Study Title: Assessment of the PM1 non-contact pachymeter

Ethics Ref: ETH2021-1765

Date and Version No: 03rd October 2022 Version 2.0

Chief Investigator:	Prof. John Lawrenson
Clinicians:	Isra Masuid, Samranjit Gill and Fardip Rashid
Sponsor:	City, University of London
Funder:	Occuity
Signatures:	

Contents

1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	Assessment of the Occuity PM1 pachymeter
Research question / hypothesis	Is the Occuity pachymeter non inferior in it's measurement of central corneal thickness compared to the ultrasound pachymeter, Lenstar and Pentacam.
Study Design	Research Study
Study Participants	Volunteers with no corneal pathology
Planned Sample Size	82-100 participants
Follow-up duration	N/A
Planned Study Period	1 month
Primary Objective	To determine whether the Occuity PM1 device is non-inferior in measuring central corneal thickness when compared to ultrasound pachymetry, the Lenstar and the Pentacam.
Secondary Objectives	The Investigation aims to assess long-term safety of the Occuity PM1 device when used under the conditions and for the purposes intended, to ensure it will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons.
Primary Endpoint	The central corneal thickness measurements taken by the three devices: Occuity PM1, the ultrasound pachymeter and Lenstar. Demonstrating that the Occuity PM1 Pachymeter is not inferior to the LenStar in terms of equivalency to a 95% confidence level using the Bland Altmen equation/approach based on +/-20micron equivalency.
Secondary Endpoints	If evidence is not sufficient to demonstrate that the PM1 Pachymeter does not perform outside of the target range, it is understood that further investigation may be required. If it is deemed that further clinical investigation(s) are required, it is understood that a new MHRA application will be undertaken.
Safety Outcomes	The type and number of adverse events, serious adverse events and any other device issues will be recorded. Adverse events and devices issues not reflected on the product label will be reported to the manufacturer and, for the Occuity product, will be dispositioned according to the Sponsor's complaint handling procedures for post-market products.
Intervention (s)	N/A

3. BACKGROUND AND RATIONALE

The cornea is a thin, transparent structure at the front of the eye; its surface, as well as the overlying tear film, is responsible for the majority of the eye's refractive power.

Accurate and precise measurement of corneal thickness is important in the diagnosis and management of many ocular diseases. In particular, the central corneal thickness (CCT) measurement is a key parameter to consider when planning for procedures such as refractive surgery, and in the diagnosis of glaucoma.

Refractive error is the leading cause of reversible visual impairment worldwide; it is therefore unsurprising corrective refractive surgery is one of the most widely performed procedures globally. In the United Kingdom, the most frequently performed refractive surgery are laser assisted surgical procedures, such as laser assisted in situ keratomileusis (LASIK), Laser epithelial keratomileusis (LASEK), and Photorefractive Keratectomy (PRK). All of these techniques involve ablating the cornea with a laser to achieve a specific shape. Having an accurate measurement of corneal thickness is therefore of utmost importance in the planning stages, as excessive ablation of the cornea can lead to corneal ectasia, a significant complication of refractive surgery .

Glaucoma is a progressive disease which causes irreversible vision loss, and with ever aging populations, it is now one of the leading causes of irreversible blindness worldwide. Although it is considered to be multifactorial in aetiology, with both genetic and acquired factors contributing to its development and progressions, it is still widely accepted that the intraocular pressure (IOP) is the only modifiable factor in its management to prevent or slow further visual loss. (5).

IOP measurement is typically done in hospital clinics using a Goldmann applanation tonometer. The pressure reading is affected by the corneal thickness – a thick cornea will give a falsely elevated IOP reading, which may result in a patient with healthy eyes being commenced on unnecessary treatment, while conversely a thin cornea may give a falsely low pressure reading, which can result in patients with glaucoma not being started on sight-saving treatment. It has been estimated that a 10% increase in CCT can result in an apparent IOP increase of 3.4mmHg (2).

Ultrasound Pachymeter

The ultrasound pachymeter (UP) is currently the gold standard method , as well as the most widely used to measure CCT. In comparative device studies, the ultrasound pachymeter has been shown to provide the most repeatable measurements . In addition, it is a small and portable handheld device, which makes it very convenient and timesaving to use during clinic appointments.

However, there are several negative aspects to the UP. First, it is necessary for the device to make direct contact with the cornea, which introduces the risk of corneal abrasions and subsequent infection. Second, anaesthetic eye drops need to be used for the patients to tolerate the corneal touch, and studies have shown that after instillation of anaesthetic eye drops, the CCT measurement is increased compared to before the use of anaesthetic, which can lead to a systematic over-reading of IOP. Third, the UP can be difficult to use, as it is necessary for the probe to contact the cornea perpendicularly, and exactly at the centre of the cornea to achieve the most accurate reading, which is difficult to achieve even with good staff training and experience. Lastly, despite the use of anaesthetic, measurement using this device

is uncomfortable, and sometimes poorly tolerated due to the corneal touch, especially by the paediatric population.

While there are optical devices available on the market which can measure CCT without the instillation of anaesthetic or corneal touch, they tend to be bulky machines which are not portable and require specialist training to use. This makes their use in busy hospital clinics and community optometry practices less feasible.

There is a clear need to develop a device which can measure CCT accurately without necessitating corneal touch and use of topical anaesthetic, as well as being easily portable. There is no such device available on the market currently, and in our search in the clinical trial databases and we did not identify any active trials investigating similar devices.

Occuity PM1 Pachymeter

The Occuity device is a new handheld, non-contact, optical pachymeter, which utilise a low power, eye safe near infrared (1310nm) beam to measure the corneal thickness.

The device has an intuitive touchscreen display interface, and a series of 9 LEDs which provides the illumination needed to align the device in front of the eye. Once alignment is achieved, the measurement can take place by pressing the start button on the touchscreen display. During preliminary testing at the parent company, it has been shown the alignment and measurement process takes less than 10 seconds in total, after which a reading will be shown on the digital display of the device. The device is reported to have high reliability (variation of approximately 10um with repeat readings of the same eye), and comparable results to the Lenstar LS900 Biometer during initial testing.

The LED light system consist of a partial ring of 9 white LEDs at a radius of 8.75mm and spaced at 30° intervals. The total power is 2.4 mWm-2 which is will within the 10 mWm-2 blue light hazard eye safety limit. The maximum power of the infrared beam is 50µW, which given the expected exposure time of less than 10 seconds, is considered Class 1 eye safe according to BS EN 60825.

Lenstar LS 900 (Haag-Streit AG, Koeniz, Switzerland)

The Lenstar is an optical device which utilises an 820mm super-luminescent diode and allows for high resolution measurements of the structures in the eye, including CCT. Its use is well established in the hospital clinic setting, and measurements do not require the use of anaesthetic drops or corneal touch. A drawback of this device is that it is large and heavy, and therefore not portable or as fast to use, unlike the ultrasound pachymeter or the Occuity PM1 device.

Pentacam (Oculus Optikgerate GmbH (Germany)

Very similar to the Lenstar, the Pentacam is an optical device which also utilises an 820mm super-luminescent diode and allows for high resolution measurements of the structures in the eye, including CCT. Its use is well established in the hospital clinic setting, and measurements do not require the use of anaesthetic drops or corneal touch. A drawback of

this device is that it is large and heavy, and therefore not portable or as fast to use, unlike the ultrasound pachymeter or the Occuity PM1 device.

4. AIMS AND OBJECTIVES

Primary Objective

To determine whether the Occuity PM1 device is non-inferior in measuring central corneal thickness when compared to ultrasound pachymetry, the Lenstar and the Pentacam.

Secondary Objective

The Investigation aims to assess long-term safety of the Occuity PM1 device when used under the conditions and for the purposes intended, to ensure it will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons.

If the evidence collected during this investigation is not sufficient to demonstrate that the PM1 Pachymeter does not perform under the conditions and for the purposes intended, it may be deemed possible that further investigation may be required. If it is deemed that further clinical investigation(s) are required, it is understood that a new MHRA application will be undertaken.

5. STUDY DESIGN

6.1 Summary of Study Design

This is a prospective, observational, non-invasive, crossover study. The participants will undergo CCT measurement using the Occuity PM1 device, Lenstar device, the Pentacam and then the Ultrasound pachymeter, which is standard of care. Measurement with ultrasound will occur last, as this will require instillation of anaesthetic drops which may confound the values obtained by the Occuity and other devices.

The participants will be recruited and will be measured by City University Clinicans. No additional visits will be required. The measurements will take place during their clinic appointment and will take approximately 30 minutes to complete.

6.2 Primary and Secondary Endpoints/Outcome Measures

The central corneal thickness measurements taken by the three devices: Occuity PM1, the ultrasound pachymeter and Lenstar. Demonstrating that the Occuity PM1 Pachymeter is not inferior to the LenStar in terms of equivalency to a 95% confidence level using the Bland Altmen equation/approach based on +/-20micron equivalency.

Occuity outlines the target range of the PM1 to be within 300-800um. This is because we have already tested this target range with known artefacts. However, the patient population which

is being evaluated will consist only of patients with no known corneal abnormalities, corrective refractive surgeries, ocular inflammatory conditions etc.

It is likely that ~95% of corneal thicknesses which are measured will be within the range of 480um to 620um, therefore ~5% will be outside of the expected range. However, despite there being no history of the pre-stated conditions, there is still the likelihood of this study being able to assess patients with thick/thin corneas as part of the scope, as this is the percentage population who naturally have very thin or very thick corneas.

Secondary Endpoint

If evidence is not sufficient to demonstrate that the PM1 Pachymeter does not perform outside of the target range, it is understood that further investigation may be required. If it is deemed that further clinical investigation(s) are required, it is understood that a new MHRA application will be undertaken.

SAFETY OUTCOMES MEASURES

The type and number of adverse events, serious adverse events and any other device issues will be recorded. Adverse events and devices issues not reflected on the product label will be reported to the manufacturer and, for the Occuity product, will be dispositioned according to the Sponsor's complaint handling procedures for post-market products.

6. STUDY PARTICIPANTS

7.1 Study Setting

The study will take place at Occuity`s office in Reading.

7.2 Overall Description of Study Participants

Patients over the age of 18, with no active corneal pathology, ocular inflammatory condition, or recent eye surgery.

7.3 Eligibility Criteria

Inclusion Criteria

The participant must meet ALL the following criteria to be considered eligible for the study:

- Male or Female, aged 18 years or above.
- Participant is willing and able to give informed consent for participation in the study.
- Able and willing to comply with all study requirements.

Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Any ocular surgery within 6 months

- Known active corneal abnormalities (e.g. Keratoconus, epithelial defects)
- Previous corrective refractive surgery (e.g. LASIK, PRK)
- Current ocular inflammatory or infectious disease (e.g. Uveitis, keratitis, corneal ulcers)
- Contact lens use within the last week
- Any contraindications to use of topical anaesthetic eye drops
- Any other pathology which the clinician or investigator believe may affect the accuracy of the CCT measurement

7. SAMPLING

To achieve a statistically significant result in this crossover, non-inferiority study, with the alpha error set at <0.025, and power at 0.95, and a non-inferiority limit of 2um, 163 eyes will be required, which would likely mean 82 to 100 participants, assuming most are able and willing to have tests performed on both eyes. Calculations are based on the formula:

$n = f(\alpha, \beta) \times 2 \times \sigma^2 / d^2$ (where σ is the standard deviation).

8. STUDY PROCEDURES

Only 1 study visit will be required.

The following procedures will be undertaken for the study, in time order:

1. Investigator to explain the study to patient, provide PIS, and obtain informed consent
2. CCT measurement using Occuity device
3. CCT measurement using Pentacam device
4. CCT measurement using Lenstar device
5. Instillation of Minims Proxymetacaine Hydrochloride 0.5% eye drops to the study eye
6. CCT measurement using Ultrasound Pachymeter

The devices will need cleaning between patients.

- The PM1 is to be cleaned with 70% isopropyl alcohol wipes to prevent patient-to-patient infection.
- The Lenstar device is to be cleaned with 70% isopropyl alcohol wipes will have the paper chin rest strip replaced.
- The Pentacam device is to be cleaned with 70% isopropyl alcohol wipes will have the paper chin rest strip replaced.
- The ultrasound probe will be wiped with a Q-tip soaked in 70% isopropyl alcohol. The tip will then be rinsed in sterile distilled water before use.

9. RECRUITMENT

Recruitment will be volunteers of Occuity who will be independently assessed and monitors by qualified clinicians from City, University of London.

10. SCREENING AND ENROLMENT

Eligible participants will be approached during their visit and will be given verbal information as well as the patient information sheet (PIS). Adequate time will be given for eligible patients

to read the PIS and make decision about participation in the study. Informed consent will be obtained by qualified study staff who have had Good Clinical Practice (GCP) training before undertaking any study specific procedures.

A copy of the signed Informed Consent Form (ICF) will be given to the patient. The original signed ICF will be kept in the site study folder and a copy of the signed ICF will be filed in the patient's notes. Consenting procedure will be clearly documented in patient's notes with date and signature.

11. RANDONMISATION

The volunteers will be randomised *a priori* into one of two sequences – those in Sequence 1 who follow the sequence Lenstar, Pentacam, PM1 then ultrasound and Sequence 2 who will follow the sequence Pentacam, PM1, Lenstar, ultrasound. The order in which subjects will be allocated to each sequence will be generated by a validated software prior to the start of the study to allocate the volunteers to each sequence.

NOTE: Ultrasound cannot be included within the randomisation as the anaesthesia required to undertake the US methodology would result in the Occuity PM1 & Lenstar measurements being unable to be recorded.

12. STUDY ASSESSMENTS

After informed consent is obtained, a short targeted medical and ocular history will be taken, which focuses on whether there is any known corneal pathology, or other ocular or systemic condition which would affect the study assessments needed.

Then the following assessments will take place:

1. CCT measurement using Occuity device
2. CCT measurement using Pentacam device
3. CCT measurement using Lenstar device
4. Instillation of Minims Proxymetacaine Hydrochloride 0.5% eye drops to the study eye
5. CCT measurement using Ultrasound Pachymeter

13. DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS FROM STUDY TREATMENT

A participant has the right to withdraw from the study at any time and for any reason and is not obliged to give his or her reasons for doing so. The participant may withdraw/be withdrawn from further study procedures at any time in the interests of the participant's health and well-being, or for any of the following reasons:

- Significant protocol deviation.
- Participant non-compliance, intentional or non-intentional, with study requirements.
- An adverse event (SAE, ADE), which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.
- Any other reason that may compromise the safety of the participant or the integrity of study data in the opinion of the investigator.

The reason for withdrawal from during the study visit will be recorded. For all SAEs/ADEs, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilised or a non-study related causality has been assigned. Any data collected prior to withdrawal will be included in the final analysis unless consent for this is withdrawn.

14. DEFINITION OF END OF STUDY

The end of study is the date of the last assessment of the last participant.

15. INTERVENTIONS

15.1 Description of Study device

The Occuity PM1 device utilises both LED lights and low intensity infrared radiation. There are a total of 9 LED lights in a partial ring, the lights are at a radius of 8.75mm and spaced at 30° intervals. The total power is 2.4 mWm-2 which is within the 10 mWm-2 blue light hazard eye safety limit.

The infrared radiation is at a wavelength of 1310nm, and the maximum power is 50µW. The expected exposure to this radiation is less than 10 seconds in total, which makes it significantly under both the 2.5mW eye safe limit for 10 second exposure and the 158µW eye safe limit for 2-hour exposure, therefore the device is Class 1 eye safe according to BS EN 60825.

To take the measurement, the device will first be held above the study eye to achieve good alignment, after which the start button can be pressed to begin the measurement process. Once completed, the measurement will be displayed on the digital touchscreen of the device.

15.2 Adherence to Study Treatment

N/A

15.3 Accountability of the Study Treatment

N/A

15.4 Concomitant Medication / Therapies

N/A

ASSESSMENT OF SAFETY

15.5 Definitions

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Significant decline in vision (Defined as irreversible loss of 10 EDTR letters)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

15.6 Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant will be reported to the REC if Chief Investigator deems the event results from, and is an unexpected effect of, administration of any of the research procedures. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form (see NRES website).

15.7 Recording and Reporting Procedures for All Adverse Events

In the event of an adverse event occurring in this study, an adverse event report form will be completed. If the adverse event has potential to cause harm to the participant, the sponsor will be informed.

16. DATA HANDLING AND RECORD KEEPING

All participants will be assigned a study specific participant number. Study data will be initially recorded on a paper case report form (CRF), which will be kept securely in the ophthalmology research office in a locked cabinet. The anonymised data will then be entered into an electronic database (Identified only by participant number), which is operated on a secure system run by the trust. The electronic database will be password protected only be accessible by authorized members of the study team. The name and any other identifying detail will NOT be included in any study data electronic file.

17. DATA ANALYSIS

17.1 Description of Analysis Populations

All participants who satisfy the eligibility criteria and are subsequently enrolled and complete the study procedures will be included in the data analysis.

17.2 Analysis of Endpoints

On completion of data collection, the primary endpoint will be analysed using paired tests or non-parametric equivalents, to compare the CCT measurement achieved using the ultrasound pachymeter and the Occuity PM1 device, and then between the values obtained from the Lenstar, Pentacam and Occuity PM1 device. The level of statistical significance will be set at $p<0.05$.

17.3 Procedure for Dealing with Missing, Unused and Spurious Data

We do not anticipate significant problems with missing, unused or spurious data. If this were to occur, the final decision as to whether the particular patient's data is included in analysis will be at the discretion of the chief investigator.

17.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

N/A

17.5 Interim analysis and criteria for early study termination

N/A

18. ETHICS

Ethical approval for all participating sites will be applied for via Optometry Proportionate Review Committee (PRC). The study will not be initiated before the protocol and all study relevant material such as the informed consent forms and PIS have received approval from the PRC. Any changes to protocol or relevant study documents will be approved by the Sponsor. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the PRC is notified as soon as possible, and an approval is requested. Minor amendments as defined by PRC as non-substantial amendment, may be implemented immediately, and the PRC informed at a later time.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each person participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study using the PIS. Participants will record their willingness to participate on the informed consent form.

The process for obtaining participant informed consent will be in accordance with the PRC guidance and any other regulatory requirements that might be introduced.

Insurance arrangements –Occuity will have clinical trial insurance in place through CNA/Hardy.

18.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

18.2 Other Ethical Considerations

Only patients that can consent for themselves will be included.

18.3 Declaration of Helsinki

The study protocol will be carried out in alliance with the Declaration of Helsinki.

18.4 ICH Guidelines for Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with relevant regulations and with the ICH Guidelines for Good Clinical Practice.

18.4 Study Sponsorship

This study will be sponsored by Occuity.

19. RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

All study procedures will take place at the Occuity Limited, Reading Offices. The equipment needed for this study are:

1. Ultrasound Pachymeter
2. Lenstar LS 900
3. Oculus Pentacam
4. Occuity PM1 Pachymeter

All four machines will be supplied by Occuity.

20. DISSEMINATION AND OUTCOME

The findings of this study will be presented at local, national and/or international scientific meetings. The findings will be submitted for peer-reviewed publication. Summary results including lay summaries may be disseminated via Trust and research department social media outlets.