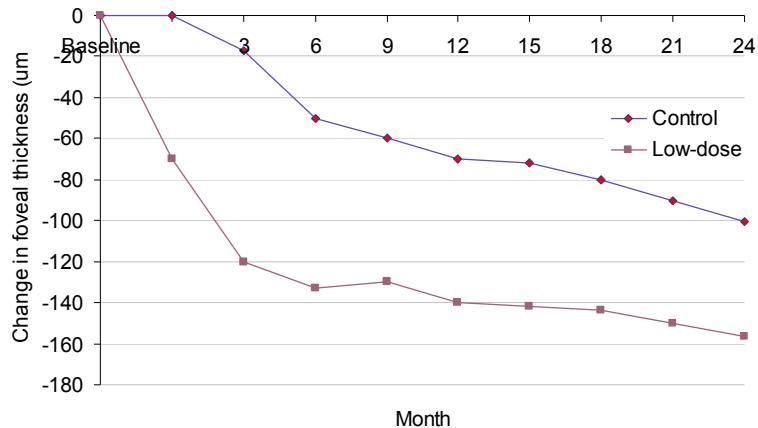


Source: Dr. Pearson presentation; Company reports

- **Decrease in Excess Foveal Thickness.**

The ability of Iluxien to result in a decrease in excess foveal thickness, as measured by OCT was also assessed. At 24-months, patients receiving the low dose of Iluxien demonstrated a mean decrease in excess foveal thickness of 156.1 microns versus 100.5 microns for the control group.

Figure 37. Decrease in foveal thickness



Source: Company reports

- **Safety**

The safety assessment in connection with the month 24 clinical readout of the FAME Study included all reported adverse events at that time, regardless of a patient's progression in the study. Some reported adverse events occurred beyond patients' month 24 follow up visits. Iluvien was well tolerated through this readout in both the low and high dose patient populations. No apparent risk of systemic adverse events to patients as a result of the use of Iluvien was found. The key adverse events related to use of Iluvien were similar to that of corticosteroids, namely: increased IOP, which may increase the risk of glaucoma and require additional procedures to manage; and cataract formation. Excluding IOP related side effects and cataracts; no significant eye related adverse events when comparing both the low dose and high dose patient populations to control. The table below summarizes the IOP related adverse events occurring in all patients randomized and treated in the study.

Figure 38. In order; Adverse Event Profile @ 24 months; Surgical Intervention to address elevated IOP for combined 2-year f/u on all patients and 40% with >2-year f/u

	Trial A & Trial B Combined		
	Control N=185	Low Dose N=375	High Dose N=393
IOP > 30 mmHg	2.70%	16.30%	21.60%
Trabeculoplasty	0.00%	1.30%	2.50%
<i>IOP-Lowering Surgeries</i>			
Trabeculectomy (filtration)	0.00%	2.10%	5.10%
Vitrectomy	0.00%	0.30%	0.50%
Other Surgery Performed	0.50%	1.60%	2.50%
Percentage of Patients Requiring One or More IOP-Lowering Surgeries	0.50%	3.70%	7.40%

Study Group	Combined	
	Low dose	High Dose
Trabeculoplasty	1.3%	2.5%
Trabeculectomy	2.1%	5.1%
Other Glaucoma procedure	1.3%	2.5%

Source: Company reports

A review of the baseline characteristics of the patient population reflects the increased risk of cataracts for diabetic patients, with 34.8% of the patients treated in the study having previously undergone a cataract surgery in the study eye. The month 24 clinical readout (which includes reported adverse events that occurred beyond patients' month 24 follow up visits) indicated that, of patients who had a natural lens (no prior cataract surgery) at baseline, 46.3% of the control group, 80.0% of the low dose and 87.5% of the high dose had cataract formation reported as an adverse event through month 24. Additionally, of the patients who had a natural lens at baseline, 23.1% of the control group, 74.9% of the low dose and 84.5% of the high dose underwent cataract surgery.

The PDUFA date for low-dose Iluvien in DME is Dec 30, 2010.

Other Studies

- **MAP Study**

This 30-patient, Phase II study is a single-blinded, randomized trial of the safety & efficacy of 0.2 and 0.5 ug/day fluocinolone acetonide in patients with exudative wet-AMD. The study is currently ongoing.

- **MAP GA Study**

This 40-patient, Phase II study is a proof of concept study of the safety & efficacy of 0.2 and 0.5 ug/day fluocinolone acetonide in patients with dry-AMD. The study is currently ongoing.

Licensing / Strategic Partnerships

Psivida Corp

In February 2005, ALIM entered into an agreement with pSivida for the use of fluocinolone acetonide in the Medidur platform. The agreement also provided ALIM with a worldwide non-exclusive license to develop and sell pSivida's proprietary delivery device to deliver other corticosteroids to the back of the eye for the treatment and prevention of eye diseases in humans (other than uveitis) or to treat DME by delivering a compound to the back of the eye through a direct delivery method through an incision required for a 25-gauge or larger needle. Further, the agreement permits pSivida to grant to any other party the right to use its intellectual property (i) to treat DME through an incision smaller than that required for a 25-gauge needle, unless using a corticosteroid delivered to the back of the eye, (ii) to deliver any compound outside the back of the eye unless it is to treat DME through an incision required for a 25-gauge or larger needle, or (iii) to deliver non-corticosteroids to the back of the eye, unless it is to treat DME through an incision required for a 25-gauge or larger needle. Alimera made initial license fee payments totaling \$750,000 to pSivida in 2004 and additional license fee payments of \$750,000 in 2005 upon the initiation of the FAME Study. Under the February 2005 agreement, both Alimera and pSivida agreed to collaborate on the development of Iluvien for DME, and share financial responsibility for the development expenses equally. Alimera retained primary responsibility for the development of the product, and therefore, were generally the party owed a balancing payment. Between February 2006 and December 2006, pSivida failed to make payments to Alimera for its share of development costs totaling \$2.0 million. For each payment not made, pSivida incurred a penalty of 50% of the missed payment and interest began accruing at the rate of 20% per annum on the missed payment and the penalty amount. In accordance with the terms of the agreement, pSivida was able to remain in compliance with the terms of the February 2005 agreement as long as the total amount of development payments past due did not exceed \$2.0 million, and pSivida began making payments again in December 2006 in order to maintain compliance with the agreement. The February 2005 agreement provided that after commercialization of Iluvien, profits, as defined in the agreement, would be shared equally. In March 2008, the agreement was amended and restated to provide Alimera with 80% of the net profits and pSivida with 20% of the net profits. Total consideration to pSivida in connection with the execution of the March 2008 agreement was \$33.8 million, which consisted of a payment of \$12.0 million, the issuance of a \$15.0 million note payable, and the forgiveness of \$6.8 million in outstanding receivables. The \$15.0 million promissory note accrued interest at 8% per annum, payable quarterly and payable in full to pSivida upon the earlier of a liquidity event as defined in the agreement (including an initial public offering), the occurrence of an event of default under our agreement with pSivida, or September 30, 2012. The outstanding receivables forgiven represented all outstanding development payments, penalties and interest totaling \$6.8 million, of which \$4.0 million was reserved for financial reporting purposes prior to the date of the amendment. The remaining \$2.8 million represented a receivable for current and unbilled development payments as of the effective date of the March 2008 agreement. As of calendar Q2-10, Alimera paid off the \$15 million note owed to Psivida. Also in connection with the amended agreement, Alimera prospectively assumed all financial responsibility for the remaining development of Iluvien. An additional milestone payment of \$25.0 million upon FDA approval of Iluvien is owed by Alimera. As a result of the amended profit sharing percentages, Alimera agreed to recover only 20% of the commercialization costs of Iluvien incurred prior to profitability, reduced from the 50% established earlier.

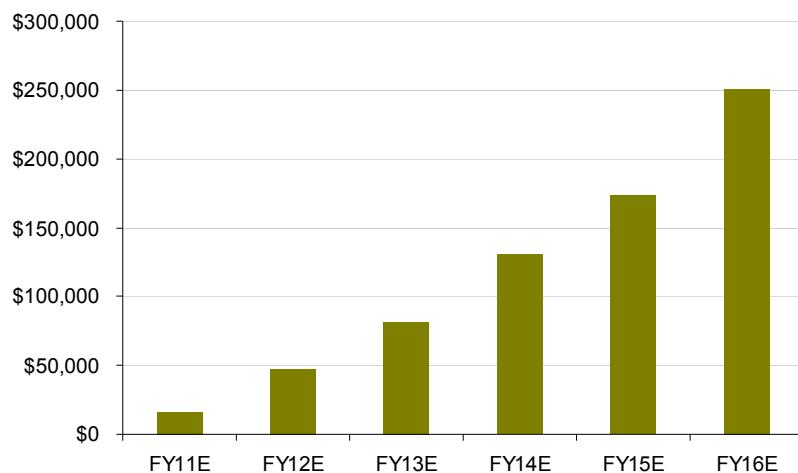
Financials

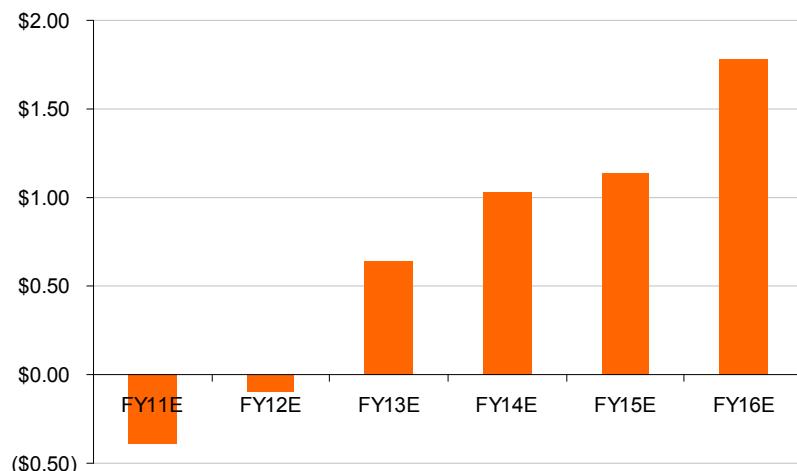
We have not bothered to forecast numbers for Q3-10 and Q4-10. Reason being, the story is really about Illuvien and how adoption occurs post-approval. We are optimistic on Illuvien's chances of regulatory approval, but in case there is a hiccup, ALIM stock could trade down significantly to near cash value which would be around \$2. Our basis for modeling the ramp rate is predicated on a few assumptions:

- Lucentis, Genentech's blockbuster drug in wet-AMD reached a 50,000 patient mark in about 5 years. Average pricing for Lucentis was around \$2000 / injection with injection protocol at 10 in the first year, 4 in the 2nd year and 4 in the 3rd year. In other words, the total Lucentis 36-month treatment regimen is estimated to be around \$36,000
- Avastin, using the existing evidence (on off-label) in wet-AMD is costing the system around \$300 / injection with quarterly injections. For a 36-month regimen, that translates into a \$5,400 cost.
- Macugen, Eyetech's drug was being sold around \$1,200 / injection
- Illuvien on the other hand, is a pseudo-device / drug platform. Hence, utilizing a direct correlation in the ramp rate would be erroneous in our mind. We are therefore assuming, for purposes of remaining conservative that the ramp would reflect more like a medical device ramp rather than a drug therapy ramp.
- While the injection for delivering Illuvien can be covered under the same codes as Ozurdex, there is no HCPCS code for Illuvien. ALIM is working on the same, and it is estimated that a code could be in place sometime by end of 2011. Our discussions with the company have highlighted that the company is working on solutions to sell Illuvien without having physicians bear the burden of the cost (till a code is in place).

Our fundamental starting point is a conservative estimate of the prevalence of DME in the U.S. around 1,000,000 with an annual incidence of about 200,000. Our field checks suggest that approximately 75% of these patients will have a laser treatment at some point, and only 50% of these existing patients will be candidates for Illuvien sustained-release therapy. A tiered penetration of high-volume / medium-volume / low-volume retina centers in the U.S. has been taken into account with cumulative penetration in the high-volume centers around 8% in 2016, and medium-volume centers around 4% in 2016. We believe that is reasonable given our earlier assumptions. At this stage, while the 36-month data is encouraging, we do not take into account repeat injections into patients, or for that matter diabetic patients whose other eye could utilize Illuvien treatment. In essence, 2016 renders approximately 38,000 Illuvien patients treated out of a pool of about 825,000. Pricing for Illuvien has been assumed to be around \$6,000 till 2014 and \$5,000 beyond that. While the company has officially stated that it expects to price Illuvien between \$5,000 - \$10,000, we do not believe the market can support the high price point. Based on these assumptions, our revenue estimates for U.S. sales for Illuvien is \$230 million in 2016 with another \$20 million contribution from OUS sales. Our OUS assumptions might be quite conservative; however we are comfortable with the numbers. Gross margins for ALIM have been assumed to be in the 85% range going down to 83% in 2016. It is certainly possible that given the cost of goods and the price point, the company might be able to command higher gross margins. Probably the key item that generates operational leverage in the model is SG&A. Based on our discussions with the company, it believes that about 30 -40 reps can handle the entire sales effort in the U.S. translated otherwise, each rep would have a territory of 10 – 12 centers. If this were not to be realized, then our numbers would be rendered wrong and we would have to revisit the story.

Figure 39. In order: Proforma Annual Revenue profile for PSDV (\$, 000); Proforma EPS profile





Source: R&R estimates

Per the agreement with pSivida, royalties due pSivida are calculated as 20% of net sales of Illuvien less direct costs for commercialization, regulatory and marketing. We have accordingly factored that in. By 2016, we estimate approximately \$35 million in net royalty payments to PSDV, which translates into approximately 14% of sales. No positive developments from the NADPH oxidase inhibitor program or for that matter the AMD program have been assumed.

ALIMERA

Proforma Revenue Model

Fiscal year ends Dec

Numbers in ,000s, except when Italicized

	ESTIMATES														
	Q2-11E	Q3-11E	Q4-11E	Q1-12E	Q2-12E	Q3-12E	Q4-12E	Q1-13E	Q2-13E	Q3-13E	Q4-13E	Q1-14E	Q2-14E	Q3-14E	Q4-14E
Total Number of DME patients - U.S. Incidence of new CSDME over prior year	1,100,000	1,150,000	1,200,000	1,250,000	1,300,000	1,350,000	1,400,000	1,450,000	1,500,000	1,550,000	1,600,000	1,650,000	1,700,000	1,750,000	1,800,000
# DME patients with prior treatment Number of de novo DME patients	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%	75% 25%
Number of independent DME surgeons - U.S. Number of surgeons / center	1,500 3	1,500 3	1,500 3	1,525 3	1,525 3	1,525 3	1,525 3	1,550 3	1,550 3	1,550 3	1,550 3	1,600 3	1,600 3	1,600 3	1,600 3
Number of retina centers treating DME - U.S.	500	500	500	508	508	508	508	517	517	517	517	533	533	533	533
High Volume centers - % Medium Volume centers - % Low Volume centers - %	10% 40% 50%	10% 40% 50%	10% 40% 50%	10% 40% 50%	10% 40% 50%	10% 40% 50%	10% 38% 50%	12% 38% 50%							
Vol of existing DME patients @ high-volume ctr	18%	18%	18%	20%	20%	20%	20%	20%	20%	20%	20%	21%	21%	22%	22%
Penetration of Illuvien in high-volume center	1.0%	1.0%	1.5%	2.0%	2.0%	2.0%	2.0%	1.8%	1.8%	1.8%	1.8%	2.0%	2.0%	2.0%	2.0%
Vol of existing DME patients @ medium-vol ctr	37%	37%	37%	35%	35%	35%	35%	35%	35%	35%	35%	34%	34%	33%	33%
Penetration of Illuvien in medium-volume center	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.5%	1.0%	1.0%	1.0%	1.0%	1.0%
Vol of existing DME patients @ low-vol ctr	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%	45%
Penetration of Illuvien in low-volume center	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Existing DME patients = candidates for Illuvien	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Potential DME patient population for Illuvien Actual Cases done using Illuvien % Penetration	412,500 743 0.2%	431,250 776 0.2%	450,000 1,215 0.3%	468,750 1,875 0.4%	487,500 1,950 0.4%	506,250 2,029 0.4%	525,000 2,105 0.4%	543,750 1,903 0.4%	562,500 2,953 0.5%	581,250 3,052 0.5%	600,000 4,260 0.7%	618,750 4,703 0.8%	637,500 4,845 0.8%	656,250 5,053 0.8%	675,000 5,198 0.8%
Re-treatment for Illuvien 3 years from initial	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OVERALL ILLUVIEN UNIT SALES ASP	743 \$6,000	776 \$6,000	1,215 \$6,000	1,875 \$6,000	1,950 \$6,000	2,029 \$6,000	2,105 \$6,000	1,903 \$6,000	2,953 \$6,000	3,052 \$6,000	4,260 \$6,000	4,703 \$6,000	4,845 \$6,000	5,053 \$6,000	5,198 \$6,000
OVERALL ILLUVIEN REVENUES - U.S. OVERALL ULLUVIEN REVENUES - O.U.S.	\$4,455 \$0	\$4,658 \$0	\$7,290 \$0	\$11,250 \$0	\$11,700 \$0	\$12,177 \$0	\$12,628 \$0	\$11,419 \$0	\$17,719 \$2,000	\$18,309 \$2,000	\$25,560 \$2,000	\$28,215 \$2,000	\$29,070 \$3,000	\$30,319 \$3,000	\$31,185 \$3,000
NET SALES	\$4,55	\$4,13	\$7,29	\$1250	\$11,700	\$12,177	\$12,628	\$13,419	\$19,719	\$20,309	\$27,560	\$31,215	\$32,070	\$33,319	\$34,185

VALUATION

We have valued ALIM using a traditional 2-stage DCF model given the stage in its life-cycle. Our DCF methodology assumes a 14% discount rate in the high-growth period and a 10% steady-state WACC. We believe these are reasonable at this stage given that the company is waiting for regulatory approval and that a reimbursement code has not yet been established. Our market risk premium is higher than historical multiples and we believe this is prudent given the structural changes in the macro-landscape. Peak Illuvien sales are modeled around \$250 million in 2016, which coincides with the timeframe where any of the new VEGF antagonists, assuming clinical trials hold up, will be entering the market.

Figure 40. DCF Analysis for ALIM

ALIM

Free Cash Flow to Firm Model
Fiscal Year ends Dec
Numbers in \$ 000

Suraj Kalia, CFA
skalia@rodm.com
212-430-1747

	PROJECTED				
	2011	2012	2013	2014	2015
Operating Income	(\$17,149)	(\$2,934)	\$20,798	\$48,650	\$66,328
Taxed at 30.0%	\$0	\$0	\$0	\$14,595	\$19,899
After Tax Operating Income	(\$17,149)	(\$2,934)	\$20,798	\$34,055	\$46,430
Less: Net Capital Expenditures	\$0	\$0	\$0	\$0	\$0
Less: Change in Working Capital	\$0	\$0	\$0	\$0	\$0
Free Cash Flow	(\$17,149)	(\$2,934)	\$20,798	\$34,055	\$46,430
Terminal Value	\$0	\$0	\$0	\$0	\$480,468
Total Free Cash Flow	(\$17,149)	(\$2,934)	\$20,798	\$34,055	\$526,898
Assumptions					
Long term debt cost	0.00%				
Tax Rate	30.00%				
WACC	14.05%				
EBITDA Multiple	8				
Beta	1.70				
Market Risk Premium	6.50%				
Risk Free Premium	3.00%				
Long term growth rate	4.00%				
Working Capital as a % of Sales	10.00%				
Steady State WACC	9.50%				
Net Present Value at December 31, 2011					
Present Value of Cash Flow	\$63,815				
Present Value of Terminal Value	\$334,201				
Company Value	\$398,017				
Plus: Cash	\$25,000				
Less: Debt	\$0				
Equity Value	\$423,017				
Shares Outstanding	31,700				
Equity Value / Share	\$13.34				
Sensitivity Analysis - Equity Value					
WACC					
Diluted Shares	31,000	15.00%	12.50%	11.00%	
	35,000	\$12.66	\$15.71	\$18.53	
	40,000	\$11.21	\$13.91	\$16.42	
		\$9.81	\$12.17	\$14.36	
Sensitivity Analysis - Equity Value					
Long-Term growth Rate					
WACC	15.00%	3.00%	4.00%	5.00%	
	12.50%	\$11.49	\$12.38	\$13.45	
	11.00%	\$13.94	\$15.36	\$17.16	
		\$16.10	\$18.12	\$20.82	

Source: R&R estimates

Risks

Regulatory risk. Market Risk. Commercialization risk.

ALIMERA**Quarterly Income Statement**

Fiscal year ends Dec 31

Numbers in \$000, except per share

Suraj Kalia, CFAskalia@rodm.com

212-430-1747

	PROJECTED																					
	Q2-11E	Q3-11E	Q4-11E	FY11E	Q1-12E	Q2-12E	Q3-12E	Q4-12E	FY12E	Q1-13E	Q2-13E	Q3-13E	Q4-13E	FY13E	Q1-14E	Q2-14E	Q3-14E	Q4-14E	FY14E	FY15E	FY16E	
Total Revenue	\$4,455	\$4,658	\$7,290	\$16,403	\$11,250	\$11,700	\$12,177	\$12,628	\$47,754	\$13,419	\$19,719	\$20,309	\$27,560	\$81,007	\$31,215	\$32,070	\$33,319	\$34,185	\$130,789	\$173,044	\$250,370	
COGS	\$668	\$699	\$1,094	\$2,460	\$1,800	\$1,872	\$1,948	\$2,020	\$7,641	\$2,281	\$3,352	\$3,453	\$4,685	\$13,771	\$5,307	\$5,452	\$5,664	\$5,811	\$22,234	\$29,417	\$42,563	
Gross Profit	\$3,787	\$3,959	\$6,197	\$13,942	\$9,450	\$9,828	\$10,228	\$10,607	\$40,113	\$11,138	\$16,367	\$16,857	\$22,875	\$67,236	\$25,908	\$26,618	\$27,655	\$28,374	\$108,555	\$143,626	\$207,807	
Operating Expenses:																						
R&D	\$2,450	\$2,562	\$4,010	\$11,171	\$3,938	\$4,095	\$3,653	\$3,157	\$14,842	\$2,684	\$2,958	\$2,031	\$2,756	\$10,429	\$3,122	\$3,207	\$3,332	\$3,419	\$13,079	\$17,304	\$25,037	
S&M	\$3,341	\$3,260	\$5,103	\$14,705	\$5,063	\$4,680	\$4,262	\$4,167	\$18,171	\$4,428	\$5,521	\$4,671	\$6,063	\$20,684	\$5,619	\$5,773	\$5,997	\$6,153	\$23,542	\$31,148	\$42,563	
G&A	\$1,300	\$1,315	\$1,350	\$5,215	\$1,375	\$1,400	\$1,425	\$1,445	\$5,645	\$1,475	\$1,500	\$1,515	\$1,525	\$6,015	\$1,551	\$1,560	\$1,575	\$1,595	\$6,281	\$6,350	\$6,500	
Royalties to PSDV	\$0	\$0	\$0	\$0	\$878	\$1,030	\$1,193	\$1,288	\$4,388	\$1,342	\$2,169	\$2,437	\$3,362	\$9,310	\$4,058	\$4,169	\$4,331	\$4,444	\$17,003	\$22,496	\$33,049	
Total OpEX	\$7,092	\$7,137	\$10,463	\$31,091	\$11,253	\$11,205	\$10,533	\$10,057	\$43,047	\$9,929	\$12,148	\$10,654	\$13,707	\$46,438	\$14,349	\$14,709	\$15,236	\$15,611	\$59,904	\$77,298	\$107,149	
Operating Income	(\$3,305)	(\$3,178)	(\$4,266)	(\$17,149)	(\$1,803)	(\$1,377)	(\$305)	\$550	(\$2,934)	\$1,209	\$4,218	\$6,203	\$9,168	\$20,798	\$11,559	\$11,909	\$12,419	\$12,763	\$48,650	\$66,328	\$100,658	
Other Inc (Exp):																						
Investment Income	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	
Total Other Inc	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	
Pretax Income	(\$3,305)	(\$3,178)	(\$4,266)	(\$17,149)	(\$1,803)	(\$1,377)	(\$305)	\$550	(\$2,934)	\$1,209	\$4,218	\$6,203	\$9,168	\$20,798	\$11,559	\$11,909	\$12,419	\$12,763	\$48,650	\$66,328	\$100,658	
Provision for Taxes	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$3,468	\$3,573	\$3,726	\$3,829	\$14,595	\$26,531	\$40,263	
Milestone Pmt - PSDV	\$0	\$0	\$0	(\$25,000)	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	
Net Income	(\$3,305)	(\$3,178)	(\$4,266)	(\$17,149)	(\$1,803)	(\$1,377)	(\$305)	\$550	(\$2,934)	\$1,209	\$4,218	\$6,203	\$9,168	\$20,798	\$8,092	\$8,337	\$8,693	\$8,934	\$34,055	\$39,797	\$60,395	
Basic / Diluted Sh	30,800	30,950	31,000	30,875	31,200	31,450	31,500	31,700	31,463	32,150	32,250	32,750	32,800	32,488	33,000	33,025	33,121	33,450	33,149	33,500	34,000	
Fully Diluted EPS	(\$0.11)	(\$0.10)	(\$0.14)	(\$0.56)	(\$0.06)	(\$0.04)	(\$0.01)	\$0.02	(\$0.09)	\$0.04	\$0.13	\$0.19	\$0.28	\$0.64	\$0.25	\$0.25	\$0.26	\$0.27	\$1.03	\$1.19	\$1.78	
Margins	Q2-11E	Q3-11E	Q4-11E	FY11E	Q1-12E	Q2-12E	Q3-12E	Q4-12E	FY12E	Q1-13E	Q2-13E	Q3-13E	Q4-13E	FY13E	Q1-14E	Q2-14E	Q3-14E	Q4-14E	FY14E	FY15E	FY16E	
Gross Margin	85.00%	85.00%	85.00%	85.00%	84.00%	84.00%	84.00%	84.00%	84.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	83.00%	
Operating Margin	NM	NM	NM	NM	NM	NM	NM	4.36%	NM	9.01%	21.39%	30.54%	33.27%	25.67%	37.03%	37.14%	37.27%	37.33%	37.20%	38.33%	40.20%	
Pretax Margins	NM	NM	NM	NM	NM	NM	NM	0.00%	NM	0.00%	0.00%	0.00%	0.00%	0.00%	11.11%	11.14%	11.18%	11.20%	11.16%	15.33%	16.08%	
Net Margin	NM	NM	NM	NM	NM	NM	NM	4.36%	NM	9.01%	21.39%	30.54%	33.27%	25.67%	25.92%	25.99%	26.09%	26.13%	26.04%	23.00%	24.12%	
Assumptions	Q2-11E	Q3-11E	Q4-11E	FY11E	Q1-12E	Q2-12E	Q3-12E	Q4-12E	FY12E	Q1-13E	Q2-13E	Q3-13E	Q4-13E	FY13E	Q1-14E	Q2-14E	Q3-14E	Q4-14E	FY14E	FY15E	FY16E	
Revenue Growth	-	-	-	-	-	162.63%	161.44%	73.22%	191.14%	19.28%	68.54%	66.79%	118.25%	69.63%	132.62%	62.64%	64.06%	24.04%	61.45%	32.31%	44.69%	
R&D as % of Rev	55.00%	55.00%	55.00%	68.11%	35.00%	35.00%	30.00%	25.00%	31.08%	20.00%	15.00%	10.00%	10.00%	12.87%	10.00%	10.00%	10.00%	10.00%	10.00%	10.00%	10.00%	
S&M as % of Rev	75.00%	70.00%	70.00%	89.65%	45.00%	40.00%	35.00%	33.00%	38.05%	33.00%	28.00%	23.00%	22.00%	25.53%	18.00%	18.00%	18.00%	18.00%	18.00%	18.00%	17.00%	
Tax Rate	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	30.00%	30.00%	30.00%	30.00%	40.00%	40.00%	

Alimera Sciences

Balance Sheet
Fiscal Year Ends Dec 31
Numbers in millions

Assets

Cash & Eqtl
Marketable Securities
Receivables, net
Inventories
Prepaid Expenses & Other Current Assets
Total Current Assets
Property, Plant & Equipment
Other Assets
Long-term deposits and loans
Total Non Cur Assets
Total Assets

Liabilities

Accounts Payable
Accrued Expenses
Other
Preferred Stock Warrant Liability
Deferred Revenue
Total Cur Liab
Long-term debt, net of current
Other
Total Long-Term Liab
Preferred
Common Stock
Additional Paid-In Capital
Warrants & equity portion of convertible debt
Accumulated Deficit
Minority Interest
Total Stockholders' Equity
Tot Liab & Stk Eq

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	Dec 2008	% chg	Dec 2009	% chg
\$17.9	-	\$14.9	-16.64%	
\$0.0	-	\$0.0	#DIV/0!	
\$0.0	-	\$0.0	#DIV/0!	
\$0.0	-	\$0.0		
\$1.6	-	\$1.4		
\$19.5	-	\$16.3	-16.27%	
\$0.8	-	\$0.3	-62.31%	
\$0.0	-	\$0.0		
\$0.0	-	\$0.0		
\$0.8	-	\$0.3	-62.31%	
\$20.3	-	\$16.6	-18.08%	

\$1.6	-	\$1.8	11.62%
\$2.3	-	\$3.3	43.59%
\$1.0	-	\$4.5	
\$0.0	-	\$0.0	
\$0.0	-	\$1.2	
\$4.9	-	\$10.7	118.65%
\$15.0	-	\$10.5	
\$13.2	-	\$0.7	
\$28.2	-	\$11.2	-60.28%
\$103.0	-	\$0.0	
\$0.1	-	\$0.3	454.90%
\$3.5	-	\$183.3	
\$0.1	-	\$0.1	
(\$119.5)	-	(\$189.0)	
\$0.0	-	\$0.0	
(\$12.9)	-	(\$5.4)	-58.18%
\$20.3	-	\$16.6	-18.26%

Alimera

Statement of Cash Flows
Fiscal year ends Dec 31
Numbers in millions

Operations

Net Income (Loss)
Depreciation / Amortization
Fair value change on preferred
Non-cash R&D expense
Stock-based compensation
Receivables
Inventories
Prepaid Expenses & Other Assets
Accounts Payable & Other Liabilities
Cash by discon. Ops
Increase in non-current financial assets
Net Cash Used by Continuing Ops

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Dec 2008	% chg	Dec 2009	% chg
(\$61.5)	-	(\$44.2)	-
\$0.2	-	\$1.1	355.60%
\$10.5	-	\$23.1	121.37%
\$17.8	-	\$0.3	-98.32%
\$0.8	-	\$0.6	-
\$0.0	-	\$0.0	-
\$0.0	-	\$0.0	-
(\$1.2)	-	\$0.6	-
\$0.6	-	\$0.2	-70.24%
\$0.0	-	\$0.7	-
\$0.1	-	\$0.2	80.00%
(\$32.7)	-	(\$17.5)	-

Investing

Investment in continuing ops
Purchases of Property, Plant & Equipment
Net Cash (Used in) Provided by Investing Activities

(\$0.6)	-	(\$0.1)	-89.84%
\$0.0	-	\$0.0	-
(\$0.6)	-	(\$0.1)	-

Financing

Proceeds from sale of Series C preferred stock
Proceeds from issuance of debt
Principal payments of long-term debt
Repayments on long-term debt
Proceeds from payments of subscription receivable
Proceeds from payments under capital lease
Proceeds from issuance of common stock, net of expenses
Cash from Financing

\$29.9	-	\$4.9	-83.64%
\$0.0	-	\$0.0	-
\$0.0	-	\$0.0	-
\$0.0	-	\$0.0	-
\$0.0	-	\$0.0	-
\$0.0	-	\$0.0	-
(\$0.2)	-	(\$0.3)	-
\$29.8	-	\$4.6	-

Increase (Decrease) in Cash

(\$3.5) - (\$12.9) -

Cash at Beginning of Year

\$20.8 - \$17.9 -14.23%

Cash at End of Year

\$17.9 - **\$4.9** -

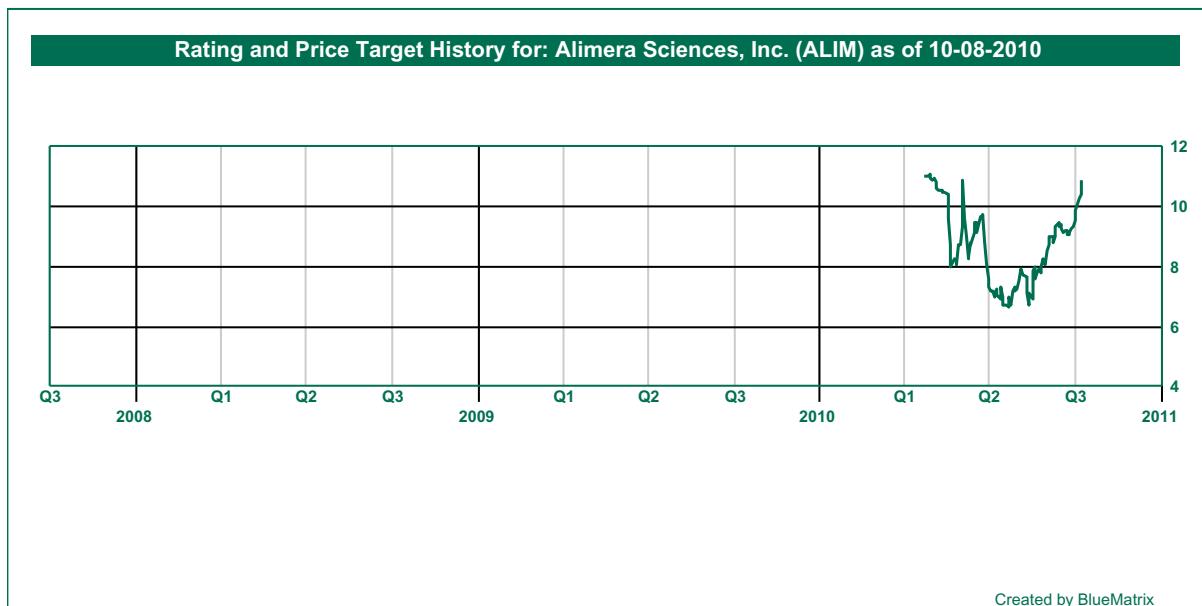
RODMAN & RENSHAW RATING SYSTEM: Rodman & Renshaw employs a three tier rating system for evaluating both the potential return and risk associated with owning common equity shares of rated firms. The expected return of any given equity is measured on a RELATIVE basis of other companies in the same sector, as defined by First Call. The price objective is calculated to estimate the potential movement in price a given equity could achieve given certain targets are met over a defined time horizon. Price objectives are subject to exogenous factors including industry events and market volatility. The risk assessment evaluates the company specific risk and accounts for the following factors, maturity of market, maturity of technology, maturity of firm, cash utilization, and valuation considerations. Potential factors contributing to risk: relatively undefined market, new technologies, immature firm, high cash burn rates, intrinsic value weighted toward future earnings or events.

RETURN ASSESSMENT

- Market Outperform (Buy): The common stock of the company is expected to outperform a passive index comprised of all the common stock of companies within the same sector, as defined by First Call.
- Market Perform (Hold): The common stock of the company is expected to mimic the performance of a passive index comprised of all the common stock of companies within the same sector, as defined by First Call.
- Market Underperform (Sell): The common stock of the company is expected to underperform a passive index comprised of all the common stock of companies within the same sector, as defined by First Call.

RISK ASSESSMENT

- Speculative - The common stock risk level is significantly greater than market risk. The stock price of these equities is exceptionally volatile.
- Aggressive - The common stock risk level is materially higher than market level risk. The stock price is typically more volatile than the general market.
- Moderate - The common stock is moderately risky, or equivalent to stock market risk. The stock price volatility is typically in-line with movements in the general market.



RATING SUMMARY

Rating	Distribution of Ratings Table		IB Serv./Past 12 Mos	
	Count	Percent	Count	Percent
Market Outperform(MO)	165	73.70%	47	28.48%
Market Perform(MP)	49	21.90%	4	8.16%
Market Underperform(MU)	5	2.20%	0	0.00%
Under Review(UR)	5	2.20%	1	20.00%
Total	224	100%	52	100%

Investment Banking Services include, but are not limited to, acting as a manager/co-manager in the underwriting or placement of securities, acting as financial advisor, and/or providing corporate finance or capital markets-related services to a company or one of its affiliates or subsidiaries within the past 12 months.

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