Hemorrhages on the optic nerve head and in the nailfold capillary bed characterize primary open-angle glaucoma (POAG). Exactly why hemorrhages occur and the wherefore of hemorrhages is enigmatic. Recent studies of patients with Alzheimer’s disease, Alzheimer’s disease.

Methods: Blood samples from age-matched control (n=3), POAG (n=3), and normal tension glaucoma (NTG; n=3) patients were obtained in acid citrate dextrone tubes; platelet rich plasma was isolated by centrifugation. Platelets were labeled with anti-CD41-PE (platelet glycoprotein IIb, alpha 2b integrin) and anti-PAC1-FITC (recognizes an activated glycoprotein IIb/IIIa epitope) and challenged with two agonists: thrombin (via protease-activated receptors [PARs]) and convulxin (via activation of glycoprotein VI receptor). Superactivated platelets are identified by the inability to bind PAC1, because its target receptor is tightly bound by fibrinogen, and phosphatidylserine exposure. After 10 minutes of incubation at 37°C the platelets were fixed with 1.5% formalin and analyzed on a Beckman Coulter Cyan ADP flow cytometer.

Results: Platelets from controls, POAG, and NTG were challenged with agonists and characterized by forward scatter and PAC1-FITC intensity. In this initial study, notably, POAG patients contained 59.4% superactivated platelets which was highly significant (P<0.001) compared to controls (29.1%). Although NTG patients displayed lower levels of super activated platelets (31.3%), this was not statistically significant when compared to POAG patients.

Conclusions: Conceivably, platelets of POAG patients are intrinsically “primed” and readily activated by agonists compared to controls. Platelet hypercoagulability may represent an etiological factor in optic nerve hemorrhages, provide a new therapeutic target, and establish a final common pathway in vascular diseases, including Alzheimer’s disease.

Commercial Relationships: Paulius V. Kuprys, None; Sean Forte, None; Christopher Wanderling, None; Loyal Walker, None; Algis Grybauskas, None; John R. Samples, None; Zibute Zaparackas, None; Beatrice Yue, None; Paul A. Knepper, None

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Program Number: 532 Poster Board Number: A0168
Presentation Time: 1:30 PM–3:15 PM

Agonistic β2-Adrenergic Receptor Autoantibodies in Ocular Hypertension and Open-Angle Glaucoma.
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Purpose: Agonistic Autoantibodies (AAB) against G protein coupled receptors (GPCR) are found in several human diseases (e. g. Asthma, arterial hypertension). β2-adrenergic receptors are involved in the regulation of aqueous humor dynamics. The aim of this study was to investigate the distribution of agonistic β2-adrenergic receptor autoantibodies (β2-AABs) in glaucoma suspects and glaucoma patients.

Methods: 92 probands were included (25 normals, 32 OHTs, 12 pre-perimetric POAGs, 23 POAGs; Erlangen Glaucoma Registry, ISSN 2191-5008, CS-2011; NTC00494923). All patients underwent complete ophthalmological examinations including examinations with Octopus G1 program. Serums probes of all patients were analyzed of β2-AABs using a bioassay (1). In this assay the alteration of the beating rate of spontaneously beating cultured neonatal rat cardiomyocytes, expressing GPCR, due to the applied serum level of AABs, is counted. Statistical analysis was done using non-parametric U-Test. The protocol was approved by the local Ethics Committee (3457).

Results: All normal showed β2-AAB levels lower than < 2 beats/ min. Using this cutoff point, patient groups showed significant percentage of β2-AABs (69% OHT, p<0.001; 78% POAG, p<0.001). β2-AAB levels revealed no significant differences (Kruskal–Wallis-
A Correlation Between Primary Open Angle Glaucoma and Renal Function

1University of Missouri Kansas City, Kansas City, MO; 2Ophthalmology, Cook County Health and Hospital Systems, Chicago, IL; 3Ophthalmology, Loyola University, Maywood, IL.

Purpose: To evaluate the relationship between renal function (serum BUN/Cr levels) in patients with primary open angle glaucoma (POAG) versus those without.

Methods: A retrospective chart review was done in order to determine the correlation between serum BUN/Cr levels and primary open angle glaucoma in patients seen at John H. Stroger Jr. Hospital of Cook County in Chicago, IL. Consecutive patient charts were reviewed retrospectively on 200 patients in each group. Exclusion criteria were ages younger than 50, no BUN/Cr levels within the last two years, or any other type of glaucoma or ocular hypertension. Patients that met these criteria were categorized as either control or POAG. The mean ages and BUN/Cr levels were determined for each group.

Results: The mean age of the control group (n=203) was 61.9 with the mean serum BUN/Cr ratio of 18.14. The mean age in the POAG group (n=189) was 66.8 with the mean serum BUN/Cr level of 16.88. Therefore the difference in mean BUN/Cr ratio was 1.26. An unpaired two-tailed T test was used to calculate the p-value, which was statistically significant with a p-value of 0.0059.

Conclusions: A correlation between renal function and POAG did exist. Our previous studies found an association between the serum electrolyte levels (Na+, K+, Cl, and Ca2+) and the prevalence of primary open angle glaucoma. The kidneys are vital organs in regulating total body electrolyte levels. This study found a correlation between renal function and POAG. Hydrogen ions are key in aqueous humor formation via active sodium transportation across the non-pigmented epithelium. Carbonic anhydrase inhibitors stop the conversion of water and CO2 into bicarbonate and hydrogen ions to reduce aqueous humor formation. These medications are often cautioned in patients with poor renal function. With this information, a patient’s renal function may have a role in aqueous humor formation and POAG.

References:
Patel K, Dworak D, Patrianakos T. Correlation of Serum Calcium Levels to Primary Open Angle Glaucoma. Abstract and Poster.
Correlation of Measures among the Time Points across Visits

Dale W. Usner, Richard Abelson.

Purpose: A general strategy for showing non-inferiority of a test product, to an existing approved product, is to demonstrate the following efficacy criteria: the upper limit of a 95% confidence interval (CI) around the difference in IOP: test product - approved product is:

a) \(< 1.5 \text{ mm Hg at all defined time points}\)
b) \(< 1.0 \text{ mm Hg at a majority of time points}\)

Historically, 1) the correlation among time points within a subject/eye and 2) the requirement of a majority of time points having an upper 95% CI \(< 1 \text{ mm Hg}\) have not been overly used when determining sample size and power. We propose a method to account for both of these points.

Methods: Multivariate normal distributions with varying assumptions around the sample size, mean differences, variances, and correlations were used; where correlations ranged from 40% to 70% as estimated from historic data. 500,000 random samples were created and 95% CIs calculated. Power was calculated as the proportion of random samples showing the upper limit of the 95% CI \(< 1.5 \text{ mm Hg}\), with a majority \(< 1.0 \text{ mm Hg}\).

Results: Power calculations from common methods either over estimate the required sample size (calculations assuming all 95% CIs must be \(< 1.0 \text{ mm Hg}\)) or under estimate the required sample size (calculations assuming only that all 95% CIs \(< 1.5 \text{ mm Hg}\)). The amount of the over estimation and under estimation depend on the assumed correlation among time points; the higher the correlation the less the over estimation and the more the under estimation of sample size.

Conclusions: When determining power and sample size for primary open angle glaucoma / ocular hypertension clinical trials, neglecting to account for the complete efficacy criteria and the correlation among time points will result in the trial requiring too many subjects/eyes or having too low power.

Commercial Relationships: Dale W. Usner, Statistics and Data Corporation (E); Richard Abelson, Statistics and Data Corporation (E)

Usability of Glaucoma Medication Eye Droppers

Thomas E. Drew, James S. Wolfsohn. Life and Health Sciences, Aston University, Birmingham, United Kingdom.

Purpose: To determine the force needed to extract a drop from a range of current glaucoma medication eye droppers and how this related to the comfortable and maximum pressure patients could exert.

Methods: The comfortable and maximum pressure patients could apply to an eye dropper (vial or unit-dose (UD)) constructed around a set of cantilevered pressure sensors (Richmond Industries, UK) and mounted above the patients eye was assessed in 40 patients aged 19-85 years repeated 3 times. A load cell amplifier (Richmond Industries, UK) mounted on a stepper motor controlled linear slide (Trinamic GmbH, Germany; Gecckodrive Inc., USA) was constructed to test the force required to extract the first 6 drops from glaucoma medication eye dropper: 4 generics latanoprost (50 μg/ml) vials of 2.5 ml, preservative free bimatoprost (0.3mg/ml) 0.4 ml UD, preservative free tafluprost (15 μg/ml) 0.3ml UD, travoprost (0.004% 40 μg/ml) vial of 2.5 ml, latanoprost (0.005%) vial of 2.5ml, bimatoprost 0.1mg/ml vial of 3ml, bimatoprost 0.3mg/ml vial of 3ml and preservative free latanoprost (50μg/ml) 0.2ml UD.

Results: The pressure that could be exerted on a dropper comfortably (30.8 ± 17.0 newtons, range 7.3 to 85.6) could be exceeded with effort (to 62.9 ± 25.6 newtons, range 33.2 to 130.9), but did not differ between repeats (ANOVA F = 2.178, p = 0.120). Comfortable and maximum pressure exerted were correlated (r = 0.769, p < 0.001), but neither were influenced strongly by age (r = 0.084, p = 0.605; r = -0.113, p = 0.489 respectively). The force needed to exert successive drops from each individual dropper design did not alter (F = 0.662, p = 0.447), but this did differ between dropper designs (F = 26.882, p < 0.001) with the force required ranging from 6.7 to 24.3 newtons. Preservative free latanoprost 50 μg/ml 0.2ml UD and latanoprost 0.005% vial of 2.5ml required significantly less force applied to exert a drop than the other eye droppers (p < 0.001).

Conclusions: Glaucoma medication droppers vary in their resistance to extract a drop and this could only be comfortably achieved by all patients with preservative free latanoprost 50 μg/ml 0.2ml UD and latanoprost 0.005% 2.5ml vial. Patients would struggle with other dropper designs and this may affect compliance and efficacy.

Commercial Relationships: Thomas E. Drew, None; James S. Wolfsohn, Thea (F)

Support: Thea Grant
Medication Utilization Analysis of Factors Affecting Nonadherence in Glaucoma

**Purpose:** The purpose of this study was to evaluate the influences of systemic disease burden and gender in long-term glaucoma medication utilization. Identification of such patients would be key to implement greater adherence measures. Socio-medical reasons may account for lower refill rates in men, but exact factors have not been elucidated. Self-reported adherence did not correlate with refill rates in this study; highlighting the requirement of objective measures to identify those at risk. This study indicates the need for a larger population study to further evaluate the influences of systemic disease burden and gender in glaucoma medication utilization.

**Commercial Relationships:** Morgan L. Pansegrau, None; Matthew Petroll, None; Inci Dersu, None

**Support:** Pat Walker Research Fund, Jones Eye Institute, University of Arkansas for Medical Sciences. Research to Prevent Blindness.

**Program Number:** 538 Poster Board Number: A0174

**Presentation Time:** 1:30 PM–3:15 PM

**Glaucma Research on Adherence to Fixed Combination Eye drops in Japan (GRACE study) : A First Report**

Toyoaki Tsumura1, 2, Yasuyuki Suzuki1, Kenji Kashiwagi1, Keiji Yoshikawa4, Hirotaka Suzumura2, Toshine Maeda3, Ryuji Takeda, Hitomi Saito8, Makoto Arai8.

1Fussa Hospital, Fussa, Japan; 2Department of Ophthalmology, University of Yamanashi, Chuo, Japan; 3Department of Ophthalmology, Tokai University Hachioji Hospital, Hachioji, Japan; 4Yoshikawa eye clinic, Machida, Japan; 5Suzumura eye clinic, Nakano, Japan; 6Maeda eye clinic, Shibuya, Japan; 7Fussa Hospital, Fussa, Japan; 8Kanto Central Hospital of The Mutual Aid Association of Public School, Setagaya, Japan.

**Purpose:** To analyze factors affecting glaucoma treatment adherence in Japanese glaucoma patients.

**Methods:** GRACE study was conducted in over 1000 institutions across Japan during June 2011 and July 2012. Subjects were primary open angle glaucoma (POAG), normal tension glaucoma (NTG), ocular hypertension (OHI) and pseudoxfoliation glaucoma (PEG) patients already undergoing eye drop treatment who received an additional prescription of fixed combination glaucoma eye drop.
for the first time. The treating physician and the patient were both requested to reply to a questionnaire on treatment adherence before, 1 month after and 6 months after prescription of fixed combination medication. Factors related to glaucoma treatment adherence at the time of the enrollment were identified using logistic regression analysis.

**Results:** Questionnaires were retrieved from 4592 patients (2122 males and 2470 females). One thousand and seventy-two institutions and 1372 physicians participated in the study. Valid replies were obtained from 3853 (83.9%), 3786 (82.4%) and 3054 (66.5%) patients before, 1 month and 6 months after prescription respectively. The mean age and male/female ratio of the 3853 patients included in the study was 68.5±12.2 years and 1794/2059, and 1991 were POAG, 1465 were NTG, 239 were OH and 158 were PEG patients. The number of prescribed eye drops was reduced after prescription of fixed combination medication (1.93±0.78 vs. 1.34±0.54, (P<0.0001). Factors related to glaucoma treatment adherence at the time of the enrollment were older age (Odds ratio (OR) 0.9848, p<0.0001), female gender (OR 0.1084, P=0.0055), fewer numbers of prescribed eye drops (OR:0.7561, p<0.0151). Agreement of adherence evaluation between the treating physician and the patient was 82.8%, and gender (P<0.0001) was the only factor related to the degree of agreement.

**Conclusions:** Questionnaire results on glaucoma treatment adherence revealed a higher rate of adherence in Japanese glaucoma patients compared to previous reports from other countries. Age, gender and number of prescribed eye drops had a significant effect on glaucoma treatment adherence at the time of the enrollment and gender was related to agreement of adherence evaluation between the treating physician and the patient.

**Commercial Relationships:** Toyoaki Tsumura, Alcon (R), MSD (R), Pfizer (F), Pfizer (R), Senju (R); Yasuyuki Suzuki, Alcon (R), MSD (R), Pfizer (R), Santen (R); Kenji Kashiwagi, None; Keiji Yoshikawa, Alcon (R), MSD (R), Pfizer (F), Pfizer (R), Santen (R), Senju (R); Hirota K Sazumura, Alcon (R), Pfizer (R), Santen (R), Senju (R); Toshie Maeda, None; Ryuj I Takeda, None; Hitomi Saito, Pfizer (R), Senju (R), Topcon (R); Makoto Araie, Alcon (C), Alcon (R), Allergan (C), Bausch & Lomb (C), Bausch & Lomb (R), Carl Zeiss-Meditec (R), Kowa (C), Kowa (R), MSD (R), Nitten (R), Otsuka (R), Pfizer (C), Pfizer (R), Santen (R), Senju (C), Senju (R), Topcon (C)

**Program Number:** 540 Poster Board Number: A0176

**Presentation Time:** 1:30 PM–3:15 PM

**Patient Adherence and Persistence with Topical Bimatoprost® 0.01% and Bimatoprost® 0.03%: an Analysis of Latanoprost Switchers**

Jonathan W. Kowalski¹, Joanna Campbell¹, Gail F. Schwartz², ³, Britni LaBounty⁴. ¹Global Health Outcomes Strategy & Res., Allergan Inc, Irvine, CA; ²Greater Baltimore Medical Center, Baltimore, MD; ³Wilmer Eye Institute, John Hopkins University, Baltimore, MD; ⁴Principled Strategies Inc., Encinitas, CA.

**Purpose:** To compare real-world adherence and persistence with bimatoprost 0.01% and bimatoprost 0.03% ophthalmic solutions in patients switching from branded latanoprost.

**Methods:** Patients receiving a first (index) prescription for bimatoprost 0.01% or 0.03% eye drops during April to June 2011 after previous treatment with branded latanoprost were identified from a longitudinal database (Source® Lx) of medical and pharmacy claims for ≥115 million patients. Treatment persistence was assessed over the first 12 months post-index using Kaplan-Meier survival analyses, assuming a 30-day grace period for prescription refill. The proportion of patients ‘on therapy’ (continuous users plus treatment restarters) was determined at 12 months. Treatment adherence was expressed as the proportion of days covered (PDC) with drug supply in the first 12 months, and as the proportion of patients with PDC >0.80. Sensitivity analyses explored the effects of varying the prescription refill gap.

**Results:** In total, 2,464 patients were included in the persistence analysis and 2,037 patients were included in the adherence analysis. Significantly more patients showed continuous 12-month treatment with bimatoprost 0.01% vs bimatoprost 0.03% [39.8% (95% CI 37.5-42.2%) vs 23.8% (95% CI 20.8-27.3%), p<0.001]. At 12 months the proportion of patients ‘on therapy’ was significantly higher in the bimatoprost 0.01% than the bimatoprost 0.03% group (61.7% vs 42.6%, p<0.001). The persistence advantage with bimatoprost 0.01% vs 0.03% was maintained at refill gaps of 15-60 days. Adherence was significantly higher with bimatoprost 0.01% than with bimatoprost 0.03% (mean PDC 0.62 vs 0.51, p<0.001), and more patients showed optimal adherence (PDC > 0.80) with bimatoprost 0.01% than with bimatoprost 0.03% (38.6% vs 25.0%, p<0.001).

**Conclusions:** A previous pharmacy claims analysis reported greater adherence and persistence with bimatoprost 0.01% vs 0.03% in ocular hypertensive patients naïve to prostaglandin/prostamide analog therapy.¹ This study supports and extends the previous research, demonstrating greater adherence and persistence with bimatoprost 0.01% than with bimatoprost 0.03% in patients switching from branded latanoprost. Sensitivity analyses using a range of refill gap assumptions support the robustness of the observed results.


**Commercial Relationships:** Jonathan W. Kowalski, Allergan, Inc. (E); Joanna Campbell, Allergan, Inc. (E); Gail F. Schwartz, Allergan, Inc. (C), Allergan, Inc. (F), Allergan, Inc. (R), Tissue Bank International (R); Britni LaBounty, Principled Strategies, Inc. (C)

**Support:** Allergan, Inc.

**Program Number:** 541 Poster Board Number: A0177

**Presentation Time:** 1:30 PM–3:15 PM

**Practice Preferences in the Management of Uveitic Glaucoma**

Ardalan Aminlari¹, Ingrid U. Scott², George C. Papachristou³, Christine Callahan⁴, Ahmad Aref⁵. ¹Ophthalmology, Penn State Hershey Eye Center, Hershey, PA; ²Ophthalmology, Illinois Eye and Ear Infirmary, Chicago, IL.

**Purpose:** This study was undertaken to ascertain practice preferences of members of the American Glaucoma Society (AGS) regarding the treatment of uveitic glaucoma. With such information, rational approaches to the management of uveitic glaucoma can be planned.

**Methods:** An anonymous survey using multiple-choice questions was constructed on www.surveymonkey.com. An email containing an explanation of the study and the survey link was sent to members of the American Glaucoma Society (AGS). Basic demographic information and practice characteristics were collected. Respondents were asked questions pertaining to their management of uveitic glaucoma, such as their preferred initial treatment of choice, surgical techniques, use of prostaglandin analogs, and changes to management if the patient were a child.

**Results:** The survey was completed by 155 of 960 AGS members for a response rate of 16.1%. 73% of respondents use a beta-blocker as first line intraocular pressure lowering therapy. A majority use prostaglandin analogs in patients with active inflammation (78%) and in patients without active inflammation (95%). 60% of respondents reported that their first line surgical choice in active inflammation is a valved implant, and 33% would use a smaller implant than they would typically use. First line surgery in patients without active inflammation is trabeculectomy with an antifibrotic (37%), valved implant (25%), or...
non-valved implant (20%). Preoperative (38.4%) and postoperative oral steroids (41.7%) are the most commonly used adjuncts to surgery. Most respondents (62%) reported they would not change their management if the patient is a child.

**Conclusions:** The majority of respondents use a topical beta-blocker as first line IOP-lowering therapy for patients with uveitic glaucoma. When additional treatment is required, and despite prostaglandin-induced inflammation reported in the literature, the majority of respondents use prostaglandin analogs, both in patients with active inflammation and without active inflammation. If surgical intervention is necessary, first line surgical procedure selected differs based on presence or absence of active inflammation, with a valved implant the most frequently selected procedure for patients with active inflammation and trabeculectomy with an antifibrotic being the most commonly selected procedure for patients without active inflammation. Most respondents would not alter their management if the patient is a child.

**Commercial Relationships:** Ardalan Aminlari, None; Ingrid U. Scott, National Eye Institute (F); George C. Papachristou, None; Christine Callahan, None; Ahmad Aref, Research to Prevent Blindness (F)

**Program Number:** 542 Poster Board Number: A0178  
**Presentation Time:** 1:30 PM–3:15 PM

**The role of the fourth drug in patients with glaucoma: is it worth it?**  
**Verena Juncal, Felipe A. Jorge, Augusto Paranhos, Tiago S. Prata.** Department of Ophthalmology and Visual Sciences, Paulista School of Medicine, São Paulo Hospital, Federal University of São Paulo, São Paulo, Brazil.

**Purpose:** To evaluate how effective is the fourth drug regarding intraocular pressure (IOP) control in patients with primary glaucomas.

**Methods:** We prospectively enrolled consecutive patients with primary glaucomas [primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG)] treated concomitantly with a topical prostaglandin analog, a beta-blocker, an alpha-adrenergic agonist and a carbonic anhydrase inhibitor. Exclusion criteria were: history of ocular trauma or surgical procedures besides cataract extraction or glaucoma surgeries, secondary glaucomas, ocular diseases other than glaucoma and poor treatment adherence. Patients were recruited from August 2013 to November 2013 for a first evaluation and were submitted to a complete ophthalmologic examination. Using Goldmann applanation tonometry, IOP was measured at 8am, 10am and 12pm. Afterwards, patients underwent a 15-day washout of the anhydrase carbonic inhibitor and had their IOP measured again at 8am, 10am and 12pm by another examiner using the same device and methodology.

**Results:** A total of 25 patients were enrolled and most were women, white, with a mean age of 66.4 ± 9.7 years old and had moderate functional damage on average. The removal of the fourth drug had a statistically significant effect on the IOP peak (increase of 1.20mmHg) and mean (increase of 1.23mmHg; p<0.01). On the other hand, it did not interfere significantly with morning fluctuation (Table 2).

**Conclusions:** Even though it was identified a statistically significant effect on the IOP peak and mean after the fourth drug removal, we believe that its clinical relevance is actually low due to the fact that most patients had an IOP increase below 20% (or below 2mmHg). Age was the only significant predictive factor of IOP change within the evaluated variables, which suggests that it might be worth it to invest on a fourth drug in the older population.

**Commercial Relationships:** Verena Juncal, None; Felipe A. Jorge, None; Augusto Paranhos, None; Tiago S. Prata, None
Synergistic Effect of Once Daily Topical 0.03% Bimatoprost and 0.5% Timolol Maleate on Intraocular Pressure Reduction in Normal Beagles

Corbin Telford, Brian C. Gilger, Jacklyn H. Salmon. North Carolina State University College of Veterinary Medicine, Raleigh, NC.

Purpose: Glaucoma is a common cause of vision loss in humans and dogs. Medical therapy is the mainstay of treatment, however, optimization of therapeutic regimens is needed. The purpose of this study was to compare the efficacy of topical 0.03% bimatoprost and 0.5% timolol as monotherapies and in combination to lower intraocular pressure (IOP) in normal dogs.

Methods: Untreated control IOPs were measured (via Tonovet® tonometer) in nine normotensive, adult, male laboratory beagles at 0, 2, 4, 8 and 24-hours post-administration daily for three days (short term; n=5) and once daily on days 3, 7, 10, and 14 of the treatment period (long term; n=4). The IOP schedule was repeated after a single daily dose (short term) or twice daily dose (long term) of 0.5% timolol, and a single daily dose of 0.03% bimatoprost or both medications (BT - separated by 5 mins.) for three days (short term) or fourteen days (long term), consecutively.

Results: In the short-term study, IOP of eyes treated with timolol was not significantly lower than baseline at any time point. In eyes treated with bimatoprost only, IOP was significantly reduced compared to baseline by 4 hours on day 2 (P=0.0404), while eyes treated with BT had significantly lower IOP than baseline by 8 hours on day 1 (P=0.0161). In the long-term study, the mean IOP of eyes treated with bimatoprost (14.0 ± 1.77 mmHg) was significantly lower than the untreated control (18.75 ± 2.85 mmHg; P=.0006). However, eyes treated with BT had mean IOP (11.56 ± 1.83 mmHg) that was significantly lower than untreated eyes (P<.0001) and eyes treated twice daily with timolol (P=.0069).

Conclusions: Once-daily bimatoprost-timolol combination therapy resulted in a more rapid reduction of IOP compared to bimatoprost monotherapy. Additionally, overall mean IOP of eyes treated with BT was significantly lower than IOP in eyes treated with timolol in normotensive beagles. This synergistic IOP-lowering effect of timolol and bimatoprost supports further clinical evaluation of this combination in glaucomatous patients.

Commercial Relationships: Corbin Telford, Allergan, Inc. (F); Brian C. Gilger, Allergan, Inc. (F); Jacklyn H. Salmon, Allergan, Inc. (F)

Support: Allergan, Inc.

Program Number: 544 Poster Board Number: A0180
Presentation Time: 1:30 PM–3:15 PM

Double-masked, randomized, dose-response study of AR-13324 Ophthalmic Solution compared to latanoprost in patients with elevated intraocular pressure

Harvey Dubiner1, Brian Levy2, Casey Kopczynski2, Gary D. Novack4. 1clayton eye, Smyrna, GA; 2Aerie Pharmaceuticals, Bedminster, NJ; 3Pharmalogic Development, San Rafael, CA.

Purpose: AR-13324 is in a new class of agents that inhibit both Rho kinase and norepinephrine transporter to increase trabecular outflow and decrease aqueous production. We evaluated two concentrations of AR-13324 compared to latanoprost for their ocular hypotensive efficacy and ocular and systemic safety.

Methods: Adult patients (N=224) with open-angle glaucoma or ocular hypertension were randomized to receive either AR-13324 0.01% or 0.02% q.d. or latanoprost q.d. for 28 days, q.d. (PM).

Results: Mean unmedicated diurnal IOP was 25 to 26 mm Hg across groups. On Day 28, in the mITT population of 221, mean diurnal
IOP was 20.1, 20.0 and 18.7 mm Hg for the AR-13324 0.01%, 0.02% and latanoprost groups, respectively, representing a decrease from baseline of 5.5, 5.7 and 6.8 mm Hg (p < 0.0001). In a planned subgroup analysis of patients with baseline IOPs <= 26 mmHg (N=106), the decrease from baseline in each group on Day 28 was 5.4, 5.8 and 6.0 mm Hg, respectively (p < 0.0001). The difference in the change from baseline between AR-13324 0.02% and latanoprost was 1.2 mm Hg (p=0.009) in the mITT population compared to 0.2 mm Hg in the subgroup with baseline IOPs <= 26 mmHg (p=0.754). These results show that AR-13324 0.02% maintained similar efficacy regardless of baseline IOP, whereas latanoprost was less effective at baseline IOPs <= 26 mmHg. The only drug-related safety finding of note for AR-13324 was conjunctival hyperemia, which was typically scored as mild to moderate and appeared to diminish throughout the study. On Day 28, 08:00 hours, the incidence of mild to moderate conjunctival hyperemia on biomicroscopic examination was 18%, 24% and 11%, respectively.

**Conclusions:** AR-13324 0.01% and 0.02% produced clinically and statistically significant reductions in IOP. On Day 28, 0.02% AR-13324 was approximately 1 mm Hg less effective than latanoprost in patients with unmedicated IOPs in the range of 22 – 36 mm Hg. However, AR 13324 0.02% had equivalent efficacy to latanoprost (within 0.2 mm Hg) in patients with baseline IOPs of 22 – 26 mm Hg. The only drug-related adverse event of note was conjunctival hyperemia which for the majority of patients was mild to moderate and transient. AR-13324 was an effective ocular hypotensive agent and well tolerated in patients with glaucoma and ocular hypertension.

**Commercial Relationships:** Harvey Dubiner (E); Brian Levy, Aerie (E); Casey Kopeczynski, Aerie (E); Gary D. Novack, Aerie (C), Glaukos (C), Mati (C), Nanyang (C)

**Clinical Trial:** NCT01731002

**Program Number:** 546 Poster Board Number: A0182

**Presentation Time:** 1:30 PM–3:15 PM

**NO-induced Regulation of Primary Human Trabecular Meshwork Cell Contractility by Latanoprostene Bunod**


**Purpose:** Prior in vivo studies demonstrated that latanoprostene bunod (LBN), a nitric oxide (NO)-donating latanoprost, results in greater IOP lowering than latanoprost (Xalatan). This study determined the effect of LBN on primary human trabecular meshwork cell (HTMC) contractility and underlying signaling pathways, to assess whether LBN may mediate this additional IOP lowering via the conventional outflow pathway.

**Methods:** The effect of LBN (1 – 100 μM) on HTMC cGMP levels was determined by ELISA ± the soluble guanylate cyclase (sGC) inhibitor ODQ. Endothelin-1 (100 nM) was used to induce HTMC contractility. To determine the effect of LBN on myosin light chain-2 (MLC-2) phosphorylation, HTMC were pre-treated with 10 - 60 μM LBN for 1 h and then endothelin-1 for 5 min. MLC-2 phosphorylation was determined by western blotting. The effects of LBN (30 and 45 μM) on endothelin-inact cytoskeletal stress fibers and the focal adhesion associated protein vinculin were determined by confocal microscopy. Endothelin-1 induced HTMC monolayer resistance in the presence of LBN (1 – 45 μM) was determined by electrical cell substrate impedance sensing, as an indicator of cell contractility. Latanoprost was used as a comparator in all studies.

**Results:** LBN (1 – 100 μM) significantly increased cGMP levels in a dose dependent manner with an EC50 of 1.54 ± 1.33 μM, while latanoprost caused a minimal increase in cGMP at 100 μM only.

The cGMP elevation was abolished by ODQ and was therefore sGC dependent. Effects of LBN on endothelin-1-induced MLC-2 phosphorylation were significantly greater than those of latanoprost. LBN caused a dramatic reduction in endothelin-1 induced actin stress fibers and vinculin localization at focal adhesions, while latanoprost was without effect. LBN significantly reduced endothelin-1 induced HTMC monolayer resistance increases to a greater extent than latanoprost over the dose range studied, indicating a greater reduction in cell contractility with LBN.

**Conclusions:** Data suggest that LBN mediates HTMC relaxation through activation of the cGMP signaling pathway and a subsequent reduction in MLC-2 phosphorylation. In all cases, effects observed with LBN were of a greater magnitude than those observed with latanoprost. This mechanism may underlie the additional IOP lowering effects of LBN over latanoprost observed in in vivo studies.

**Commercial Relationships:** Megan E. Cavet, Bausch + Lomb (E); Thomas R. Vollmer, Bausch + Lomb (E); Karen Harrington, Bausch + Lomb (E); Karl VanDerMeid, Bausch + Lomb (E); Mary Richardson, Bausch + Lomb (E)

**Program Number:** 547 Poster Board Number: A0183

**Presentation Time:** 1:30 PM–3:15 PM

**Switch from BAK-preserved to preservative-free latanoprost decreases anterior chamber flare in POAG patients**

Philippe G. Kestelyn', Dirk De Bacquer", Anna Stevens'. 1 Ophthalmology, University Ghent, Gent, Belgium; 2 Public Health, University Ghent, Gent, Belgium.

**Purpose:** We previously showed that BAK-preserved and preservative-free timolol both increase flare measurements, but that the increase in BAK treated eyes is significantly higher than in preservative-free treated eyes (Stevens et al. Acta Ophthalmologica, 2012). To corroborate the hypothesis that BAK induces low grade inflammation in the anterior chamber, we designed another study to investigate whether switching from BAK-preserved to preservative-free latanoprost in patients with POAG would reduce the flare levels.

**Methods:** Clinical trial. We measured baseline flare values in 22 patients with primary open angle glaucoma who took BAK-preserved latanoprost for at least 6 months. We then switched all patients to preservative-free latanoprost and took flare measurements at month 1 after the switch.

**Results:** Baseline flare value : 6.59 photons/millisecond Flare values 1 month after the switch : 5.71 photons/millisecond Decrease in flare : -0.882 (-1.441 to -0.323) F-statistic mixed models p = 0.0038

**Conclusions:** The switch from BAK-preserved to preservative-free latanoprost indeed reduced the flare values. This finding confirms our hypothesis that BAK induces low grade inflammation in the anterior segment since both preservative -free betablockers and latanoprost generate lower flare values than the BAK-preserved drugs. The potential implications of long term low grade inflammation due to chronic use of BAK preserved drugs are not yet clear but raise important questions:
- Is BAK potentially harmful to the trabecular meshwork cells?
- Is BAK implicated in the slow loss of efficacy of glaucoma medications over time?
- Could the low grade inflammation account for the higher failure rate of filtering surgery in patients on BAK-preserved glaucoma medication?
- Our findings obtained over a short period of time certainly justify further research on the potential toxicity of BAK at the level of the anterior chamber and the trabecular meshwork in glaucoma patients since they are exposed to this substance for years or decades.
Commercial Relationships: Philippe G. Kestelyn, None; Dirk De Bacquer, None; Anna Stevens, None

Clinical Trial: B670201316847

Program Number: 548 Poster Board Number: A0184
Presentation Time: 1:30 PM–3:15 PM

Efficacy of Latanoprostene Bunod Ophthalmic Solution, 0.024%, in Lowering Intraocular Pressure Over 24-Hours in Normal Japanese Subjects (KRONUS)

Makoto Arai1, Tuyen Ong1, Baldo Scassellati-Sforzolini1, Quintus Ngumah1, Jason L. Vittitow1, Robert N. Weinreb2. 1Kanto Central Hospitals, Mutual Aid Assoc of Public Sch Teachers, Setagaya-Ku, Japan; 2Ophthalmology, University of Tokyo School of Medicine, Tokyo, Japan; 3Clinical Affairs, Bausch+Lomb, Bridgewater, NJ; 4Ophthalmology and Hamilton Glaucoma Center, University of California, San Diego, La Jolla, CA.

Purpose: To evaluate the efficacy of latanoprostene bunod, 0.024% in reducing and maintaining IOP over 24 hours in normal Japanese subjects. In Phase 2 dose-ranging studies in USA (VOYAGER) and Japan, 0.024% latanoprostene bunod was the safest and most efficacious dose, demonstrating significantly greater IOP reduction compared with latanoprost, 0.005%.

Methods: This was a single-arm, single-center, open-label, clinical study of 24 healthy Japanese male volunteers. A baseline IOP profile was established in both eyes in the sitting position at 8 PM, 10 PM, 12 AM, 2 AM, 4 AM, 8 AM, 10 AM, 12 PM and 4 PM using a Goldmann applanation tonometer. Following the baseline visit, both eyes were treated with 0.024% latanoprostene bunod QD at approximately 8 PM for 14 days. For each subject’s right eye, the change and change from baseline in sitting IOP at each time point was assessed on Day 14. A one-sampled paired t-test was used to determine statistical significance.

Results: The mean age of the volunteers was 26.8 (range 20-39) years. Mean IOPs (± SD) on Day 0 were: 14.4mmHg (1.7), 13.9mmHg (1.5), 13.4mmHg (1.4), 13.0mmHg (1.3), 13.2mmHg (1.6), 14.0mmHg (1.7), 13.7mmHg (1.5), 13.5mmHg (1.7) and 13.4mmHg (1.6) with a 24-hour mean IOP of 13.6 mmHg (1.6). On Day 14 pressures were: 11.5mmHg (1.8), 9.8mmHg (1.4), 9.8mmHg (1.2), 9.9mmHg (1.2), 9.9mmHg (1.5), 9.8mmHg (1.7), 9.6mmHg (1.3), 9.4mmHg (1.3) and 10.1mmHg (1.1) with a 24-hour mean IOP of 10.0 mmHg (1.5). Intraocular pressures were taken at 8 PM, 10 PM, 12 AM, 2 AM, 4 AM, 8 AM, 10 AM, 12 PM and 4 PM, respectively. A 14-day QT treatment with 0.024% Latanoprostene bunod reduced IOP at all time points (p < 0.001) with a mean 24-hour reduction of 3.6mmHg (1.5) or 26% from the baseline. Peak and trough IOP lowering occurred at 8 AM and 8 PM (12 and 24 hours following instillation) with a mean reduction of 4.2mmHg (1.8) or 30% and 2.8mmHg (2.2) or 20%, respectively. No significant adverse events were encountered.

Conclusions: Latanoprostene bunod, 0.024% dosed QD for 14 days significantly lowered IOP in normal Japanese subjects during the entire 24 hour period from 13.6 to 10.0 mmHg, corresponding to 27% reduction in mean 24-hour IOP. The current result suggests potential of this compound in providing sustained 24-hour IOP reduction to glaucoma patients not only with elevated, but also with normal IOP.

Commercial Relationships: Makoto Arai, Alcon (C), Alcon (R), Allergan (C), Bausch & Lomb (C), Bausch & Lomb (R), Carl Zeiss-Meditec (R), Kowa (C), Kowa (R), MSD (R), Nitten (R), Otsuka (R), Pfizer (P), Pfizer (R), Santen (C), Santen (R), Senju (C), Senju (R), Topcon (C); Tuyen Ong, Bausch+Lomb (E); Baldo Scassellati-Sforzolini, Bausch+Lomb (E); Quintus Ngumah, Bausch+Lomb (E); Jason L. Vittitow, Bausch+Lomb (E); Robert N. Weinreb, Acrie (F), Alcon (C), Allergan (C), Amakem (C), Bausch+Lomb (C), Carl Zeiss-Meditec (C), Genentech (F), Heidelberg Engineering (F), Konan (F), Lumenis (F), National Eye Institute (F), Nidek (F), Optovue (F), Topcon (C)

Clinical Trial: NCT01895985

Program Number: 549 Poster Board Number: A0185
Presentation Time: 1:30 PM–3:15 PM

Randomized Clinical Trial Of The Efficacy And Safety Of Preservative-free Tafluprost And Preservative-free Timolol In Patients With Open-angle Glaucoma (OAG) Or Ocular Hypertension (OHT) In India

Almira Chabi, Robert Lupinacci, Christine Baranak, W. Joseph Herring. Merck, North Wales, PA.

Purpose: Prostaglandin analogs are frequently first-line IOP-lowering therapy in patients with OAG and OHT. Most topical ocular hypotensives contain the preservative benzalkonium chloride, which may be associated with decreased ocular tolerability in some patients. We compared the efficacy and safety of tafluprost, a preservative-free (PF) prostaglandin analog, with PF timolol in India.

Methods: Randomized, double-masked, Phase III clinical trial (NCT01254604) in patients with OAG and OHT. After discontinuation and washout of existing ocular hypotensive treatment, patients who had IOP ≥24 mmHg at least once in the previous 3 months were randomized to either PF tafluprost (PF TAF) 0.0015% or PF timolol (PF TIM) 0.5%. IOP was measured 3 times during the day (0800, 1600, 2400 hrs) at baseline and weeks 2 and 4. The primary hypothesis was that PF TAF would be non-inferior to PF TIM in mean diurnal IOP change from baseline to week 4. The study was powered for a non-inferiority margin of 1.5 mmHg.

Results: A total of 190 patients were randomized and 173 completed (PF TAF = 95, 87 and PF TIM = 95, 86 respectively). Baseline diurnal mean IOPs were 24.8 mmHg in the PF TAF group and 24.9 mmHg in the PF TIM group. At week 4 decreased a mean of -8.3 mmHg (95% CI ranged between -9.0 and -7.6) for PF TAF and decreased a mean of -6.6 mmHg (95% CI ranged between -7.3 and -5.9) for PF TIM. At weeks 2 and 4, the upper limits of the 2-sided 95% CIs for the difference between treatments in IOP-lowering were less than the pre-specified non-inferiority margin. In fact, the CIs were < 0 at both weeks 2 and 4 suggesting PF TAF superiority to PF TIM with respect to diurnal IOP change from baseline.

Conclusions: The percentages of PF TAF and PF TIM patients reporting ocular pain/stinging/irritation and pruritus were (6.5% vs. 5.3%; nominal p = 0.742) and (7.5% vs. 3.2%; nominal p = 0.188) respectively. The percentages of PF TAF and PF TIM patients reporting conjunctival hyperemia (determined by aggregation of all terms suggestive of conjunctival hyperemia) were 9.7% vs. 4.3% (nominal p = 0.145).

Commercial Relationships: Almira Chabi, Merck & Co., Inc. (E); Robert Lupinacci, Merck & Co., Inc. (E); Christine Baranak, Merck & Co., Inc. (E); W. Joseph Herring, Merck & Co., Inc. (E)
Support: Merck & Co.

Clinical Trial: NCT01254604

Program Number: 550 Poster Board Number: A0186
Presentation Time: 1:30 PM–3:15 PM

Efficacy and Tolerability of BAK-Free Travoprost in Patients With Open-Angle Glaucoma Previously on Latanoprost

Joao F. Lopes1, Douglas A. Hubatsch1. 1Hospital, Santiago, Chile; 2Chile University, Salvador Hospital, Santiago, Chile; 3Alcon Laboratories, Inc., Fort Worth, TX.
Purpose: To assess the efficacy and tolerability of benzalkonium (BAK)–free travoprost in patients with open-angle glaucoma or ocular hypertension who were previously on latanoprost monotherapy.

Methods: This 12-week, multicenter, open-label, single-group study (NCT01510145) conducted in Argentina, Chile, and Colombia included patients ≥18 years with ocular hypertension or open-angle glaucoma in ≥1 eye who had been on latanoprost 0.005% monotherapy for ≥4 weeks before screening. Patients discontinued their latanoprost therapy and self-administered 1 drop of BAK-free travoprost 0.004% (preserved with polyquad) every evening at approximately 8 PM for 12 weeks. Assessments included change from baseline to week 12 in intraocular pressure (IOP), ocular surface health (assessed using the Ocular Surface Disease Index [OSDI], with scores ranging from 0 [no disability] to 100 [complete disability]), and ocular hyperemia (assessed from 0 [no hyperemia] to 3 [severe hyperemia]). Adverse events (AEs) and discontinuations due to AEs were reported.

Results: 191 patients were eligible for the study, and 173 patients completed the study. Mean IOP decreased by 5.4% from 14.8 mmHg at baseline to 13.8 mmHg at week 12 (P<0.001). The percentage of patients achieving the target IOP of ≤18 mmHg increased from 89.5% (171/191) at baseline to 93.3% (166/178) at week 12. From baseline to week 12, the mean OSDI score improved by 14.9% (decreasing from 22.2 to 13.7 mmHg; P<0.001). The mean ocular hyperemia score decreased from 0.94 at baseline to 0.74 at week 12. 42 AEs were reported in 15.2% (29/191) of patients. The most commonly reported AEs were eye irritation (3.7%), eye pruritis (3.1%), and eye pain (2.6%). Most AEs (31/42) were mild in severity, and there were no serious AEs. 6 patients discontinued from the study because of eye-related AEs.

Conclusions: BAK-free travoprost preserved with polyquad decreased IOP from baseline and was well tolerated over 12 weeks in patients with open-angle glaucoma or ocular hypertension who were previously on BAK-containing latanoprost.

Commercial Relationships: Joao F. Lopes, Alcon Laboratories, Inc (R); Douglas A. Hubatsch, Alcon Laboratories, Inc (E)

Support: This study was sponsored by Alcon.

Clinical Trial: NCT01510145

Program Number: 551 Poster Board Number: A0187

Presentation Time: 1:30 PM–3:15 PM

24-hour diurnal intraocular pressure (IOP) evaluation in eyes with POAG or ocular hypertension treated with unoprostone isopropyl as measured in both the sitting and supine position

Alan L. Robin, MD, Ophthalmology & Intl Health, Johns Hopkins Univ, Baltimore, MD; Ryuji Ueno, MD, PhD, Sucampo Pharmaceuticals, Inc., Bethesda, MD; Ryuji Ueno, Sucampo Pharma Americas, LLC; Sucampo Pharmaceuticals, Inc (I)

Purpose: To assess the 24-hour IOP lowering effect of unoprostone isopropyl ophthalmic solution (UIOS) 0.15% dosed BID.

Methods: We enrolled 10 subjects with either POAG or ocular hypertension who had untreated IOPs ≥23 mm Hg and <32 mm Hg in at least one eye.

Technicians administered one drop of UIOS 0.15% at 6 am and 10 pm daily for three days. While the patient was in the sitting position, IOP was measured using Goldmann tonometry; at the same time points, a Perkins tonometer was used to measure IOP with the patient supine. We measured IOP in both the supine and seated positions at Baseline and on Day 3 at the following time points: 0.75, 2, 4, 6, 10, 14, 18, and 22 hours after the 6 am dose.

Results: The mean age of the subjects was 70.5 years. On Day 3, the mean change in 24-hour diurnal IOP from Baseline in the sitting position was 4.7±1.0 mm Hg (P<0.001). Overall, after three days of BID dosing, IOP reduction measured in the sitting position appears uniform and relatively flat over 24-hours. Mean change in nighttime IOP, assessed in the sitting position after the second daily-dose, is also statistically significantly lower post-treatment versus baseline (P<0.001).

On Day 3, the mean change in 24-hour diurnal IOP from Baseline in the supine position was 4.2±0.8 mm Hg (P<0.001). Overall, after three days of dosing twice daily, IOP reduction measured in the supine position appears relatively flat over 24-hours. Mean change in nighttime IOP, assessed in the supine position after the second daily-dose, is also statistically significantly lower post-treatment versus baseline (P<0.001).

Conclusions: In this study, after three days of dosing, the 24-hour IOP curves of patients treated with unoprostone isopropyl 0.15% ophthalmic solution appear to be relatively flat and suggest around the clock efficacy with BID dosing. The IOP reduction was greater during the day than at night.
Difference of intraocular pressure lowering effects among 3 Prostaglandin analogs for Korean glaucoma and ocular hypertension patients


Purpose: To compare intraocular pressure (IOP) lowering effects of tafluprost, travoprost, and bimatoprost respectively for Korean glaucoma patients.

Methods: Seventy-eight patients, 147 eyes, diagnosed with normal tension glaucoma (NTG), ocular hypertension (OHT), or primary open-angle glaucoma (POAG), received 0.0015% tafluprost, 0.004% travoprost or 0.01% bimatoprost respectively once daily. We compared and analyzed IOP and the change of IOP at baseline, after a week and after a month.

Results: Of all 147 eyes, there were 72 eyes of NTG, 35 eyes of OHT, 7 eyes of POAG, and 10 eyes of other glaucoma in tafluprost group. There were 24 eyes of NTG, 2 eyes of POAG, and 7 eyes of other glaucoma in travoprost group. There were 14 eyes of NTG, 4 eyes of POAG, and 2 eyes of other glaucoma in bimatoprost group. In tafluprost group, the average IOP was 16.2 ± 3.2 mmHg at baseline, 12.5 ± 2.6 mmHg (p<0.0001) after 1 week, and 12.4 ± 2.8 mmHg (p<0.0001) after 1 month. In travoprost group, the average IOP was 15.1 ± 2.2 mmHg at baseline, 11.0 ± 2.7 mmHg (p<0.0001) after 1 week, and 12.7 ± 2.2 mmHg (p<0.0001) after 1 month. In bimatoprost group the IOP was 16.9 ± 2.8 mmHg at baseline, 11.9 ± 2.2 mmHg (p<0.0001) after 1 week, and 13.7 ± 3.5 mmHg (p<0.0001) after 1 month, which all showed statistically significant IOP reduction. No meaningful correlation between baseline IOP and the change of IOP was shown in the travoprost group (p=0.191, r=0.234) and bimatoprost group (p=0.395, r=0.201). However in tafluprost group (p=0.03, r=0.305), as the baseline IOP was higher, the change of IOP was higher significantly.

Conclusions: Tafluprost, travoprost and bimatoprost were all effective in IOP lowering effects until one month for Korean glaucoma and ocular hypertension patients. Travoprost and bimatoprost showed consistent IOP reduction regardless of baseline IOP. Otherwise in tafluprost group, as the baseline IOP was higher, the change of IOP was higher significantly.

Commercial Relationships: Seung Jae Lee, None; Youngdon Kim, None; Haksu Kyung, None

Program Number: 553 Poster Board Number: A0189
Presentation Time: 1:30 PM–3:15 PM
Comparison study of the intraocular-pressure reduction efficacy and safety between bimatoprost and latanoprost-timolol-fixed combination in Japanese open-angle glaucoma patients who switched from latanoprost

Yuko Maruyama1, Yoko Ikeda1, 2, Kazuhiko Mori1, Morio Ueno1, Haruna Yoshikawa1, Shigeru Kinoshita1. Ophthalmology, Kyoto Prefectural Univ of Med, Kyoto, Japan; 2Oike-Ganka Ikeda Clinic, Kyoto, Japan.

Purpose: To prospectively evaluate and compare the intraocular pressure (IOP) reduction efficacy and safety between bimatoprost (Bim) and latanoprost (Lat)-timolol-fixed combination (LTFC) in Japanese open-angle glaucoma patients.

Methods: This study involved 62 eyes of 62 Japanese open-angle glaucoma patients (37 females and 25 males, mean age: 66.9±13.3 years) who had used Lat monotherapy for more than 4 weeks, and randomly divided them into two groups; 1) Bim group and 2) LTFC group. Both groups were switched from Lat to Bim or LTFC for 12 weeks. Written informed consent was obtained from all patients.

IOP, conjunctival injection score (grade 0-3), corneal epitheliopathy score (area density classification; AD score), and tear film break-up time (BUT) were evaluated at 0, 4, and 12 weeks post switching, respectively. If both eyes were available, right-eye data was used. The Paired t-test and Mann Whitney U test were used for statistical analysis.

Results: Of the 62 patients, 49 were analyzed for IOP reduction and safety and 13 dropped out of the study. At 0, 4, and 12 weeks, mean IOP of the Bim group (26 eyes) and LTFC group (23 eyes) were 13.2, 11.5, and 11.6 mmHg, and 13.4, 11.7, and 11.5 mmHg, respectively. In both groups, the mean IOP had already significantly decreased at 4 weeks compared with week 0 (P<0.0001 in both groups). Comparisons between the two groups showed no significant differences. The conjunctival injection scores were 0.6±0.5 at baseline, and 1.1±0.8 (Bim group) and 0.6±0.5 (LTFC group) at 12 weeks. The conjunctival injection score at 12 weeks was higher in the Bim group than in LTFC group (P=0.0171). The corneal AD scores (total score of area and density grade) were 1.6±1.5 at baseline, and 1.7±1.4 (Bim group) and 1.7±1.4 (LTFC group) at 12 weeks, and BUT was 6.0±4.2 seconds (sec) at baseline, and 5.8±4.4 sec (Bim group) and 5.4±4.0 sec (LTFC group) at 12 weeks. There were no significant differences between the two drugs in relation to AD score and BUT.

Conclusions: The findings of this study show that Bim and LTFC have equal efficacy for the reduction of IOP. Safety comparisons between the two drugs showed that only the conjunctival injection score at 12 weeks was higher in the Bim group than in the LTFC group.

Commercial Relationships: Yuko Maruyama, None; Yoko Ikeda, None; Kazuhiko Mori, Ocular Instruments Inc. (P), Santen Pharmaceutical Co. (P); Morio Ueno, Santen Pharmaceutical Co. (P), Senju Pharmaceutical Co. (P); Haruna Yoshikawa, None; Shigeru Kinoshita, Alcon (R), AMO (R), HOYA (R), Otsuka Pharmaceutical Co. (C), Santen Pharmaceutical Co. (P), Senju Pharmaceutical Co. (P)

Clinical Trial: UMIN000004595

Program Number: 554 Poster Board Number: A0190
Presentation Time: 1:30 PM–3:15 PM
Latanoprost prevents TGF-β2-induced collagen deposition and promotes contraction in trabecular meshwork cells

Georges Kalouche1, 2, Michael Bakria1, Celine Boucher1, Patrick Averen1, Stephane Melik-Parsadaniantz1, Caroline Leriche1, Thomas Debeir3, Xavier Vige2, Christophe Baudouin1, William H. Rostene1.

1Institut de la Vision UMRS 968 /INSERM / UPMC, Paris, France; 2Sanofi Research & Development, Chilly-Mazarin, France; 3Sanofi Fovea, Paris, France.

Purpose: Latanoprost is the first-line medication in the treatment of glaucoma but its direct action on the trabecular meshwork (TM), the main site of resistance to the aqueous humor outflow, is still controversial. In this study, the authors examined the effects of latanoprost on collagen accumulation and contraction of human TM cells.

Methods: Primary human TM cells were pretreated with vehicle (DMSO 0.1%) or latanoprost acid (1 µM) and incubated with TGF-β2 (2 ng/ml). After 96h, collagen I, F-actin and phospho-myosin light chain (p-MLC) immunolabelings were analyzed by quantitative immunocytochemistry. Total RNA from treated TM cells were isolated at 6, 24 and 48h, and qPCR were performed to detect the mRNA of collagen I(Coll1A1), metalloproteinase (MMP)-1, and lysyl oxidase (LOX).

Results: TGF-β2 induces a deposition of collagen I in TM cell culture which is inhibited by latanoprost (p<0.01). Batimastat, a broad spectrum MMP inhibitor, does not prevent the latanoprost-
dependent inhibition of collagen deposition. Furthermore, TGF-β2 time-dependently up-regulates collagen I, LOX and MMP-1 mRNA expressions which are not modulated by pretreatment with latanoprost. In addition, latanoprost induces a time-dependent contraction of TM cells as evidenced by an increased staining for F-actin and p-MLC. Latanoprost does not potentiate the TGF-β2-dependent increase in F-actin staining.

**Conclusions:** Latanoprost inhibits collagen deposition induced by TGF-β2 in a MMP independent manner. mRNA of collagen I, LOX and MMP-1, respectively involved in collagen degradation and cross-linking, are not modulated by latanoprost. These results suggest that latanoprost can act on the TM by decreasing collagen deposition independently of MMPs as opposed to its effects on uveoscleral tissues. However, latanoprost by activating the actomyosin system seems to induce a concomitant contraction of TM cells which could antagonize its intraocular pressure (IOP) lowering effect. Further studies would evaluate the contribution of latanoprost-dependent TM cells contraction on IOP.

**Commercial Relationships:** Georges Kalouche, Sanofi (E), Sanofi (F); Michael Bakria, Sanofi (F); Celine Boucher, Sanofi (F); Patrick Avenet, Sanofi (E); Stephane Melik-Parsadaniantz, None; Caroline Leriche, Sanofi (E); Thomas Debeir, Sanofi Fovea (E); Xavier Vige, Sanofi (E); Christophe Baudouin, Sanofi (F); William H. Rostene, Sanofi (F)

**Support:** Sanofi

**Program Number:** 555 **Poster Board Number:** A0191

**Presentation Time:** 1:30 PM–3:15 PM

**Prostaglandin EP4 Increases Outflow Facility in Calf Eyes Using a Whole Eye Organ Perfusion (WEOP) Model**

Lindsey H. Millard, Andriy Pashko, Claes Bavik, Ryo Kubota. Acucela, Seattle, WA.

**Purpose:** Models using animal eyes are relevant for glaucoma research. Between species, however, physiologic and pharmacologic signaling differences present obstacles in determining the tissue most analogous to humans for studying intraocular pressure (IOP) regulation through the conventional outflow pathway. Here, we aimed to determine whether enucleated calf eyes responded similarly to a selective prostaglandin EP4 (PG-EP4) agonist when perfused into a whole-eye ex-vivo model as previously published using mice and human eyes.

**Methods:** Paired post-mortem calf eyes received within 4 hrs and prepared for organ-culture were perfused at 10 mmHg constant pressure. Once a stable baseline was established, the contents of the anterior chamber were exchanged with either drug (L-902.688, 16 nM) or vehicle (PBS with glucose). After 2-4 hrs of perfusion post-exchange, both eyes were perfusion-fixed with 8% PFA at 10 mmHg for 30 min. Whole globes were stored in 4% PFA for 2-4 days; then the corneo-scleral regions of the eyes were embedded in paraffin, sectioned and stained (hematoxylin and eosin) for histological examination.

**Results:** Baseline outflow facility for control and drug-treated eyes was similar (1.6 ± 0.3 versus 1.8 ± 0.2 µl/min/mmHg). In drug-treated eyes, outflow facility was increased by 55 ± 9% (n=6, p < 0.01) over contralateral vehicle-treated eyes. Histological analysis showed no significant differences in tissue morphology or integrity between control and drug-treated eyes. Notably, results in our drug-treated calf eyes were comparable to the outflow facility increases observed in WEOP studies in mice (106%; Boussommer-Callega 2012) and human (69%; Millard 2011) eyes.

**Conclusions:** Comparing the outflow facility measurements observed here to those from previous studies in mice and humans, we conclude that the PG-EP4 pharmacology of conventional outflow pathway in the calf eye is similar to both mice and humans to regulate IOP. These results demonstrate the utility of calf eyes in the whole-eye ex-vivo model to test other compounds expected to target the conventional outflow pathway.

**Commercial Relationships:** Lindsey H. Millard, Acucela, Inc. (E); Andriy Pashko, Acucela, Inc. (E); Claes Bavik, Acucela, Inc. (E); Ryo Kubota, Acucela, Inc. (E), Acucela, Inc. (I)

**Program Number:** 556 **Poster Board Number:** A0192

**Presentation Time:** 1:30 PM–3:15 PM

**Subgroup Analysis of the IOP-Lowering Effect of Fixed-Combination Brinzolamide 1%/Brimonidine 0.2% in the 3-Month Study NCT01297517**

Jason Bacharach1,2, Douglas A. Hubatsch3, Howard Barnebey4.

1North Bay Eye Associates, Petaluma, CA; 2Glancoma, California Pacific Medical Center, San Francisco, CA; 3Alcon Laboratories, Inc., Fort Worth, TX; 4Speciality Eyecare Centre, Seattle, WA.

**Purpose:** To determine if intraocular pressure (IOP)-lowering effect observed with fixed-dose combination brinzolamide 1%/brimonidine 0.2% (BBFC) in the full NCT01297517 study cohort was consistent across different subgroups.

**Methods:** NCT01297517 was one of two phase 3, parallel-arm, double-masked, multicenter, 3-month studies used for regulatory approval of BBFC. This preplanned descriptive statistical analysis compared IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) across the following subgroups after 3 months of treatment: (1) baseline intraocular pressure (24-27 or 28-36 mmHg), (2) age (<65, >65, 65-75, 75-85 years), (3) gender, and (4) ethnicity. IOP was recorded at 8 am, 10 am, 3 pm, and 5 pm.

**Results:** A total of 660 patients were enrolled in the original study, and IOP lowering with BBFC was statistically superior to the components at all time points. Subgroup analyses of IOP at 8 am (10-hour trough IOP) after 3 months of treatment are reported in this abstract. Mean IOP in high/low baseline IOP BBFC arm subgroups ranged from 18.4±2.97 to 22.9±4.56 mmHg. In comparison, mean IOP ranged from 19.7±3.64 to 23.5±4.14 mmHg in the brinzolamide arm and from 20.9±3.71 to 26±3.83 mmHg in the brimonidine arm. The lower and higher ends of each range are mean IOPs for subgroups with baseline IOP of 24-27 mmHg and 28-36 mmHg, respectively. Patients aged 65-75 years had mean IOP levels of 19.6±3.87, 20.2±4.00 and 22.8±4.63 mmHg with BBFC, brinzolamide, and brimonidine, respectively; patients aged 75-85 years showed mean IOP levels of 20.4±4.03, 20.5±3.81, and 22.5±3.89 mmHg in each of the arms at 8 am. There was no apparent gender bias in efficacy of BBFC compared with its components, nor was there a bias toward any particular ethnic group (Caucasian, African American or Hispanic). The AE profile of BBFC was similar to that of the components. This subgroup efficacy analysis demonstrated that BBFC has a similar IOP profile across all subgroups analyzed as was observed in the full cohort. IOP with BBFC was lower than with the individual components across all time points and all subgroups analyzed.

**Conclusions:** BBFC is an effective IOP-lowering therapy for patients with OAG or OHT irrespective of baseline IOP, age, sex and ethnicity (Caucasian, African American or Hispanic).

**Commercial Relationships:** Jason Bacharach, Alcon (C); Douglas A. Hubatsch, Alcon (E); Howard Barnebey, Alcon (C)

**Clinical Trial:** NCT01297517
Efficacy and Tolerability of Switching to Brinzolamide/Timolol Fixed Combination From Brimonidine/Timolol Fixed Combination in Latin America

Arturo A. Alezzandrini1, Douglas A. Hubatsch2, Rene Alfaro3.
1University of Buenos Aires, Buenos Aires, Argentina; 2Alcon Laboratories, Inc., Fort Worth, TX; 3Colegio Mexicano de Oftalmologia and Sociedad Mexicana de Oftalmologia, San Miguel Chapultepec, Mexico.

Purpose: To assess the efficacy and tolerability of twice-daily fixed-combination brinzolamide 1%/timolol 0.5% (BRINZ/TIM-FC; AZARGA®, Alcon Laboratories, Inc., Fort Worth, TX, USA) in patients with open-angle glaucoma or ocular hypertension in Latin America previously on brimonidine 0.2%/timolol 0.5% (BRIM/TIM-FC; COMBIGAN®, Allergan, Inc., Irvine, CA, USA) fixed-combination therapy

Methods: This 8-week, open-label, prospective study was conducted at 6 sites in Argentina, Chile, and Mexico and enrolled patients ≥18 years with primary, exfoliative, or pigment-dispersion open-angle glaucoma or ocular hypertension who had intraocular pressure (IOP) ranging from 19–35 mmHg in ≥1 eye at baseline (on BRIM/TIM-FC). Patients instilled 1 drop of BRINZ/TIM-FC in the study eye twice daily, at 8 AM and 8 PM, for 8 weeks. The primary efficacy endpoint was the mean change in IOP from baseline to week 8, and the secondary efficacy endpoint was the percentage of patients reaching target IOP (≤18 mmHg) at week 8. Exploratory endpoints included patient and investigator preference for treatment assessed using a global preference response questionnaire at week 8. Safety assessments included adverse events (AEs). IOP change was analyzed using Wilcoxon signed rank tests.

Results: In total, 50 patients (mean age, 67 ± 12 years) received BRINZ/TIM-FC and were included in the intent-to-treat population. A significant reduction in mean ± SD IOP from baseline was observed after 8 weeks of treatment with BRINZ/TIM-FC (−3.60 ± 3.01 mmHg; P < 0.0001); the mean percentage reduction in IOP from baseline to week 8 was 17.1%. Overall, 55.3% of patients reached the target IOP of ≤18 mmHg. Significantly more patients (89.4%) and investigators (95.7%) preferred BRINZ/TIM-FC to BRIM/TIM-FC (both P < 0.0001; exact binomial test). Thirteen AEs were observed, of which 8 were related to BRINZ/TIM-FC; the most common treatment-related AEs were eye irritation (n = 4) and abnormal sensation in the eye (n = 2).

Conclusions: BRINZ/TIM-FC significantly reduced IOP when used as replacement treatment in patients previously treated with BRIM/TIM-FC and was preferred to BRIM/TIM-FC. The safety profile of BRINZ/TIM-FC was comparable with previously reported studies; no AEs were identified other than those already associated with topical β-blockers and carbonic anhydrase inhibitors.

Commercial Relationships: Arturo A. Alezzandrini, None; Douglas A. Hubatsch, Alcon Laboratories, Inc. (E); Rene Alfaro, None
Support: Alcon Laboratories, Inc.
Clinical Trial: NCT01518244
The neuroprotective protein Stanniocalcin-1 (STC-1) has ocular hypotensive properties in the human anterior segment organ culture model


**Purpose:** Current therapies for glaucoma lower intraocular pressure but do not provide neuroprotection. STC-1 is a multi-functional protein that has recently been shown to be neuroprotective for photoreceptors and ganglion cells in vivo. In this study, we evaluated the ocular hypotensive properties of STC-1.

**Methods:** Paired human eyes (n=5) were obtained from the MN Lions Eye Bank. Following bisection of the eyes at the equator and removal of the iris, lens and vitreous, the anterior segments were clamped in a modified petri dish, placed at 37°C in a 5% CO2 atmosphere and perfused with Dulbecco’s Modified Eagle’s Media (DMEM) at the normal human flow rate of 2.5 μl/min. Upon stabilization of baseline IOP, one eye received an anterior chamber exchange with DMEM containing STC-1 (5, 50 or 500 ng/ml) while the fellow eye received an anterior chamber exchange with DMEM alone. Pressures were continuously monitored with a transducer connected to the second access cannula built into the dish and recorded with a custom designed computerized system. Histology was analyzed by transmission electron microscopy and evaluated by masked observation.

**Results:** All anterior segments perfused with STC-1 at 500 ng/ml had increased outflow facility (0.15 ± 0.03 to 0.27 ± 0.09 μl/min/mmHg, n=5, P=0.02) compared to baseline. In contrast, paired controls treated with vehicle showed no change in outflow facility (0.20 ± 0.03 to 0.20 ± 0.02 μl/min/mmHg, n=5, P=0.76). Anterior segments perfused with STC-1 at 5 ng/ml (0.15 ± 0.04 to 0.15 ± 0.04 μl/min/mmHg, n=2) and 50 ng/ml (0.14 ± 0.05 to 0.18 ± 0.07 μl/min/mmHg, n=4) had no significant effect on outflow facility (P=0.09). Morphological analysis showed similar cell numbers in the trabecular meshwork and Schlemm’s canal. No major disruptions of the juxtacanalicular region or the basement membrane of Schlemm’s canal inner and outer wall were observed.

**Conclusions:** STC-1 increased outflow facility in the human anterior segment culture model. STC-1 appears to be a novel molecule that can both reduce IOP and provide neuroprotection.

**Commercial Relationships:** Gavin W. Roddy, None; Cindy K. Bahler, None; Bradley H. Holman, None; Michael P. Fautsch, None

Support: NIH grant EY21727; Research to Prevent Blindness; Mayo Foundation

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**Tolerability, Safety and Pharmacokinetics of ONO-9054, a novel FP/EP3 dual receptor agonist: a 14 day study in subjects with ocular hypertension or open angle glaucoma**

Cheryl L. Rowe-Rendleman, ONO Pharma (E); Douglas T. Ross, ONO Pharma (E); Akifumi Fujii, ONO Pharma (E); Takafumi Ouchi, ONO Pharma (E); Andrew Wood, ONO Pharma (E)

**Purpose:** A randomized double masked clinical trial was performed to evaluate the safety, tolerability and pharmacokinetics (PK) of ONO-9054 a novel IOP lowering drug that targets both the prostaglandin FP and EP3 receptors in the eye.

**Methods:** 48 subjects with ocular hypertension or early open-angle glaucoma were recruited to 4 cohorts and randomized 1:3 to placebo or one of 4 active doses of ONO-9054 at 3, 10, 20 or 30 μg/mL. Adverse events (AEs) and tolerability were assessed during the study period from Days 1-19, and at follow up on Day 25. Blood samples taken for PK were collected by venipuncture from predose thru 6 hours post dose.

**Results:** Seventeen subjects had 23 AE’s, of which 21 were regarded as mild and the remaining 2 as moderate. The most frequent systemic AE was headache (3/48). All ocular AEs were mild except for 2 moderate cases of anterior uveitis which could not be definitely related to the drug. After 14 days of dosing all patients were graded with no or mild hyperemia. The Cmax and AUClast of ONO-AG-367 increased approximately dose proportionally from 3.0 to 30 μg/mL but there were no signs of accumulation.

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**Conclusions:** In our analysis all subjects on ONO-9054 experienced a reduction in IOP to 18 mmHg or less after 14 days dosing. At higher doses of the drug, IOPs of 16 mmHg or less were more frequent.

**Commercial Relationships:** Alon Harris, Adom (I), Alcon (R), BioLight (C), Merck (C), MSD (R), Nano Retina (C), ONO Pharmaceuticals (C), Pharmalight (C), Suncampo (C); Cheryl L. Rowe-Rendleman, ONO Pharma (C); Douglas T. Ross, ONO Pharma (E); Akifumi Fujii, ONO Pharma (E); Takafumi Ouchi, ONO Pharma (E); Andrew Wood, ONO Pharma (E)

**Clinical Trial:** NCT01670266
Conclusions: These data indicate that ONO-9054 is safe and well tolerated at concentrations up to 30 µg/mL. The profile of AEs is similar to that reported for currently prescribed prostaglandin analogues and the tolerability profile suggests that hyperemia may be lower. PK results indicate that neither ONO-9054 nor its active metabolite accumulate in blood and this dual agonist may become a useful tool in glaucoma medical therapy.

Commercial Relationships: Cheryl L. Rowe-Rendleman, Ono Pharma USA (C); Akifumi Fujii, Ono Pharma USA (E); Takafumi Ouchi, Ono Pharma USA (E); Funmitaka Suto, Ono Pharma USA (E); Douglas T. Ross, Ono Pharma USA (E); Andrew Wood, Ono Pharma USA (E)

Clinical Trial: NCT01670266

Program Number: 562 Poster Board Number: A0198

Presentation Time: 1:30 PM–3:15 PM

Decorin, an anti-fibrogenic and fibrolytic glycoprotein, reduces established trabecular meshwork scarring and intraocular pressure and protects retinal function in a rat model of glaucoma Lisa J. Hill!, Richard J. Blanch!, Ben Mead!, Peter J. Morgan-Warren!, Hannah Bofield!, Shabbir Mohamed!, Robert A H Scott!, Martin Berry!, Wendy Leadbeater!, Ann Logan!. 'Neurotrauma and Neurodegeneration Section, University of Birmingham, Edgbaston, United Kingdom; 2Department of Ophthalmology, University Hospital Birmingham, Birmingham, United Kingdom.

Purpose: Chronically raised intraocular pressure (IOP) is a major risk factor for the development of Primary Open Angle Glaucoma (POAG). Reduced outflow of aqueous humour secondary to fibrosis in the Trabecular Meshwork (TM) elevates IOP causing Retinal Ganglion Cell (RGC) death and blindness. Currently, reduction of IOP is recognised as the only modifiable risk factor. Decorin, a naturally occurring proteoglycan has anti-fibrogenic and fibrolytic properties that suppress scar formation and reverse established scarring in the CNS. Acting as a direct antagonist of pro-fibrogenic Transforming Growth Factor beta (TGF-β), Decorin also causes scar dissolution by activating proteases that lyse collagen, fibronectin and laminin. Hence, we suggest that Decorin is an alternative treatment strategy for POAG that has the potential to prevent progressive visual loss, by reducing IOP through reducing resistance to AqH outflow through MMP-induced dissolution of TM fibrosis and protecting RGC from death.

Methods: Rats received bi-weekly intracameral injections of 5ng/µl TGF-β (to induce TM fibrosis and raise IOP) or PBS (controls) for 30d. TGF-β injections were stopped at 16d when TM fibrosis was established and IOP had become consistently raised and thereafter rats were injected intracamerally with 5mg/ml Decorin or PBS. IOP were measured throughout and eyes harvested at 30d for immunohistological analysis of laminin and fibronectin to assess levels of TM fibrosis and of MMP to assess fibrolysis. RGC function was assessed using Visual Evoked Potentials (VEP) and survival was quantified in retinal whole mounts using FluoroGold back-labeling.

Results: A significant increase in IOP was observed by 16d in the TGF-β group, which became significantly raised by 14d until 30d compared to PBS. This increase in IOP induced a 30% loss of RGC numbers compared to PBS and a significant decrease in retinal function. By 30d, Decorin injections reduced established TM fibrosis (p<0.05) by enhancing levels of active MMP, lowered the IOP to baseline levels and preserved RGC viability.

Conclusions: Decorin lowered IOP by reversing established TM fibrosis and protecting RGC function in this model. Thus, intracameral Decorin treatment has the potential to be developed into as an effective therapy for patients with established progressive POAG.

Commercial Relationships: Lisa J. Hill, None; Richard J. Blanch, None; Ben Mead, None; Peter J. Morgan-Warren, None; Hannah Bofield, None; Shabbir Mohamed, None; Robert A H Scott, None; Martin Berry, None; Wendy Leadbeater, None; Ann Logan, None

Program Number: 563 Poster Board Number: A0199

Presentation Time: 1:30 PM–3:15 PM

Comparison of effect of oral lomerizine and methylcobalamin on visual field defect in primary open angle glaucoma and normal tension glaucoma

Kazuyoshi Kitamura¹, Tatsuya Chiba¹, Fumihiko Mabuchi¹, Satoshi Kogure², Fumiko Kashiwagi², Shigeo Tsukahara², Kenji Kashiwagi².

¹Ophthalmology, University of Yamanashi, Chuo, Japan; ²Kogure Eye Clinic, Showa, Japan; ³Kashiwagi Eye Clinic, Kofu, Japan.

Purpose: To compare effect of orally administered lomerizine and methylcobalamin on visual field defect in primary open angle glaucoma (POAG) and normal tension glaucoma (NTG).

Methods: Adult patients with POAG or NTG whose intraocular pressure (IOP) was controlled under 18 mmHg were randomly prescribed 10 mg of lomerizine or 1500 µg of methylcobalamin per day. Static visual field testing, fundus examination and IOP, blood pressure (BP), and pulse rate (PR) measurements were carried out every four months up to three years. Change in mean deviation (MD) slope in eyes showing much faster deterioration was compared between lomerizine group and methylcobalamin group as a primary outcome measure.

Results: Of 120 enrolled subjects, 101 subjects (49 males and 52 females; 63.1±1.4 years) satisfied the study protocol. Only one patient quit the study due to nausea in the lomerizine group. There were no significant difference in the lomerizine group and the methylcobalamin group regards as the entry characteristics. MD slopes of the lomerizine group and the methylcobalamin group were -0.41±0.3 and -1.0±0.9 dB, respectively (P<0.001). Oral lomerizine did not effect on BP and PR, and no significant difference in IOP and BP, and PR were observed between the two groups during the follow up period.

Conclusions: Lomerizine significantly reduced deterioration of glaucomatous visual field loss than methylcobalamin.

Commercial Relationships: Kazuyoshi Kitamura, None; Tatsuya Chiba, None; Fumihiko Mabuchi, None; Satoshi Kogure, None; Fumiko Kashiwagi, None; Shigeo Tsukahara, None; Kenji Kashiwagi, None

Clinical Trial: UMIN000003182

Program Number: 564 Poster Board Number: A0200

Presentation Time: 1:30 PM–3:15 PM

Phase 2 of bamosiran (SYL040012), a novel RNAi based compound for the treatment of increased intraocular pressure associated to glaucoma

Victoria Gonzalez⁴, Kadi Palumaa⁵, Krista Turman⁶, Francisco José Muñoz⁷, Jens Jordan⁸, Julian Garcia⁸, Fernando Ussá⁸, Alfonso Antón⁹, Esperanza Gutierrez⁹, Javier Moreno-Montanes⁹.

⁴Sylentis, Madrid, Spain; ⁵Institut Catala de Retina, Barcelona, Spain; ⁶Hospital Universitario Clínico San Carlos, Madrid, Spain; ⁷Hospital Universitario 12 de Octubre, Madrid, Spain; ⁸Clinica Universidad de Navarra, Pamplona, Spain; ⁹Hospital Universitario Ramón y Cajal, Madrid, Spain; ¹₀Instituto de Oftalmobiología Aplicada, Valladolid, Spain; ¹¹East Tallinn Central Hospital, Tallinn, Estonia; ¹₂Universitätsklinikum Freiburg, Freiburg, Germany; ¹₃Eye Clinic Dr. Krista Turman, Tallinn, Estonia.

Purpose: The aim of this study was to assess the tolerability and intraocular pressure (IOP) lowering effect of three different doses of
SYL040012 eye drops administered QD over a period of 14 days to subjects with increased IOP or glaucoma.

**Methods:** This phase 2 study was a multi-center, randomized, parallel-design, placebo-controlled, double masked clinical trial. 89 patients were randomized to one of following groups: 80 μg/eye/day (0.2%), 300 μg/eye/day (0.75%), 900 μg/eye/day (2.25%) SYL040012 or placebo. Local and systemic tolerability as well as effect on IOP were evaluated. Local tolerability was assessed by performing conjunctival and corneal examinations on a daily basis; full ophthalmic examinations were performed prior to the first and after the last administration. The effect on IOP was evaluated by performing a 24h IOP curve prior to the first administration and on day 14. The study was conducted in accordance with the ICH Guidelines on Good Clinical Practices and following national regulations as well as the tenets that had their origin on the Declaration of Helsinki. The study was registered on www.clinicaltrials.gov (NCT01739244) and EU Clinical Trial Register (EudraCT Number:2011-001849-33). Subjects signed a written consent form stating they understood and agreed to participate in the study.

**Results:** SYL040012 at the dose of 300 μg/eye/day caused a statistically significant reduction in IOP at day 14 when compared to placebo. This reduction was also statistically significant when compared to the IOP curve performed during the screening period. The compound was very well tolerated with only a 14.6% of the patients reporting an adverse event; most of these events (80%) were of mild intensity. No differences among groups were observed in terms of adverse events. The most frequent adverse event was headache. The only severe adverse event registered throughout the clinical trial was hyponatremia in one patient treated with SYL040012 at the dose of 300 μg/eye/day; this event was not considered to be related to the investigational product.

**Conclusions:** In conclusion, the results of this phase 2 study indicate that the dose of 300 μg/eye/day of SYL040012 significantly reduced IOP when compared to basal values and to placebo. Systemic and local tolerance to all studied doses of SYL040012 was good; with a very low rate of adverse events.

**Commercial Relationships:** Victoria Gonzalez, Sylentis (E), Sylentis (I); Kadi Palumaa, None; Kristur Turman, None; Francisco José Muñoz, None; Jens Jordan, None; Julian Garcia, None; Fernando Ussa, None; Alfonso Antón, None; Esperanza Gutierrez, None; Javier Moreno-Montanes, None

**Support:** CDTI program, Spanish Govement

**Clinical Trial:** NCT01739244

**Program Number:** 565 Poster Board Number: A0201

**Presentation Time:** 1:30 PM–3:15 PM

**Initial Clinical Evaluation of Safety, Tolerability and Pharmacodynamics of the Locally-Acting ROCK Inhibitor AMA0076**

**Methods:** A First-in-Human (FIH) study with an initial AMA0076 formulation and a subsequent Phase 1b study with optimized formulations were completed. The FIH study was a multicenter, randomized, double-masked, placebo-controlled dose-escalation study with AMA0076 (or matching placebo) applied topically for 28 days in 82 POAG/OHT patients aged 30-85. The Phase 1b study was a single center, randomized, double-masked, placebo-controlled, repeat-dose, 3 period cross over study in which 21 healthy male and female subjects aged 35-65 were randomized. Each treatment period in the Phase 1b study entailed 1 week of BID topical ocular administration (14 active : 7 placebo) with a washout period of 1 week between treatment periods. Safety evaluation in both studies included AE reporting, vital signs, ECG, laboratory, and visual acuity assessments. Both studies also included biomicroscopy, hyperemia grading (according to a standardized photographic scale), and IOP determinations obtained at baseline and end of treatment at the same diurnal timepoints (pre-dose, 2, 4, and 8 hours post-dosing).

**Results:** AMA0076 was safe and generally well tolerated in both studies. No SAEs were reported. There was no discernible difference in non-ocular AEs or other systemic assessments (vitals, ECG, laboratory) by treatment group in either study. All ocular AEs in both studies resolved without sequelae. At the optimal IOP-lowering dose in each study, all ocular AEs were rated as mild in intensity, with a rate of mild, transient hyperemia in the FIH study and the Phase 1b study of 0% and 28.6%, respectively. In these dose regimens, a decrease in mean diurnal IOP compared to placebo was achieved (p=0.020 and p<0.005, respectively).

**Conclusions:** The optimal dose of AMA0076 demonstrated IOP reduction without significant hyperemia in both clinical studies. No other ROCK inhibitor has demonstrated this finding in the clinic. Therefore, AMA0076, due to its Localized Drug Action, has the potential to optimize the use of ROCK inhibition to lower IOP in patients with glaucoma and ocular hypertension.

**Commercial Relationships:** John Hall, Amakem NV (E); Kenneth N. Sall, None; James H. Peace, None; Douglas Day, None; Michael Tepedino, None; Jason Bacharach, None; Anwar Zaman, None; Stuart Mair, None; Steve Pakola, Amakem NV (E)

**Clinical Trial:** NCT01693315

**Program Number:** 566 Poster Board Number: A0202

**Presentation Time:** 1:30 PM–3:15 PM

**Hypotensive effect of melatonin and its analogues in different animal models**

Hanah A. Alkozi, Alejandro Martinez-Aguila, Begoña Fonseca, Almudena Crooke, Maria Jesus Perez de Lara, Jesus Pintor.

Biochemistry and molecular biology IV, Universidad Complutense de Madrid, Madrid, Spain.

**Purpose:** To demonstrate the potential use of melatonin and its analogues in decreasing IOP which is often elevated in glaucoma.

**Methods:** Different animals were used along this study: New Zealand white rabbits, normotensive and hypotensive by the Trendelenburg position (80 deg. head down). Mice, normotensive control model C57BL/6J and glaucomatous model DBA/2J. Hypertensive monkeys with laser induced unilateral glaucoma (data taken from a study done by Serle JB et al., 2004). Normotensive humans during cataract surgery (data taken from Ismail and Mowafi, 2009). Melatonin or analogues were topically applied except in the case of humans which was a single oral dose of 10 mg. All animals were kept with free access to food and water; they were submitted to controlled 12h/12h light/dark cycle. IOP measurements were taken by TonoPen (rabbits), TonoVet (rabbits) and Tomolab (mice). Single doses of the agonist at a concentration of 100 μM (10


Results: Melatonin application reduced IOP in normotensive rabbits by 22.0% ± 1.6%, when compared to control animals, while melatonin analogue 5- methoxy carbonylamine N-acetyl tryptamine (5-MCA-NAT) had a reduction until 42.5% ± 1.6%. The effect of the latter lasted more than 8 hours, and also a long-term effect, till 3 days, was measured. In glaucomatous mice when applying melatonin it was also possible to detect a reduction of 33.4% ± 2.5% in IOP. This open the possibility to search for other glaucoma models such as the monkey laser induced glaucoma. In this sense, and as indicated by Serle et al., (2004), when 5-MCA-NAT is applied to hypertensive monkeys it resulted in a reduction of 19.2% ± 2.1% in IOP. Finally, when administering melatonin to normotensive humans there was also a reduction of 32.0% ± 3.2% over the patient’s initial IOP values (Ismail and Mowafi, 2009).

Conclusions: Melatonin and its analogues have already displayed an important pharmacological ability reducing intraocular pressure starting from simple experimental animals, moving towards glaucomatous models and finally tested in humans. This is clearly indicating that melatonin and analogues are new promising molecules for the treatment of elevated IOP often associated with glaucoma.

Commercial Relationships: Hanan A. Alkozi, None; Alejandro Martinez-Aguila, None; Begoña Fonseca, None; Almudena Crooke, None; Maria Jesus Perez de Lara, None; Jesus Pintor, None

Support: SAF 2010/16024 and RETICS RD12/0034/0003

Program Number: 567 Poster Board Number: A0203
Presentation Time: 1:30 PM–3:15 PM
The Association Between Normal Optic Nerve Cupping, Normal Visual Fields and Marijuana Use
Edwin R. Swann. Duke Raleigh Hospital, Duke Health Systems, Raleigh, NC.

Purpose: The purpose of this study was to test for the association between normal optic nerve cupping, normal visual fields (VF) and a history of having smoked marijuana. The null hypothesis was that there is no difference in the odds of having a vertical cup disc ratio (C/D ratio) of less than 0.5, or normal VF in subjects who report a history of having smoked marijuana compared to those who had not smoked it.

Methods: The 2005-2008 NHANES data were imported into Stata/IC version 10.0 (StataCorp LP, College Station, Texas). Variables analyzed were: “ever smoke marijuana”, “the vertical C/D ratio” of each eye, race/ethnicit, gender, and age. Another variable examined was normal Humphrey Matrix VF as defined by an NHANES algorithm. The variable vertical C/D ratio was used to create a dichotomous variable “C/D ratio < 0.5”. The variables for ever smoke marijuana, C/D ratio < 0.5 and normal VF were used to create dichotomous variables to represent those variables for each subject instead of for each eye. The logistic regression models for the dependent variables C/D ratio < 0.5 and normal VF were created using a backward elimination process. The model with C/D ratio < 0.5 as a dependent variable had remaining variables ever smoked marijuana and gender as independent variables. The model with normal VF as the dependent variable had a remaining variable of ever smoked marijuana. Permission to allow use of de-identified data from the NHANES in other studies was obtained from subjects at the time of their enrollment.

Results: The adjusted odds ratio of subjects with a vertical C/D ratio < 0.5 was 1.26, 95% CL (1.03 – 1.58) with a “P” value = 0.037.

The odds ratio of subjects with a normal VF who had smoked marijuana compared to those who had not was 1.4, 95% CL (0.91 – 2.16) with a “P” value = 0.119.

Conclusions: This study shows a statistically significant increase in the odds of subjects with C/D ratios<0.5 having a history of having smoked marijuana. There was a lack of statistical significance for the odds of having a normal VF test in subjects who reported having smoked marijuana possibly related to the smaller sample size.

These results suggest that the use of marijuana may have a protective influence on the optic nerve. Croxford (2003) has reported that cannabinoids “may be potent neuroprotective agents.” Further studies could reveal that marijuana has neuroprotective properties.

Table listing the number of observations for each variable.

<table>
<thead>
<tr>
<th>Ever Smoked Marijuana</th>
<th>Number</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>2,747</td>
<td>44.47</td>
</tr>
<tr>
<td>Yes</td>
<td>3,430</td>
<td>55.53</td>
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<td>Total</td>
<td>6,177</td>
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<table>
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<tr>
<th>Cup Disc Ratio &lt; 0.5</th>
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</tr>
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</tr>
<tr>
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<tr>
<th>Normal Visual Fields</th>
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<tr>
<td>Female</td>
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Figure 1
ARVO 2014 Annual Meeting Abstracts

Table showing the crude and adjusted odds ratios for subjects with cup/disc ratios less than 0.5 and for subjects with normal visual fields who self-reported having smoked marijuana.

<table>
<thead>
<tr>
<th>Ever Smoke Marijuana or Hashish</th>
<th>Crude Analysis Odds Ratio (95% CI)</th>
<th>Adjusted Analysis Odds Ratio (95% CI)</th>
<th>Crude Analysis p value</th>
<th>Adjusted Analysis Odds Ratio p value</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1.24 (1.00 – 1.55)</td>
<td>1.26 (1.03 – 1.58)</td>
<td>0.046</td>
<td>0.029</td>
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<tr>
<td>No</td>
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</table>

<table>
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<th>Gender</th>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.651 (0.89 – 1.24)</td>
<td>1.16 (0.92 – 1.45)</td>
<td>0.530</td>
<td>0.194</td>
</tr>
<tr>
<td>Male</td>
<td>Reference Group</td>
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</table>

<table>
<thead>
<tr>
<th>Ever Smoke Marijuana or Hashish</th>
<th>Crude Analysis Odds Ratio With Normal Visual Field (95% CI)</th>
<th>Crude Analysis p value</th>
<th>Adjusted Analysis Odds Ratio p value</th>
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<tr>
<td>Yes</td>
<td>1.40 (0.91 – 2.16)</td>
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Figure 2

Commercial Relationships: Edwin R. Swann, None