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A randomized, active-controlled, parallel, double-blind study on the safety, ocular tolerability and efficacy of Piiloset Trehalose Emulsion Eye Drop in adult patients with moderate or severe dry eye

STATISTICAL ANALYSIS PLAN

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1 Abbreviations

AE adverse event

ETDRS early treatment diabetic retinopathy study

IBI interblink interval

IER Institute of Eye Research

IOP intraocular pressure

OPI ocular protection index

OSDI ocular surface disease index

ITT intent-to-treat

PP per-protocol

SADE serious adverse device effect

SAE serious adverse event

SAP statistical analysis plan

TBUT tear film break-up time

USADE unanticipated serious adverse device effect

ANOVA Analysis of variance

MedDRA Medical dictionary of regulatory authorities

2 Study objective(s)

The study is comprised of three parts. Part 1 of the study aims to investigate safety and ocular tolerability of trehalose emulsion eye drops. Primary objective of Part 1 of the study is:

to evaluate the safety and ocular tolerability of trehalose emulsion eye drops administered on one eye four times a day for one day.

Part 2 of the study aims to investigate the safety, ocular tolerability and efficacy of trehalose emulsion eye drops administered for 10 days compared to control eye drops. Primary objective of Part 2 of the study is:

to evaluate the safety, ocular tolerability and efficacy (OSDI, tear osmolarity, tear film break-up time) of trehalose emulsion eye drops administered on both eyes three times a day for 10 days as a change from baseline and compared to control eye drops.

The secondary objective of Part 2 of the study is:

to evaluate the efficacy (blink rate, corneal and conjunctival staining) of trehalose emulsion eye drops administered on both eyes three times a day for 10 days as a change from baseline and compared to control eye drops.

Part 3 of the study aims to investigate the safety, ocular tolerability and efficacy of trehalose emulsion eye drops administered for 30 days compared to control eye drops. Primary objective of Part 3 of the study is:

to evaluate the safety, ocular tolerability and efficacy (OSDI, tear osmolarity, tear film break-up time) of trehalose emulsion eye drops administered on both eyes three times a day for 30 days as a change from baseline and compared to control eye drops.

The secondary objective of Part 3 of the study is:

to evaluate the efficacy (blink rate, corneal and conjunctival staining) of trehalose emulsion eye drops administered on both eyes three times a day for 30 days as a change from baseline and compared to control eye drops.

3 Design and type of the study

This is a prospective, single-site, randomized, active-controlled, parallel, double-blind, single and multiple dose study to evaluate the safety, ocular tolerability and efficacy of Piiloset Trehalose Emulsion Eye Drop in the adult patient population with moderate or severe dry eye for up to 30 days.

4 Sample size considerations

A total number of 64 adult patients (both males and females) will be included in the study as follows:

In Part 1 of the study, a total of 3 subjects to obtain preliminary information on the acute safety and ocular tolerability of the treatment from all 3 completing subjects (n=3). In Part 2 of the study, nine subjects to obtain preliminary information on the long-term safety, ocular tolerability, and efficacy of the daily treatments from at least 8 completing subjects (n=8). In Part 3, 52 subjects to obtain information on the long-term safety, ocular tolerability, and efficacy of the daily treatments from at least 44 (83%) completing subjects allocated in two randomized treatment groups (n=22).

No subject will be allowed to participate in more than one Part of the study.

5 Statistical hypotheses

The purpose of this study is to evaluate ocular safety and tolerability in 3 different study Parts conducted sequentially. For the study part 3 a sample size calculation was conducted with OSDI as the parameter of interest. The evaluation of the study will be based on the total evidence collected.

The null-hypothesis to be tested is

H_0 : There is no difference between study products in OSDI scores.

H_1 : There is a significant difference in OSDI scores in favour of the investigational product.

Statistical analyses will be performed primarily on the ITT population. The PP population will be used as a secondary dataset.

6 Analysis sets

6.1 Intention-to-treat (ITT) set

The ITT population includes all randomized subjects who have received the study medication at least once and who have subsequent efficacy measurements available.

6.2 Safety dataset

The safety population will include all randomized subjects who have received the study medication at least once from whom at least one safety measurement is obtained after randomization.

6.3 Per protocol (PP) set

The PP population excludes subjects with significant protocol deviations, including withdrawn subjects. Protocol deviations will be assessed prior to database lock.

7 General statistical considerations

The aim of study is to investigate the safety, ocular tolerability and efficacy of Piiloset Trehalose Emulsion Eye Drop in adult patients with moderate or severe dry eye.

No imputations will be done for missing observations. If not stated otherwise, a two-sided p-value less than 0.05 will be considered statistically significant.

No interim analyses are planned.

8 Demographic and other baseline characteristics

The comparability of the treatment groups will be assessed by the demographic and baseline characteristics. These include but are not restricted to

- Age
- Gender
- Weight
- History of ocular surgery, trauma, refractive laser vision correction, infection, allergy
- Topical and/or systemic therapies for the preceding 4 weeks
- Allergy to any constituent of the investigational
- Current or planned pregnancy and nursing

Demographic and baseline characteristics of the subjects will be tabulated with descriptive statistics. The disposition of the subjects (and eyes) will be summarized.

9 Concomitant medication/treatment

Concomitant medications reported during the study will be listed.

10 Extent of exposure and compliance

Exposure and compliance will be reported descriptively using the information available in the database.

11 Analysis of efficacy

11.1 Primary efficacy variables

11.1.1 OSDI

The OSDI questionnaire comfort rating used as an efficacy endpoint will be performed

• before the 1st treatment in all Parts; and

• at end-of-study visit in Parts 2 (Day 10) and 3 (Day 30).

11.1.2. Biomarkers

Biomarkers to be assessed as primary efficacy endpoints will be determined

• at screening visit;

• before the 1st treatment in all Parts; and

• at end-of-study visit in Parts 2 (Day 10) and 3 (Day 30).

Biomarkers used as primary efficacy endpoints are a part of the physical examination of the eyes and include the following methods:

• tear osmolarity

• tear film break-up time (TBUT)

Ocular comfort ratings (OSDI) by the subjects will be summarized by study day and treatment (Parts 2 and 3). The results will be presented separately for Parts 2 and 3.

The comparisons between treatment groups in Part 2 after ten days treatment will be conducted using standard statistical methodology for paired data (e.g. paired t-test for continuous variables and Wilcoxon signed rank test for variables in ordinal scale) between eyes (study treatment administered in other eye and control treatment to contralateral eye).

The comparisons between treatments in all ocular measurements (including biomarkers and physical examination of eye parameters) in Part 3, which are the primary basis of evaluation of study objectives, are done using the parallel group design. Analysis of variance model will be used to evaluate the difference in the change from baseline in OSDI between treatment groups. Similar method will be used for tear osmolarity and tear film break-up time. In case the normality assumption is violated then Wilcoxon rank sum test will be used instead.

11.2 Secondary efficacy variables

The secondary efficacy parameters include the following assessments:

11.2.1. Biomarkers

Biomarkers to be assessed as secondary efficacy endpoints will be determined

- at screening visit;
- before the 1st treatment in all Parts; and
- at end-of-study visit in Parts 2 and 3.

The biomarkers are a part of the physical examination of the eyes and include the following methods:

- blink rate (blinks per minute)
- corneal staining (Oxford grading)
- conjunctival staining (Oxford grading)

Blink rate is further converted to the interblink interval (IBI) and used with TBUT for calculation of the ocular protection index (OPI = TBUT/IBI) (Ousler et al. 2008).

Similar methods than in the primary variables will be used for the secondary variables. ANOVA model will be used for blink rate and Wilcoxon rank sum test will be used for the staining variables.

12 Analysis of safety and tolerability

The safety population having received the study treatment and with any follow-up data will be considered evaluable for safety and tolerability for the corresponding Part of the study.

In Part 1, the ocular safety and tolerability of trehalose emulsion eye drops will be evaluated as a within-subject comparison to the untreated eye and to baseline. In Part 2, the evaluation will be performed as a within-subject comparison to the control eye and to baseline. In Part 3, the evaluation will be performed between subjects receiving trehalose emulsion eye drops in comparison with subjects receiving control eye drops and to baseline.

Physical examination of the eye parameters will be summarized descriptively by eye in all Parts of the study. The ocular safety and tolerability of the treatments evaluated at the end-of-study visit will be summarized by study day, treatment and eye.

A. Physical examination of the eyes

Physical examination of the eyes will be performed

• at screening;

• in Part 1 at baseline (before the 1st dose) and after the 4th dose;

• in Part 2 at baseline (Day 1, before the 1st dose) and after the last dose; and

• in Part 3 at baseline (Day 1, before the 1st dose) and after the last dose.

Methods:

• Visual acuity (ETDRS)

• Digital photography of the anterior eye

• Bulbar redness (IER grading)

• Lid redness (IER grading)

• Intraocular pressure (IOP)

If feasible statistical analysis using similar methods than for efficacy variables can be conducted for these parameters.

12.1 Adverse events

AEs will be summarized for each treatment group and study Part by severity, causality, and duration. Ocular AEs will be reported separately. All SAEs (including SADE and USADE) will be listed with all relevant information.

13 Completion and premature discontinuation

Completion and premature discontinuation will be listed and the reasons for premature discontinuation will be presented.

14 Deviations from the analyses planned in the study protocol

There are no deviations from analyses planned in the protocol.

15 Execution of statistical analyses

Statistical analyses will be performed by 4Pharma Ltd.

16 Hardware and software

Statistical analysis, tables and patient data listings will be performed with SAS® version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

17 References

Clinical Study Protocol, Final Protocol, Amended 060418, Oy Finnsusp Ab.