CLINICAL STUDY

VISUMAX™ FEMTOSECOND LASER SMALL INCISION LENTICULE EXTRACTION FOR THE CORRECTION OF HIGH MYOPIA

STUDY NUMBER: LOVC-004

clinicaltrials.gov: NCT02528123

Date: 01/02/2016

SUMMARY

Product name: VisuMax SMILE	Name of investigator (surgeon) and location of site: Dan Reinstein, Glenn Carp, London, UK
TITLE OF THE STUDY: VisuMax femtosecond laser small incision lenticule extraction (SMILE) for the correction of high myopia.	
DEVELOPMENT PHASE: Investigator Initiated Trial (IIT)	
METHODOLOGY: Prospective, single-center, non-randomized, including primary and secondary endpoints	
GENERAL OBJECTIVE: The objective of this clinical trial is to evaluate the safety and effectiveness of the Carl Zeiss Meditec VisuMax™ femtosecond laser small incision lenticule extraction (SMILE) procedure for the reduction or elimination of myopia for manifest refraction spherical equivalent (MRSE) up to -14.00 D with maximum 7.00 D cylinder (myopia with or without astigmatism).	
NUMBER OF PATIENTS: 187 eyes	
INVESTIGATIONAL DEVICE : VisuMax femtosecond laser	
DURATION OF TREATMENT: The overall treatment phase for all patients will be about 24 months DURATION OF FOLLOW-UP FOR EACH PATIENT: 1 year START OF STUDY: February 2016 Interim Report: February 2017 FINAL REPORT: September 2019	
MAIN INCLUSION CRITERIA: - Patients with high myopia with or without astigmatism for MRSE between -9.00 D and -14.00 D, who would like to undergo SMILE surgery with the VisuMax femtosecond laser system MAIN EXCLUSION CRITERIA: - Patients, who are not medically suitable for laser refractive surgery	

LIST OF ABBREVIATIONS AND DEFINITIONS

Astigmatism	Refractive error, caused by an irregularly shaped cornea with one meridian being significantly more curved than the meridian perpendicular to it
Cap	Corneal tissue above the refractive lenticule that remains intact except for a small incision through which the refractive lenticule is removed
CDVA	Corrected Distance Visual Acuity
CE	Conformité Européenne
CZM	Carl Zeiss Meditec
D	Diopter
eCRF	electronic Case Report Form
EMR	Electronic Medical Record
GCP	Good Clinical Practice
HOA	Higher Order Aberrations
LASIK	Laser in situ Keratomileusis
MPG	Medizinproduktgesetz - Medical Devices Act
Myopia	Nearsighted or shortsighted
MRSE	Mean Refractive Spherical Equivalent (=sphere + cylinder/2)
PRK	Photorefractive Keratectomy
RST	Residual Stromal Thickness
SAE	Serious Adverse Event
SLT	Sub-lenticule Thickness
SMILE	Small Incision Lenticule Extraction
Spherical Aberration	Aberration, where parallel light rays do not have the same focus after they pass through an optical system In the Zernike Polynomial expansion the coefficient is: Z_4^0
TUST	Total Uncut Stromal Thickness
UDVA	Uncorrected Distance Visual Acuity

1 BACKGROUND INFORMATION

1.1 INVESTIGATIONAL DEVICE

The following devices and software options have to be used during the clinical investigation:

→VisuMax femtosecond laser (device) for therapeutic and refractive applications of corneal surgery.[1]

The VisuMax has CE approval for treating myopia and myopia with astigmatism up to -10D sphere and 5D cylinder.[2]

The focus of this Investigator Initiated Trial is on the treatment option SMILE for high myopia and high myopia with astigmatism up to -14D spherical equivalent and 7D cylinder.

→SMILE treatment option (software-license)

2.0 STUDY RATIONALE

Laser refractive surgery has been established for more than 25 years[3, 4] for the treatment of low to high myopia. While PRK was defined as a first generation of laser refractive surgery, LASIK was the second generation. In the 1990s many studies were published reporting PRK and LASIK correction of very high myopia (up to -32.00 D in some cases),[5-10] however, these early treatments were associated with low predictability, significant regression of the refractive correction, and induced night vision disturbances.[11-13] During this period, it was found that these issues were for the most part due to the use of small optical zones and minimal transition zones,[14, 15] as well as the non-aspheric nature of the Munnerlyn ablation profiles that were resulting in high induction of spherical aberration[16] and producing serious changes in night vision (glare and halos) and loss of contrast sensitivity. The introduction of aspheric profiles in the early 2000s resulted in significant reduction of the induction of spherical aberration along with improved safety in contrast sensitivity.[17, 18] At around the same time, many studies investigated the influence of the optical zone diameter, and demonstrated that small optical zones were one of the major risk factors for night vision complaints.[19-21] It was also shown that larger optical zones significantly reduced the amount of aberrations post-operatively and provided better outcomes and greater stability. Recent studies have shown that treatment of high myopia (<-10 D) using larger optical zones and aspheric profiles is safe and effective. [3, 4, 22-25]

A further concern of treating high level of myopia was the increased risk of keratectasia. Keratectasia can be induced either by excessive tissue removal or by tissue removal in an already ectatic cornea such as a keratoconic cornea. It has now been established and is accepted in the community of refractive surgeons that the residual stromal thickness of uncut stroma under a LASIK flap should be no thinner than 250 µm and the total uncut stromal thickness for a postop PRK treatment should be no thinner than 300 µm. The major contributor to the risk of excessive keratectomy is the variation in flap thickness.[26-28] Improvements in microkeratome design and the introduction of femtosecond lasers for flap creation have significantly reduced the variation in flap thickness.[29-32] Femtosecond lasers also add the ability to create very thin flaps (down to 80 µm using the VisuMax[33]), which has further reduced the risk of leaving less than 250 µm of residual stromal thickness.

There have also been significant improvements in diagnostic techniques, and a lot of effort has been directed towards improving methods of screening for keratoconus preoperatively.[34-38]

The combination of knowledge of safety limits, improved safety calculations and improved keratoconus screening has dramatically reduced the risk of ectasia.

SMILE, as the third generation of refractive laser surgery, performed using the VisuMax femtosecond laser system, is established for treatments of myopia and myopia with astigmatism with CE approval for sphere up to -10.00 D and cylinder up to 5.00 D.[2] Refractive predictability, safety and patient satisfaction after SMILE have been reported to be high and comparable to results in previous studies of femtosecond LASIK for moderate to high myopia.[39, 40]

SMILE involves passing a dissector through a small 2–3 mm incision to separate the lenticular interfaces created by the femtosecond laser and allow the lenticule to be removed, thus eliminating the need to create a flap. This means that less anterior corneal lamellae are severed in SMILE, which has two main advantages. First, it is known that vertical cuts (e.g. flap sidecut) have more biomechanical impact than horizontal cuts. Recently, Knox Cartwright et al[41] performed a study on human cadaver eyes that compared the corneal strain produced by a LASIK flap, a sidecut only, and a delamination cut only. The authors demonstrated that the increase in strain was equivalent between a LASIK flap cut and a sidecut alone. In contrast, the increase in strain after a delamination cut only was lower than after a LASIK flap or sidecut only. Applying this finding to SMILE, since no anterior corneal sidecut is created, there will be a reduced impact on corneal strain in SMILE compared to thin flap LASIK. Second, it is known that that the cohesive tensile strength (i.e., how strongly

the stromal lamellae are held together) of the stroma decreases from anterior to posterior within the central corneal region, with the anterior 40% stromal lamellae being the strongest region of the cornea, whereas the posterior 60% of the stroma are at least 50% weaker.[42, 43] In addition to cohesive tensile strength, tangential tensile strength (i.e., stiffness along the stromal lamellae) and shear strength (i.e., resistance to torsional forces) have both been found to vary with depth in the stroma. Kohlhaas et al.[44] and Scarcelli et al.[43] found that the tangential tensile strength was greater for the anterior stroma than posterior stroma, each using different methodology. Applying this knowledge to SMILE, since the anterior stroma remains uncut, the strongest part of the stroma continues to contribute to the strength of the cornea postoperatively, in contrast to both photorefractive keratectomy (PRK) and LASIK where the strongest anterior stroma is affected.

In order to model these differences in corneal tensile strength between LASIK and SMILE, we recently developed a mathematical model based directly on the Randleman[42] depth dependent tensile strength data to compare the postoperative tensile strength between PRK, LASIK and SMILE.[45] The total tensile strength after PRK, LASIK and SMILE was calculated as the area under the regression line for the depths of the stroma that remain uncut in each type of procedure. The model demonstrated that the postoperative tensile strength would be greater after SMILE than after both PRK and LASIK.

In summary, considering the safety of subtractive corneal refractive surgical procedures in terms of tensile strength represents a paradigm shift away from classical residual stromal thickness limits. Ideally, a parameter such as total tensile strength, which takes the nonlinearity of the strength of the stroma into account, seems more appropriate than residual stromal thickness as the limiting factor for corneal refractive surgery. At least, a simpler and more conservative way of modelling the total postoperative tensile strength is to calculate the Total Uncut Stromal Thickness (TUST). In SMILE, the TUST is the addition of the uncut stromal thickness in the cap and the Sub-Lenticule Thickness (SLT) defined as the remaining stromal thickness below the lenticule. This is different to LASIK, where only the RST is taken into account as all lamellae in the anterior stroma are cut as a result of the flap.

Knowing that a RST of 250 µm is safe for LASIK, the minimum total uncut stromal thickness (TUST) was conservatively set to 300 µm for the present study, with a minimum sub-lenticule thickness of 220 µm.

As described earlier, the results of SMILE up to -10.00 D have been shown to be similar to those achieved by LASIK. However, there is reason to expect the results of SMILE to be superior to LASIK for very high myopia because all of the potential errors associated with

excimer laser ablation are avoided, such as stromal hydration,[46] laser fluence projection and reflection losses,[47, 48] and other environmental factors.[49] In SMILE, the tissue removal is defined only by the accuracy of the femtosecond laser, which is not affected by any changes in environmental conditions. Therefore, the accuracy of the lenticule interfaces will be independent of the overall thickness of the lenticule (i.e. the amount of correction), meaning that the potential error due to the surgery will be the same for low and high myopia.

These factors should also reduce the induction of higher order aberrations, particularly spherical aberration, compared to LASIK as has been shown for moderate myopia.[50, 51] The induction of spherical aberration should be reduced both by the increased contribution of the anterior stroma thereby reducing the peripheral stromal expansion postoperatively,[52, 53] as well as the elimination of the laser fluence projection and reflection losses that degrade the peripheral ablation.[47, 48]

Therefore, the introduction of SMILE has the potential to improve the outcomes of corneal refractive surgery for very high myopia in terms of accuracy, safety, and quality of vision (induction of aberrations). This study will investigate safety and effectiveness for high myopia with sphere -10.00 D or higher treated by SMILE with the VisuMax femtosecond laser system.

3.0 STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of the Carl Zeiss Meditec VisuMax™ femtosecond laser SMILE procedure for the reduction or elimination of myopia with spherical equivalent from -9.00 D to -14.00 D with a maximum cylinder of 7.00 D (high myopia with or without astigmatism). The secondary objective of the study is to establish appropriate safety parameters for SMILE surgery given that they have been set to be the same as LASIK.

4.0 STUDY ENDPOINTS

4.1 MAIN ENDPOINT

1. Standard deviation of SE_{postop}-SE_{target} at each follow-up time point (represent the scatter of the refractive outcome)
2. Difference in keratometry between the 3 months and 12 months' time points to be the same as for group of matched LASIK eyes.

4.2 SECONDARY ENDPOINTS

The secondary, descriptive endpoints will include:

3. Cumulative UDVA distribution at each time point compared to pre-operative CDVA (efficacy diagram A[54]).
4. Distribution of lines difference between post-operative UDVA and pre-operative CDVA in order to normalize the improvement in visual acuity between eyes (efficacy diagram B[54]).
5. Change in CDVA as a loss-of-line distribution at each time point (safety diagram C[54]) including the percentage of eyes with CDVA unchanged or lines gained, and the percentage of eyes with a loss of 2 or more lines.
6. Cumulative distribution of CDVA at each time point.
7. Stability of spherical equivalent refraction (SE) (diagram F[54]):
   The mean and standard deviation at each time point will be calculated, as well as the percentage of eyes with a change of 0.5 D and 1.0 D between 1-month- and 3-months follow-up, and between 3-months and 12-months follow-up.
8. Predictability of spherical equivalent including linear regression analysis of achieved SE depending on attempted SE (diagram D[54]).
9. Spherical equivalent refractive accuracy (diagram E[54]):
   Distribution of SE_{postop}-SE_{target} at each follow-up time point.
10. Refractive astigmatism as a distribution of pre- and post-operative astigmatism at each follow-up time point (diagram G[54]).
11. Side effects and complications at each time point (numbers and percentages) according appendix 1.
12. Standard analysis of corneal aberrations with focus on spherical aberration with ATLAS pre- versus post-operative and stability of corneal aberrations post-operative for all follow-up visits with an ATLAS.
13. Cylinder vector analysis according to the Alpins method[55] including predictability of the target induced astigmatism vector relative to the surgically induced astigmatism vector, and the distribution of the angle of error (angle between the target induced astigmatism vector and surgically induced astigmatism vector) (diagrams H and I[54]).

5.0 STUDY DESIGN

This is a prospective single-center clinical trial in which a maximum of 187 eyes will be consented, enrolled, and treated with the VisuMax™ femtosecond laser.

Study subjects will be followed for 12 months. Subjects will be screened for eligibility, and informed consent will be obtained from those who meet screening criteria and are interested in participating in the study. Eligible subjects will be examined preoperatively to obtain a medical history and to establish a baseline ocular condition. Baseline and postoperative measurements will include manifest refraction, cycloplegic refraction, distance visual acuity (best corrected and uncorrected using ETDRS charts), slit-lamp examination, fundus examination, corneal topography and wavefront, corneal tomography (front and back corneal surface), central corneal pachymetry, dynamic pupillometry (dark, scotopic, and mesopic), whole-eye wavefront analysis, mesopic contrast sensitivity, and intraocular pressure (IOP).

All baseline and postoperative measurements will be done in accordance to the daily routine procedure of the clinic for standard SMILE treatments.

Retreatments of the study eye will not be allowed during the course of the study.

6.0 STUDY POPULATION

6.1 INCLUSION CRITERIA

6.1.1 General inclusion criteria

Only patients who are medically suitable for corneal refractive surgery can be included in the study.

As general inclusion criteria the following aspects are defined:

- Subjects should be 21 years of age or older
- Contact lens wearers must stop wearing their contact lenses at least four weeks per decade of wear before baseline measurements in case of hard contact lenses and one week before baseline measurements in case of soft contact lenses.

6.1.2 Inclusion criteria specific to the protocol

- Eyes with high myopia spherical equivalent between -9.00 D up to -14.00 D, with cylinder up to 7.00 D will be included.

- Calculated sub-lenticule thickness (SLT) ≥220 µm
- Calculated total uncut stromal thickness (TUST) ≥300 µm
- The corrected distance visual acuity will be 20/40 or better in each eye pre-operatively.
- Patient will be able to understand the patient information and willing to sign an informed consent.
- Patient will be willing to comply with all follow-up visits and the respective examinations as specified in the flow-chart.

6.2 EXCLUSION CRITERIA

6.2.1 General exclusion criteria

- Previous intraocular or corneal surgery of any kind on the eye being treated
- Patient not being able to lie flat in a horizontal position
- Patient not being able to tolerate local or topical anesthesia
- Autoimmune diseases
- Sicca syndrome, dry eye
- Herpes viral (herpes simplex) infections
- Herpes zoster
- Diabetes
- Pregnant or nursing women (or who are planning pregnancy during the study)
- Patients with a weight of > 135 kg
- Any residual, recurrent or acute ocular disease or abnormality of the eye, e.g.
  - Cataract
  - Suspected glaucoma
  - Corneal disease
  - Corneal thinning disorder, e.g. keratoconus,
  - Pellucid marginal corneal degeneration
  - Dystrophy of the basal membrane
  - Corneal oedema
  - Exudative macular degeneration
  - Infection
- Any residual, recurrent, or active abnormality of the cornea to be treated, e.g.
  - Existing corneal implant
  - Corneal lesion

- Unstable refraction
- Connective tissue disease
- Dry eye

The complete list of contraindications is included in the Surgical Information Package provided to the patient by the London Vision Clinic before surgery. Furthermore, the contraindications related to a SMILE treatment correspond to those reported in the medical literature for laser refractive surgery.

7.0 STUDY PROCEDURES

7.1 PRE-OPERATIVE ASSESSMENT

Note: As soon as the first screening for each patient is done and the patient is enrolled in the study, patient data will be pseudonymized. Only the investigator and monitor will be able to identify the patient name if necessary.

Informed consent and permission to use data for analysis and publication have to be obtained from each patient prior to the pre-operative assessment.

A full ophthalmologic examination will be performed on all patients prior to surgery as described in the schedule of assessments (chapter 8.2).

7.2 OPERATIVE PROCEDURES

The treatment protocol will provide information as described in the schedule of assessments and as usually done in daily practice for SMILE.

Schedule of Assessments

Examination **Days to treatment**	**preOP** **-60 to -1**	**OP**	**1d** **1 to 2**	**1m** **21 to 42**	**3m** **75 to 110**	**12m** **305 to 440**
Patient Demographics, medical history	**X**					
Informed consent	**X**					
Pupil diameter (Procyon)	**X**					
Intraocular pressure (IOP) (Goldmann)	**X**					**X**
Fundus examination	**X**					**X**
Cycloplegic refraction	**X**					
Subjective refraction	**X**		**X**	**X**	**X**	**X**
Contrast sensitivity	**X**				**X**	**X**
Slitlamp examination	**X**	**X**	**X**	**X**	**X**	**X**
Corneal topography and wavefront (ATLAS)	**X**		**X**	**X**	**X**	**X**
Corneal tomography (Pentacam)	**X**				**X**	**X**
Wavefront (WASCA)	**X**				**X**	**X**
Optical quality (HD Analyzer)	**X**				**X**	**X**
Corneal & epithelial thickness (RTVue OCT)	**X**				**X**	**X**
Ocular Response Analyzer	**X**					**X**
Severe side effects / complications		**X**	**X**	**X**	**X**	**X**
UDVA	**X**		**X**	**X**	**X**	**X**
CDVA	**X**			**X**	**X**	**X**
Patient questionnaire for night vision disturbances	**X**				**X**	**X**
Light Disturbance Analysis (LDA)	**X**				**X**	**X**
Treatment protocol and videos		**X**				
Laser settings		**X**				

Note: All described examinations are usually done in daily routine practice.

8.0 AVERSE EVENT REPORTING

DEFINTION OF AN ADVERSE EVENT (AE)

An AE is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

REPORTING OF AES

Patients will be instructed by the investigator to report the occurrence of any AE. The investigator assesses and records all AEs observed during the AE reporting period which is defined as postoperative until the end of the study. Any event considered as related to the procedure will be reported regardless of timing.

DEFINITION OF SERIOUS ADVERSE EVENT (SAE) SAES DURING STUDY PERIOD

A SAE includes any of the events listed in Table 1 below and occurring between registration and until completion of the study.

Table 1 SAE Definitions

	Comments
Fatal	All events resulting in death
Life-threatening	The patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death
Requires inpatient hospitalization (> 24 hours)	Events not considered to be SAE are hospitalizations > 24 hours and occurring under the following circumstances: - elective surgery (planned before entry into the trial) - part of the normal treatment or monitoring of the trial treatment - hospitalization for social reasons (e.g. in rehabilitation home) - progressive disease
Prolongs hospitalization	Prolongation of an existing hospitalization
Disabling	Includes persistent or relevant disability or incapacity
Secondary malignancy	Any new malignancy other than a relapse of the current tumour
Congenital anomaly	Birth defect of offspring
Other medically significant condition	Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above

SAEs after End of Trial Treatment

During the follow-up phase, the following events have to be reported as SAE:

- fatal, life-threatening and other medically significant events possibly, probably or definitely related to late effects of trial treatment
- disabling events possibly, probably or definitely related to late effects of trial treatment
- secondary malignancy
- congenital anomaly

DEFINITION OF SERIOUS ADVERSE DRUG REACTIONS (SADRS)

SADRs are all SAEs considered to be related (possibly, probably, definitely) to the trial treatment.

RECORDING OF SAES

Any SAE must be recorded by completion of an SAE form within 24 hours of becoming aware of the SAE.

REPORTING OF SAES TO THE REGULATORY AUTHORITIES

The London Vision Clinic will report all SAEs to the regulatory authorities as required by local and national guidelines.

An overview of expected adverse events and serious adverse events is shown in appendix 1.

8.1 SURGICAL COMPLICATIONS

If any surgical complication occurs, the surgeon will finish the treatment of the patient as usually done in daily routine practice for SMILE. This patient might be excluded from the efficacy analysis if the surgical problem can be defined as a reason for low predictability or loss of lines of CDVA. However, the patient will be still included in the safety investigation and will be reported in the intermediate and final report. If necessary, single patients will be described in detail as case reports.

An overview of intraoperative surgical complications, is shown in appendix 1.

8.2 RETREATMENT

To avoid any permanent risk of under- or overcorrection for the patient, a retreatment will be performed if necessary as done in daily routine practice. However, retreatments will not be performed earlier than the 12-month time point in order to collect the study data.

9.0 STATISTICS

9.1 STATISTICAL METHODS

The main criterion and secondary criteria represent the standard analysis of refractive and visual outcomes and will be analyzed according to the Standard Graphs for Reporting Refractive Surgery, as recommended by the Journal of Refractive Surgery.[54]

9.2 DETERMINATION OF SAMPLE SIZE

The main criterion for the study is to evaluate the standard deviation of the SE_{postop}-SE_{target}, which represents the scatter of the refractive outcome. This metric was chosen in place of the predictability of the refractive correction as a mean under or overcorrection can be adjusted for simply using a nomogram, so the scatter is an indicator of the best possible refractive predictability.

To calculate the sample size for this study, the standard deviation of the refractive outcome will be compared to that reported for LASIK for an equivalent range of myopia. In a previous study of 480 eyes using the MEL80 excimer laser for myopia between -8.00 and -14.00 D, we found the standard deviation of the spherical equivalent refraction 1 year after LASIK to be 0.70 D.[56] A one-tailed F-test will be used to test if the variances of the two populations are equal, or that the variance of SMILE is not greater than the variance of LASIK, using a difference of 0.15 D in standard deviation.

Null hypothesis: Variance(LASIK) = Variance(SMILE)

Test hypothesis: Variance(LASIK) < Variance(SMILE)

Given standard deviations of 0.70 and 0.85 D, the ratio of variances is 1.47. Using an α error probability of 0.05 and a statistical power (1-β error probability) of 0.8, the a priori sample size calculation indicates that a population size of 168 eyes is required.

The 1 year follow-up rate for routine refractive surgery patients at London Vision Clinic has been >90%, so it is reasonable to expect this level of follow-up would be achieved for the study population. Therefore, a total population of 187 eyes is required.

10 DATA MANAGEMENT

The data will be entered directly into the London Vision Clinic EMR software (Nextech) during the patient examination. This includes all measurements made by the ophthalmologist/optometrist as well as images of all automated eye scans obtained (e.g. corneal topography, aberrometry, etc). The data are then exported from the EMR database and transferred electronically by an automated process to a study database (in Microsoft Excel 2010) which will be used for the final analysis. See appendix 2 for details. All data will be fully pseudonymized. Plausibility checks are programmed in the study database to catch 1st order errors, which are then checked manually.

11 MONITORING

Monitoring visits will be performed periodically throughout the study to ensure that the data captured in the study database is correct.

All the data will be checked for any patients presenting with one or more serious adverse events or who withdraw or are withdrawn prematurely from the clinical investigation.

100% monitoring of the informed consent forms will be done.

Random Sample Monitoring will be performed on 50% of the data collected.

12 ETHICAL PRINCIPLES

12.1 REFERENCE DOCUMENTS

This clinical trial will be carried out in accordance with the ethical principles stated in the Helsinki Declaration (and its subsequent modifications), the recommendations consolidated by the International Conference of Harmonization in respect of Good Clinical Practice, ISO 14155 and the local and national applicable regulations.

12.2 PROVISION OF INFORMATION TO PATIENTS AND CONSENT

Patients may participate in this investigation only after being informed by the investigator of the nature of this investigation and of its objectives, risks, disadvantages and benefits,

prerequisites and obligations, confidentiality, specific risks covered by law in order to protect their integrity and notification of the investigation to the Ethics Committee.

No examination, outside of those performed for standard refractive surgery patients, relating to this investigation will be carried out before the written consent has been received. The patients will receive a copy of the study consent form. Only subjects who have the legal capacity, are able to understand the nature, significance and objectives of the clinical investigation, and are able to make a decision can be included in the study. Moreover, any subject whose freedom is impaired by an administrative or court order cannot be selected to participate in the study.

12.3 RESPECT OF ANONYMITY

A unique identification code, assigned by the investigator (automatically assigned within the EMR software), will be used as means of pseudonymization for each patient participating in this investigation, in order to protect his or her identity. This patient identification code will be used instead of the patient's name for any communication of data or reporting of adverse reactions by the investigator. The patient identification consists of numbers:

Example: 13991

12.4 SUBMISSION TO THE ETHICS COMMITTEE AND COMPETENT AUTHORITIES

Approval will be obtained prior to the start of the study according to local regulations.

13 ACCESS TO DATA AND ARCHIVING

13.1 PERSONNEL PARTICIPATING IN THE INVESTIGATION

The investigator is responsible for filing all the documents related to the IIT. The investigator must employ a sufficient number of qualified personnel and have the required facilities available to him/her for the provisional duration of the investigation in order to conduct the study properly and in complete safety. The investigator must ensure that the personnel involved in the IIT are sufficiently well informed about the protocol, the study products, their responsibilities and their functions in the IIT.

13.3 ARCHIVING

After the normal or premature termination of the investigation, the essential study documents will be archived confidentially according to local regulations and GCP guidelines.

14 REPORTS AND PUBLICATION

All data or results from this IIT are the property of London Vision Clinic.

APPENDIX 1: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS REPORTING

ADVERSE EVENTS[1]

The following adverse events, although not an all-inclusive list, should be considered to be reportable.

Any adverse event (AE), whether ascribed to the surgical procedure or not, have to be identified by an updated version of the CRF.

- Diffuse lamellar keratitis (Grade 2 or above)
- Corneal infiltrate or ulcer
- Corneal epithelial defect only at 1 month or later
- Corneal edema (Grade 2 or above) only at 1 month or later
- Epithelium in the interface with loss of 2 lines or more CDVA
- Decrease in CDVA of greater than or equal to 2 lines at 3 months or later
- Any other vision-threatening event
- Ocular penetration
- Ectasia
- Others (describe)

Additional possible adverse events:

- Foreign body sensation only at 3 months or later
- Pain at 3 months or later
- Ghost/double images in the operative eye
- Dry eye at 6 months or later
- Significant night vision disturbances at 6 months or later

SERIOUS ADVERSE EVENTS

Any Serious Adverse Event (SAE), whether ascribed to the surgical procedure or not, will be communicated promptly (within 24 hours after knowledge) according to local regulations and GCP guidelines.

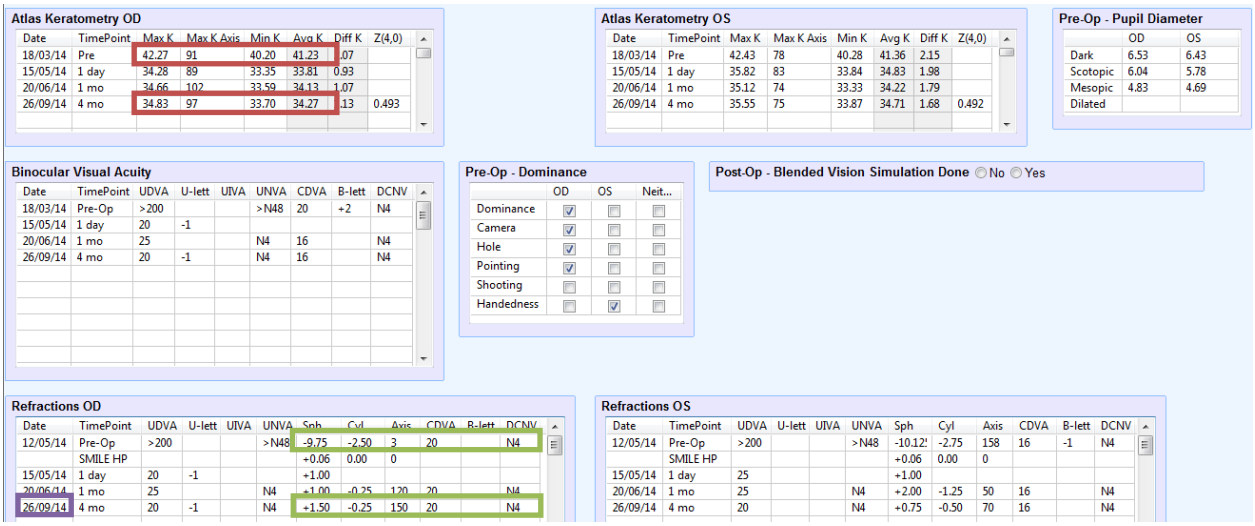
- death
- life-threatening illness or injury

[1] American National Standard ANSI Z80.11-2007

- a permanent impairment of a body structure or a body function
- in-patient hospitalization or prolongation of existing hospitalization
- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- fetal distress, fetal death or a congenital abnormality or birth defect
- device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate

APPENDIX 2: NEXTECH EMR DATA MANAGEMENT

Below is an example screen shot of the EMR source data entry. Further tables are included to record all other data to be collected.



Below is an example screen shot of the data after it has been transferred into Excel for analysis. Highlighted values demonstrate the successful transfer of the data (refraction, keratometry, date).

Preop values:

DOB	NextechID	Sex	Enh	Eye	PreSph	PreCyl	PreAx	PreCDVA	PreDCNV	PreSphEq	RoomDist	PreMaxK	PreMaxKAx	PreMinK	PreAvgK
05/05/74	53791	M		OD	-9.75	-2.50	3	20	4	-11.00	53791OD	42.27	91	40.20	41.23
05/05/74	53791	M		OS	-10.13	-2.75	158	16	4	-11.50	53791OS	42.43	78	40.28	41.36

Postop values:

3mDate	3mTimePoint	3mUDVA	3mBinocUDVA	3mUIVA	3mBinocUIVA	3mUNVA	3mBinocUNVA	3mMaxK	3mMaxKAx	3mMinK	3mAvgK	3mSph	3mCyl	3mAx	3mCDVA	3mDCNV	3m150VA	3mSphEq
26/09/14	4.5	20	20			4	4	34.83	97	33.70	34.27	1.50	-0.25	150	20	4		1.38
26/09/14	4.5	20	20			4	4	35.55	75	33.87	34.71	0.75	-0.50	70	16	4		0.50

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