304 Clinical Trials and Drug Studies II
Tuesday, May 09, 2017 8:30 AM–10:15 AM
Ballroom 4 Paper Session
Program #/Board # Range: 2459–2465
Organizing Section: Glaucoma

Program Number: 2459
Presentation Time: 8:30 AM–8:45 AM
Safety and Efficacy of 0.1% Nepafenac versus 1% Prednisolone acetate Eye Drops after Laser Iridotomy - A Prospective, Randomized Trial
kavitha srinivasan[1], Keerthi Gayam[1], Swati Upadhyaya[1], Rengaraj Venkatesh[1], Pradeep Ramulu[2]. [1]Glaucoma, Aravind Eye Hospital, Pondicherry, India; [2]Wilmer Eye Institute, Baltimore, MD.
Purpose: Steroid abuse is very common in developing countries like India because of easy availability and low cost. Here we compared the safety and efficacy of 0.1% Nepafenac, a topical nonsteroidal anti-inflammatory drop, with 1% Prednisolone acetate in controlling inflammation after YAG laser peripheral iridotomy (LPI) in primary angle closure suspects (PACS)
Methods: We randomized 152 PACS aged 40-70 years undergoing bilateral LPI to 0.1% Nepafenac or 1% Prednisolone eye drop in both eyes after LPI. Medications were given 4 times daily for 7 days and then twice daily for an additional 7 days. Investigators and patients were masked to the type of medication issued. Outcome measures were the degree of anterior chamber (AC) cell, flare on slit-lamp biomicroscopy using standardized uveitis nomenclature grading and changes in intraocular pressure (IOP) measured with Goldmann applanation tonometry. Postoperative assessments were completed at 2 and 4 weeks
Results: Study groups were comparable in terms of age, gender, comorbid illness, baseline IOP and total laser energy ($p>0.6$ for all). One patient in Nepafenac group had 1+ cells at 2 wks; at 4 wks eyes were quiet in both groups. Within 2 days of stopping eye drop rebound iritis was seen in 4 patients in Prednisolone group, which subsided at 4 wks with additional medication, but it was not seen with any Nepafenac treated patients ($p=0.037$). IOP differences from baseline to 2 wks were significantly higher in Prednisolone group than the Nepafenac group (+2.8 vs +0.5 mm Hg; $p=0.003$), though at 4 wks IOPs were not significantly different than baseline in either group ($p>0.1$ for both), and did not differ between the 2 groups (+0.56 vs +0.18 mm Hg in Prednisolone and Nepafenac groups respectively, $p=0.499$). By 2 wks 6-15 mm Hg IOP elevation from baseline was seen in 3 subjects in Nepafenac,10 in Prednisolone group ($p=0.075$); 2 in Prednisolone and none in Nepafenac had IOP elevation >15 mm Hg ($p=0.188$). By 4 wks none in either group had IOP elevation >15 mm Hg. Eight subjects in Prednisolone, but none in Nepafenac group needed repeat LPI ($p=0.003$)
Conclusions: Nepafenac is as effective as Prednisolone acetate in controlling post-LPI iritis with less impact on IOP and lesser chances of rebound iritis and iridotomy closure
Commercial Relationships: kavitha srinivasan, None; **Keerthi Gayam**, None; **Swati Upadhyaya**, None; **Rengaraj Venkatesh**, None; **Pradeep Ramulu**, None
Clinical Trial: REF/2016/11/012649

Program Number: 2460
Presentation Time: 8:45 AM–9:00 AM
Ocular Hypotensive Efficacy of Netarsudil Ophthalmic Solution 0.02% Over a 24-Hour Period: A Pilot Study
James H. Peace[1], Casey Kopczynski[2], Theresa G. Heah[3]. [1]United Medical Research Institution, Inglewood, CA; [2]Research and Development, Aerie Pharmaceuticals, Durham, NC; [3]Clinical Research and Medical Affairs, Aerie Pharmaceuticals, Bedminster, NJ.
Purpose: Netarsudil (previously known as AR-13324) is a Rho kinase and norepinephrine transporter inhibitor that appears to lower intraocular pressure (IOP) by increasing outflow through the trabecular meshwork and decreasing episcleral venous pressure. The ocular hypotensive efficacy of netarsudil in subjects with ocular hypertension (OHT) or open-angle glaucoma (OAG) has been demonstrated in multiple studies in which IOP was measured during the diurnal period. Based upon its novel pharmacology, we sought to evaluate its efficacy in nocturnal period relative to the diurnal period.
Methods: This was a pilot, double-masked, randomized, single-center, placebo-controlled study comparing netarsudil ophthalmic solution to its vehicle, dosed once daily in the evening (20:00-22:00). Eligible were subjects with OHT or OAG with unmedicated IOP between 17 and 30 mmHg. After qualification, patients were randomized 2:1 to netarsudil or vehicle and baseline habitual IOP was measured over a 24-hour period. Patients then self-administered the medication for 7 days and returned on day 8 for another 24-hour IOP measurement. The study was planned for 12 patients, and had power to detect a 2.5 mmHg treatment difference.
Results: All 12 patients enrolled completed the study. The study population was established patients, all previously on ocular hypotensive therapy, and was 50% female, with a mean age of 64.4 ± 8.6 years, 75% black, and 17% Hispanic. Mean baseline IOPs were similar for the netarsudil and vehicle groups and ranged from 21.0 to 24.8 mmHg, with the highest IOPs recorded from midnight to 06:00 hours. After 7 days of dosing, netarsudil achieved statistically significant reductions in mean IOP of 2.6 to 5.0 mmHg across the 8 measured time points ($p < 0.01$ to < 0.001). Mean diurnal IOP (09:00 to 18:00 hours) and mean nocturnal IOP (21:00 to 06:00 hours) were reduced by 3.5 mmHg and 3.5 mmHg, respectively, for netarsudil compared to 0.4 mmHg and 0.9 mmHg, respectively, for vehicle. There were no safety issues reported.
Conclusions: In patients with OAG or OHT, once-nightly netarsudil ophthalmic solution 0.02% had ocular hypotensive activity throughout 24 hours and was equally effective at lowering IOP in the nocturnal and diurnal periods. There were no safety issues.
Commercial Relationships: James H. Peace, Aerie Pharmaceuticals (C), Alcon (C), Allergan (C); **Casey Kopczynski**, Aerie Pharmaceuticals (E); **Theresa G. Heah**, Aerie Pharmaceuticals (E)
Clinical Trial: NCT02874846

Program Number: 2461
Presentation Time: 9:00 AM–9:15 AM
A double-masked, randomized, parallel study of Netarsudil Ophthalmic Solution, 0.02% QD compared to timolol maleate ophthalmic solution, 0.5% BID in patients with elevated intraocular pressure (ROCKET-4)
Albert S. Khouri[1], Theresa Heah[2], Casey Kopczynski[3], Gary D. Novack[3, 4]. [1]Ophthalmology, Rutgers - New Jersey Med Sch, Newark, NJ; [2]Aerie Pharmaceuticals, Inc, Bedmnister, NJ; [3]PharmaLogic Development, Inc, San Rafael, CA; [4]Departments of Ophthalmology and Pharmacology, University of California, Davis, CA.

Purpose: Netarsudil is a Rho kinase and norepinephrine transporter inhibitor that appears to lower intraocular pressure (IOP) by enhancing trabecular outflow and reducing episcleral venous pressure (Kiel and Kopczynski, 2015; Wang et al, 2015). In controlled trials, once-daily netarsudil 0.02% has demonstrated effectiveness at lowering IOP in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) (Bacharach et al, 2015; Lewis et al, 2016; Katz et al, 2016). The objective of this study was to further evaluate the efficacy and safety of netarsudil relative to timolol.
Methods: This was a double-masked, randomized, parallel-group trial in subjects with OAG or OHT treated with netarsudil 0.02% QD or timolol 0.5% BID. Subjects had unmedicated IOP >20 mmHg and < 30 mmHg at 08:00 hr, and > 17 mmHg and < 30 mmHg at 10:00 and 16:00 hrs. Subjects with contraindications to timolol were excluded. The primary efficacy endpoint was non-inferiority to timolol in the per-protocol population with baseline IOP < 25 mm Hg. Reported here is a planned 3-month interim analysis.
Results: Enrolled were 708 subjects, of which 423 were in the primary efficacy population. Completing 3 months were 88% (189/214) and 95% (199/209) of subjects in the netarsudil and timolol groups, respectively. Mean IOP at baseline visits was similar among the treatment groups, ranging from 20.7 to 22.4 mmHg. Over the 3-month treatment period, netarsudil demonstrated non-inferiority to timolol across all time points, with mean IOP ranging from 16.3 to 17.8 mmHg for netarsudil and 16.7 to 17.6 for timolol. In a pre-specified analysis, netarsudil also demonstrated non-inferiority in subjects with baseline IOP < 28 mmHg. The most frequent adverse event was conjunctival hyperemia, which was reported in 148 subjects (42.2%) in the netarsudil group and 24 (6.7%) in the timolol group. When present, conjunctival hyperemia was predominately of mild (117/148) or moderate severity (29/148). No drug-related systemic adverse events were reported for netarsudil.
Conclusions: Once-daily netarsudil was non-inferior to twice-daily timolol in patients with baseline IOP < 25 mm Hg (primary) and patients with baseline IOP < 28 mmHg (secondary). Mild conjunctival hyperemia was the most frequent adverse event.
Commercial Relationships: Albert S. Khouri, Allergan (S), Glaukos (S), NJ Health Foundation (F), Alcon (S), Aerie Pharmaceuticals, Inc (F), Allergan (F); **Theresa Heah**, Aerie Pharmaceuticals, Inc. (I), Aerie Pharmaceuticals, Inc (E); **Casey Kopczynski**, Aerie Pharmaceuticals, Inc. (I), Aerie Pharmaceuticals, Inc (E); **Gary D. Novack**, Aerie Pharmaceuticals, Inc (C)
Support: Aerie Pharmaceuticals, Inc
Clinical Trial: NCT02558374

Program Number: 2462
Presentation Time: 9:15 AM–9:30 AM
3-month Interim Report of a Prospective 12-month Safety and Efficacy Study of Topical PG324 (Fixed Combination of Netarsudil 0.02% and Latanoprost 0.005%) Compared to the Individual Components in Subjects with Elevated Intraocular Pressure
Janet B. Serle[1], Richard A. Lewis[3, 2], Casey Kopczynski[2], Theresa Heah[2]. [1]Ophthalmology, Mount Sinai School of Medicine, New York, NY; [2]Aerie, Bedminster, NJ; [3]Sacramento Eye Consultants, Sacramento, CA.
Purpose: To assess the safety and efficacy of a fixed-dose combination of netarsudil 0.02% and latanoprost 0.005% (PG324) to its components in patients with elevated IOP.
Methods: A double-masked, active-controlled, parallel, randomized study in patients with open-angle glaucoma or ocular hypertension with unmedicated IOP (mmHg) >20 and <36 at 08:00 hours and >17 and <36 at 10:00 and 16:00 hours. Patients were dosed QD (PM) with PG324, netarsudil or latanoprost for 12 months. IOP was measured at 08:00, 10:00 and 16:00 hours at week 2, week 6 and month 3. Ocular and systemic side effects were collected, a 0 to 3 grading scale was used to assess hyperemia. Statistical analysis was performed using SAS Version 9.2 or higher.
Results: Enrolled were 718 patients of which 85% (201/238), 82% (201/244) and 95% (223/236) completed three months of dosing in the PG324, netarsudil and latanoprost groups, respectively. Mean baseline IOP was similar across the groups and ranged from 22.4 to 24.8 mm Hg. Mean treated IOPs ranged from 14.8 to 16.0 mm Hg, 17.2 to 19.0 mm Hg and 16.7 to 17.8 mm Hg, respectively, with PG324 IOP reductions achieving statistical superiority to netarsudil and latanoprost at all 9 time points across the Week 2, Week 6 and Month 3 visits ($p < 0.0001$). Mean IOP reductions in the PG324 group were 1.8 to 3.0 mm Hg greater than in the netarsudil group, and 1.3 to 2.5 mm Hg greater than in the latanoprost group. At Month 3, 44% of PG324 subjects achieved mean diurnal IOPs of ≤15 mm Hg compared to 23% and 25% of netarsudil and latanoprost subjects, respectively ($p < 0.0001$). The most frequent adverse events were conjunctival hyperemia (53%, 41% and 14%, respectively) and conjunctival hemorrhage (11%, 14% and 0.4%, respectively), which were of mild severity and sporadic frequency for the majority of subjects. There were no drug-related serious or systemic adverse events.
Conclusions: The fixed dose combination of PG324 provided clinically and statistically significantly greater ocular hypotensive efficacy than its individual components, netarsudil and latanoprost. The safety profile of PG324 was similar to that of netarsudil alone. This fixed dose combination addresses the issues of patient compliance and enhanced ocular hypotensive efficacy.
Commercial Relationships: Janet B. Serle, Aerie (I), Aerie (C), Richter (C), Bausch & Lomb (C); **Richard A. Lewis**, Aerie (E); **Casey Kopczynski**, Aerie (E); **Theresa Heah**, Aerie (E)
Clinical Trial: NCT02558400

Program Number: 2463
Presentation Time: 9:30 AM–9:45 AM
West Indies Glaucoma Laser Study: 12-Month Efficacy of Selective Laser Trabeculoplasty (SLT) in Afro-Caribbeans with Glaucoma
Tony Realini[1], Hazel Shillingford-Ricketts[2], Darra Burt[3]. [1]Ophthalmology, West Virginia University, Morgantown, WV; [2]Harlsbro Medical Center, Roseau, Dominica; [3]Eye Care Saint Lucia, Castries, Saint Lucia.
Purpose: To characterize the 12-month IOP-lowering efficacy of SLT when used as sole therapy for the management of primary open-angle glaucoma (POAG) in an Afro-Caribbean population.
Methods: Subjects with established POAG based on optic nerve and visual field damage were recruited from St. Lucia and Dominica and randomized to 1 of 3 groups: prompt washout followed by SLT; 3-month delay followed by washout and SLT; or 6-month delay followed by washout and SLT. The latter 2 groups continued current medical therapy for 3 or 6 months, respectively, between randomization and washout. Baseline IOP was the mean of values obtained on 2 different days after a 4-6 week washout of all IOP-lowering medications. Bilateral 360-degree SLT was performed in 1 session. Post-treatment assessments took place 1 hour, 1 week, and 3, 6, 9, and 12 months. IOP was measured twice at each visit with a Perkins tonometer using a modified OHTS protocol by an operator masked to target IOP. Target IOP was a ≥20% reduction in IOP from post-washout baseline. Failure occurred when IOP was above target on 2 consecutive assessments and was followed by retreatment.

Results: 78 subjects were randomized and 72 underwent treatment (1 had low washout IOP, 5 withdrew consent before treatment). Mean IOP at enrollment was 15.3 ± 3.5 mmHg and 15.3 ± 3.6 mmHg in right and left eyes, which rose to 20.9 ± 3.4 mmHg and 20.7 ± 3.1 mmHg, respectively, after washout. Mean IOP at 3, 6, 9 and 12 months ranged from 12.5 mmHg to 14.6 mmHg ($p<0.0001$ in each eye at each time point), representing IOP reductions from post-washout baseline ranging from 29.2% to 39.6%. IOP in the delayed treatment groups were unchanged between randomization and washout ($p=0.08$), ruling out regression to the mean as an explanation for the observed post-SLT IOP reductions. Survival analysis revealed a 78% survival rate (IOP at or below target in both eyes) at 12 months following initial SLT. Considering those who failed initial SLT and underwent retreatment, the 12-month survival rate for one or more SLT treatments rose to 97%. Common side effects included transient photophobia and discomfort.
Conclusions: SLT safely provides significant IOP reduction when used as monotherapy in Afro-Caribbean eyes with POAG. SLT can play a significant role in preventing glaucoma vision loss and blindness in people of African Descent living in resource-limited regions.
Commercial Relationships: Tony Realini, Inotek (C), Alcon (F), Bausch & Lomb (C), Aerie (F), Alcon (C);
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Program Number: 2464
Presentation Time: 9:45 AM–10:00 AM
Risk factors for glaucoma progression in the United Kingdom Glaucoma Treatment Study (UKGTS)
Panayiota Founti[1], Ana Quartilho[1], Catey V. Bunce[1, 2], Caroline J. Dore[1, 3], Jibran Mohamed-Noriega[1, 4], David Garway-Heath[1]. [1]National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom; [2]Department of Primary Care & Public Health Sciences, King's College London, London School of Hygiene & Tropical Medicine, London, United Kingdom; [3]Comprehensive Clinical Trials Unit, University College London, London, United Kingdom; [4]Departamento de Oftalmología, Hospital Universitario, UANL, México, Monterrey, Mexico.
Purpose: To identify factors associated with visual field (VF) deterioration in the United Kingdom Glaucoma Treatment Study (UKGTS).
Methods: The UKGTS is the first randomised, double-masked, placebo-controlled, multicentre trial on the visual field (VF) preserving effect of medical treatment in open-angle glaucoma (OAG). Five hundred sixteen participants with previously untreated OAG were randomized to either latanoprost 0.005% or placebo. Eligibility criteria were modeled on those for the Early Manifest Glaucoma Trial. The observation period was 2 years, with subjects monitored by VF testing, among other procedures, at 11 visits. VF deterioration was based on the Guided Progression Analysis pattern deviation maps. Frailty models (extension of the Cox proportional model) were fitted to compute the hazard ratios (HRs) and respective 95% confidence intervals (CIs) for time to progression whilst accounting for the correlation within sites. Model selection was guided by backwards stepwise selection conducted on the model containing all variables which were significant at the 0.2 level in the univariable analysis.
Results: Treatment with latanoprost reduced the HR for VF deterioration by 54% (HR, 0.46; 95% CI, 0.30-0.73, $p=0.001$). Progression factors were higher baseline mean intraocular pressure (HR, 1.05 per mmHg; 95% CI, 1.004-1.106, $p=0.03$) and disk haemorrhage at any visit (HR, 1.68; 95% CI, 1.09-2.60, $p=0.02$). Smoking (current or previous) was associated with reduced HR for VF deterioration (HR, 0.63; 95% CI, 0.41-0.98, $p=0.04$). No other factors were found to be statistically significant in the multivariable analysis.
Conclusions: In the UKGTS, treatment with latanoprost halved progression risk. Previously reported progression factors for OAG were incorporated in the model, and only disc haemorrhage and baseline intraocular pressure were confirmed. The association of smoking history requires further exploration to assess for potential confounding.

Multivariable model fitting study site as a random effect

Variables	Hazard Ratio (95% CI)	P-value
Treatment assignment (latanoprost vs placebo)	0.46 (0.30-0.73)	0.001
Baseline GAT Mean IOP (mmHg)	1.05 (1.004-1.106)	0.03
Corneal hysteresis (mmHg)	0.92 (0.82-1.03)	0.16
Refractive Error (dioptres)	1.05 (0.98-1.13)	0.18
Disk Haemorrhage (any eye, any visit) (yes vs no)	1.68 (1.09-2.60)	0.02
Both eyes eligible (yes vs no)	1.48 (0.96-2.28)	0.07
History of Heart Attack (yes vs no)	0.24 (0.03-1.78)	0.16
Current or previous smoking (yes vs no)	0.63 (0.41-0.98)	0.04

Commercial Relationships: Panayiota Founti; **Ana Quartilho**, None; **Catey V. Bunce**, None; **Caroline J. Dore**, None;
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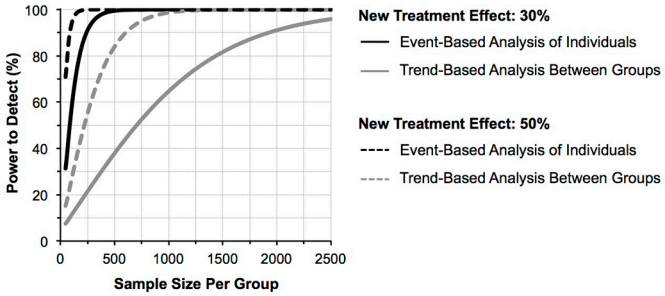
Clinical Trial: ISRCTN96423140

Program Number: 2465
Presentation Time: 10:00 AM–10:15 AM
Improving the Feasibility of Glaucoma Clinical Trials With Trend-Based Analysis of Visual Field Change Between Groups as an Endpoint
Zhichao Wu[1, 5], Balwantray C. Chauhan[2], David Garway-Heath[3], David P. Crabb[4], Jonathan Crowston[5], Felipe Medeiros[1]. [1]Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego, La Jolla, CA; [2]Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada; [3]National Institute for Health Research Biomedical Research Centre, Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, United Kingdom; [4]Optometry and Visual Science, City University London, London, United Kingdom; [5]Centre for Eye Research Australia, Royal Victoria Eye and Ear Hospital, The University of Melbourne, East Melbourne, VIC, Australia.
Purpose: As glaucoma is often a slowly progressive disease, there have been concerns about the feasibility of short-term clinical trials evaluating new treatments for this disease, as the required sample size could be prohibitively large. The United Kingdom Glaucoma Treatment Study has shown that differences between a new treatment and placebo can be demonstrated with relatively short follow-up. However, as the effect size between new and existing treatments are likely smaller, a correspondingly larger sample size for short-term trials would be required. This study sought to determine the required sample size for such short-term trials using visual field event-based endpoints, and whether it can be reduced using trend-based analysis.
Methods: Sample sizes were determined by running computer simulations reconstructing 24-2 visual field results over time, after

extracting real-world estimates of point-wise variability according to different threshold levels and rates of change from a cohort of 321 eyes of 240 glaucoma participants followed under routine clinical care for a mean of 10 years. “Real-world” visual fields were reconstructed in a similar manner described by Russell et al (PLoS ONE, 2013). A clinical trial lasting 2 years with testing every 3 months was simulated, assuming that the new treatment halted visual field change in various percentages of participants (or “responders”). Treatment efficacy was evaluated by: a) Difference in the incidence of point-wise event-based progression (similar to the commercially available Guided Progression Analysis) and b) Difference in rate of visual field mean deviation (MD) change between groups using linear mixed models.

Results: To detect the effect of a new treatment that halted progression in 30% of the participants under routine clinical care (equal to a 30% reduction in MD rate of change) with 90% power for example, 1924 participants would be required per group using event-based analysis, but only 240 participants per group if linear mixed models were used. A plot of the power to detect against the sample size in each group is shown in the Figure (grey and black respectively for the two methods).

Conclusions: Feasibility of future glaucoma clinical trials can be substantially improved by evaluating differences in the rate of visual field change between groups.



Commercial Relationships: Zhichao Wu, None; **Balwantray C. Chauhan**, None; **David Garway-Heath**, None; **David P. Crabb**, None; **Jonathan Crowston**, None; **Felipe Medeiros**, Novartis (C), Heidelberg Engineering (F), Reichert (C), Allergan (F), Reichert (F), Carl Zeiss Meditec (F), National Eye Institute (F), Topcon (F), Alcon (F), Valeant Pharmaceutical (C), Optovue (F), Bausch & Lomb (F), Allergan (C), Carl Zeiss Meditec (C)

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