

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

<b>Submission date</b> 21/01/2021	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 02/02/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 10/10/2022	<b>Condition category</b> Eye Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## 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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2. Mr Sebastiano Giuffrida (Public)

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## Contact information

### Type(s)

Scientific

### Contact name

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**Additional identifiers****EudraCT/CTIS number**

2016-001823-30

**IRAS number**

212841

**ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

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 ( $\Delta$ ), 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

## **Secondary study design**

Randomised controlled trial

## **Study setting(s)**

Hospital

## **Study type(s)**

Treatment

## **Participant information sheet**

See additional file ISRCTN12199908\_PIS\_English\_v2.0\_09Oct2018

## **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 measure**

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.

## **Secondary outcome measures**

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

**Overall study start date**

17/01/2008

**Completion date**

04/10/2021

## **Eligibility**

**Key inclusion criteria**

1. Subject must be able and willing to give informed consent
2. Aged  $\geq 12$  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  $\geq 6$  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  $\geq 6$  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

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

Planned Sample Size: 130; UK Sample Size: 70

**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

England

Italy

Poland

United Kingdom

## Study participating centre

**Moorfields Eye Hospital NHS Foundation Trust**

162 City Road

London

United Kingdom

EC1V 2PD

## Study participating centre

**Central Manchester University Hospitals NHS Foundation Trust**

Trust Headquarters

Cobbett House

Manchester Royal Infirmary

Oxford Road

Manchester

United Kingdom

M13 9WL

## Study participating centre

**University Hospital Southampton NHS Foundation Trust**

Mailpoint 18

Southampton General Hospital

Tremona Road

Southampton

United Kingdom

SO16 6YD

## Study participating centre

**Ospedale San Raffaele**

Via Olgettina, 60

Milan

Italy

20132



**Study participating centre**  
**Ospedale SS Giovanni e Paolo**  
Sestiere Castello, 6777  
Venice  
Italy  
30122

**Study participating centre**  
**Medical University of Silesia**  
Poniatowskiego 15  
Katowice  
Poland  
40055

## **Sponsor information**

**Organisation**  
SIFI Medtech (Italy)

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**Sponsor type**  
Industry

**Website**  
<http://www.sifimedtech.com/>

**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, Ευρωπαϊκή Επιτροπή, Европейская комиссия, Evropské komise, Commission européenne, Choimisiúin Eorpaigh, Europskoj komisiji, Commissione europea, La Commissione europea, Eiropas Komisiju, Europos Komisijos, Európai Bizottság, Europese Commissie, Komisja Europejska, Comissão Europeia, Comisia Europeană, Európskej komisii, Evropski komisiji, Euroopan komission, Europeiska kommissionen, 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

**Publication and dissemination plan**

Planned submission to the regulatory authorities for licensing and publication in a peer-reviewed journal.

**Intention to publish date**

30/06/2023

**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?
<a href="#">Participant information sheet</a>	version v2.0	09/10/2018	02/02/2021	No	Yes
<a href="#">Protocol file</a>	version 2.0	08/10/2018	10/10/2022	No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No