Clinical Study:

# A PROSPECTIVE, OPEN, MULTICENTRE CLINICAL TRIAL WITH ONE COHORT ANALYSING THE EFFICACY AND SAFETY OF MINIJECT IN PATIENTS WITH OPEN ANGLE GLAUCOMA UNCONTROLLED BY TOPICAL HYPOTENSIVE MEDICATIONS (ISM04)

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# Clinical Investigational Plan

A PROSPECTIVE, OPEN, MULTICENTRE CLINICAL TRIAL WITH ONE COHORT ANALYSING THE EFFICACY AND SAFETY OF MINIJECT IN PATIENTS WITH OPEN ANGLE GLAUCOMA UNCONTROLLED BY TOPICAL HYPOTENSIVE MEDICATIONS

Synopsis
according to EN ISO 14155:2011

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| Medical Device Name: | MINIject |
| Clinical Trial Identifier: | ISM04 |
| CIP Version: | Version 3.0 |
| Release date | 17-JUL-2017 |

# Synopsis

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| **Acronym** | **MINIject Study** |
| **Title** | A prospective, open, multicenter clinical trial with one cohort analyzing the efficacy and safety of MINIject in patients with open angle glaucoma uncontrolled by topical hypotensive medications |
| **Sponsor** | iSTAR Medical S.A.<br>Avenue Sabin, 6<br>1300 Wavre, Belgium |
| **Ethical Aspects** | Glaucoma is a complicated disease in which damage to optic nerve leads to progressive, irreversible vision loss. Glaucoma is the second leading cause of blindness. Glaucoma can be treated with eye drops, pills, laser surgery, traditional surgery or a combination of these methods. The goal of any treatment is to prevent loss of vision by lowering the IOP because vision loss from glaucoma is irreversible.<br>If a surgery is needed the currently available options (trabeculectomy, available implants) do not promise a long-term effect and new devices are requested. STARflo MINIject is a promising new developed glaucoma device with a new structure and unique working method. |
| **Study purpose** | The aim of this study is to assess the efficacy and safety of the MINIject system in patients diagnosed with open angle glaucoma uncontrolled by topical hypotensive medications. |
| **Investigational Device and procedure** | MINIject is an integrated system comprising a minimally-invasive Glaucoma Drainage Implant and a Delivery Tool.<br>The Delivery Tool is configured for inserting the implant into the sub-scleral location through an ab-interno minimally-invasive approach. It is single-use.<br>**Device options to be evaluated in this study**:<br>Implant CS 600 with Curved Shaft.<br>**Intervention:**<br>The intervention is to be performed stand-alone. |
| **Indication** | MINIject is indicated in adult, male and female patients diagnosed with open angle glaucoma, and where the progression of glaucoma is not adequately controlled by topical hypotensive medications.<br>MINIject is intended to be used to reduce the intraocular pressure (IOP) by channeling aqueous humor out of the anterior chamber to a sub-scleral location, thus enhancing the physiological uveoscleral outflow. |

# Synopsis

**Design**

Baseline and evaluation time points:

| Screening / Baseline | Follow-up 1 day / 1 week / 2 weeks / 1 Month / 3 Months | Follow-up 6 / 12 / 18 / 24 Months |
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| patient inclusion | Safety evaluation | safety and efficacy evaluation |
| medicated diurnal IOP baseline | single point IOP measurement | medicated diurnal IOP |

This prospective, non-comparative, open, multi-center, interventional clinical investigation is designed as one cohort study and intended to show the efficacy and safety of the MINIject system consisting of the CS 600 MINIject implant and the delivery tool with curved shaft.

In total 25 patients will be enrolled in approximately 5 sites in Panama, India and Europe (France or Germany).

The study will evaluate the efficacy and safety of the implant and IOP lowering effects with or without glaucoma medications. The procedure will be a stand-alone surgery. Overall, the patient will be asked to attend at 10 visits and perform several examinations up to 24 months after surgery.

The primary efficacy objective of the present study is to show the IOP reduction under medication 6 months after surgery compared to medicated diurnal IOP at screening.

The sponsor will evaluate the ease of use of the delivery tool based on questionnaires completed by the surgeons after surgery.

**Primary study objective**

The primary objective is to show a reduction in medicated diurnal IOP between screening/baseline visit and medicated diurnal IOP at 6 months after surgery.

**Secondary study objectives**

To test the reduction in medicated diurnal IOP between screening/baseline visit and medicated diurnal IOP 12 months and 24 months after surgery.

To assess the safety of the MINIject in terms of nature and severity of Adverse Events (AE/SAE), Adverse Device Effects (ADE/SADE) and Unanticipated Adverse Device Effect (UADE)*.

To assess the rate of peripheral and central corneal endothelial cells density-loss.

To assess the rate defined as:

- Complete success: diurnal IOP ≤ 21mmHg and > 5mmHg with a minimum 20% diurnal IOP reduction from baseline without the need for glaucoma hypotensive medication.
- Qualified success: diurnal IOP ≤ 21mmHg and > 5mmHg with a minimum 20% diurnal IOP reduction from baseline with the concomitant use of glaucoma hypotensive medication.

To assess the reduction of the number of hypotensive active ingredients compared to screening visit.

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| | * referring to expected AEs for implantable glaucoma devices as listed in ANSI Z80.27.2014 and FDA Guidance Premarket Studies of Implantable Minimally Invasive Glaucoma surgical (MIGS) Devices. |
| **Assessed Parameter** | The assessed parameters are listed in detail in Table 1 at the end of this synopsis. |
| **Patient selection** | **Inclusion criteria**<br>Any patient is eligible for inclusion in this clinical investigation if all of the following criteria apply:<br>Males or females, 18 years of age or older.<br>Diagnosis of primary or secondary open angle glaucoma during screening/baseline visit or earlier.<br>Grade 3 (open, 20-35 degrees) or grade 4 (wide open, 35-45 degrees) according to Shaffer Angle Grading System.<br>Glaucoma not adequately controlled by one to four different topical hypotensive medication(s), given each for at least one month, as confirmed by 21 mmHg ≤ IOP ≤ 35 mmHg in the study eye at screening and baseline visits.<br>Patient must be willing and able to return for scheduled study-related examinations.<br>Patient must provide written informed consent.<br><br>**Exclusion criteria**<br>Any patient is not eligible for inclusion in this clinical investigation if one or more of the following criteria apply:<br>Diagnosis of glaucoma other than open angle glaucoma (e.g. angle closure glaucoma) in the study eye.<br>Grade 2 (narrow, 20 degrees), grade 1 (extremely narrow, less or equal to 10 degrees) and grade 0 (closed or slit) according to Shaffer Angle Grading System.<br>Neovascular glaucoma in the study eye.<br>Corneal opacity or iridocorneal angle not visible through gonioprism in the study eye, preventing correct placement of the implant.<br>Prior glaucoma surgery in the study eye, patient treated with argon laser trabeculoplasty or selective laser trabeculoplastry in the study eye may be eligible if treatment performed ≥ 90 days before screening visit.<br>Visual field defect in the 10 degree central field in the study eye.<br>Anticipated need for ocular surgery or retinal laser procedure in the study eye in the 12 months following surgery.<br>Anterior chamber anatomic configuration of high risk for development of angle closure glaucoma in the study eye. |

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| | Clinically significant corneal disease (e.g., corneal dystrophy) in the study eye.<br><br>Pre-existing ocular or systemic pathology that, in the opinion of the physician, is likely to cause postoperative complications following implantation of the device in the study eye.<br><br>Evidence of crystalline lens subluxation or luxation in the study eye.<br><br>Evidence of vitreous loss in the anterior chamber in the study eye.<br><br>Clinically significant intra-ocular inflammation or infection, presence of ocular disease such as uveitis, ocular infection, severe dry eye, severe blepharitis, active proliferative/inflammatory retinopathy in the study eye.<br><br>Presence of silicone oil in the study eye.<br><br>Patients treated with systemic acetazolamide within 3 days before screening visit.<br><br>Patients with poor vision (LogMar score: +1.0) in non-study eye, unless there is an expected benefit for the study eye, in the opinion of the investigator.<br><br>Participation in any study involving an investigational drug or device within the past 3 Months.<br><br>Only for women of childbearing potential: positive urine pregnancy test at screening.<br><br>Individuals under tutorship or trusteeship. |
| **Quality Assurance** | During the clinical investigation, the sites will be visited by CRO staff to review the progress of the clinical investigation, review the data collected, conduct source data verification, (according to ISO 14155:2011(E); define the extend of source data verification) perform device accountability, identify issues and address their resolution. The aim of the monitoring of the clinical investigation is to ensure that the data collected is authentic, accurate and complete, to ensure the safety of the subjects and that the subject's rights are protected, and to ensure that the clinical investigation is performed according to the approved clinical investigation plan and all applicable regulations and guidelines. |
| **Sample Size** | Sample size is obtained by a paired sample t-test, 2-sided, with alpha of 0.05 and power of 0.9. The difference of interest is taken equal to 5.2 mmHg. Under the conservative assumption that 25% of subjects will drop out of the study, this treatment effect will be reduced to 0.75*5.2 = 3.9 mmHg if all patients are included in an ITT analysis. The variance of the difference in IOP between the month 6 visit and baseline is assumed to be at most equal to $3^2+5^2=34$, hence the standard deviation is taken equal to 5.83. Under these assumptions, the sample size required is equal to 25 patients. |
| **Statistical rationale for sample** | An IOP reduction ≥ 20% has been previously used as success criterion and thus can be defined as clinically meaningful. |

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| **size calculation** | The mean baseline IOP of 26.0 mmHg ± 3.0 used for calculation is derived from published study results involving comparable study population; subjects with OAG uncontrolled by medication(s).<br><br>The mean IOP at 6 months is estimated to 20.8 mmHg ± 5, the standard deviation is derived from published study results involving comparable devices.<br><br>Based on these assumptions, the estimated sample size of 25, in order to obtain 16 completed subjects at 6 Months follow-up (endpoint for the primary objective). |

## FLOW CHART

| GENERAL ASSESSMENTS | Visit 0<br>Screen/ Baseline<br>Day - 42 to -1 | Visit 1<br>Surgery<br>Day 0 | Visit 2<br>1 Day<br>Day 1 | Visit 3<br>1 week<br>Day 5-9 | Visit 4<br>2 weeks<br>Day 12-16 | Visit 5<br>1 Month Safety evaluation<br>Day 21-35 | Visit 6<br>3 Months<br>Day 70-98 | Visit 7<br>6 Months Safety & Efficacy evaluation<br>Day 168-196 | Visit 8<br>12 Months Safety & Efficacy evaluation<br>Day 335-425 | Visit 9<br>18 Months Safety & Efficacy evaluation<br>Day 510-600 | Visit 10<br>24 Months Safety & Efficacy evaluation<br>Day 700-790 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Signed informed consent | X | | | | | | | | | | |
| Demography/ relevant medical and ocular history/Glaucoma diagnosis | X | | | | | | | | | | |
| Inclusion /exclusion criteria | X | | | | | | | | | | |
| Urine pregnancy test (women of childbearing potential only) | X | | | | | | | | | | |
| Concomitant ocular & non-ocular medications, | X | X | X | X | X | X | X | X | X | x | X |
| AE/SAE recording | X | X | X | X | X | X | X | X | X | x | X |
| Implantation | | X | | | | | | | | | |
| Implant position assess by investigator's judgment | | X | | | | | | | | | |
| Record video of surgery | | X | | | | | | | | | |
| Ease of use feedback questionnaires completed by investigator | | X | | | | | | | | | |
| QOL questionnaire, CIGTS sub-part | X | | | | | | | X | X | x | X |

# Synopsis

| OCULAR ASSESSMENTS | Visit 0<br>Screening/ Baseline<br>Day -42 to -1 | Visit 1<br>Surgery<br>Day 0 | Visit 2<br>1 day<br>Day 1 | Visit 3<br>1 week<br>Day 5-9 | Visit 4<br>2 weeks<br>Day 12-16 | Visit 5<br>1 Month<br>Safety evaluation<br>Day 21-35 | Visit 6<br>3 Months<br>Day 70-98 | Visit 7<br>6 Months<br>Safety & Efficacy evaluation<br>Day 168-196 | Visit 8<br>12 Months<br>Safety & Efficacy evaluation<br>Day 335-425 | Visit 9<br>18 Months<br>Safety & Efficacy evaluation<br>Day 510-600 | Visit 10<br>24 Months<br>Safety & Efficacy evaluation<br>Day 700-790 |
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| BCVA | X | | X | X | X | X | X | X | X | x | X |
| IOP, Goldmann Appl. Tonometry, diurnal (8:00 AM, 12:00 AM, 4:00 PM) | X | | | | | | | X | X | x | X |
| IOP (Single time point) | | | X | X | X | X | X | | | | |
| Visual field testing (Octopus or Humphrey) | X | | | | | X | X | X | X | x | X |
| Optic disc photograph of the optic nerve | x | | | | | x | x | x | x | x | x |
| Vertical C/D ratio | X | | | | | X | X | X | X | x | X |
| Central corneal thickness (pachymetry) | X | | | | | | | X | X | x | X |
| Gonioscopy, angle grading using Shaffer grading | X | | | | | | | | | | |
| Recording Gonioscopy image | | X | | | | X | | | | | |
| Slit lamp examination | X | | X | X | X | X | X | X | X | x | X |
| Dilated fundus examination | X | | X | X | | X | | X | X | x | X |
| Peripheral and central specular microscopy | X | | | | | | | X | X | x | X |
| Eye symptoms | X | | X | X | X | X | X | X | X | x | X |
| Assess Implant position (UBM) | | | | X | | | | X | X | x | X |

Table 1: Flow chart for cohort, general and ocular assessments. All ocular assessments (except BCVA) are to be done on study eye only, except at screening visit, where the assessments are to be done on both eyes.