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)	EMEA-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 patientswere 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 (±2h) 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 needlewere 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 needlewere 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) Conjunctival redness subjects affected / exposed occurrences (all) Erythema of eyelid subjects affected / exposed occurrences (all) Ocular hyperaemia subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 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	Section: 6.4.1. Inclusion criteria Old text: 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 New text: 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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported