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Comparing topical (eye drop) PHMB 0.08% only to PHMB 0.02% with propamidine 0.1% combination therapy for Acanthamoeba keratitis

Submission date 21/01/2021	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 02/02/2021	**Overall study status** Completed	
Last Edited 10/10/2022	**Condition category** Eye Diseases	

Plain English summary of protocol

Background and study aims
Acanthamoeba keratitis (AK) is an uncommon but severe infection of the cornea (the protective outer layer of the eye). Over 90% of cases occur in contact lens users and result from exposure to contaminated fluids. The highest proportion of international cases is in the UK (50 to 200 new cases per year in England) and is likely due to contamination of domestic tank-stored water. The infection can cause pain and inflammation and is difficult to clear, with the current best treatment curing only 70% of patients in 12 months.

Polyhexamethylene biguanide (PHMB) is an antiseptic with antiviral and antibacterial properties used in contact lens cleaning solutions and to treat AK. This study will compare the current best treatment, a combination of PHMB 0.02% and propamidine 0.1%, against the new formulation PHMB 0.08%, for the treatment of Acanthamoeba keratitis.

Who can participate?
People aged 12 years and older with a diagnosis of Acanthamoeba keratitis

What does the study involve?
Participants will be allocated at random (like a coin toss) to receive either PHMB 0.08% eye drops or PHMB 0.02% and propamidine 0.1% combination eye drops to be used 16 times a day for 21 days, and then 6 times a day until symptoms resolve. Neither patients nor doctors will know which of the two trial medications the patients have received.

Participants will be asked to complete health questionnaires and undergo evaluation using a slit lamp eye test at the start of the study, then weekly for 3 weeks, then monthly until one month after symptoms resolve, followed by a final visit 3 months later. Participation in the trial will be for a maximum of 12 months.

Additionally, at the start and the end of the study, participants will have clinical eye photography and ophthalmoscopy eye examination, as well as providing blood and urine samples. Where appropriate, participants may be also asked to complete pregnancy tests throughout the course of the study.

What are the possible benefits and risks of participating?
A possible benefit is that participants have a 50:50 chance of being treated with a new formulation of PHMB (0.08%) which may be more efficacious than treatment with the current widely used PHMB 0.02% with propamidine combination treatment.

Patients have their travel reimbursed and will receive trial medications for no cost.

Where is the study run from?
Participating hospitals in London (UK), Manchester (UK), Southampton (UK), Venice (Italy), Milan (Italy), and Katowice (Poland)

When is the study starting and how long is it expected to run for?
From January 2008 to October 2021

Who is funding the study?
The European Commission, SIFI S.p.A. (Italy), and the National Institute for Health Research (NIHR) (UK)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2016-001823-30

Integrated Research Application System (IRAS)
212841

Protocol serial number
CPMS 33467, IRAS 212841, European Commission HEALTH-F5-2012-305661

Study information

Scientific Title
Randomized, assessor-masked, active-controlled, phase 3 study to evaluate efficacy, safety and tolerability of 0.08% polyhexamethylene biguanide (PHMB) ophthalmic solution in comparison with 0.02% PHMB + 0.1% propamidine combination therapy in subjects affected by Acanthamoeba keratitis

Acronym
ODAK Phase 3 (043/SI)

Study objectives
1. The clinical resolution rate at 12 months (CRR_12) of subjects treated with 0.08% polyhexamethylene biguanide (PHMB) monotherapy, is superior, or worse by no more than an acceptable pre-defined 0.20 noninferiority margin (Δ), compared to the CRR_12 of 0.02% PHMB + 0.1% propamidine combination therapy
2. Adverse events, and those relating to toxicity in particular, are less with PHMB 0.08% monotherapy compared to the comparator
3. Time to a cure is shorter in subjects receiving PHMB 0.08% monotherapy compared to the comparator

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/06/2017, London - City & East Research Ethics Committee (Bristol REC Centre, Whitefriars Level 3, Block B, Lewins Mead, Bristol, BS1 2NT; +44 (0)207 104 8171; cityandeast.rec@hra.nhs.uk) ref: 17/LO/0371

Study design
Assessor-masked randomized active-controlled Phase 3 study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acanthamoeba keratitis

Interventions
Participants will be recruited from participating hospitals, and their subsequent study visits will take place in the same hospitals. Routine baseline investigations for Acanthamoeba keratitis are carried out. These include in vivo confocal microscopy (IVCM), a corneal surface cell sample taken for culture and identification of Acanthamoeba DNA by polymerase chain reaction (PCR). Corneal surface cells sampling is carried out with local anaesthetic to minimise discomfort. After the anaesthetic wears off variable mild to severe pain can be experienced. After these investigations, consenting participants can enter the trial.

After obtaining oral and written informed consent, participants will be screened according to the inclusion criteria will be randomized to one of the two study medications (Polyhexamethylene biguanide (PHMB) 0.08% with placebo or PHMB 0.02% with propamidine 0.1%) in a 1:1 ratio. The randomization schedule will be generated using a computer program and verified for accuracy using strict quality control procedures. Eligible participants will receive a masked treatment assignment with a unique randomization code based on the randomization list. The assigned randomization code will be captured in the electronic Case Report Form (eCRF). This randomization code does not disclose any treatment assignment.

Participants will be asked to use the study medication intensively (16 drops daily) for 21 days, then reduced to 4 drops daily from day 21 until symptoms resolve. Participants will visit the hospital every week in the first month, followed by additional monthly visits until the Acanthamoeba keratitis infection has been resolved. When the participant has finished treatment, they will be asked to visit the hospital after 1 month and 3 months for a follow-up check. Visits will last 1-2 h each. Participants will undergo a standardised clinical assessment using slit-lamp evaluation at every visit which is the same as for patients outside the trial. In addition to standard assessment, trial participants will be asked to complete two questionnaires about their general health status (EQ-5D) and visual ability (VFQ-25) at every visit. If applicable, urine pregnancy tests will be done every month, during the visits.

Participants will be assessed using clinical eye photography and ophthalmoscopy at the baseline visit and when trial therapy is ended. Assessments of general health status (blood pressure, pulse rate, and body temperature) will be also measured at the baseline visit and when trial therapy is ended.

Participants who have a relapse of the infection during the trial will have repeat corneal sampling. Participants who are deteriorating, or who require surgery or immunosuppressive therapy will be discontinued from the trial. Participants whose symptoms have not resolved by 11 months will be discontinued from the trial.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
polihexanide 0.08%, polihexanide 0.02% with propamidine 0.1%

Primary outcome(s)
1. Clinical resolution rate at 12 months from randomization (CRR_12) measured using slit-lamp examination at baseline, weekly between weeks 1 and 4 until symptoms resolve, monthly between 1 and 11 months until symptoms resolve, and 1 and 3 months post-discontinuation of treatment. CRR_12 is defined as the percentage of subjects with an absence of signs of clinical inflammation (conjunctival redness, corneal inflammation (seen as a cellular infiltrate +/- oedema) on slit-lamp examination maintained for 1 month after discontinuing all study therapies, and confirmed by a repeat examination 3 months after discontinuing all study therapies.

Key secondary outcome(s))
1. Best-corrected visual acuity (BCVA) measured using spectacles with a pinhole (at the final visit there will be full refraction with spectacles and, for participants with central scarring, vision will be tested with a rigid contact lens) at baseline and on discontinuation of treatment
2. Acanthamoeba keratitis signs measured using slit-lamp examination to detect the following at baseline, weekly between weeks 1 and 4 until symptoms resolve, monthly between 1 and 11 months until symptoms resolve, and 1 and 3 months post-discontinuation of treatment:
2.1. Presence or absence of corneal scarring
2.2. Ulceration severity, ulceration location (epithelial or stromal), and presence or absence of ulceration
2.3. Anterior chamber inflammation grade (0–4)
3. Overall health and eyesight measured using the Euroqol 5 dimension (EQ-5D) quality of life questionnaire and the Visual Function Questionnaire 25 (VFQ25) at baseline, weekly between weeks 1 and 4 until symptoms resolve, monthly between 1 and 11 months until symptoms resolve, and 1 and 3 months post-discontinuation of treatment
4. Safety measured using the following at baseline, weekly between weeks 1 and 4 until symptoms resolve, monthly between 1 and 11 months until symptoms resolve, and 1 and 3 months post-discontinuation of treatment (unless otherwise stated):
4.1. Adverse events tabulated together with the detailed outcomes of the discontinued subjects by 3 months post-discontinuation of treatment
4.2. Clinical laboratory tests of routine blood tests (U&E, LFT's, and haematology parameters) at baseline and termination
4.3. Intraocular pressure (IOP) determined by tonometry
4.4. Rate of pupil, cataract, vitreous, optic disc, and retinal abnormalities determined by slit lamp examination and ophthalmoscopy
4.5. Worsening of the corneal epithelial defect and definable inflammatory signs (development of ring abscess and hypopyon despite >30 days of treatment with the study drug) determined by

slit lamp examination
4.5. Rate of subjects with a relapse measured by slit lamp examination for clinical signs of increasing inflammation (including one or more of: scleritis, conjunctival inflammation, corneal inflammation, corneal ulceration, and anterior chamber inflammation)
4.6. Rate of subjects requiring surgery (including amniotic membrane transplants, superficial keratectomy, application of cyanoacrylate glue, therapeutic penetrating, lamellar keratoplasty, cataract surgery, evisceration, or enucleation) tabulated together with the detailed outcomes of the discontinued subjects by 3 months post-discontinuation of treatment
4.7. Rate of subjects requiring non-study therapies, such as topical steroids and NSAIDs tabulated together with the detailed outcomes of the discontinued subjects by 3 months post-discontinuation of treatment
4.8. Rate of subject discontinuation from study to permit alteration of anti-amoebic therapy or for other unrelated specified reasons
4.9. Incidence of secondary complications (such as significant corneal neovascularization, corneal scarring, corneal perforation, scleritis, secondary glaucoma, cataract, or retinopathy) tabulated together with the detailed outcomes of the discontinued subjects by 3 months post-discontinuation of treatment

Completion date
04/10/2021

Eligibility

Key inclusion criteria
1. Subject must be able and willing to give informed consent
2. Aged ≥12 years, subjects <18 years will only be enrolled in selected study sites
3. Able to understand and willing to comply with study procedures, restrictions, and requirements as judged by the investigator
4. Clinical findings consistent with Acanthamoeba keratitis
5. Confocal microscopy findings consistent with Acanthamoeba keratitis (performed within 7 days prior to study entry or as part of screening procedures)
6. Previously used antibiotics, antiviral and antifungal drugs, or anti-inflammatory drugs treatment for Acanthamoeba keratitis
7. Women of childbearing potential who agree to remain either sexually inactive (sexually abstinent for 14 days prior to the first study drug dose continuing through 28 days after the last study drug dose) or using the same highly effective contraceptive method (results in <1% failure rate when used consistently and correctly) for at least 28 days following the last study drug dose
8. Women of non-childbearing potential who have undergone sterilization procedures and have had these procedures ≥6 months prior to the first study drug dose
9. Non-vasectomized men with a partner of childbearing potential who agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days beyond the last dose of study drug and a partner who agrees to comply with points 7 and 8
10. Vasectomized men who have had their vasectomy ≥6 months prior to study start who agree use a condom during sexual intercourse, or men who have had a vasectomy <6 months prior to study start who agree to follow the same restrictions as described in point 9
11. Men who agree not to donate sperm from the first study drug dose until 90 days the last dose of the study drug

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Documented history and/or clinical signs of concomitant presence of an ocular infection caused by viruses (such as herpes simplex virus) or fungi
2. Treated with drugs having effects on Acanthamoeba cysts prior to study entry, including biguanides (PHMB, chlorhexidine) and diamidines (propamidine, hexamidine)
3. Require systemic immunosuppression for Acanthamoeba associated scleritis
4. Require urgent surgical intervention for advanced Acanthamoeba keratitis in either eye (such as for advanced corneal thinning/melting)
5. Known or suspected allergy to biguanides, diamidines, or intolerance to any other ingredient of the investigational treatments
6. Immunodeficiency disease or taking systemic immunosuppressive therapy
7. Major systemic disease or other illness that would, in the opinion of the investigator, compromise the subject's safety or interfere with the collection or interpretation of study results
8. Pregnancy, planned pregnancy, or breast-feeding
9. Participating in another interventional clinical study with an experimental or unapproved /unlicensed therapy or has participated in another interventional clinical study within the 4 weeks prior to this study

Date of first enrolment
17/08/2017

Date of final enrolment
05/10/2020

Locations

Countries of recruitment
United Kingdom

England

Italy

Poland

Study participating centre

Moorfields Eye Hospital NHS Foundation Trust
162 City Road
London
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Study participating centre
Central Manchester University Hospitals NHS Foundation Trust
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Study participating centre

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Sponsor information

Organisation
SIFI Medtech (Italy)

ROR
https://ror.org/00jts5t62

Funder(s)

Funder type
Government

Funder Name
European Commission

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version v2.0	09/10/2018	02/02/2021	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 2.0	08/10/2018	10/10/2022	No	No