Randomized, Double-Masked, Placebo-Controlled Multiple-Dose Phase 1 Study to Evaluate the Safety and Tolerability of Different Doses of Preservative-free Polyhexamethylene Biguanide (PHMB) Ophthalmic Solution in Healthy Subjects

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The primary objective of the study is to establish the ocular safety and tolerability, and systemic safety of 3 different concentrations of preservative-free PHMB in healthy subjects.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Eye disorders
Study type	Interventional

Summary

ID

NL-OMON42469

Source
ToetsingOnline

Brief title
ODAK Phase I (042/SI)

Condition

- Eye disorders
- Protozoal infectious disorders

Synonym
Acanthamoeba keratitis, AK

Research involving

Human

Sponsors and support

Primary sponsor: SIFI SpA
Source(s) of monetary or material Support: European Union (FP7 project)

Intervention

Keyword: Acanthamoeba keratitis, eye infection, healthy subjects, PHMB

Outcome measures

Primary outcome

The determination of the sample size is based on the following:

a total number of 80 evaluable subjects (24 per PHMB treatment group and 8 in placebo group) is considered sufficient for the purpose of the present study for the following reasons:

Based on the binomial probability distribution function, if no serious adverse events (SAEs) are observed in a group of 24 subjects, it can be concluded (with 95% confidence) that the true SAE rate is unlikely to be higher than 11.8%.

Safety and tolerability of 3 different concentrations will be compared to placebo (3 null hypotheses):

* No difference between dose 1 and placebo

* No difference between dose 2 and placebo

* No difference between dose 3 and placebo

Assuming a dropout rate of 10%, the study will aim to recruit 90 subjects.

Secondary outcome

Plasma PHMB concentrations will be presented in a descriptive way.

Study description

Background summary

No formal hypothesis testing is planned.

The Orphan Drug for Acanthamoeba Keratitis (ODAK) project consortium is investigating the potential of polyhexamethylene biguanide (PHMB) as a safe and effective drug for the treatment of the rare eye disease Acanthamoeba keratitis. This debilitating infectious disease is caused by a commonly occurring protozoan and in the absence of treatment can result in blindness. There are currently no approved drugs to treat this disease.

PHMB is a poly-cationic polymer composed by hexamethylene biguanide units (n varies 2 to 40 with a mean of 5.5). Biguanides are an important class of cationic surface-active antimicrobial agents, which have been used for the preservation of many aqueous formulations in addition to the use as disinfectants and antiseptics. PHMB is currently used as an environmental biocide and antiseptic in a variety of products including wound care dressings, contact lens cleaning solutions, perioperative cleansing products and swimming pool cleaners. It has a broad spectrum of activity, being effective against gram-positive and gram-negative bacteria. At a cellular level in Escherichia coli, PHMB interacts with the cytoplasmic membrane, causing leakage of cellular components and inhibition of respiratory enzymes considered essential for survival.1.

PHMB has been shown to have excellent in vitro activity against a broad range of fungal pathogens. Antimicrobial effectiveness has been demonstrated on Acanthamoeba polyphaga, Acanthamoeba castellanii and Acanthamoeba hatchet. Against these protozoa, PHMB acts by binding of its highly charged positive molecules to the mucopolysaccharide plug of the ostiole. This results in penetration through the ostiole to the internalized amoeba, where the drug binds to the phospholipid bilayer of the amoeba cell membrane causing membrane damage, cell lysis and death. PHMB is effective and well tolerated at concentrations of 200 to 600 mg/L (0.02%-0.06%) when used as treatment of patients with Acanthamoeba keratitis.

Study objective

The primary objective of the study is to establish the ocular safety and tolerability, and systemic safety of 3 different concentrations of preservative-free PHMB in healthy subjects.

Study design

Randomized, Double-Masked, Placebo-Controlled Multiple-Dose Phase 1 Study to Evaluate the Safety and Tolerability of Different Doses of Preservative-free Polyhexamethylene Biguanide (PHMB) Ophthalmic Solution in Healthy Subjects.

Intervention

The study consists of an eligibility screening visit, 1 treatment period including short ambulant visits, and a follow-up visit.

In total 90 subjects will be assigned to one of the following 4 treatment groups in a ratio of 3:3:3:1:
Group 1: 0.04% PHMB, n=27
Group 2: 0.06% PHMB, n=27
Group 3: 0.08% PHMB, n=27
Group 4: placebo, n=9

In each group, subjects will receive the study drug/placebo 12 times daily (1 drop every hour, daytime only) for 7 days (Days 0-6) and, if well tolerated, followed by 6 times daily (1 drop every 2 hours, daytime only) for an additional 7 days (Days 7 to 13). On Day -1, subjects will receive 2 test applications of the study drug/placebo, separated by 1 hour. The study drug/placebo will be applied to one eye only (right eye).

Study burden and risks

Eligibility screening will take place according to the inclusion and exclusion criteria on Day -7 to -1. After screening, the subjects will be randomized to one of the treatment groups. The study drug will be applied to the right eye only. On Day -1, subjects will arrive at the clinical research center for the baseline assessments and will receive instructions on how to apply the study drug. Subjects will receive 2 test applications, separated by 1 hour, to test for tolerability. After an observation time of 15 minutes following the second application, subjects will leave the clinical research center. On Days 0 to 13, study drug will be applied at home. Subjects will return to the clinical research center for ambulant visits on Days 7 and 14. The follow-up medical examination will be performed on Day 21.

The subject will visit the hospital 4 or 5 times over a period of 4 weeks, including screening.
A visit will take 2 to about 4 hours. The following will take place:

* We will measure the weight and height - at screening.
* We will measure the blood pressure and heartbeat - at each visit.
* We will analyse urine to check for side effects - at each visit.
* We will draw blood to check for side effects; this will be done at each visit, two tubes each time.
* We will draw blood to see how well PHMB is absorbed in the blood. This will be done at two visits, two tubes each time.
* We will do ocular safety assessments - at four visits
* We will ask to complete questionnaires about ocular surface tolerance (OSDI) and symptoms of ocular discomfort (VAS) - at four visits.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subject must have bilateral best corrected visual acuity >6/10.
Subject must have intraocular pressure (IOP) 14-21 mmHg.
Subject*s ophthalmologic examination must be without abnormalities.

Exclusion criteria

1. Subject with presence of bacterial ocular infections.
2. Subject with presence of any concomitant ocular pathology.
3. Subject performs activities likely to result in an irritated conjunctiva during the study (including heavy alcohol intake, swimming in chlorinated water and heavy smoking).
4. Subject wearing contact lenses at screening until follow-up.
5. Subject with ocular surface fluorescein staining score >3.
6. Subject who used topical or systemic antibiotics, antihistamines, decongestants and non-steroidal anti-inflammatory agents as well as steroids within 7 days before screening.
7. Subject with known or suspected allergy to biguanides or intolerance to any other ingredient of the test treatments.
8. Subject who underwent ocular surgery.
9. Subjects participating in another clinical study or who had participated in a clinical study in the preceding 30 days.
10. Subjects who have only one functional eye.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2015

Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	polihexanide (Polyhexamethylene Biguanide, PHMB)

Ethics review

Approved WMO Date:	14-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002979-15-NL
CCMO	NL54396.018.15