# STUDY REPORT SYNOPSIS

Intraocular pressure and tolerability Study of Preservative Free Bimatoprost 0.03% Unit Dose (BUDPF) or preservative free Latanoprost 0.005% Unit Dose (LUDPF) (Monoprost®) in patients with Ocular hypertension or glaucoma: A Randomized, single masked, 3 month cross-over, Investigator led, European multicentre Trial (SPORT)

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| **PROTOCOL No.:** | ECR-GLC-2013-06 (SPORT) |
| **ACRONYM:** | SPORT |
| **EudraCT Number / ClinicalTrials.gov Number:** | 2013-003490-10 / NCT01975714 |
| **SPONSOR:** | AIBILI (EVICR.net) |
| **REPORT VERSION Nº:** | 0 |
| **REPORT VERSION DATE:** | 2015/11/10 |

Investigator(s) : Ingeborg Stalmans – UZ Leuven



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# 1 Synopsis

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| **Sponsor**<br>AIBILI (Coordinating Centre of EVICR.net) | |
| **Coordinating Investigator**<br>Ingeborg Stalmans, UZ Leuven | |
| **Name of Active Ingredient:** Preservative Free Bimatoprost 0.03% Unit Dose; Preservative free Latanoprost 0.005% Unit Dose | |
| **Title of Study:** Intraocular pressure and tolerability Study of Preservative Free Bimatoprost 0.03% Unit Dose (BUDPF) or preservative free Latanoprost 0.005% Unit Dose (LUDPF) (Monoprost®) in patients with Ocular hypertension or glaucoma: A Randomized, single masked, 3 month cross-over, Investigator led, European multicentre Trial (SPORT) | |
| **Investigators:** Anton Hommer, Francesca Cordeiro, Francesco Oddone, Gordana Sunaric Megevand, Ingeborg Stalmans, Luca Rossetti, Luísa Ribeiro. | |
| **Study centre(s):**<br>EVICR.net Clinical Site 01 - Centre for Clinical Trials AIBILI, Coimbra, Portugal<br>EVICR.net Clinical Site 16 – Centre for Clinical Trials, San Paolo Hospital, Milan, Italy<br>EVICR.net Clinical Site 18 – Department of Ophthalmology, University Hospitals Leuven, Leuven, Belgium<br>EVICR.net Clinical Site 20 – G.B.Bietti Eye Foundation – IRCCS, Rome, Italy<br>EVICR.net Clinical Site 83 – Hommer Ophthalmology Institute, Vienna, Austria<br>EVICR.net Clinical Site 84 – ICORG - Imperial College Ophthalmologic Research Group, London, United Kingdom<br>EVICR.net Clinical Site 85 – Clinical Research Centre Mèmorial A de Rotschild, Geneva, Switzerland | |
| **Publication (reference):** Not applicable | |
| **Studied period (years):** 1 year, 4 months<br>**First enrolment:** 22-Oct-2013<br>**Last completed:** 17-Feb-2015 | **Phase of development:** Phase IV study |
| **Objectives:** This cross-over study investigated the efficacy and safety of BUDPF and LUDPF in a clinical setting and may influence these drugs' future use in Europe. The primary objective was to compare the difference in mean IOP values between the 2 groups at 6 months | |
| **Methodology:** Prospective, randomized, investigator-masked, cross-over clinical study carried out at 7 European centers (members of EVICR.net), of efficacy and safety of BUDPF and LUDPF for 3 months in patients treated with preserved prostaglandins for at least 6 weeks. | |
| **Number of patients (planned and analysed):** Planned 67 patients. Included and analysed 67 patients. | |
| **Diagnosis and main criteria for inclusion:**<br>*Inclusion Criteria*<br>1. A patient suffering from ocular hypertension, XFG or POAG that has been on a preserved prostaglandin monotherapy for at least 6 weeks and needs treatment in both eyes<br>2. At pre-screening and screening visit (09:00 ± 1 hr) the IOP is less than or equal to 21 mm Hg in both eyes.<br>3. Patient is older than 39 years and younger than 85 years<br>4. 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<br>*Exclusion Criteria*<br>1. Unwilling to sign informed consent;<br>2. Not at least 40 years old;<br>3. Ocular condition that are of safety concern and that can interfere with the study results;<br>4. Visual field defects with an MD value above -12dB with Humphey or above +12dB with Octopus on either eye;<br>5. Contact lens wearer; | |

6. Closed/barely open anterior chamber angles or history of acute angle closure on either eye as assessed by gonioscopy;
7. Ocular surgery (other than glaucoma surgery) or argon laser trabeculoplasty within the past three months on either eye;
8. Glaucoma surgery within the past 6 months on either eye;
9. Ocular inflammation/infection occurring within three months prior to pre-trial visit on either eye;
10. Patients with pigmentary glaucoma on either eye;
11. Patients with Neovascular glaucoma on either eye;
12. Concomitant topical ocular medication that can interfere with study medication on either eye;
13. Known hypersensitivity to any component of the trial drug solutions;
14. Other abnormal condition or symptom preventing the patient from entering the trial, according to the Investigator's judgement;
15. Refractive surgery patients at any time;
16. Women who are pregnant, are of childbearing potential and are not using adequate contraception or are nursing;
17. Inability to adhere to treatment/visit plan;
18. Have participated in any other clinical trial (i.e., requiring informed consent) involving an investigational drug within one month prior to pre-trial visit

**Test product, dose and mode of administration, batch number:**
Each patient received the following medication throughout his participation in the clinical trial:

- BUDPF (0.03%) eye drops once-daily, evening administration (21:00).
- LUDPF (0.005%) eye drops once-daily, evening administration (21:00).

**Duration of treatment:** 6 months (2 periods of 3 months)

**Reference therapy, dose and mode of administration, batch number:**
Not applicable.

**Criteria for evaluation:**
All patients included in the study were used for the Intent to Treat (ITT) population analysis.

**Efficacy:**

- Intraocular Pressure

**Safety:**

- Best Corrected Visual Acuity;
- Slit lamp biomicroscopy;
- Ocular tolerability;
- Optic nerve assessment.

**Statistical methods:** The sample size calculation was based on the assumption that a difference in mean IOP of 1 mmHg between the 2 treatment groups is clinically relevant. About 60 patients were calculated to be needed in this crossover study, given a type I error of 0.05 and a statistical power of 80%, with a standard deviation of 2.8 mmHg. Assuming approximately 10% rate of withdrawals, 67 patients were included and randomized. The worst eye (defined as the eye with highest baseline IOP) was defined as study eye and included in the statistical analysis. Statistical analysis was performed in R programming environment. Linear mixed modeling was used to account for repeated measures on the same subject (patient random effect) and clustering of observations from the same center (center random effect). Fixed effects included treatment and baseline IOP (which was included either as a continuous covariate or as a level of the treatment fixed effect).

**SUMMARY - CONCLUSIONS**
This study demonstrates BUDPF to be superior to LUDPF in reducing IOP at 6 months, a finding reinforced in the intra-subject IOP comparison, which was possible to perform based on the cross-over study design. Moreover, as far as we are aware, this is the first head-to-head comparison of preservative-free prostaglandin drugs in glaucoma. The major advantage of the cross-over design is it enables intra-subject differences in

treatment arms to be compared in a more precise fashion. Another strength of this study is its multicenter nature, which increases the validity of the data by reducing the centre-specific effects. A potential disadvantage of a cross-over design is that carry-over effects from the previous treatment period may be difficult to control. However, after adjusting for the centre effect in this study, the carry-over effect was not found to affect the final comparison outcomes. Furthermore, as each arm of the study was for a period of 3 months, these effects are probably minimised.

An interesting finding seen in our study was that the difference in efficacy was not present at 3 months. This finding could be explained by several factors. First, centre variability can play a role. Second, various prostaglandin analogues may take different time spans to reach their maximal effectiveness. A longer study period might have provided more insights into this observation. Indeed, the relatively short study periods are to be considered a limitation of this trial. Longer follow-up would have added information on not only efficacy but also safety. Finally, the preselection of patients who had already been treated with a prostaglandin analogue may have lead to a selection bias. Not only were these patients by definition responders to prostaglandin analogues, but they were also patients with an acceptable tolerability profile. This may in part explain the very low hyperemia rates observed in this trial, and have led to a reduced difference in tolerability between the two study drugs.

Of note, great care was taken to make this study as objective as possible. For this purpose, the design was single masked (the investigator was not aware of the treatment) and the data analysis was done prior to unmasking the treatment arms by an independent statistician who was not involved in patient management.

In summary, our results show a difference in IOP lowering efficacy of 1,6 mmHg between unpreserved bimatoprost and latanoprost. As the importance of IOP lowering in reducing glaucoma progression has been demonstrated, these results can have significant impact in glaucoma management.

Date of the report: 10 Nov 2015