



Clinical trial results:

A phase I study to evaluate the pharmacokinetics, safety and tolerability of preservative free tafluprost ophthalmic solution (0.0015%) in pediatric patients diagnosed with glaucoma or ocular hypertension.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-004302-26 |
| Trial protocol | GB HU SK PL |
| Global end of trial date | 03 July 2017 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 07 March 2019 |
| First version publication date | 07 March 2019 |
| Summary attachment (see zip file) | CSR Synopsis (Tafluprost PK-pediatric study_CSR synopsis.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 201350 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Santen Oy |
| Sponsor organisation address | Niittyhaankatu 20, PO BOX 33, Tampere, Finland, FIN-33721 |
| Public contact | Tommi Pesonen, MSc, 4Pharma Ltd, +358 22835700, |
| Scientific contact | Auli Ropo, MD, PhD, Santen Oy, Global Medical Affairs, +358 32848863, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001187-PIP01-11 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 December 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 July 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the pharmacokinetics (PK) of preservativefree tafluprost 0.0015% eye drops in paediatric patients of at least 36 week gestation and 1 month postnatal to under 18 years of age diagnosed with paediatric glaucoma or ocular hypertension (OHT).

Protection of trial subjects:

This was an open-label, multicenter Phase I study in pediatric patients diagnosed with glaucoma or OHT. The planned enrollment of at least 18 pediatric patients proceeded in a sequential manner beginning with the oldest age group: First at least five 12 to <18 years old patients were enrolled. These were followed by at least five 3 to <12 years old patients and then at least eight 1 month to <3 years old patients.

A PK and safety assessment committee (PKSAC) reviewed all relevant data before patients could be enrolled to a younger age cohort. Official minutes of the PKAC meetings for these two decision-making steps were transcribed. The IECs/IRBs and health authorities were noted as appropriate. As a safeguard, individual data of the youngest age cohort was evaluated in complementary ad hoc meetings. The study medical monitor and statistician, as well as Sponsor's representatives (from the disciplines of clinical science, PV, and PK) were the members of the PKSAC. The PI was also included in all communications and decision-making by the PKSAC.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 24 June 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 18 |
| EEA total number of subjects | 5 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 4 |
| Children (2-11 years) | 8 |
| Adolescents (12-17 years) | 6 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 8 centers in the United States and Europe. A total of 20 pediatric patients were screened for the study. A total of 18 patients were enrolled to this study, six patients in each age group.

Pre-assignment

Screening details:

Eligible patients were on IOP-lowering medication, or had not used it for ≥ 4 weeks prior to the study, or were treatment naïve.

All eligible patients were assigned to receive the following open-label treatment on Day 1 for a period of 7-9 days.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 18 |
| Number of subjects completed | 18 |

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|--|--------------------|
| Arm title | Tafluprost 0.0015% |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | tafluprost |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ocular use |

Dosage and administration details:

The once daily dosing of tafluprost eye drops was based on the latest SmPC. Each patient received one drop of tafluprost 0.0015% once daily at 08:00 (± 2 h) in both eyes for 7-9 days.

| | |
|---------------------------------------|--------------------|
| Number of subjects in period 1 | Tafluprost 0.0015% |
| Started | 18 |
| Completed | 17 |
| Not completed | 1 |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | overall trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 18 | 18 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 4 | 4 | |
| Children (2-11 years) | 8 | 8 | |
| Adolescents (12-17 years) | 6 | 6 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 8.4 | | |
| standard deviation | ± 5.73 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 9 | 9 | |
| Age group | | | |
| Age group 1: 12 years to <18 years old | | | |
| Age group 2: 3 years to <12 years old | | | |
| Age group 3: 1 month to <3 years old | | | |
| Units: Subjects | | | |
| Age group 1 | 6 | 6 | |
| Age group 2 | 6 | 6 | |
| Age group 3 | 6 | 6 | |

Subject analysis sets

| | |
|----------------------------|----------------|
| Subject analysis set title | Safety dataset |
|----------------------------|----------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All enrolled patients were included in the Safety dataset.

| | |
|----------------------------|------------|
| Subject analysis set title | PK dataset |
|----------------------------|------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The patient with improper entry and the patients using the butterfly needle were excluded from the PK dataset.

| Reporting group values | Safety dataset | PK dataset | |
|---|----------------|------------|--|
| Number of subjects | 18 | 11 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 4 | 3 | |
| Children (2-11 years) | 8 | 5 | |
| Adolescents (12-17 years) | 6 | 3 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 8.4 | 7.3 | |
| standard deviation | ± 5.73 | ± 6.04 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 4 | |
| Male | 9 | 7 | |
| Age group | | | |
| Age group 1: 12 years to <18 years old | | | |
| Age group 2: 3 years to <12 years old | | | |
| Age group 3: 1 month to <3 years old | | | |
| Units: Subjects | | | |
| Age group 1 | 6 | 3 | |
| Age group 2 | 6 | 3 | |
| Age group 3 | 6 | 5 | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Tafluprost 0.0015% |
| Reporting group description: - | |
| Subject analysis set title | Safety dataset |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All enrolled patients were included in the Safety dataset. | |
| Subject analysis set title | PK dataset |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The patient with improper entry and the patients using the butterfly needle were excluded from the PK dataset. | |

Primary: Pharmacokinetic parameter tmax

| | |
|--|---|
| End point title | Pharmacokinetic parameter tmax ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: Tafluprost acid concentrations were measured at the end of tafluprost dosing period. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The PK of tafluprost acid was characterized by pediatric age group. Thus, no formal hypotheses were set for the study. PK variables were summarized by age group.

| End point values | PK dataset | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 11 | | | |
| Units: minutes | | | | |
| Age group 1 | 10 | | | |
| Age group 2 | 10 | | | |
| Age group 3 | 10 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic parameter Cmax

| | |
|--|---|
| End point title | Pharmacokinetic parameter Cmax ^[2] |
| End point description: | |
| End point type | Primary |
| End point timeframe: Tafluprost acid concentrations were measured at the end of tafluprost dosing period. | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The PK of tafluprost acid was characterized by pediatric age group. Thus, no formal hypotheses were set for the study. PK variables were summarized by age group.

| End point values | PK dataset | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 11 | | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Age group 1 | 22.9 (± 7.3) | | | |
| Age group 2 | 39.0 (± 20.4) | | | |
| Age group 3 | 72.0 (± 53.2) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic parameter tlast

| | |
|-----------------|--|
| End point title | Pharmacokinetic parameter tlast ^[3] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Tafluprost acid concentrations were measured at the end of tafluprost dosing period.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The PK of tafluprost acid was characterized by pediatric age group. Thus, no formal hypotheses were set for the study. PK variables were summarized by age group.

| End point values | PK dataset | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 11 | | | |
| Units: minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Age group 1 | 23.3 (± 11.5) | | | |
| Age group 2 | 16.7 (± 11.5) | | | |
| Age group 3 | 34.0 (± 25.1) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic parameter AUC 0-last

| | |
|-----------------|---|
| End point title | Pharmacokinetic parameter AUC 0-last ^[4] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Tafluprost acid concentrations were measured at the end of tafluprost dosing period.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The PK of tafluprost acid was characterized by pediatric age group. Thus, no formal hypotheses were set for the study. PK variables were summarized by age group.

| End point values | PK dataset | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 11 | | | |
| Units: pg/mL*min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Age group 1 | 383.4 (± 267.4) | | | |
| Age group 2 | 456.8 (± 555.3) | | | |
| Age group 3 | 1661.0 (± 1705.5) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All enrolled patients were included in the Safety dataset.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Enrolled |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events | Enrolled | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Enrolled | | |
|---|-----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 18 (33.33%) | | |
| Investigations | | | |
| IOP increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |
| Goniotomy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|--|----------------------|--|--|
| Ear pain subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Conjunctival redness subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Erythema of eyelid subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Ocular hyperaemia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 18 September 2015 | <p>Section: 6.4.1. Inclusion criteria</p> <p>Old text:</p> <p>1. Patient is a non-smoking male or female ≤ 17 years of age on the day of signing the informed consent with the first day of study drug dosing to occur prior to the 18th birthday. Infants must be of ≥ 36 weeks gestational age and at least 1 month of age</p> <p>New text:</p> <p>1. Patient is a non-smoking male or female ≤ 17 years of age on the day of signing the informed consent with the first day of study drug dosing to occur prior to the 18th birthday. Infants less than 12 months old must be of ≥ 36 weeks gestational age and at least 1 month of age</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported