SYNOPSIS

Name of Sponsor/Company Santen Oy	Individual trial table referring to part of the dossier	(For National Authority use only)
Name of finished product: Preservative-free tafluprost 0.0015% eye drops	Volume:	
Name of active ingredients: Tafluprost (AFP-168)	Page:	

Title of trial:
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

Investigators and trial centers:
The study was conducted at eight centers in the United States and Europe (Hungary, Slovenia, UK, and Poland).

Publication (reference): Not applicable

Date of first patient enrolled: 1 July 2014 (Pre-study visit) **Date of last patient completed:** 3 July 2017 (Post-study visit)	**Phase of development:** I

Objective(s):
The primary objective of this study was to evaluate the pharmacokinetics (PK), as well as the safety and tolerability, of preservative-free tafluprost 0.0015% eye drops in pediatric patients diagnosed with glaucoma or ocular hypertension (OH).

Methodology:
Open-label, multinational, multicenter, phase I study in pediatric patients. The study comprised three age groups: 12 to <18 years old patients, 3 to <12 years old patients, and 1 month to <3 years old patients. The enrollment proceeded in a sequential manner from the oldest age group to the youngest. A PK and safety assessment committee (PKSAC) reviewed all relevant data before patients could be enrolled to a younger age cohort.

The primary evaluation of pharmacokinetics (PK) was based on tafluprost acid plasma concentrations following 8 days repeated administration of 0.0015% tafluprost eye drops. The assessment of repeated dose tolerability and safety (AEs, visual acuity, biomicroscopy, ophthalmoscopy, IOP, vital signs, 12-lead ECG and laboratory safety tests), in turn, warranted further clinical investigations in the target population.

Number of patients:
Eighteen pediatric patients were enrolled to the study as planned: six 12 years to <18 years old patients (≥5 patients planned), six 3 years to <12 years old patients (≥5 patients planned), and six 1 month to < 3 years old patients (≥8 patients planned). The clinical phase was prolonged by 2 years to meet the planned number of youngest patients.

Diagnosis and main criteria for inclusion:
Eligible patients were of any race and either sex, 1 month to <18 years old, and at least 36 weeks of gestational age if <12 months old. The patients were diagnosed with primary or secondary pediatric glaucoma or OH in one or both eyes. The patients had a history/presence of elevated IOP (≥22 mmHg) in at least one eye. The patients switched (directly or following a short washout) from their prior OH medication to tafluprost, or had appropriate washout (≥4 weeks) prior to tafluprost, or were treatment-naïve.

Test product, dose and mode of administration, batch number(s):
Preservative-free tafluprost 0.0015% eye drops (1 drop per eye) into both eyes once daily at 8:00 (± 2h). Batch numbers 144374 (US; expiry date November 2016) and 157501 (Europe; expiry date November 2018).

Reference therapy, dose and mode of administration, batch number(s):
Not applicable.

Name of Sponsor/Company Santen Oy	Individual trial table referring to part of the dossier	(For National Authority use only)
Name of finished product: Preservative-free tafluprost 0.0015% eye drops	Volume:	
Name of active ingredients: Tafluprost (AFP-168)	Page:	

Duration of treatment:
Tafluprost eye drops were dosed for 8 (±1) days into both eyes.

Criteria for evaluation:
PK
Steady-state tafluprost acid concentrations in plasma on Day 8, and the resulting PK parameters: $AUC_{0\text{-}last}$, C_{max}, t_{max}, and t_{last}. $t_{1/2}$ and $AUC_{0\text{-}\infty}$ could be calculated only for a subset of patients

Safety and tolerability
Treatment discontinuations, exposure to tafluprost, AEs, ocular safety measures (visual acuity, biomicroscopy, ophthalmoscopy and IOP) and systemic safety measures (vital signs, 12-lead ECG and safety laboratory tests)

Statistical methods:
Descriptive statistical methods were used. IOP changes from baseline were analyzed using a paired t-test.

Results:
PK (N=11)
A total of 18 pediatric patients were enrolled in the study. Unfortunately, one site in the US had used butterfly needles for drawing blood (instead of intravenous cannulas). Tafluprost acid had probably been absorbed in the soft plastic material of the connecting tube. Six patients from this site were excluded from the pharmacokinetic (PK) dataset in addition to one patient with improper entry (prematurely born child). Thus, the final PK dataset included 11 patients: three patients in the two youngest age groups (1 month to <3 years old patients and 3 to <12 years old patients) and five patients in the oldest age group (12 to <18 years old patients). The PK results are therefore contingent upon the small sample sizes.

Tafluprost was dosed once daily into both eyes for a period of 8 (±1) days. Tafluprost acid plasma concentrations were measured at the end of the dosing period prior to the last dose, and at 10, 30 and 60 minutes post dosing. As in adults (Uusitalo et al, 2008), the highest tafluprost acid plasma concentrations were typically seen at 10 minutes post dosing across all age groups. The maximum concentrations (C_{max}) were on average 22.9 pg/mL for 12 to <18 years old patients, 39.0 pg/mL for 3 to <12 years old patients and 72.0 pg/mL for 1 month to <3 years old patients. The average C_{max} of 12 to <18 years old patients was comparable with that seen in adults (26.6 pg/mL; Uusitalo et al, 2008). The 1 month to <3 years old patients, in turn, had around 3-fold increase in average C_{max} compared to the adults. A 5-fold increase was reported with latanoprost (Raber et al, 2011). The two highest (>100 pg/mL) concentrations were seen in the youngest patients who were also lightest in weight. Controversially, the overall lowest C_{max} (11.4 pg/mL) was seen for a 2-year-old patient.

Tafluprost acid was eliminated rapidly from the blood circulation, such that concentrations above 10 pg/mL (the lower limit of quantification) were typically not seen beyond 30 minutes post dosing in any of the age groups. This was reflected in the areas under the concentration curves: $AUC_{0\text{-}last}$ values were on average 383.4 pg/mL*min for 12 to <18 years old patients, 456.8 pg/mL*min for 3 to <12 years old patients and 1661.0 pg/mL*min for 1 month to <3 years old patients. The average $AUC_{0\text{-}last}$ of the 12 to <18 years old patients was slightly lower than that seen in adults (431.9 pg/mL*min). The 1 month to <3 years old patients, in turn, had around 4-fold increase in average $AUC_{0\text{-}last}$ compared to the adults. A 7-fold increase was reported with latanoprost (Raber et al, 2011).

Expectedly, age and weight were highly correlated in the present study. Therefore, also patient's weight can be used as a surrogate when estimating the increase in tafluprost acid systemic exposure.

Safety (N=18)
All 18 enrolled patients were included in the Safety dataset, six patients in each age group. A prematurely born, 6-month-old patient was removed from therapy after three days dosing of tafluprost. All other patients had 8 (±1) days exposure to tafluprost into both eyes.

Name of Sponsor/Company Santen Oy	Individual trial table referring to part of the dossier	(For National Authority use only)
Name of finished product: Preservative-free tafluprost 0.0015% eye drops	Volume:	
Name of active ingredients: Tafluprost (AFP-168)	Page:	

Ten AEs in six patients were reported during the study. All AEs were treatment-emergent and no SAEs were reported. Seven of the AEs were ocular and three were non-ocular. The AEs were predominantly mild in severity. Only one moderate AE (related IOP increase in the right eye on day 2, resolved to a decrease of 7.5 mmHg on day 8) in a 12-year-old patient was reported in addition to the severe AE in a 10-year-old patient (related ocular hyperemia in both eyes during the first two dosing days). The remaining related ocular AEs (eye pain, conjunctival redness, and erythema of eyelid) were also typical with PGAs. Headache was the only related non-ocular AE; it was reported concurrently with eye pain. Notably, no related AEs were reported in the youngest age group with the highest systemic exposure to tafluprost acid. A pre-planned goniotomy was though done to a 4-month-old patient on day 8.

Visual acuity remained stable during the study, and no changes >0.2 LogMAR were seen in patients for whom the measurement was available. Most of the biomicroscopic findings seen prior to tafluprost dosing were in the conjunctiva for patients aged from 12 to <18 years (83.3%) and patients aged from 3 to <12 years (50.0%), and in the cornea for patients aged from 1 month to <3 years (66.7%). None of the patients had aggravated biomicroscopic findings during treatment with tafluprost, and only two patients experienced new findings: a 9-year-old patient had mild redness in the conjunctiva and lids of both eyes, and another 9-year-old patient had mild erythema in the lids of both eyes. The last finding was not reported as an AE. Ophthalmoscopy findings were seen merely in the optic nerve (glaucomatous cupping). None of the patients experienced aggravated or new findings during tafluprost treatment.

All treated and diagnosed eyes were included in the pharmacodynamic analysis of IOP. In addition, a breakdown to switch patients (with no or short washout period; N=5) and non-switch patients (N=13) was applied. Exceptionally, all but one of the switch patients had one or two IOP therapies in addition to a PGA prior to commencing tafluprost. Apart from a 2-year-old patient (who used a PGA, beta-blocker and carbonic anhydrase inhibitor prior to tafluprost) all IOPs of the switch patients remained adequately controlled during tafluprost treatment. This specific patient had IOP increases of 6 mmHg (left eye) and 7 mmHg (right eye) on Day 8. Remarkably, he also had the overall lowest systemic exposure to tafluprost acid (C_{max}=11.4 pg/mL). The IOP increases were not reported as an AE. The largest IOP decrease in the switch group (7.5 mmHg in right eye) was seen with the 12-year-old patient discussed in the AE paragraph. He had a prior combination of PGA and beta-blocker, and an intermediate systemic exposure to tafluprost acid (C_{max}=29.5 pg/mL). The IOPs of the non-switch patients decreased steadily, and a mean change of 3.5 mmHg from Day 1 to 8 was observed in the worse eye (N=11; p=0.013). Very few increases were seen in this subgroup; the largest increase (3 mmHg) was seen in the left eye of a 22-month-old patient, but the IOP remained controlled (13 mmHg) with tafluprost. The IOP of the fellow eye (without a diagnosis) decreased by the same amount during the tafluprost period.

No clinically relevant findings attributable to tafluprost were seen in vital signs, 12-lead ECG, and laboratory safety parameters. The most prominent increases (decreases) in heart rate and blood pressure were seen in the abovementioned switch patients with the highest increase (decrease) in IOP. Neither incident was reported as an AE.

Conclusions:
Tafluprost eye drops, instilled eight days into both eyes at adult dose, were well tolerated and provided good IOP control in pediatric patients of all ages diagnosed with glaucoma or OH. The steady state tafluprost acid levels suggested that appropriate systemic safety margin was preserved across the pediatric age groups.

Date of the report:
20 December 2017