STUDY REPORT

Intraocular pressure and tolerability Study of Preserved Bimatoprost 0.01% (BIMMD) or Tafluprost Unit Dose Preservative Free 15microgram/ml (TUDPF) (Saflutan), in patients with Ocular hypertension or glaucoma suitable for prostaglandin therapy:

A Randomized, single masked, 3 month cross-over, Investigator led, European multicentre Trial, II (SPORT II)

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Study Report

Approval				
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1. Table of contents for the individual clinical study report

2. List of tables and list of figures

3. List of abbreviations and definition of terms

AIOL	Accommodating Intraocular Lens
BCVA	Best Corrected Visual Acuity
BUMD	Preserved Bimatoprost
BAK	Benzalkonium chloride
CI	Confidence Interval
CRF	Case Report Form
EC	Ethics Committee
EU GMP	European Union Good Manifacturing Practice
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	Intraocular Pressure
MD	Mean Deviation
PI	Principal Investigator
PIOL	Phakic Intraocular Lens

POAG	Primary Open-Angle Glaucoma
TUDPF	Tafluprost Unit Dose Preservative Free
XFG	Exfoliative Glaucoma

4. Ethics

The trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and its amendment in October 2000, Edinburgh, Scotland, the European Guidelines on Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) Guidelines

4.1 Informed consent procedures

The Investigator ensured that each patient was fully informed about the nature and objective of the study and possible risks associated with participation. Patients indicated assent to participate in the study by personally signing and dating the written informed consent form. The process of obtaining informed consent was documented in the patient's source documents. The informed consent form used in this study, and any changes made during the course of the study, were prospectively approved by the Ethics Committees (EC). The Investigator retained the original of each patient's signed informed consent form and gave a copy to the patient.

Eligible patients were only included in the study after providing written (witnessed, where required by law or regulation), EC-approved informed consent. In cases where the patient's representative gave consent, the patient was informed about the study to the extent possible given his/her understanding. If the patient was capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent was obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol).

Women of child bearing potential were informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study.

Study was listed at the www.ClinicalTrials.gov, 21 days after 1st patient screened, OR 21 days after 1st patient randomized, whichever comes first.

5 Investigators and study administrative structure

The Coordinating Investigator was Ingeborg Stalmans from UZ Leuven, the Sponsor was UZ Leuven. Luca Rossetti from *Azienda Ospedaliera de San Paolo, Milan* led the statistics team.

6 Introduction

Prostaglandin analogues are the most widely used first line treatment for glaucoma.

Several prostaglandin analogues are available, which differ in their efficacy and tolerability profile.

Intolerability can be caused by the active compound and/or the preservative. Therefore, several prostaglandin analogues have been developed without preservatives. However, some compounds are dependent on preservatives to penetrate into the eye, and therefore to maintain their efficacy.

The current study has been designed to investigate the efficacy and tolerability of two prostaglandin analogues: preservative-free tafluprost 15 microgram/ml versus bimatoprost 0.1 mg/ml which contains 0.02% of benzalkonium chloride (BAK) as a preservative. This cross-over study will shed new light on the efficacy and tolerability of two currently used prostaglandin analogues which have not been compared head to head so far, and on the relative impact of active ingredient versus BAK on tolerability and efficacy. This study will investigate the efficacy and safety of BUMD and TUDPF in a clinical setting and may influence these drugs' future use in Europe.

7 Study objectives

Primary outcome

The primary objective is to compare the difference in mean IOP values between the 2 groups at 6 months.

Secondary outcome

- the difference in IOP values between the groups in *change from baseline IOP* at month 3 and month 6 respectively;
- the difference in *mean IOP* between the 2 groups at 3 months;
- the difference in IOP between the 2 groups at each time points at months 3 and 6;
- *Safety endpoints* will be; visual acuity, adverse events, slit lamp biomicroscopy, ocular tolerability and optic nerve assessment.

8 Investigational plan

8.1 Overall study design and plan-description

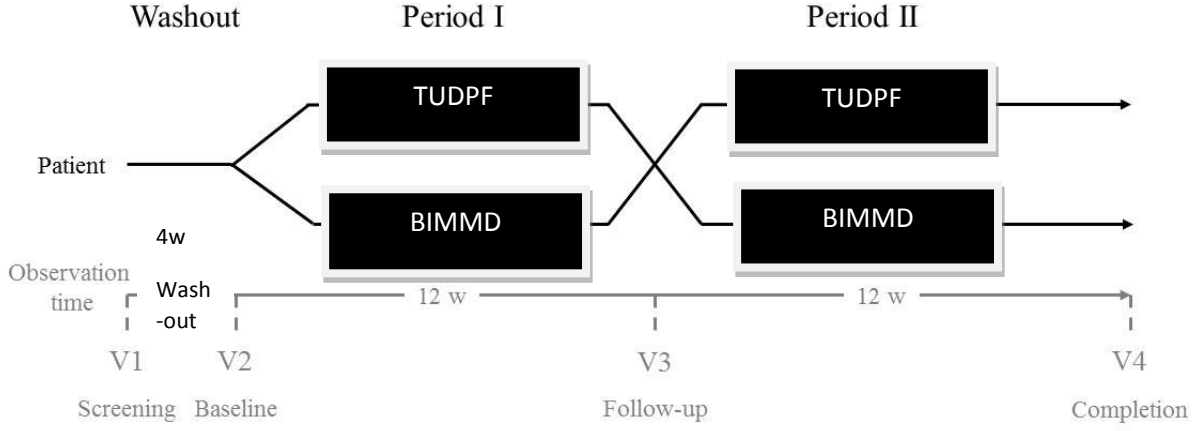

Figure 1 - Study design.

8.2 Discussion of study design, including the choice of control groups

- This is a prospective, randomized, investigator-masked, crossover comparison;
- Patients with ocular hypertension or glaucoma (XFG or POAG) and who consent to participate will be enrolled in this study
- Patients will be scheduled for a screening visit IOP assessment (IOP measurements at 08:30, 12:30 and 16:30 (±1 hour).
- Patients who are on therapy at the screening visit and who consent to participate will undergo a washout period for 4 weeks (depending on therapy) before the baseline visit; To avoid exposing the patient to any additional risks of a second wash-out, the patients will be switched from the first to the second therapy without additional wash-out. Since the wash-in and wash-out of prostaglandin analogues is known to be around 4 weeks, and the second treatment period is 3 months, no influence of the first treatment of the final study assessment is expected.
- Patient under the washout period can be given brinzolamide (Azopt®) if needed, Azopt should then be discontinued 5 days before baseline visit;
- After the screening visit (and after washout period for treated patients) patients will be scheduled to undergo a baseline visit IOP assessment (IOP measurements at 08:30, 12:30 and 16:30 (±1 hour with a minimum of 3 hours between readings) and will then be randomized for Period 1 to receive either BIMMD drops once in the evening (20:30) or TUDPF drops once in the evening (20:30) for 3 month
- After 3 month, patients will be switched for Period 2, to the opposite treatment (e.g. switched to either BIMMD or TUDPF) to be dosed in the evening;
- After another 3 months they will undergo the final evaluation of IOP levels and of tolerability;
- Intermediate safety visits may be scheduled at the discretion of the investigator.

8.3 Selection of study population

67 patients with ocular hypertension or open angle glaucoma (including those with pseudoexfoliation) and who consent to participate were enrolled in this study.

8.3.1 Inclusion criteria

- A patient suffering from ocular hypertension, XFG or POAG and needs treatment in both eyes
- Patient is at least 18 years
- Patient is able and willing to participate in the study for the whole duration of the follow up and is willing to sign the consent form.

8.3.2 Exclusion Criteria

- Unwilling to sign informed consent;

- Younger than 18 years old;
- Ocular condition that are of safety concern and that can interfere with the study results;
- Visual field defects with an MD value above -15dB on either eye on Humphrey (or the equivalent in Octopus) and/or threatening fixation
- Contact lens wearer;
- Closed/barely open anterior chamber angles or history of acute angle closure on either eye as assessed by gonioscopy;
- Ocular surgery (other than glaucoma surgery) or argon laser trabeculoplasty within the past three months on either eye;
- Glaucoma surgery within the past 6 months on either eye;
- Ocular inflammation/infection occurring within three months prior to pre-trial visit on either eye;
- Concomitant topical ocular medication that can interfere with study medication on either eye;
- Known hypersensitivity to any component of the trial drug solutions;
- Other abnormal condition or symptom preventing the patient from entering the trial, according to the Investigator's judgement;
- Refractive surgery patients at any time;
- Women who are pregnant, are of childbearing potential and are not using adequate contraception or are nursing;
- Inability to adhere to treatment/visit plan;
- Have participated in any other Interventional clinical trial (i.e., requiring informed consent) involving an investigational drug within one month prior to pre-trial visit.

8.3.3 Withdrawal of subjects

A subject becoming pregnant would be withdrawn from the trial treatment A subject would be withdrawn from the trial treatment if, in the opinion of the investigator, it was medically necessary, or if it was the wish of the subject. If a subject did not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

8.4 Treatment of subjects

8.4.1 Study products

BIMMD bottles were supplied by Allergan as a courtesy to the investigators and TUDPF vials were bought by the Sponsor.

Labeling and packaging (masking with a new outer box) of trial medication was handled and the trial medication distributed by the Sponsor in accordance with the EU GMP Annex 13 and EU GCP, or the Sponsor can delegate this task to another qualifying center.

Each patient will receive the following medication throughout his participation in the clinical trial, according to the study design (**Fout! Verwijzingsbron niet gevonden.**):

- 1 set (3 boxes) of BIMMD, each box containing 1 bottle with a labeling that states once-daily, evening administration (20:30).
- 1 set (3 boxes) of TUDPF, each box containing 30 Unit dose vials with a labeling that states once-daily, evening administration (20:30).

One additional back-up box of each medication for each period per patient will be stored at study center.

The labeling of the outer box will not expose the treatment but just state patient number and period (I or II).

Patients will be instructed to bring these boxes back to the hospital at their next study visit and destruction of left over vials will be handled in accordance with the EU GCP, by each study site pharmacy (or delegated by the study site pharmacy to a site which meets this requirement).

8.4.2 Prior and Concomitant Therapy

No other topical ophthalmic medication that can interfere with study medication, could be used in either eye during the complete study period.

No systemic medication which is known to affect IOP (e.g. beta-adrenergic antagonists etc.) could be initiated or altered during the study.

Other therapy considered necessary for the patient's welfare could be given at the discretion of the Investigator. All such therapy was recorded in the Case Report Form (CRF).

No other drug under investigation could be used concomitantly with the trial drug. The patients were not allowed to participate concurrently in any other clinical trial.

8.4.3 Treatment Compliance

The patients were instructed by their Investigator how and when to apply their medication.

8.5 Clinical Safety Assessments

8.5.1 Flow Chart

The table below evidences (in bold) the specific safety variables and their collection schedule. Patients should be seen for all visits on the designated day or as close as possible.

Study Phase	Screening	Baseline Start Period 1	Follow-up Start Period 2	Completion
Visit Number	1	2	3	4
Study Week	(-4 weeks)*	0	W12	W24
Allowed Window (in days)		5	5	5

Ocular History	X			
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Pregnancy test	X	(X)	(X)	(X)
IOP (08:30; 12:30 and 16:30 ± 1 hour)	X	X	X	X
Visual Fields		X		X
BCVA + Refraction	X	X	X	X
Slit Lamp Examination	X	X	X	X
Gonioscopy	X			
Lid Examination	X	X	X	X
Ophthalmoscopy	X	X	X	X
Randomisation		X		
Medication Dispensing (D) and / or Retrieval (R)	D	D	D/R	R
Conc. Medications /Non-Drug Therapies	X	X	X	X
Adverse Events		X	X	X

X: obligatory

(X): only if legally required by local regulatory framework

Table 1 – Flow Chart

8.5.2 Visual fields

A visual field was performed using the Humphrey or Octopus perimeter at baseline and at exit visit

8.5.3 Visual Acuity and Refraction

Best corrected Snellen Visual Acuity was determined and recorded at the screening visit, at the baseline visit and at the 3 and 6 month visits.

A clinically relevant decrease in best corrected Visual Acuity compared to the pre-trial visit was reported as AE.

8.5.4 Lid and slit lamp examination (biomicroscopy)

Lid and slit lamp examinations was performed at the screening visit, at the baseline visit, at the month 3 and 6 visit.

Skin and margins of upper and lower lids were examined. Deposition of pigment on the corneal endothelial layer or the lens capsule or any abnormalities of the lids, conjunctiva (palpebrae and bulbi), cornea, anterior chamber, iris and lens was described in the CRF and be graded mild, moderate or severe. Conjunctival hyperemia was scored using the Allergan scoring chart for hyperemia. Aphakia or intraocular lens (AIOL, PIOL or iris clip) was specified. Cells present in a slit of 2 mm were graded as mild=1 (3-5 cells), moderate=2 (6-20 cells) or severe=3 (>20 cells).

8.5.5 Ophtalmoscopy

At the screening visit, at the baseline visit, at the month 3 and 6 visit, ophthalmoscopy was performed to examine the status of the optic nerve head. The vertical cup/disc ratio was scored and the presence of optic disc hemorrhages was recorded.

9 Statistical Analysis

9.3 Demographics

On a total of 69 subjects recruited, 66 were randomized. One subject (P303) was a screening failure. Patients P106 and P115 left the study before randomization.

All subjects that had at least one measurement under treatment (either at 3 or 6 months) and both a Screening and Baseline visit (to assess the correct inclusion criteria) were included and analysed.

On a total of 66 subjects randomized, the final analysis included 64 subjects, 33 for arm A and 31 for arm B. One subject (P103) was excluded since it did not have any measurement at 3 or 6 months. Another subject (P211) was excluded since it did not have any measurements at Screening and Baseline.

One subject was missing the measurements at 3 months (P411), while another was missing the measurements at 6 months (P415). These two subjects were included in the analysis.

A total of 30 males and 36 females were analysed. The age at baseline was 70.1 ± 8.3 years (Mean ± SD). The Mean Deviation at baseline was -0.59 ± 4.33 dB. The cup-to-disc ratio at baseline was -0.55 ± 0.22. No significant differences in baseline conditions could be detected between the two arms.

In total, before the study, prostaglandin eye drops were used by 26 subjects in Arm A (of which 3 used fixed combination with Timolol) and 25 in Arm B (1 in combination with Timolol). Additionally, 5 subjects in Arm A and 4 in Arm B were on Timolol alone, while 1 in Arm A and 2 in Arm B where without any treatment before the study. Only one subject used Brinzolamide, in Arm A.

Prostaglandin distribution was as follows: 30 subjects (15 in Arm A and 15 in Arm B) used Bimatoprost; 30 subjects (15 in Arm A and 15 in Arm B) used Bimatoprost; 15 (9 in Arm A and 6 in Arm B) used Latanoprost; 4 (1 in Arm A and 3 in Arm B) used Travoprost; 2 (1 in Arm A and 1 in Arm B) used Tafluprost.

9.4 Time course analysis

This analysis was carried out using a linear mixed model. Predictors in the linear model were the Period ("Screening", "Baseline", "3 Months", "6 Months") and the randomisation Arm ("A" or "B"). The interaction between the Arm and the Period were used to estimate and compare the two arms at different time points.

Random effects were used to account for repeated measurements on the same Subject (both across visits and within the same visit, as the protocol scheduled three measurements per day) and clustered observations from different Centres (as nested random effects). Therefore, incomplete cases could be included (i.e. missing visits or missing IOP measurements within the visit). For all analysis, when multiple pairwise comparisons are reported, their p-values have been corrected using the Tukey-Kramer method.

No significant differences could be found between the two Arms at Screening and Baseline. Arm B did not have a significantly lower IOP at 3 Months ($p = 0.0632$) but had a significantly higher IOP at 6 months ($p = 0.0307$). A carryover effect was not evident, as the mean estimates after the cross-over switch were very similar for the same medication regardless of the Arm sequence (see next paragraph). Results are reported in Table 2 and depicted in Figure 2.

The random effect to account for clustering by centres was significant ($p = 0.003188$) indicating significant variations among centres. This issue is further explored in the next paragraph.

	Screening	**Baseline**	**3 Months**	**6 Months**
Arm A	15.22	20.26	14.71	13.34
(IOP [95% CI], mmHg)	[13.52, 16.92]	[18.56, 21.96]	[13.01, 16.41]	[11.64, 15.05]
Arm B	15.68	20	13.46	14.79
(IOP [95% CI], mmHg)	[13.95, 17.41]	[18.27, 21.74]	[11.72, 15.19]	[13.06, 16.53]

Table 2. Mean IOP at different time points.

No significant differences could be detected at Screening and Baseline between the two groups. Both differences at 3 and 6 months were significant and opposite in signs. The table reports the mean estimate and, in brackets, the 95% Confidence Interval (CI) limits. Only the difference at 6 months was significant between the two arms. Notice that although the 95% CI for the estimates partially overlap at 6 Months, the 95% CI for the difference did not include 0 (i.e. the test was significant at 0.05). The blue line and dots represent the time course of Arm A, while the red line and dots represent estimates for Arm B.

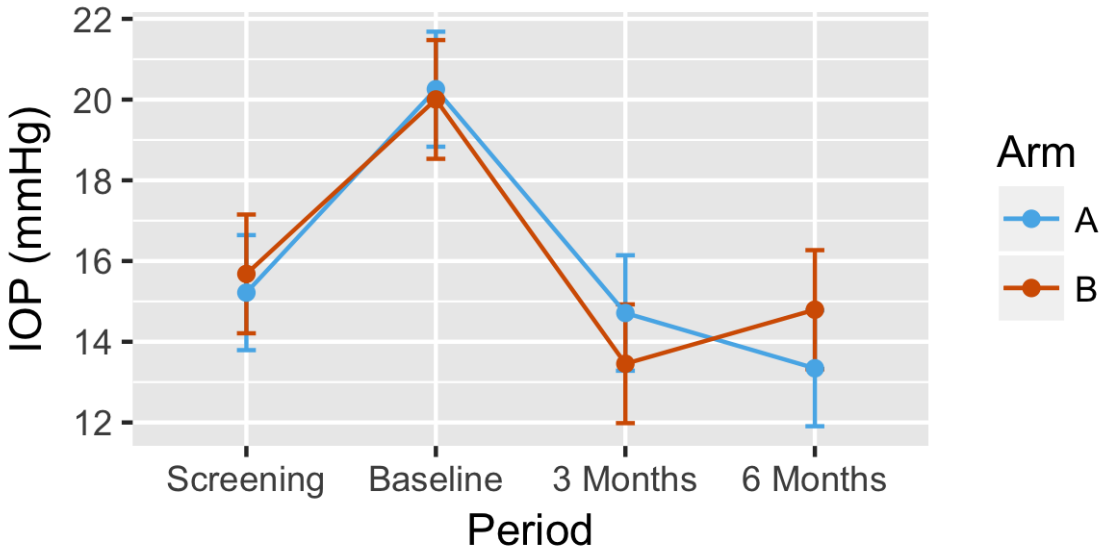

Figure 2. Mean IOP at different time points, representation of what is reported in Table 2.

No significant differences could be detected at Screening and Baseline between the two groups. Differences at 3 and 6 months were opposite in signs. Only the difference at 6 months was significant between the two arms. Notice that although the 95% CI for the estimates partially overlap at 6 Months, the 95% CI for the difference did not include 0 (i.e. the test was significant at 0.05). The blue line and dots represent the time course of Arm A, while the red line and dots represent estimates for Arm B.

9.5 Analysis by medications (Drugs)

The same approach was used to analyse the overall differences of the two Drugs across the whole trial (excluding the Screening visit). This was achieved by using a mixed model similar to the one in the previous paragraph, but using the Treatment (a factor, with levels “Null”, “Drug 1” or “Drug 2”) and the Arm of treatment (“A” or “B”) as predictors. Drug 1 is defined as the first drug in Arm A. Drug 2 is defined as the first drug in Arm B. The interaction between the Treatment and the Arm was used to test whether the Arm sequence could influence the effect of either medication (this would be indicative of a significant carryover effect). Since no significant effect could be detected due to the Arm sequence ($p = 0.8757$), we assumed no carryover effect and just used the Treatment as the sole fixed predictor.

Since a large proportion of the participants was on Bimatoprost treatment before the study, we also explored whether being on Bimatoprost could have any additional effect that could bias the results. We used a mixed model with a two-way interaction (between the Treatment and the pre-study medication). The pre-study medication effect had two levels, either “Bimatoprost” or “Else”. We could not find any significant effect of being on Bimatoprost before the study on the effect of the two drugs ($p = 0.8757$) used in the study. We also analysed the subset of subjects on either Latanoprost or Bimatoprost (the two most common pre-study medications) and found no significant effect of previous treatment with Bimatoprost over Latanoprost on the final results ($p = 0.4894$).

We then tested whether the Centre had a significant influence on the effect of either medication. This was done by using a mixed model similar to the previous one, but using the Centre and the

Treatment (plus their interaction) as predictors, with the Subject as the only random effect. This interaction was significant ($p < 0.0001$).

To further investigate the specific variations, we used a sum-to-zero contrast in the model so that each Centre baseline and its effect on IOP reduction were compared to the overall mean IOP (at baseline) and the overall mean effect on IOP lowering for each medication.

We observed significant variations in the baseline. Specifically, Centres 2 (1.71 [0.14 – 3.27] mmHg) and 5 (3.89 [1.14 – 2.65] mmHg) had a Baseline IOP that was significantly higher than the overall mean ($p < 0.05$), while it was significantly lower for Center 1 (-1.93 [-3.27, -0.58] mmHg) and 3 (-3.91 [-5.75, -2.07] mmHg).

Compared to the average IOP lowering effect of Drug 1, a reduced effect was observed for Centre 3 (1.96 [0.60, 2.71], $p = 0.00586$), while a significantly larger effect was observed for Centre 5 (-3.72 [-4.67, -2.78], $p < 0.0001$).

Compared to the average IOP lowering effect of Drug 2, a reduced effect was observed for Centre 1 (1.65 [0.62, 2.74], $p = 0.00233$) and Centre 3 (2.74 [1.32, 4.15], $p = 0.00016$), while a significantly larger effect was observed for Centre 5 (-3.94 [-4.93, -2.95], $p < 0.0001$).

Figure 3 reports Centre variations at 3 Months and 6 Months for the two arms.

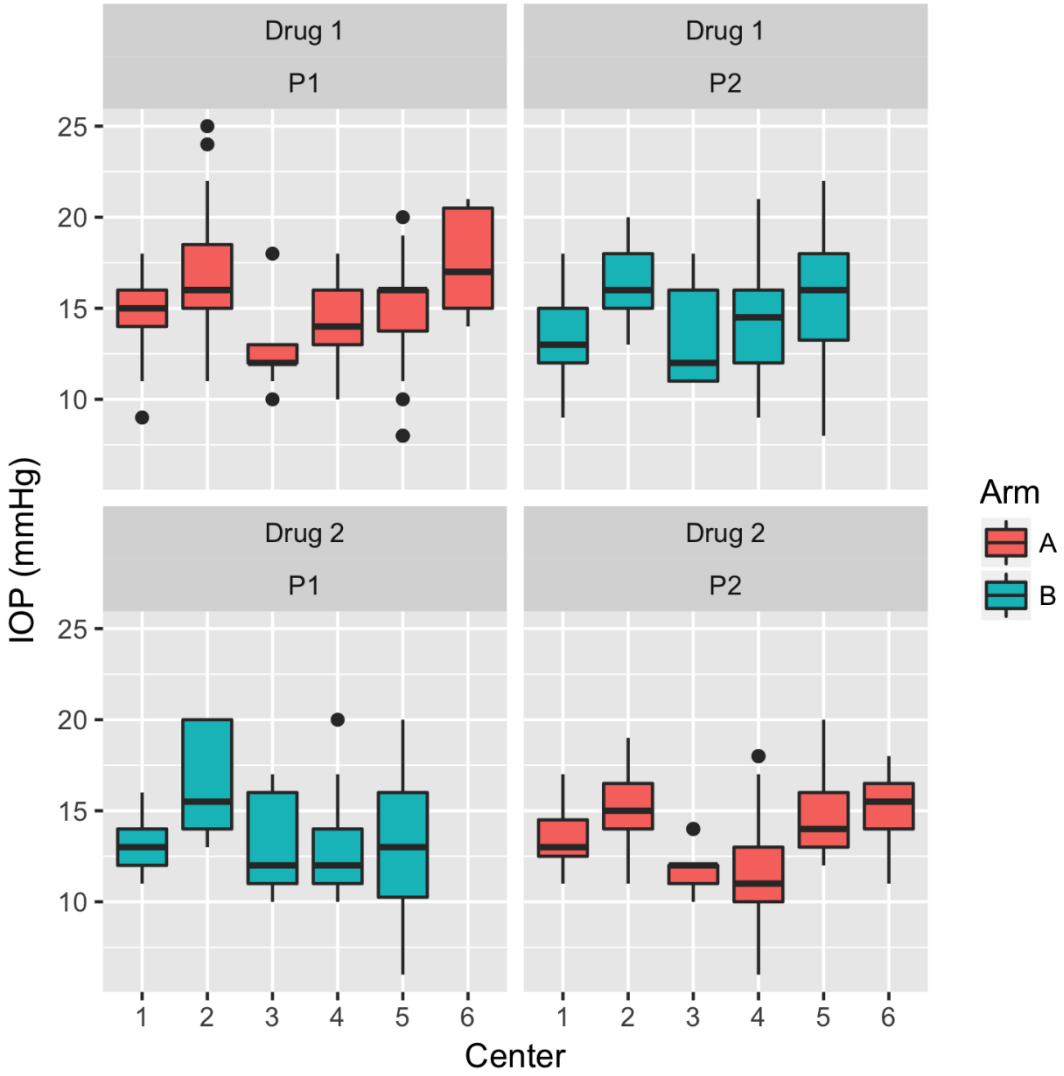

Figure 3. Box plots showing the distribution of IOP values for different groups at 3 Months (P1) and 6 Months (P2) for the two drugs at different centres. Centre 6 had two subjects and they were both assigned to Arm A.

Hence, the final model included nested random effects for the Subject and the Centre (to account for the observed variations) and Treatment as the sole fixed effect. The results are reported in Table 3. Both medications lowered the IOP significantly compared to Baseline (5.38 mmHg for Drug 1 and 6.75 for Drug 2, $p < 0.0001$). The mean difference between the two medications was 1.37 mmHg ($p < 0.0001$).

The proportional reduction was also analysed (percentage reduction). This was achieved using a generalized linear model (GLM) with a Gamma error distribution and a logarithmic link function. As with logarithmic variable transformations, the linear comparisons are performed in the log scale and translate to proportional changes in the linear scale. However, the use of GLM models the log of the mean (i.e. the actual variable) instead of the mean of the log (as it would happen with data transformation). Random effects were included as for the previous models. Results are reported in

Table 3. Compared to baseline, Drug 1 reduced the IOP by 27% ($p < 0.0001$) while Drug 2 by 33% ($p < 0.0001$). IOP with Drug 2 was 9% lower than with Drug 1 ($p < 0.0001$). Effects were different across centres, especially in terms of differential effects of the two drugs, although always in a consistent direction (Drug 2 was more effective than Drug 1).

		IOP Reduction [95% CI]		
		mmHg	**%**	**Corrected p**
Average	**Drug 1 - Baseline**	5.4 [4.87, 5.92]	27 [24, 29]	**<.0001**
(n = 64)	**Drug 2 - Baseline**	6.73 [6.21, 7.25]	33 [31, 35]	**<.0001**
	Drug 1 - Drug 2	1.34 [0.81, 1.86]	9 [6, 12]	**<.0001**
Center 1	**Drug 1 - Baseline**	3.8 [2.79, 4.82]	21 [16, 26]	**<.0001**
(n = 14)	**Drug 2 - Baseline**	4.53 [3.51, 5.54]	25 [2, 29]	**<.0001**
	Drug 1 - Drug 2	0.73 [-0.3, 1.75]	4 [-2, 1]	0.3459
Center 2	**Drug 1 - Baseline**	4.7 [3.46, 5.95]	22 [16, 28]	**<.0001**
(n = 9)	**Drug 2 - Baseline**	5.7 [4.46, 6.95]	26 [2, 32]	**<.0001**
	Drug 1 - Drug 2	1 [-0.24, 2.24]	5 [-2, 12]	0.2573
Center 3	**Drug 1 - Baseline**	2.67 [-4.45, 6]	17 [9, 25]	**0.004**
(n = 6)	**Drug 2 - Baseline**	3.44 [-5.97, 7.53]	22 [14, 29]	**<.0001**
	Drug 1 - Drug 2	0.78 [-0.75, 2.3]	5 [-4, 14]	0.2264
Center 4	**Drug 1 - Baseline**	5.09 [4.07, 6.1]	26 [21, 3]	**<.0001**
(n = 15)	**Drug 2 - Baseline**	6.8 [5.82, 7.77]	36 [32, 39]	**<.0001**
	Drug 1 - Drug 2	1.71 [0.69, 2.73]	13 [8, 19]	**0.0031**
Center 5	**Drug 1 - Baseline**	8.35 [7.47, 9.23]	37 [33, 4]	**<.0001**
(n = 18)	**Drug 2 - Baseline**	10.12 [9.22, 11.02]	44 [41, 47]	**<.0001**
	Drug 1 - Drug 2	1.77 [0.87, 2.67]	12 [7, 17]	**0.0004**
Center 6	**Drug 1 - Baseline**	3.17 [0.53, 5.81]	17 [1, 29]	0.0838
(n = 2)	**Drug 2 - Baseline**	6.5 [3.5, 9.5]	32 [18, 44]	**0.0002**
	Drug 1 - Drug 2	3.33 [0.33, 6.33]	19 [2, 33]	0.0804

Table 3 – Proportional IOP reduction (percentage reduction)

9.6 Safety analysis

No significant changes occurred for BCVA (EDTRS charts) and visual field defect (Mean Deviation in dB) during the whole trial. Only one subject in Arm A showed an increase in the cup-to-disc ratio (from 0.75 to 0.80) at the last visit, but the Mean Deviation at the visual field was not decreased compared to baseline.

Table 4 reports the score increase from baseline for slit lamp assessment. The mode of the score was calculated only on the subjects that showed an increase (except for the Iris score, where no increase was observed). No formal analysis was conducted due to the low number of occurrences.

		Score Increase				
		Lid	**Cornea**	**Conjuctiva**	**Iris**	**Lens**
N Subjects	**Arm A**	0	3	2	0	0
	Arm B	2	3	2	0	2
Max score		1	2	2	0	1
Mode		1	1	1	0	1

Table 4 - Score increase from baseline for slit lamp assessment

The Hyperemia score did not change significantly between the two treatments (Wilcoxon paired test, p = 0.78). No significant changes from the Baseline could be detected with either medication at 3 Months. The mean of the Hyperemia score was 0.38 [0.05, 0.73] for Drug 1 (0.44 [0.10, 0.78] at 3 Months), while it was 0.41 [0.07, 0.74] for Drug 2 (0.41 [0.071, 0.75] at 3 Months).

10 Conclusion

Our data shows that BIMMD can offer some advantage in IOP reduction compared to TUDPF with minimal to no increase in side effects, including hyperemia. Further longitudinal study with long term administration of the two drugs will be needed to asses long term adverse effects and whether such additional IOP reduction indeed results in a better control of disease progression.