CLINICAL INVESTIGATION PLAN

Prospective, Investigator Initiated Feasibility Study to Evaluate the Safety, and Indicative Effectiveness of Gebauer™ Lenticules in Patients Suffering from Severe Keratoconus or Post LASIK Ectasia

Clinical Investigation Plan No.: 2019OPH108

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SIGNATURE PAGE:

Study Title	**Prospective, Investigator Initiated Feasibility Study to Evaluate the Safety, and Indicative Effectiveness of Gebauer™ Lenticules in Patients Suffering from Severe Keratoconus or Post LASIK Ectasia**
Clinical Investigation Plan Number	**2019OPH108**
Version No	**1.5**
Date	**30 March 2020**
Statement	**We, the undersigned have read and understood the protocol specified above and agree to conduct the study according to the protocol and comply with its obligations to comply with ethical, safety and regulatory considerations**
Signature of Principal Investigator	**MR. ILANGO**
	Signature: _____
	Date: _____
Signature of Technical Collaborator	**MR. STEFFEN GEBAUER**
	Signature: _____
	Date: _____

1. STUDY SYNOPSIS

Title:	Prospective, Investigator Initiated Feasibility Study to Evaluate the Safety, and Indicative Effectiveness of Gebauer™ Lenticules in Patients Suffering from Severe Keratoconus or Post LASIK Ectasia.
Device:	Gebauer™ Lenticule (corneal Implant made of highly purified, optically transparent corneal collagen fibers of porcine origin).
Intended Use:	The Gebauer™ Lenticule corneal implant device is a custom-made device intended for patients suffering from keratoconus or post-LASIK ectasia. The device is expected to reinforce and stabilize the patient's cornea, so that a more consistent refraction is induced and a penetrating human cornea donor transplantation may be avoided or postponed.
Study Design:	Prospective open-label, investigator initiated feasibility clinical investigation for a custom-made device which is in full compliance with the Medical Device Regulations and the Medical Device Directives.
Study Objectives:	To evaluate the safety and indicative effectiveness of Gebauer™ Lenticule implanted in subjects suffering from keratoconus or post-LASIK Ectasia.
Study Hypothesis:	Treatment with the Gebauer™ Lenticule is safe and results in improvement of vision by stabilizing the cornea and improving the refractive regularity.
Study Population:	Men and women aged 18 or over and less than 80 years old, suffering from keratoconus or post-LASIK ectasia, who meet the inclusion/ exclusion criteria and provided written Informed Consent will be enrolled in the study.
Enrollment:	A total of 15 subjects will be enrolled.
Investigational Sites:	A single site will participate in this study.
Study Duration:	Completion of active enrolment is anticipated to last approximately 1-3 months. The primary endpoint will be achieved when the last study subject has completed his/her 6 months follow-up. For the assessment of long-term tolerability, subjects will be invited to additional follow-up visits after 1 and 2 years. The total duration of the study is expected to be 9 months (6 months follow-up), respectively, 27 months (2 years follow-up)

Primary Safety Endpoint:	• The frequency and severity of all treatment-related adverse events, during implantation of the Gebauer™ Lenticule and throughout the post implantation observation period.
Secondary Safety Endpoints	• Changes in IOP during observation period • Changes in corneal transparency and lenticule transparency during observation period • Inflammation of cornea or sclera during observation period • Changes to the corneal epithelium during observation period • Changes to conjunctiva, iris/pupil, lens during observation period • Changes to ocular pain/discomfort during observation period.
Primary Endpoints for Effectiveness:	• Changes in corneal topography (central K-reading results): at baseline vs. post implantation observation period • Changes in central corneal thickness at baseline vs. post implantation corneal thickness (cornea plus lenticule) • Patient satisfaction with received treatments and outcome.
Secondary Endpoints for Effectiveness	• Best corrected visual acuity during the observation period • Investigator's overall procedure evaluation • Suitability of pocket size • Duration of surgical procedure • Requirement of specific post surgical measures (suturing after implantation, bandage contact lens, antibiotic and immunosuppressive treatments).
Study Treatment:	Subjects will be implanted with the Gebauer™ Lenticule. The device will be implanted into a corneal stromal pocket using a manual or femtosecond laser pocket formation.

Inclusion Criteria:	1. Diagnosis of severe keratoconus in patients who would prefer to avoid corneal transplant surgery / penetrating keratoplasty **OR** Diagnosis of severe post-LASIK Ectasia in patients who would prefer to avoid corneal transplant surgery / penetrating keratoplasty 2. In terms of general health, patients must be free of diagnosed terminal illnesses (life expectancy of ≥ 2 years). 3. Patients must be aged 18 years or over and less than 80 years old 4. Patients' contact lenses must have been removed at least one-week prior to surgery for soft lenses and two weeks prior to surgery for hard lenses 5. Subject understands the study requirements and the treatment procedures and provides written Informed Consent before any study-specific tests or procedures are performed 6. Patient must be able and willing to complete all study visits and comply with the study-specific requirements.
Exclusion Criteria	1. History or presence of any ocular pathologies that may interfere with the planned surgical treatment, including corneal epithelial problems 2. Previous corneal transplantation or corneal implant in the designated eye 3. Cataract with anticipated surgical intervention (IOL implantation) within 2 years 4. Active inflammation and/or infection of the eye or the eye lid 5. Patients with IOP <10 mmHg or >21 mmHg 6. Professionally diagnosed and currently treated autoimmune diseases 7. Current strong symptoms of any allergy 8. History of major organ transplantation and/or current continuing immunosuppressive treatment 9. History of blood transfusion within the last 12 months 10. Subject who is currently participating or has participated in another investigational clinical study within the past 60 days 11. Pregnancy and lactation.
VISITS AND PROCEDURE:	**Procedural Information**

	There will be one screening visit /baseline visit followed by surgery visit and at least 4 follow-up study visits. **Baseline Evaluation (Day - 30 To -1)** The pre-procedure data can be collected from 30 days to 1 day prior to the surgical procedure. Obtaining Informed Consent Form is mandatory before any study related procedure is performed. The visit will include subject's eligibility assessment for inclusion and exclusion criteria as described in Section 7. Ophthalmic medical history will be taken including subject's ophthalmic complaints and medications use. The following examinations will also be performed for both eyes: 1. Intraocular pressure (IOP) measurement 2. Best corrected visual acuity 3. Corneal transparency (slit lamp) 4. Photodocumentation of corneal status 5. Inflammation of cornea or sclera 6. Central corneal thickness measurement (OCT) 7. Corneal topography (K-reading map) 8. Assessment of corneal epithelium 9. Assessment of conjunctiva 10. Assessment of iris / pupil 11. Assessment of lens 12. Assessment of ocular pain 13. Assessment of patient satisfaction with treatments and outcome **Day 0 Surgery – Flap creation** For eligible subjects the creation of the flap surgery will be scheduled according to clinical discretion of the responsible ophthalmic surgeon, and in compliance with the provisions described in this Clinical Investigation Plan. The main steps are listed here: 1. Under topical anesthesia, a mid-stromal pocket will be created using either a femtosecond laser dissection technique or a manual technique. In patients suffering from post-LASIK ectasia, manual techniques will be applied to re-open the pre-existing LASIK flap in the form of a pocket. **Day 0 (+ 30 days) Surgery – Implantation**

	For eligible subjects the implantation of the Gebauer Lenticule surgery will be scheduled according to clinical discretion of the responsible ophthalmic surgeon, up to 30 days after flap creation, and in compliance with the provisions described in this Clinical Investigation Plan. The main steps are listed here: 1. Under topical anesthesia, the corneal vertex will be marked with gentian violet using the first Purkinje image as a reference while asking the patient to fixate on the microscope light. 2. The Gebauer™ Lenticule implant is then gently inserted and fully expanded with no wrinkles into the pocket through the pocket opening. 3. The implant is then centered with the corneal vertex. 4. Immediately post implantation, essential surgical data will be recorded including procedural details (start and end time), orientation, dimensions and closure method of pocket, use of bandage contact lens, device ease of use, procedure complications and medications prescribed. The subject will be discharged after the procedure or will be hospitalized for one day according to physician discretion. Post- operatively, antibiotic eye drops will be prescribed for 2 weeks, and steroid eye drops (e.g. PredForte; Allergan) will be prescribed 2 hourly for 2 weeks, along with optional lubricating drops. Safety Monitoring will be performed (recording of adverse events and medications). **Follow-up Study Visits Post-Surgery** Subjects will be followed up frequently for a period of 6 months with ophthalmic assessments at day 1-3; 28 days (+/- 7days), 3 months (+/- 14 days), 6 months (+/- 28 days), and optionally 12 and/or 24 months. In addition 2 weekly, telephone assessments will be conducted up to 3 months. **Long-Term Follow-up Study Visits Post-Surgery** Patients will be invited to come back to the hospital for two optional long-term follow-up visits 1 and 2 years post implantation. The results of these long-term follow-up visits will be reported separately in an addendum report, independently from the basic follow-up period of 6 months. **Treatment Assessments done at each follow-up visit will be as follows:**

	All Follow-Ups Post-Surgery It is recommended to perform all the ophthalmic examination on the same hour ± 3 hours along the day in all the follow-up visits. At each follow-up visit, the clinical investigator will perform a detailed ophthalmic examination on the treated and the untreated eye with includes the following: 1. Intraocular pressure (IOP) measurement 2. Best corrected visual acuity 3. Corneal transparency (slit lamp) 4. Lenticule transparency (slit lamp) 5. Photodocumentation of corneal status 6. Inflammation of cornea or sclera 7. Signs of immunological rejection 8. Central corneal thickness measurement (OCT) 9. Corneal topography (K-reading map) 10. Assessment of corneal epithelium 11. Assessment of conjunctiva 12. Assessment of Iris / Pupil 13. Assessment of Lens 14. Assessment of ocular pain 15. Assessment of patient satisfaction 16. Assessment of conjunctiva 17. Assessment of iris / pupil 18. Assessment of lens 19. Assessment of ocular pain 20. Assessment of patient satisfaction with treatments and outcome In addition to that, safety Monitoring will be performed (recording of adverse events and medications).
Statistical Considerations	**Sample Size**: The present study is an open-label feasibility clinical research investigation study and will mainly be analyzed with descriptive statistics. No formal sample size calculation has been performed, the sample size of 15 subjects is considered sufficient to enable the estimation of the study endpoints.
	Statistical Analysis: The present investigational study is mainly descriptive in nature. Nevertheless, when relevant, the required significance level of findings will be 5%. All statistical tests will be two-

	sided. If statistical tests are performed, nominal p-values will be presented. Where confidence limits are appropriate, a two-sided 95% confidence interval will be constructed.

2. INTRODUCTION

2.1 BACKGROUND

Keratoconus is a bilateral, progressive disorder characterized by ectasia and thinning of the cornea, causing compromised visual function [1]. Rigid contact lens fitting and intracorneal ring segment implantation are valuable options for improving the optical performance in mild to moderate stages of keratoconus [2]. In cases of advanced keratoconus, if contact lenses are not tolerated or if no acceptable visual acuity is achieved with contact lenses, then either a deep anterior lamellar keratoplasty (DALK) or a penetrating keratoplasty (PK) is recommended [41].

Post-LASIK ectasia is a condition similar to keratoconus where the cornea starts to bulge forwards at a variable time after LASIK, PRK, or SMILE corneal laser eye surgery. It is one of the most devastating complications after Laser In situ Keratomileusis (LASIK). Post-LASIK ectasia is considered in patients who developed increasing myopia, with or without increasing astigmatism, loss of uncorrected visual acuity, often loss of best-corrected visual acuity, with keratometric steepening, with or without central and paracentral corneal thinning, and topographic evidence of asymmetric inferior corneal steepening after LASIK procedure [43].

Corneal collagen cross-linking with riboflavin(CXL) is a promising treatment modality which strengthens the corneal stroma and thereby halts further progression [3]. It provides long term stabilisation of the cornea, so that corneal transplantation may be deferred or precluded. This procedure appears to be safe in keratoconic/ectatic eyes with central corneal thickness (CCT) of at least 400 µm, and in which the preoperative maximum keratometry (Kmax) value does not exceed 58 diopters (D) [4]. Recently there has been a development to expand the use of ultraviolet cross-linking into eyes with thinner corneas by means of a variety of modifications to the original procedure, of which the use of hypo-osmolar riboflavin solution is the most common[5]. However, the risk of complications or failure seems higher in thinner and steeper corneas [6,7].

Another possibility to avoid corneal transplantation in keratoconus/ectasia eyes may be by reshaping the cornea using intracorneal ring segments [8, 42]. ICRs, however, may be associated with potential risks of extrusion, misalignment, infection, perforation, and tissue reactions[9].

Nevertheless, patients with advanced keratoconus or post-LASIK ectasia may benefit from stabilizing the cornea and halting the progression to preserve visual acuity, while deferring DALK or PK and thereby avoiding the cascade of complications of these procedures[10, 11].

A novel technique of Bowman layer transplantation for advanced keratoconus has been found to stabilize the cornea, potentially delaying or avoiding the need for whole corneal transplantation [12]. Although the surgical technique and lamellar dissection currently require a potentially steep learning curve and the exact plane at which the donor is implanted is unknown.

A variety of therapeutic approaches using tissue engineering strategies have been considered to replace a portion or whole of corneal tissue in keratoconus [13]. Collagen equivalents hold great potential in treating keratoconus. It would improve the biomechanical strength of corneal stroma thereby stabilizing and halting the disease process even in advanced keratoconus, postponing or avoiding the need for corneal transplantation. They could also increase the thickness of the cornea, converting patients who may be unsuitable for collagen crosslinking due to thin corneas into

suitable patients by an increase in corneal thickness.

Treatment of the condition has included use of Intrastromal corneal ring segments [19] and corneal transplantation [20], however recently, collagen cross-linking has become a routine procedure [21]. Collagen cross linking involves removal of the epithelial layer of the cornea followed by the application of riboflavin and ultraviolet light which on reaction leads to the formation of chemical bonds between the collagen fibrils, thus strengthen the cornea and ceasing the progression of the disease [22]. The treatment may become a successful procedure in treating keratoconus or Post-LASIK ectasia, it is associated with side effects such as infection due to delayed re-epithelialisation [23, 24], endothelial damage, haze [25] and herpes reactivation [26].

2.2 STUDY RATIONALE

Gebauer Medizintechnik GmbH has developed the Gebauer™ Lenticule, a corneal implant that will be used to treat, among others, keratoconus and post-LASIK ectasia. The Gebauer™ Lenticule is a corneal stromal implant, manufactured from transparent corneal collagen of animal origin which has been cleared of all donor's cells and related cellular remnants such as lipids, proteins, sugars or genetic materials (DNA and RNA). The product represents a disc-shaped (approx. 7 mm in diameter and 0.1 mm thickness) piece of highly purified porcine collagen fibres formed to a given profile and thickness. The Gebauer™ Lenticule will be implanted into the corneal stroma of the diseased eye and is expected to improve the mechanical stability of the corneal tissue while not impairing the vision.

The procedure is an additive procedure after other treatment options have been exhausted. And the procedure is reversible, i.e., the implant can be removed in the unexpected case of local intolerance, and the initial vision from before the implantation can be restored. Due to the transparency of the cornea, the implant can be seen and inspected at all times, which is beneficial for monitoring purposes.

This is an Investigator initiated feasibility study to investigate the safety and indicative effectiveness of the Gebauer™ Lenticule in stabilizing the keratoconic/ectatic cornea. Keratoconus is a disease seen quite commonly with prevalence rates of about 1 in 2000. Additionally, keratoconus affects patients in the most productive phase of life, around 15 years.

Post-LASIK ectasia is one of the most devastating complications after Laser In situ Keratomileusis (LASIK).

Several of these patients will eventually need corneal transplantation due to inability to arrest the progression of keratoconus or due to unsuitability for collagen crosslinking due to thin corneas. The implantation of the Gebauer™ Lenticule could potentially address both of these problems and delay or even avoid this highly invasive human corneal transplantation.

3. SUMMARY OF PRECLINICAL BIOCOMPATIBILITY TESTING

Objective: For the demonstration of biocompatibility, a series of biological endpoints has been tested and/or evaluated in compliance with the requirements of EN ISO 10993-1. At the end of this process, a summarizing expert opinion ("Declaration of Compliance with EN ISO 10993-1") was prepared which finally concluded on the biocompatibility of the final Gebauer™ Lenticules under evaluation.

Methods: A combination of experimental testing and evaluation of scientific literature in compliance with the EN ISO 10993 series of standards and within a risk management process as of EN ISO 14971 was applied. At the end of the process, a "Declaration of Compliance with EN ISO 10993-1", currently named "Overall Biological Risk Assessment", as of ISO 10993-1 Chapter 7, was prepared [44].

Summary of Test Reports: Based upon a strategic and risk-based assessment of the biological endpoints to be experimentally investigated for the Gebauer™ Lenticules, tests for cytotoxicity and chemical analyses using GC/MS and ICP-OES have been performed. The following summaries have been provided in the Overall Biological Risk Assessment [44]:

The potential of **cytotoxicity** of the Gebauer™ Lenticules was investigated in compliance in accordance with EN ISO 10993-5 (UL MDT report 11520828 1.1, For sample preparation, the provisions of EN ISO 10993-12 were fulfilled. The materials were extracted for 24 hours at 37 °C with sterile culture medium containing 10 % fetal calf serum at a ratio of 0.1 g per ml.

In summary, the tested Gebauer™ Lenticules showed no cytotoxic effects after dynamic extraction in culture medium. Under the conditions of the test, the undiluted extract of the Gebauer™ Lenticules caused no growth. This result corresponded to a biological reactivity score value of "0" according to USP 39 <87>.

Based upon the above results and evaluation arguments it is concluded that the investigational Gebauer™ Lenticules have no cytotoxic properties in terms of EN ISO 10993-5, relating to potentially toxic substances extractable from the Gebauer™ Lenticules under investigation.

In order to perform a **chemical material characterization** in order to detect potential organic and inorganic leachable substances which may be released from the final Gebauer™ Lenticules, the final products were subjected to a polar, mid-polar and non-polar extraction followed by **GC/MS**, respectively, by **ICP-OES analyses** of the respective extracts (UL MDT report 11520828 2.1

The study was performed within the scope of a material characterization as requested by ISO 10993-18. For sample preparation, the provisions of EN ISO 10993-12 were fulfilled. The dynamic extraction was performed for 72 h at 37°C and at a ratio of 0.1 g per ml, using the following extraction vehicles: 0.9% saline

in water, isopropyl alcohol, and n-hexane. After the extraction of the investigational lenticules, aliquots of the extracts were analyzed by means of GC/MS, respectively by means of ICP-OES.

In summary, the **GC/MS investigation** revealed that none of the investigated extracts of the Gebauer™ Lenticules exhibited any product-related organic peaks. This indicates that no potentially toxic organic leachable substances were released from the final products under the conditions of the test. Therefore, no toxicological risk assessment as described in ISO 10993-17 was required.

With regard to the **ICP-OES investigation**, the Gebauer™ Lenticules revealed small amounts of leaching calcium (5.98 µg/device), magnesium (1.56 µg/device), copper (0.005 µg/device), iron (0.005 µg/device), potassium (15.6 µg/device), sulphur (28.7 µg/device) and strontium (0.009 µg/device) in the analyzed extracts in quantities higher than the untreated extraction vehicle.

In summary, considering the intended purpose of the Gebauer™ Lenticules under evaluation, the observed amounts and identities of leaching metal ions are evaluated to be clinically uncritical.

Based upon the study results obtained in this GC/MS and ICP-OES investigation, and considering the fact that the investigational Gebauer™ Lenticules only consists of purified porcine collagen fibers, the manufacturer Gebauer Medizintechnik GmbH decided that animal experimental tests for irritation, systemic toxicity, material-mediated pyrogenicity, and additional tests for genotoxicity can be waived both in view of scientific considerations relating to the known biocompatibility of porcine collagen and in view of the current animal protection regulations as described in EN ISO 10993-2.

Conclusion: As documented in a formal “Declaration of Compliance” / “Overall Biological Risk Assessment” as requested in EN ISO 10993-1 Chapter 7, and based upon both experimental study results and evaluation arguments, and considering the provisions of the current version of the harmonized standard EN ISO 10993-1 as well as FDA Guidance "Use of International Standard ISO 10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process", dated 16. June 2016, it is concluded that the investigational Gebauer™ Lenticules can be evaluated biocompatible if manufactured appropriately and applied in compliance with their intended use as outlined in the manufacturer's Technical Documentation and in this Clinical Investigation Plan.

4. DEVICE DESCRIPTION

4.1 DESIGN

The Gebauer™ Lenticule is a corneal Implant made of highly purified, transparent collagen of animal origin. The Gebauer™ Lenticules undergo a complex manufacturing process followed by a validated terminal UV-sterilization step. The result is a co-planar implant which is free of cells and their remnants.

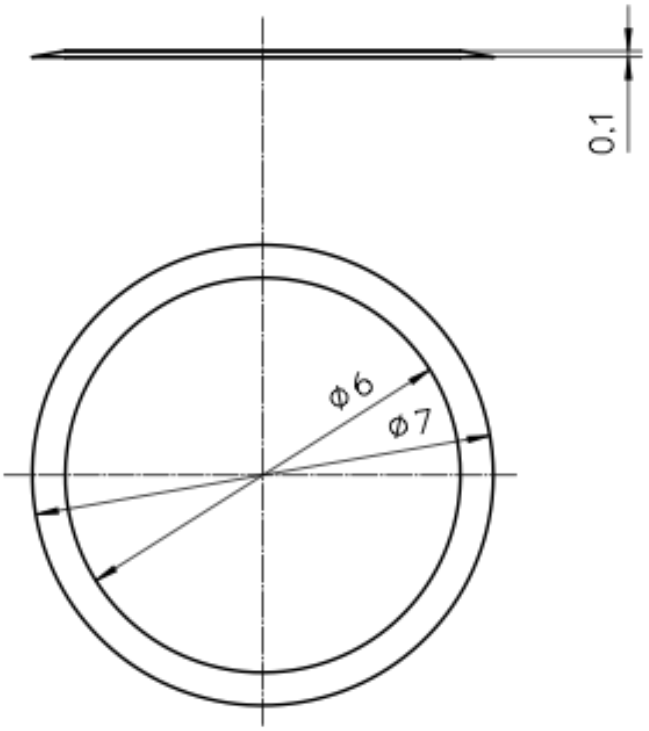

Figure 1: The Gebauer™ Lenticule implant - Example

4.2 DEVICE PRINCIPLE OF OPERATION

The Gebauer™ Lenticule represents a corneal stromal implant device which is intended to be implanted in a patient's cornea in order to change its thickness and/or to change the cornea's anterior curvature and/or to replace defective, compromised or vacant stromal tissue.

4.3 INTENDED USE

The Gebauer™ Lenticule is intended for ophthalmic lenticular intrastromal keratoplasty (or keratophakia). Thereby it is intended to be implanted in a patient's cornea in order to change its thickness and/or to change the cornea's anterior curvature and/or to replace defective, compromised or vacant stromal tissue. Based upon this intended purpose, the various Gebauer™ Lenticule geometries can be used for the following clinical conditions/indications:

1) Co-planar lenticules of variable thicknesses and diameters: E.g. for the treatment of keratoconus or post-LASIK Ectasia.
2) Curved lenticules of different diameters and variable spherical and astigmatic geometries: E.g., for the treatment of ametropia / refractive errors.

Based upon these general therapeutic fields, the current clinical study is intended to investigate the effectiveness and safety of Gebauer™ Lenticules in the treatment of patients suffering from either severe keratoconus or post-LASIK Ectasia.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 OBJECTIVES

The objective of this study is to evaluate the safety and indicative effectiveness of Gebauer™ Lenticule when implanted in subjects suffering from keratoconus or post-LASIK ectasia. Therefore, numerous clinical endpoints have been identified, based upon scientific literature, to investigate both safety and effectiveness aspects of the GebauerTM Lenticules (see below Chapter 5.2).

5.2 CLINICAL ENDPOINTS

5.2.1 PRIMARY SAFETY ENDPOINTS

The following primary safety endpoints have been determined and will be systematically documented in the Case Report Form for each patient visit:

- Signs of immunological rejection during the post implantation observation period
- The frequency and severity of all treatment-related adverse events, during implantation of the Gebauer™ Lenticule and throughout the post implantation observation period.

5.2.2 SECONDARY SAFETY ENDPOINTS

The following secondary safety endpoints have been determined and will be systematically documented in the Case Report Form for each patient visit:

- Changes in IOP during observation period
- Changes in corneal transparency and lenticule transparency during observation period
- Inflammation of cornea or sclera during observation period
- Changes to the corneal epithelium during observation period
- Changes to conjunctiva, iris/pupil, lens during observation period
- Changes to ocular pain/discomfort during observation period

5.2.3 PRIMARY ENDPOINTS FOR EFFECTIVENESS

The following primary endpoints for effectiveness have been determined and will be systematically documented in the Case Report Form for each patient visit:

- Changes in corneal topography (central K-reading results): at baseline vs. post implantation observation period
- Changes in central corneal thickness at baseline vs. post implantation corneal thickness (cornea plus lenticule)
- Patient satisfaction with received treatments and outcome

5.2.4 SECONDARY ENDPOINTS FOR EFFECTIVENESS

The following secondary endpoints for effectiveness have been determined and will be systematically documented in the Case Report Form for each patient visit:

- Best corrected visual acuity during the observation period
- Investigator's overall procedure evaluation
- Suitability of pocket size
- Duration of surgical procedure
- Requirement of specific post surgical measures (suturing after implantation, bandage contact lens, antibiotic and immunosuppressive treatments)

6. STUDY DESIGN AND STUDY DURATION

This investigator-initiated clinical research study is an open-label, single site clinical investigation, which follows the Good Clinical Practice guidelines as described in EN ISO 14155.

The primary aim of this study is to assess the safety and effectiveness of the Gebauer™ Lenticules after corneal implantation in patients suffering from severe keratoconus or post-LASIK ectasia. Specific clinical endpoints, as documented in Chapter 5.2 above, have been identified in order to systematically investigate and document particularly relevant aspects of clinical safety and effectiveness of this innovative treatment option.

Subjects with severe keratoconus or post-LASIK ectasia are eligible for this study. Only subjects who have signed the informed consent form and meet all the eligibility criteria listed in Chapter 7.1 and 7.2 below will be qualified for enrollment. The study will encompass a total of 15 subjects who will complete the follow-up schedule as described in this Clinical Investigation Plan.

In summary, as listed in Chapter 8.7.5, after patients were enrolled in the study, a detailed ophthalmological examination is performed, in order to document the current status of both patient eyes (Baseline Day -30 – Day -1). On Day 0, a flap is created in the eye at the Optimax clinic, then on Day 0 (+ 30 days) patients are implanted with the GebauerTM Lenticule on 1 diseased eye. The untreated eye serves as a reference during the complete observation period.

After implantation, subjects will be followed up frequently for a period of 6 months with ophthalmic assessments at day 1-3; 28 days (+/- 7days), 3 months (+/- 14 days) and 6 months (+/- 28 days). In addition 2 weekly, telephone assessments will be conducted up to 3 months. After this period, the primary clinical investigation report will be issued.

In addition to that, two further optional patient visits are planned to investigate long-term safety and effectiveness of the Gebauer™ Lenticules. Therefore, 1 and 2 years post implantation, patients will be invited to come back to the hospital for additional ophthalmic examinations. The results of these long-term follow-up visits will be in separate addendum reports, independently from the basic clinical investigation report.

For this clinical investigation, the following time frame is anticipated: Completion of active enrolment is expected to require approximately 1-3 months. The primary endpoints will be achieved when the last study subject has completed his/her 6 months follow-up. For the assessment of long-term tolerability, subjects will be invited to additional follow-up visits after 1 and 2 years. Therefore, the total duration of the study is expected to be 9 months (for completion of the 6 months follow-up period), respectively, 27 months (for completion of the 2 years follow-up period).

7. STUDY POPULATION

Men and women aged 18 or over and less than 80 years old, suffering from keratoconus or post-LASIK ectasia, who meet the inclusion/ exclusion criteria and provided written Informed Consent will be enrolled in the study.

7.1 INCLUSION CRITERIA

Candidates for participation in the study must meet all of the following inclusion criteria:

- Diagnosis of severe keratoconus in patients who would prefer to avoid corneal transplant surgery / penetrating keratoplasty

  OR
- Diagnosis of severe post-LASIK Ectasia in patients who would prefer to avoid corneal transplant surgery / penetrating keratoplasty
- In terms of general health, patients must be free of diagnosed terminal illnesses (life expectancy of ≥ 2 years).
- Patients must be aged 18 years or over and less than 80 years old
- Patients' contact lenses must have been removed at least one-week prior to surgery for soft lenses and two weeks prior to surgery for hard lenses
- Subject understands the study requirements and the treatment procedures and provides written Informed Consent before any study-specific tests or procedures are performed
- Patient must be able and willing to complete all study visits and comply with the study-specific requirements

7.2 EXCLUSION CRITERIA

Candidates for participation will be ineligible for the study if any of the following conditions apply:

- History or presence of any ocular pathologies that may interfere with the planned surgical treatment, including corneal epithelial problems
- Previous corneal transplantation or corneal implant in the designated eye
- Cataract with anticipated surgical intervention (IOL implantation) within 2 years
- Active inflammation and/or infection of the eye or the eye lid
- Patients with IOP <10 mmHg or >21 mmHg
- Professionally diagnosed and currently treated autoimmune diseases
- Current strong symptoms of any allergy
- History of major organ transplantation and/or current continuing immunosuppressive treatment
- History of blood transfusion within the last 12 months

- Subject who is currently participating or has participated in another investigational clinical study within the past 60 daysPregnancy and lactation

8. STUDY PROCEDURES

8.1 SUBJECT SCREENING

Subjects will be selected from the physician's usual patients practice. All subjects meeting the inclusion/exclusion criteria and having signed the Informed Consent Form will be evaluated by the Investigator according to the study protocol.

Any pre-procedure assessment or tests that are required before entering subjects to the study (history and ophthalmic examinations, laboratory tests) will be analyzed and interpreted at the study site.

A screening log will be maintained by the site for all the subjects screened. This list includes both enrolled and non-enrolled patients.

Every effort will be made to correctly establish eligibility of the participants prior to enrolment. Subjects who do not meet all inclusion/exclusion criteria as listed in Chapter 7.1 and 7.2 will not be enrolled in the study.

Where the participant’s first language is not English, the Site’s interpreting services will be utilised as per Site’s standard protocols.

8.2 INFORMED CONSENT PROCEDURE

The background and purpose of the proposed study and its potential risks and benefits will be explained to the subject under the care of the Investigator. The subjects must be informed about their right to withdraw from the Study at any time and for any reason without sanctions, regulatory consequences, or loss of benefits to which the subject is otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care.

Written Informed Consent must be obtained for all subjects who are potential study candidates before any study-specific tests or procedures are performed. Subjects who meet general entry criteria will be asked to sign the study-specific Informed Consent Form, which has previously been approved by an Ethics Committee (EC). Before signing, the responsible doctor will explain the details of the planned clinical investigation and will inform about potential alternative treatments. Furthermore, the responsible doctor will explain that a patient might be excluded from participating in the study, irrespective of signing the informed consent form, based upon medical examination.

8.3 SUBJECT INSURANCE

Standard NHS Indemnity only will apply for the protocol and study design and clinical negligence.

GEBAUER MEDIZINTECHNIK GmbH providing the devices hold professional liability for the device and its use.

8.4 SUBJECT ENROLMENT

A Screening/Enrolment Log will be maintained to document selected information about candidates who meet or fail to meet the entry criteria. Subjects meeting all eligibility requirements will be eligible to advance in the study, and they will be assigned a 3 digit Subject Identification Number. If the subject does not meet all of the eligibility requirements, the subject's participation is denied.

All subjects who meet the eligibility requirements will be invited to participate. Subjects will be considered enrolled into the study after:

1. A signed Informed Consent has been obtained.
2. The subject has met all of the inclusion and none of the exclusion criteria.
3. The screening assessments results have been approved by the Chief Investigator

8.5 PROCEDURAL INFORMATION

There will be one screening visit followed by the surgical flap creation visit, then the implantation visit and 4 compulsory follow-up study visits. In addition 2 weekly, telephone assessments will be conducted up to 3 months. In addition to that, 2 optional long-term follow-up visits are planned, 1 and 2 years after implantation.

8.5.1 BASELINE EVALUATION (DAY - 30 TO DAY -1)

The pre-procedure data can be collected from 30 days to 1 day prior to the surgical procedure. Obtaining Informed Consent Form is mandatory before any study related procedure is performed. The visit will include subject's eligibility assessment for inclusion and exclusion criteria as described in Section 7. Ophthalmic medical history will be taken including subject's ophthalmic complaints and medications use.

The following examinations will also be performed for both eyes:

- Intraocular pressure (IOP) measurement
- Best corrected visual acuity
- Corneal transparency (slit lamp)
- Photodocumentation of corneal status
- Inflammation of cornea or sclera
- Central corneal thickness measurement (OCT)

- Corneal topography (K-reading map)
- Assessment of corneal epithelium
- Assessment of conjunctiva
- Assessment of iris / pupil
- Assessment of lens
- Assessment of ocular pain
- Assessment of patient satisfaction with treatments and outcome

8.5.2 Day 0 Surgery - Flap Creation

For eligible subjects the Flap creation surgery will be scheduled according to clinical discretion of the responsible ophthalmic surgeon, and in compliance with the provisions described in this Clinical Investigation Plan. The main steps are listed here

- Under topical anesthesia, a mid-stromal pocket will be created using either a femtosecond laser dissection technique or a manual technique. In patients suffering from post-LASIK ectasia, manual techniques will be applied to re-open the pre-existing LASIK flap in the form of a pocket.

8.5.3 Day 0 (+ 30 days) Surgery - Implantaion

For eligible subjects the Implantation of the Gebauer™ Lenticule surgery will be scheduled according to clinical discretion of the responsible ophthalmic surgeon up to 30 days after the flap creation, and in compliance with the provisions described in this Clinical Investigation Plan. The main steps are listed here

- Under topical anesthesia, the corneal vertex will be marked with gentian violet using the first Purkinje image as a reference while asking the patient to fixate on the microscope light.
- The Gebauer™ Lenticule implant is then gently inserted and fully expanded with no wrinkles into the pocket through the pocket opening.
- The implant is then centered with the corneal vertex.
- Immediately post implantation, essential surgical data will be recorded including procedural details (start and end time), orientation, dimensions and closure method of pocket, use of bandage contact lens, device ease of use, procedure complications and medications prescribed.

The subject will be discharged after the procedure or will be hospitalized for one day according to physician discretion.

Post- operatively, antibiotic eye drops will be prescribed for 2 weeks, and steroid eye drops (e.g. PredForte; Allergan) will be prescribed 2 hourly for 2 weeks, along with optional lubricating drops.

Safety Monitoring will be performed (recording of adverse events and medications)

8.5.4 Follow-up Study Visits Post-surgery

Subjects will be followed up frequently for a period of 6 months with ophthalmic assessments at day 1-3; 28 days (+/-7days), 3 months (+/-14 days), 6 months (+/-28 days). In addition to that, patients will be invited to come back to the hospital for two optional long-term follow-up visits 1 and 2 years post implantation. The results of these long-term follow-up visits will be reported separately in an addendum report, independently from the basic follow-up period of 6 months.

Post surgical assessments performed at each follow-up visit will be as follows:

It is recommended to perform all the ophthalmic examination on the same hour ± 3 hours along the day in all the follow-up visits.

At each follow-up visit, the clinical investigator will perform a detailed ophthalmic examination on the treated and the untreated eye which includes the following:

- Intraocular pressure (IOP) measurement
- Best corrected visual acuity
- Corneal transparency (slit lamp)
- Lenticule transparency (slit lamp)
- Photodocumentation of corneal status
- Inflammation of cornea or sclera
- Signs of immunological rejection
- Central corneal thickness measurement (OCT)
- Corneal topography (K-reading map)
- Assessment of corneal epithelium
- Assessment of conjunctiva
- Assessment of Iris / Pupil
- Assessment of Lens
- Assessment of ocular pain
- Assessment of patient satisfaction with treatments and outcome

In addition to that, safety Monitoring will be performed (recording of adverse events and medications).

8.5.5 FOLLOW UP TELEPHONE ASSESSMENTS

Subjects will have 2 weekly telephone assessments up to 3 months post surgery.

The assessments performed at each telephone follow-up will be as follows:

- Assessment of ocular pain
- Assessment of patient satisfaction with treatments and outcome
- Recording of adverse events
- Recording of medications

8.5.6 PROCEDURAL FAILURES

Failure to perform the procedure with the Gebauer™ Lenticule will be recorded on the CRF as an operative failure. In the event of operative failure to treat or if the surgery had to be terminated unsuccessfully for whatever reasons, a detailed explanation of the circumstances will be recorded and an adverse event form will be filed. The patient will be followed until final decision.

It shall be noted that the Investigator must return any damaged or unused study devices within 24 hours post surgery to the manufacturer of the product, GEBAUER MEDIZINTECHNIK GmbH, Monbachstraße 7/1, D-75242 Neuhausen, Germany.

8.5.7 DOCUMENTATION OF THE SURGICAL PROCEDURES

The following data will be recorded during or immediately after performing the procedure:

- Date of procedure, start and end time
- Gebauer™ Lenticule Identification (Product Number/Batch number)
- IOP of treated eye before surgery
- Method of corneal pocket formation
- Suitability of pocket size
- Orientation / opening of pocket
- Potential suturing after implantation
- Potential use of bandage contact lens
- Antibiotic and immunosuppressive treatments
- Overall implantation success
- Investigator's overall procedure evaluation
- Date of discharge from hospital post surgery
- Any procedural adverse events

All relevant information is recorded in the CRF's**.**

8.5.8 POST IMPLANTATION MEDICAL TREATMENTS

Post- operatively, antibiotic eye drops will be prescribed for 2 weeks, and steroid eye drops (e.g., PredForte; Allergan) will be prescribed 2 hourly for 2 weeks (along with optional lubricating drops), and subsequently in tapering doses. All treatment-related medication will be documented in the Concomitant Medications Form.

8.5.9 SUMMARY SCHEDULE OF VISITS AND PROCEDURES

In the below Table, a summary of all planned patient visits and related procedures is provided:

Assessment Procedure	Baseline (-30 – 1 d)	Flap creation (0d)	Implantation (0 ± 30 d)	Follow-up 1 (1 – 3 d)	Telephone Follow-up 1 (14 ± 2 d)	Follow-up 2 (28 ± 7 d)	Telephone Follow-up 2 (42 ± 2 d)	Telephone Follow-up 3 (56 ± 2 d)	Telephone Follow-up 4 (70 ± 2 d)	Telephone Follow-up 5 (84 ± 2 d)	Follow-up 3 (3 M ± 14 d)	Follow-up 4 (6 M ± 28 d)	Long Term Follow-ups (1, 2 y etc.)
Informed Consent	X												
Inclusion & Exclusion Criteria	X												
Ophthalmic medical history	X												
Intraocular pressure (IOP) measurement	X	X	X	X		X					X	X	X
Best corrected visual acuity	X			X		X					X	X	X
Corneal transparency (slit lamp)	X			X		X					X	X	X
Lenticule transparency (slit lamp)				X		X					X	X	X

Photodocumentation of corneal status	**X**			**X**		**X**					**X**	**X**	**X**
Inflammation of cornea or sclera	**X**			**X**		**X**					**X**	**X**	**X**
Signs of immunological rejection				**X**		**X**					**X**	**X**	**X**
Central corneal thickness measurement (OCT)	**X**			**X**		**X**					**X**	**X**	**X**
Corneal topography (K-reading map)	**X**			**X**		**X**					**X**	**X**	**X**
Assessment of corneal epithelium	**X**			**X**		**X**					**X**	**X**	**X**
Assessment of conjunctiva	**X**			**X**		**X**					**X**	**X**	**X**
Assessment of iris / pupil	**X**			**X**		**X**					**X**	**X**	**X**
Assessment of lens	**X**			**X**		**X**					**X**	**X**	**X**
Assessment of ocular pain	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Assessment of patient satisfaction with treatments and outcome	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Request for custom-made device for participant	**x**												
Device Implantation			**x**										
Antibiotic eye drops prescribed			**x**										
Steroid eye drops prescribed along with optional lubricating drops.			**x**										
Flap creation		**x**											
Lenticule Implantation & CRF		**x**	**x**										
Ophthalmic Examination CRF	**x**	**x**	**x**	**x**		**x**					**x**	**x**	**x**
Documentation of Concomitant Medication (Ophthalmic or General)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Documentation of AE / SAE	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

9. INDICATIONS FOR DEVICE REMOVAL

The Gebauer™ Lenticule should be removed from the subject's eye in the following circumstances:

- Uncontrolled cornea erosion
- Cornea melting
- Cornea perforation
- Severe infection (contamination of Implant)
- In case the cornea becomes thinner than 75% of its normal thickness a close follow-up should be performed. When cornea becomes less than 50% of its normal thickness the Gebauer™ Lenticule should be removed.
- Inflammatory processes as red eye
- Peripheral neo-vascularization
- Other symptoms of activation of immunological pathways
- Any condition in the discretion of the PI that may be resulting from the implantation of Gebauer™ Lenticule and deemed to have a long term effect on the eye.

10. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. To prevent premature withdrawal from the study each participant will be properly informed about the study procedures and visits before his/her enrollment. Each case of premature withdrawal will be properly recorded. Wherever possible, subjects will be followed for safety and will be encouraged to return for follow-up visits and for any unresolved adverse events.

No subject will be removed from the study unless the subject has withdrawn his/her consent before treatment or no treatment was ever attempted.

Subjects withdrawn from the study, for any reason, who have not completed the 6-month follow-up visit, will be replaced by enrollment of additional subject. In any case, no more than additional 20% of the original study size will be enrolled.

11. ASSESSMENT OF STUDY PARAMETERS

11.1 MEASUREMENT OF INTRAOCULAR PRESSURE

Goldmann applanation tonometry (GAT) is considered the gold standard for IOP measurement; its accuracy is, however, influenced by corneal thickness, curvature, and biomechanical properties, such as rigidity, viscosity, elasticity, hydration, which have shown to have high interindividual variability and to be affected by corneal pathology and surgery.

The iCare is a new handheld tonometer, which is based on the impact-induction principle also known as rebound tonometry. The main advantages of this device include its quick and simple use, and that local anesthesia and slit lamp are not needed. The iCare tonometer has shown good reproducibility and correlation with GAT and is designed not to be influenced by corneal properties.

In iCare rebound tonometer, a very light-weight probe is used to make a momentary contact with the cornea. In the rebound technology, motion parameters of the probe are recorded during the measurement. An induction based coil system is used for measuring the motion parameters. An advanced algorithm combined with the state of the art software analyzes deceleration and the contact time of the probe while it touches the cornea. Deceleration and the contact time of the probe change as a function of IOP. In simple terms, the higher the IOP, the faster the probe decelerates and the shorter the contact time.

Alternatively, other standard tonometers can be used to measure the intraocular pressure.

Intraocular pressure will be measured at baseline and at each follow-up visit.

11.2 BEST CORRECTED VISUAL ACUITY

Best Corrected Visual Acuity (BCVA) will be assessed using ETDRS/LogMAR

BCVA will be measured at baseline and at each follow-up visit.

11.3 SLIT LAMP ASSESSMENT AND PHOTOGRAPHY

Slit lamp photography is used to document the microscopic and obscure details of the transparent, translucent and opaque structures of the anterior segment, of the implanted Gebauer^{TM} Lenticule and surrounding areas of the eye.

Often conditions affecting the anterior segment of the eye are of a subtle nature and can only be documented using a Slit Lamp Bio microscope with an attached camera. Slit Lamp Photography utilizes a variety of magnifications, angles of view and types of illumination to highlight the areas of interest. This is especially useful in following progression or changes in specific pathology such as new vessels, cataracts and pterygium.

The slit lamp photography will be performed at baseline and at each follow-up visit.

11.4 CENTRAL CORNEAL THICKNESS Measurement (OCT)

Optical coherence tomography (OCT) provides high resolution images of the cornea and anterior segment. It is based on the principle of partial coherence interferometry. It has the benefits of being a rapid, non-contact method requiring less expertise to perform. It is capable of visualizing fine corneal structures such as the corneal epithelium, Bowman's layer, and corneal endothelium.

It helps to visualize various cross sections of the cornea and assess the depth and location of the Gebauer™ Lenticule implant and to discern its relation with the anterior corneal cap and the underlying stromal bed.

Anterior Segment OCT will be performed at baseline and at each follow-up visit.

11.5 CORNEAL TOPOGRAPHY

Corneal topography is a computer assisted diagnostic tool that creates a three-dimensional map of the surface curvature of the cornea.

Topographers can be Placido disc systems or slit-scanning devices.

Placido disc topography systems do not actually measure elevation; rather, they derive anterior corneal elevation data by reconstructing actual anterior curvature measurements via sophisticated algorithms. Slit-scanning or elevation devices directly measure the elevation of both the anterior and posterior cornea via time domain or light-based analysis. Scheimpflug tomographers can analyze the very center of the cornea and image both the anterior and posterior corneal surfaces.

The Pentacam is a hybrid Placido-Scheimpflug device that rotates around the eye 180 degrees in 2 seconds, producing 50 images of both corneal surfaces and 138 000 elevation points to create a 3-D representation of the cornea.

Alternatively, other standard corneal topographers can be used.

Corneal topography will be performed at baseline and at each follow-up visit.

12. STUDY DURATION

The duration of each subject's involvement with the study is expected to be 7-25 months from the time of enrollment and signing of the informed consent document. Each participant will come for treatment/follow-up visits at baseline, procedure day, and all other 4 follow-up visits post procedure. Telephone visits will be conducted 2-weekly up to 3 months. Unscheduled visits may be scheduled additionally if required for medical reasons.

Completion of active enrolment is anticipated to last approximately 1-3 months. The primary endpoints will be achieved when the last study subject has completed his/her 6 months follow-up. For the assessment of long-term tolerability, subjects will be invited to additional follow-up visits after 1 and 2 years. Therefore, the total study duration is 9, respectively, 27 months.

13. STATISTICAL CONSIDERATIONS

13.1 STUDY DESIGN AND OBJECTIVES

The study is planned as an open-label, investigator initiated feasibility clinical study to assess the safety and efficacy of the Gebauer™ Lenticule implant in subjects suffering from keratoconus or post-LASIK ectasia. Therefore, only 15 patients are intended to be investigated.

13.2 STUDY ENDPOINTS

The primary and secondary clinical endpoints for the evaluation of product safety and effectiveness are listed in detail in Chapter 5 of this Clinical Investigation Plan.

13.3 JUSTIFICATION OF SAMPLE SIZE

The present study is an open-label investigator initiated feasibility clinical study and will mainly be analysed with descriptive statistics. No formal sample size calculation was performed, the sample size of 15 subjects is considered sufficient to enable the estimation of the study endpoints.

13.4 BLINDING

This is an open label study. No blinding of patients and/or investigators is intended.

13.5 DATA ANALYSIS SETS

13.5.1 FULL ANALYSIS SET (FA)

The full analysis set (FA analysis) will consist of all subjects enrolled in the study. All variables described in the Case Report Form will be evaluated systematically

13.5.2 ANALYSIS SET FOR EFFECTIVENESS (EF)

The effectiveness analysis set will consist of all subjects who were implanted with the Gebauer™ Lenticule.

13.6 STATISTICAL ANALYSIS OF ANALYSIS SETS

The FA analysis set will serve as the main set for the safety assessments.

The EF analysis set will serve as the main set for the effectiveness assessments.

13.7 STATISTICAL ANALYSIS

13.7.1 GENERAL CONSIDERATIONS

Statistical analyses will be performed using appropriate statistical tools.

Baseline characteristics, together with safety analyses will be performed on all subjects from the FA analysis set. Baseline values are defined as the last valid value prior to first treatment.

The present study is mainly descriptive, nevertheless, when relevant, the required significance level of findings will be 5%. All statistical tests will be two-sided. If statistical tests are performed, nominal p-values will be presented. Where confidence limits are appropriate, a two-sided 95% confidence interval will be constructed.

For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test may be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test may be used as appropriate.

13.7.2 DEMOGRAPHIC AND OTHER BASELINE VARIABLES

Demographic and baseline condition related characteristics will be tabulated. Continuous variables such as age and BMI will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage.

13.7.3 DISPOSITION OF SUBJECTS

Treatment tolerability will be presented, the number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of Adverse Events will be presented. Time to withdrawal may also be assessed and presented by Kaplan-Meier curves if relevant.

13.7.4 EFFECTIVENESS ANALYSIS

A repeated measures analysis (RMA) of variance model (SAS proc MIXED) may be used to assess the pain score change over time. The observed changes over time (e.g. in IOP levels or in pain score) will be modeled as a function of time with baseline results or scores entered as a covariate. Adjusted means of such variables at each time-point will be extracted from the RMA model respective 95% confidence intervals and level of significance (which assesses whether the change at that time point is significantly different from zero).

Change in corneal topography, corneal thickness, corneal clarity (the three primary endpoints for effectiveness) and all other secondary endpoints for effectiveness may be analyzed and presented in a similar manner.

13.7.5 SAFETY ANALYSIS

The primary safety variables, i.e., the occurrence of signs of immunological rejection during the post implantation period, as well as the cumulative incidence (and 95% CI) of treatment-related adverse events (AEs) observed during and after implantation of the Gebauer™ Lenticule and throughout the follow-up period, will be presented in tabular format. Related adverse events include: corneal perforation, melting, uncontrolled inflammation, severe infection

A detailed list of all adverse events will be presented. The adverse event rate will be compiled with respect to frequency, nature, severity of the event, and relationship to the study device. In addition, listings of all safety measures will be produced.

13.7.6 POOLING

Subgroup analysis of the primary efficacy endpoints by the site will be used to evaluate the poolability of the results if the study is performed in more than one site.

13.7.7 HANDLING OF MISSING DATA

No imputation of missing data is planned.

13.7.8 INTERIM ANALYSIS AND LONG-TERM FOLLOW-UP ANALYSES

No interim analyses are planned for this study.

After the last patient completed his/her 6 months follow-up visit, the statistical analysis of the full analysis set is performed and reported in an integrated study report.

For the optional follow-up visits 1 and 2 years after implantation, separate statistical analyses will be performed and reported in separate addendum reports.

14. RISK BENEFIT ANALYSIS

14.1 BENEFITS

The purpose of this clinical investigation is to evaluate the safety of implanting the Gebauer™ Lenticule in subjects with keratoconus or post-LASIK ectasia.

The Gebauer™ Lenticule device is indicated for use as an implantable device, which shall change the thickness and surface curvature of the patient's cornea so that a change in corneal thickness and refraction is induced.

The Gebauer™ Lenticule has several advantages in treating keratoconus and post-LASIK ectasia as compared to alternative treatment options as described in Chapters 2.1 and 2.2. above:

- The GebauerTM Lenticule is a transparent, biocompatible corneal implant which can be

expected to mechanically stabilize the diseased corneal tissue without impairing the patient's vision nor his/her intraocular pressure

- The implanted collagen fibers are similar to the collagen fibers present in the natural human corneal stroma. Therefore, the implant material is expected to be fully accepted by the corneal tissue and to be integrated in its metabolism
- As the Gebauer™ Lenticule is devoid of foreign cellular components such as cell walls, foreign proteins, lipids and foreign genetic information (DNA/RNA), the risk of immunological rejection is much lower than for human cornea donor tissue transplantation.

14.2 RISKS

Risks that may be associated with implantation of the Gebauer™ Lenticule are similar in nature to those encountered with other corneal surgeries. These risks include:

- Anterior or posterior synchie
- Cornea abrasion, opacity
- Device Detachment and further surgical manipulation
- Cornea thinning and perforation
- IOP elevation due to procedure or steroids
- Infection
- Inflammation
- Cataract induction
- Retinal detachment
- Device rejection

15. SAFETY PARAMETERS

Safety assessments include sings of immunological rejection during the post implantation observation period and adverse events/serious adverse events. These variables are classified as primary safety endpoints. Further to this, changes in IOP, corneal /lenticule transparency, inflammation, changes to the corneal epithelium, conjunctiva, iris/pupil or the intraocular lens as well as changes to ocular pain/discomfort have been classified as secondary safety variables.

The reporting time period for safety variables starts with the baseline ocular examination and ends with the last follow-up results obtained after 6 months, respectively, after 2 years post implantation.

15.1 DEFINITIONS OF ADVERSE EVENTS

An adverse event is any untoward and unintended sign, symptom or disease temporally associated with the use of an investigational device or other protocol-imposed intervention, regardless of the suspected cause. Conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF. Changes in a chronic condition of disease that are consistent with natural disease progression are NOT adverse events and also should not be recorded on the AE pages of the CRF.

15.2 SERIOUS ADVERSE EVENTS (SAE)

An AE should be classified as an SAE and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE places the subject at immediate risk of death)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)
- It is considered sight-threatening by the investigator

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.
- Clinical events to be considered and reported as SAE's include (but are not limited to):
- Infectious keratitis
- Serious allergic reaction

15.3 UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence. UADEs also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

15.4 ADVERSE EVENT ASSESSMENT AND DOCUMENTATION

All subjects who have been exposed to the study treatment will be evaluated for adverse events. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents and CRF using standard medical terminology.

All adverse events will be evaluated beginning with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the subject's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form.

All AEs will be characterized by the following criteria:

- Consecutive number
- Diagnosis, Signs & Symptoms
- Seriousness
- Date of onset
- Severity (Scores 1 – 4 as defined below)
- Outcome (Scores 1 – 6 as defined below)
- Date of resolution or date of last assessment

- Action taken (4 activities as listed below)
- Relationship of AE to device
- Relationship of AE to procedure

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If more than one distinct adverse event occurs, each event shall be recorded separately.

Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension □□fainting and fall to floor□□head trauma□□neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

15.5 CLASSIFICATION OF ADVERSE EVENTS BY INTENSITY/SEVERITY

All adverse events are to be graded on a four-point scale (mild, moderate, marked, severe) for intensity/severity. Unless otherwise defined, the definitions are as follows:

- **Mild:** Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities.
- **Moderate:** Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.
- **Marked:** Considerable discomfort with limitation in daily activities, some assistance usually required; medical intervention/therapy usually required.
- **Severe:** Extreme discomfort and limitation in daily activities, significant assistance required; significant medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events listed above.

It shall be noted that expected / anticipated events, as described in this clinical investigation plan (e.g. relating to the physiological healing process after implantation) are not considered as an adverse event. Typical adverse events are unexpected in nature, in severity or in the context of the procedures required in the course of this clinical investigation.

15.6 CLASSIFICATION BY SERIOUSNESS

All AEs will be evaluated as to whether they are serious or non-serious. For AEs and SAEs, the following definitions apply:

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or medical device, and which does not necessarily have a causal relationship with the respective treatments. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally or permanently associated with the use of an investigational product, whether or not related to this product or related treatments.

The regulatory definition of a **Serious Adverse Event (SAE)** is an event that is fatal or life-threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment/damage, or an event that results in or prolongs hospitalization (congenital anomaly, cancer). Serious Adverse Events may or may not be related to the device.

15.7 CLASSIFICATION BY OUTCOME

The clinical outcome of an AE will be classified as follows:

- Resolved
- Resolving
- Unresolved
- Resolved with sequelae
- Unknown / lost to follow-up
- Death

15.8 ACTION TAKEN

The actions taken as a consequence of an AE/SAE are specified as follows:

- None
- Medical Intervention
- Surgical Intervention
- Other treatment

15.9 RELATEDNESS TO THE DEVICE AND RELATED PROCEDURES

The Chief Investigator will evaluate if the AE is related to the Gebauer™ Lenticule or to applicable procedures required for this clinical investigation. Relationships are defined in the following manner:

Not related: Evidence indicates no plausible direct relationship to the study device, respectively, to applicable study-related procedures, such that:

A clinically plausible temporal sequence is inconsistent with the onset of the AE and device administration; and/or a causal relationship is considered biologically implausible (e.g., the AE can be attributed to concurrent/underlying illness, other drugs, or procedures).

Related: Evidence indicates a reasonable temporal sequence of the event with the study device administration and/or with study-related procedures:

There is a clinically plausible time sequence between onset of the AE and study treatment administration; and/or there is a biologically plausible mechanism for study treatments causing or contributing to the AE; and/or the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures.

Possibly related: When considering the above criteria, a causal relationship is classified "possibly related", if the above described relationship is unclear.

15.10 SERIOUS ADVERSE EVENT AND UNANTICIPATED ADVERSE DEVICE EFFECT REPORTING

Serious Adverse Events (SAE) and unanticipated adverse device effects (UADE) must be reported to the Sponsor as soon as possible and within 24 hours after the investigator first learns of the event and to the collaborator, Gebauer Medizintechnik GmbH as soon as possible and no later than 2 days after the investigator first learns of the event. Furthermore, following national requirements, involved ethical committees and/or health authorities must be informed.

For initial reports, investigators should record all case details that can be gathered within the reporting timeframe.

Relevant follow-up information should be submitted to the Sponsor and Gebauer Medizintechnik GmbH as soon as it becomes available and/or upon request. For some events, the sponsor or its designee or the medical monitor may follow-up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the study sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

The applicable regulations have to be followed for safety reporting to regulators:

Any SAE, including laboratory test abnormalities, clinical trial related injury or death, regardless of causal relationship, must be immediately recorded in CRF AE/SAE forms within 24 hours after the Investigator becomes aware of the SAE. The SAE will be reported to the responsible authorities within **24** hours.

15.10.1 REPORTING OF FATAL SAES

Investigator to report fatal SAE within **24 hours** of becoming aware to

i. Sponsor
ii. Collaborator
iii. Chairman of EC
iv. Responsible Authority

Investigator to submit the analysis report (causality assessment) within **14 days** of becoming aware of the event to:

i. Sponsor
ii. Collaborator
iii. Chairman of EC
iv. Responsible Authority

15.10.2 REPORTING OF NON-FATAL SAES

Investigator to report non-fatal SAE within **24 hours** of becoming to:

i. Sponsor
ii. Collaborator
iii. Chairman of EC
iv. Responsible Authority

Investigator/Sponsor to submit the analysis report (causality assessment) within **14 days** of becoming aware of the event to:

i. Chairman of EC
ii. Responsible Authority

The contact details sending notifications:

Sponsor:

Mrs Sarah Glover, R&D Directorate Manager

Research & Development Directorate, The Chestnuts, New Cross Hospital, Wolverhampton, WV10 0QP

Email: sarah.glover7@nhs.net

Phone: 01902 695065

Collaborator:

Mr. Steffen Gabeauer

Gebauer Medizintechnik GmbH, Monbachstrasse 7/1, 75242 Neuhausen, Germany

Tel: +49 (0)7234 9421 0, sgebauer@gebauermedical.com

Detailed and complete Follow-up information relating to a SAE must be reported similarly to the EC within **14 days** of its occurrence along with appropriate documentation. The patient should be observed and monitored carefully until the condition resolves or stabilizes.

All deaths are to be thoroughly investigated and reported. Autopsy reports are to be obtained, if possible.

The Chief Investigator is also being responsible for reporting SAEs to the Ethics Committees overseeing the study within the required timeframe.

In case it is established by the EC etc., that the injury is related to the Investigational Product or study procedure, the collaborator will provide compensation to the trial participant and intimate the details of the compensation provided within **30 days** of release of such order by the Authority on the quantum of compensation to be provided.

16. DATA MONITORING AND QUALITY CONTROL

16.1 REQUIRED DATA

All required data for this study will be collected on standardized CRF's.

16.2 DATA COLLECTION AND TRACKING

Qualified study staff at the clinical site will perform primary data collection drawn from source-document (hospital chart) reviews. The Sponsor will decide the extent of clinical monitoring required as per Sponsor SOPs, including review of CRF's with verification to source documentation.

16.3 EXPECTED COMPLETION, SUBMISSION OF CASE REPORT FORMS AND REPORTS

The Investigator will complete CRF's in a timely fashion, preferably on the day of the patient visit but not later than 7 days after subject enrolment, Implantation or follow-up visit. This will support data quality and reliability.

Serious Adverse Event forms should be faxed to the Investigator/Sponsor within 24 hours of the Investigator's knowledge of the event.

All raw data completed per protocol requirements or as a result of interim follow-up will be prepared and sent to the Investigator/Sponsor within 7 days of completion.

17. DEVICE ACCOUNTABILITY AND DISPOSITION RECORD

Each study device will be provided by Gebauer Medizintechnik GmbH and once received by the Investigator will be kept in a secure location. The secure location will have restricted access and the study devices will be kept separate from other medical devices. The study devices will only be handled by trained personnel.

The Investigator will not supply the study device to any individual not involved in the investigation. The study device will be inventoried at regular intervals during the study, and all unused devices will be returned to the Collaborator when study enrolment is closed.

A form will be maintained by the site that will log the model, lot number, and date of receipt by the site. As the devices are used, the site will record the subject initials or study identification number and date of use. A space will be provided for recording returned devices and the reason for the return.

18. RECORD RETENTION

All study records and reports will remain on file at the site for a minimum of 15 years after completion of this trial, and will further be retained in accordance with local and international guidelines as identified in the clinical study agreement. Study records are to be discarded only upon notification by the Sponsor. The Investigator must contact the Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be contacted if the Investigator plans to leave the investigational site.

19. STUDY RESPONSIBILITIES

19.1 INVESTIGATOR RESPONSIBILITY/PERFORMANCE

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice. The Investigator will provide current copies of the study protocol to all Sub-Investigators or other site personnel responsible for study conduct.

Upon completion or termination of the study, the Investigator will submit a final written report to the Sponsor and the collaborator, Gebauer Medizintechnik and the reviewing EC. The report should be submitted within ten (10) months of study completion or termination.

The Investigator will provide Gebauer Medizintechnik or designee with copies of all EC actions regarding the study.

Investigator will also inform the national regulatory authority in case of completion /termination of the study.

19.2 SHIPMENT OF STUDY DEVICES

The Collaborator and Manufacturer Gebauer Medizintechnik GmbH will ship devices only to the Chief Investigator as per signed study agreements, and provide the Investigators with the information necessary to conduct the study. The Chief Investigator will obtain necessary permission to obtain the import license to import the devices from the national Regulatory Authority.

19.3 STUDY DATA REPORTING AND PROCESSING TRAINING

The training of appropriate clinical site personnel will be the responsibility of the Investigator/ Sponsor or designee for the conduct of the study. The Investigator is responsible for ensuring that his/her staff conduct the study according to the protocol. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present a formal training session to study site personnel which will review the instructions for use of the device, the Investigational Plan, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor or designee

through the regular site monitoring. The collaborator will provide training on the use and implantation of the device to the site personnel.

19.4 MONITORING AT THE INVESTIGATIONAL SITE

This is an Investigator initiated study. The Sponsor will perform any monitoring in line with Sponsor SOPs. Monitoring is performed ensure that the study is executed according to ISO 14155 Good Clinical Practice Guidelines, that the protocol and applicable regulations are complied with and that national legal regulations are followed.

During monitoring visits, the monitor will perform a one hundred percent (100%) review of all Inclusion/Exclusion criteria, informed consent, all reports of device malfunction, all events meeting criteria for expedited event reporting as well as safety and efficacy endpoints. Key variables (demographics, inclusion/exclusion criteria, and safety) on the CRF's will be compared with each subject's source documents. Any discrepancies will be noted and resolved. The data analysis will be conducted at the Institution.

19.5 STUDY MANAGEMENT

The study will be co-ordinated by the Chief Investigator at a single site.

The research study group consisting of the research team listed on the delegation log will meet at regular intervals (every six month or earlier if required).

The Trial Steering Committee consisting of the Chief Investigator, independent peer not involved in the study directly and a representative from Gebauer Medizintechnik GmbH will meet at six-monthly intervals, but more frequently during the first 9 months of the study during the active implantation phase.

19.6 STUDY FUNDING

This study is being funded and the implants provided free of charge by Gebauer Medizintechnik GmbH.

20. SOURCE DOCUMENTATION

Regulations require that Investigators maintain information in the study subject's medical records

which corroborate data collected on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by Sponsor's monitors, EC and/or regulatory inspectors:

Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.

- Medical record documenting that Informed Consent was obtained for the subject's participation in the study.
- Description of device procedure (material used, drugs administered during the procedure, date, time, clinical findings, including supporting data).
- Dated and signed notes for each study subject visit, including results of examinations.
- Notations on abnormal lab results and their resolution.
- Dated printouts or reports of special assessments.
- Description of adverse events and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse events).
- Notes regarding other medications taken during the study (including start and stop dates).
- Study subject's condition upon completion of or withdrawal from the study.

Whenever possible, study-related information/variables as listed in the Case Report Form must be entered directly into the patient's Case Report Form, using this document as the primary source document.

21. AMENDING THE PROTOCOL

This protocol is to be followed exactly, and will only be altered by written amendments. Administrative changes that do not affect the subject benefit/risk ratio (e.g., editorial changes for clarity) may be made without any further approvals. Any change that would require alteration of the Informed Consent form must receive approval from all persons who approved the original protocol and from the EC prior to implementation. Following approval, the protocol amendment(s) will be distributed to all protocol recipients with instructions to append them to the protocol.

22. PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the Investigational Plan or the Investigator Agreement. Investigators are required to obtain prior approval from Sponsor before initiating deviations from the Investigational Plan or protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation.

Deviations shall be reported to the Sponsor regardless of whether medically justifiable, preapproved by Sponsor, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the CRF's. Non-subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement, screening log not submitted as specified, etc.), will be reported to Sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their EC in accordance with their specific EC reporting policies and procedures.

Regulations (ISO 14155) require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol. The site will receive from the Sponsor a list of site-specific study deviations on an annual basis as part of the Annual Progress Report and as part of the Final Report upon completion of the study.

23. STUDY CLOSEOUT

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits and the CRF's and queries have been completed). all CRF's, , and any unused study materials will be collected and returned to the Sponsor. Any unused study devices will be returned to the collaborator. The Monitor will ensure that the Investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the EC of study closure.

It shall be noted that the investigator – whenever possible - is requested to perform a terminal ocular examination and document the findings in the "Ophthalmic Examination Questionnaire", even if a patient terminates his participation due to an adverse event or does not come for the intended final follow-up visit after 6 months.

24. AUDITS/INSPECTIONS

In the event that audits are initiated by the Sponsor (or it's designate), or national/international regulatory authorities, the Investigator shall allow access to the original medical records and provide all requested information.

25. PUBLICATION POLICIES

At the conclusion of the study, a manuscript will be prepared for publication in a reputable scientific journal. The analysis of other pre-specified and non-pre specified endpoints will be performed by the Chief Investigator. Such analyses, as well as other proposed investigations will require the approval of Sponsor. Many secondary manuscripts are anticipated. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all will require the approval of the Sponsor.

26. ETHICAL AND REGULATORY CONSIDERATIONS

26.1 ROLE OF THE SPONSOR

This clinical research study is an investigator-initiated trial. Therefore, the manufacturer of the GebauerTM Lenticule, Gebauer Medizintechnik GmbH, is only delivering the test devices, provides specific indemnity, gives technical support and training on the devices and acts as collaborator. The Sponsor of the study is the Royal Wolverhampton NHS Trust. It is the sole responsibility of the Chief Investigator to conduct the study in compliance with ISO 14155 Good Clinical Practice requirements, and to take any measures that the study meets the regulatory requirements of international regulatory agencies and is performed in compliance with national law.

For this particular clinical investigation, the Chief Investigator will ensure compliance to international regulations and guidelines including ISO 14155 and the Declaration of Helsinki in the conduct of the study. Additionally, country specific laws / regulations concerning clinical investigations, including requirements to file a patient insurance contract, will be followed as applicable.

26.2 GENERAL DUTIES

The Chief Investigator is responsible for obtaining EC and appropriate national regulatory approvals. The Investigator needs to ensure that documentation of EC approvals prior to the shipping of devices, proper clinical site monitoring, patient informed consent is obtained. Additionally, the Chief Investigator is responsible to comply with this Clinical Investigation Plan, to completely fill in the Case Report Forms in a reliable and timely manner and to provide quality data that allow for a meaningful evaluation of the received clinical data. Furthermore, the Chief Investigator is responsible to inform the EC of unanticipated adverse device effects, serious adverse events, and serious deviations from the study protocol as appropriate.

26.3 ETHICS COMMITTEE

A copy of the protocol, proposed Informed Consent form, other written subject information and any proposed advertising material etc. must be submitted to the EC for written approval.

All proposed changes to the clinical protocol must be reviewed and approved by the Sponsor. The Sponsor and the Ethics Committee must approve significant changes in writing; these changes will be considered as Protocol Amendments. All changes must be consistent with the specific country law. A significant change is one which may increase risk or present new risk to the subject, or which may adversely affect the validity of the Study. The Investigator should notify the EC of deviations from the protocol or reportable SAEs/UADEs occurring at the site and other SAE/UADE reports received from Sponsor in accordance with local procedures.

The Investigator will be responsible for obtaining EC approval throughout the duration of the

study. The Investigator, if a member of the EC, may not participate in the approval decision for this study. This non–participation should be noted in the approval letter.

No devices or supplies will be shipped to the Investigator until the EC approval has been given in writing and the Sponsor is supplied with copies of the EC approval document and the Informed Consent document to be used.

26.4 SUBJECT CONFIDENTIALITY

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code (ID number and subject name code) will be used that allows identification of all data reported for each subject.

Data relating to the study may be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data is treated confidentially and that the subject's privacy is guaranteed.

Collection of any subject data will comply with all aspects of the Data Protection Act and GDPR.

Any information which would allow individual patients or clinicians to be identified, will not be released into the public domain.

27. SUPPLEMENTAL APPLICATIONS

As appropriate, Sponsor or designee will submit changes in the Investigational Plan to the appropriate international regulatory authorities and Investigators to obtain EC re-approval.

28. SUBMITTING REPORTS

Sponsor (through the Chief Investigator) will submit the required reports identified as required by local and international regulations. This includes unanticipated adverse device effects, withdrawal of EC or other regulatory approval, current Investigators list, annual progress reports, recall information and final reports.

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30. APPENDIX

ACRONYMS

Acronym	Definition
AE	Adverse Event
AEOI	Adverse Events of Interest
AS-OCT	Anterior Segment Optical Coherence Tomography
BCDVA	Best Corrected Distance Visual Acuity
BMI	Body Mass Index
CCT	Central Corneal Thickness
CRF	Case Report Form
CXL	Corneal collagen cross-linking with riboflavin
DALK	Deep Anterior Lamellar Keratoplasty
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
EF	Efficacy
EN ISO	European Adopted ISO Standard
ETDRS	Early Treatment Diabetic Retinopathy Study.
FA	Full Analysis Set
FDA	Food and Drugs Administration
GAT	Goldmann Applanation Tonometry
GC/MS	Gas Chromatography/Mass Spectroscopy
GCP	Good Clinical Practice
HERF	Hyderabad Eye Research Foundation

ICH	International Council on Harmonization
ICP-OES	Inductively Coupled Plasma (ICP-OES)
ICR	Intracorneal Ring
ID	Identification
IEC	Institutional Ethics Committee
IIS	Investigator Initiated Study
IOP	Intra Ocular Pressure
IRB	Institutional Review Board
ISO	International Organization of Standardization
KPs	Keratic Precipitates
RMA	Repeated Measures Analysis
SAE	Serious Adverse Event
SEIs	Subepithelial Immune Infiltrates
PK	Penetrating Keratoplasty
UADE	Unanticipated Adverse Device Effects
USP	US Pharmacopeia
VA	Visual Acuity