21 July 2022
EMA/683847/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Jinarc

tolvaptan

Procedure no: EMEA/H/C/002788/P46/009

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On May 2022, the MAH submitted a completed paediatric study for Jinarc, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

This application contains the final clinical study report on the study 156-12-298 carried out as part of the tolvaptan paediatric investigation plan (EMEA-001231-PIP02).

Study 156-12-298 is a phase 3b, two-part, multicenter, one year randomized, double-blind, placebo-controlled trial of the safety, pharmacokinetics, tolerability, and efficacy of tolvaptan followed by a two-year open-label extension in children and adolescent subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD).
There are no regulatory consequences identified by the MAH.
The trial is among the requirements of the EU Paediatric Investigation Plan (PIP) for tolvaptan and was the first trial of tolvaptan in a paediatric ADPKD population.

The purpose of this randomized, double-blind, placebo-controlled trial conducted over 3 years was to assess the effects of titrated oral tolvaptan in a paediatric and adolescent ADPKD population. The assessments included pharmacodynamics (PD), pharmacokinetics (PK), efficacy (including total kidney volume [TKV]), and long-term safety (including growth and development) and tolerability.
Trial 156-12-298 was compliant with the key binding elements agreed upon in the PIP decision EMEA-001231-PIP02-13-M08:

- Study 6, requested in the PIP, was a double-blind, randomised, placebo-controlled trial to assess the effects of titrated oral tolvaptan on renal size, pharmacokinetics and safety in children from 4 years to less than 18 years of age diagnosed with autosomal dominant polycystic kidney disease; followed by an open label extension phase to collect additional safety and efficacy data (156-12-298).

Study 6

Study identifier(s)	**156-12-298**
Study design features and main objectives	Double-blind, randomised, placebo-controlled trial to assess the effects of titrated oral tolvaptan on renal size, pharmacokinetics and safety in children from 4 years to less than 18 years of age diagnosed with autosomal dominant polycystic kidney disease; followed by an open label extension phase to collect additional safety and efficacy data
Study population and subset definition	Male and female patients aged 4 to less than 18 years who have been diagnosed with ADPKD 3 age subsets: • 15 to less than 18 years; • 12 to less than 15 years; • 4 to less than 12 years.
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	At least 60 patients enrolled in total: • at least 15 male and 15 female patients from 15 to less than 18 years; • at least 10 male and 10 female patients from 12 to less than 15 years.

Study duration for participants	• 12 months double-blind treatment duration (Phase A) • Open-label extension phase for further 24 months (Phase B)
Dosage, treatment regimen, route of administration	• Initial dose (0.3 to 0.75 mg/kg) must be at maximum two thirds of the adult starting dose (adjusted for body weight) and given in a split dosing twice daily regimen • Dose up-titration after one week of dosing based on tolerability. Subjects permitted to down-titrate per tolerance as needed during the study
Control(s)	Placebo
Primary endpoint(s) with time point(s) of assessment	In Phase A, change from baseline in spot urine osmolality and specific gravity (pre-morning dose) after one week of daily dosing
Main secondary endpoint(s) with time(s) of assessment	• 24 hours fluid balance prior to up-titration • Description of proportions at each Tanner Stage by gender and age compared to normative populations at baseline, 6 months and 12 months during the placebo-controlled phase, and every 6-months during the open-label extension phase • Description of changes from baseline percentiles for height and weight by gender and age at baseline, 6 months and 12 months during the placebo-controlled phase, and every 6-months during the open-label extension phase • Change from baseline in estimated glomerular filtration rate (GFR) based on serum creatinine at each visit • Change from baseline in height-adjusted total kidney volume (TKV) at 12 months after the placebo-controlled phase • Change from baseline in height-adjusted TKV at 12 months and at 24 months treatment in open-label extension phase • 24 hours urine volume in those subjects who have dense PK sampling (at least 20 subjects)
Statistical plan including study conduct and analysis	Descriptive statistics
Other	Close monitoring of potential interactions of tolvaptan with diuretics with particular focus on dehydration and decrease in renal function. Data on compliance to taking the tablet with the intended volumes of water must be collected in those children dosed at the hospital.
Plan for specific follow-up (not part of completion of this study)	None
External data safety monitoring board	Required
Date of initiation	Not determined by the PDCO

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 156-12-298 is part of a clinical development program (PIP EMEA-001231-PIP02). No indication on if and when a variation of the application is provided.

Information on the pharmaceutical formulation used in the study Oral tolvaptan 7.5-, 15-, and 30-mg immediate-release tablets with matching placebo were used in Trial 156-12-298. No paediatric-specific or extemporaneous formulation was used.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for:

- study 156-12-298

2.2.2. Clinical study

Trial 156-12-298

Description

Study 156-12-298 is a Phase 3b, Two-part, Multicenter, One Year Randomized, Double-blind, Placebo-controlled Trial of the Safety, Pharmacokinetics, Tolerability, and Efficacy of Tolvaptan followed by a Two Year Open-label Extension in Children and Adolescent Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Table 5.2-1 Listing of Clinical Studies

Type of Trial (Trial Phase)	Protocol Number Location of Trial	Trial Report Location	Trial Objective(s)	Trial Design and Type of Control	Investigational Medicinal Product; Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Subjects	Treatment Duration	Trial Status; Type of Report
Safety, PD, PK, and efficacy (Phase 3b)	156-12-298 Belgium, Germany, Italy, and the UK	Section 5.3.5.1 [Report body] [Synopsis]	**Primary:** long-term safety **Secondary:** PD, PK, and efficacy	Multicenter, randomized, double-blind, placebo-controlled (Phase A), followed by open-label extension (Phase B)	Tolvaptan; split-dose tolvaptan or matching placebo PO (Phase A), split-dose tolvaptan PO (Phase B) Phase A starting dose by weight: 15/7.5 mg 30/15 mg 45/15 mg Up-titration by weight after 1 week if tolerated: 30/15 mg 45/15 mg 60/30 mg	Phase A: N = 91 Phase B: N = 81	Aged 4 to 17 years inclusive with a diagnosis of ADPKD	Phase A: 12 months Phase B: 24 months	Complete; Report body and Synopsis

ADPKD = autosomal dominant polycystic kidney disease; PD = pharmacodynamics; PK = pharmacokinetics; PO = oral; UK = United Kingdom.

Methods

Study design

The trial comprised 2 phases.

Phase A was a randomized, double-blind, placebo-controlled phase to compare tolvaptan with placebo. The duration of treatment was 12 months. It was open to subjects between the ages of 4 and 17 years, inclusive. Subjects between the ages of 12 and 17 years were stratified by age and sex in the following cohorts:

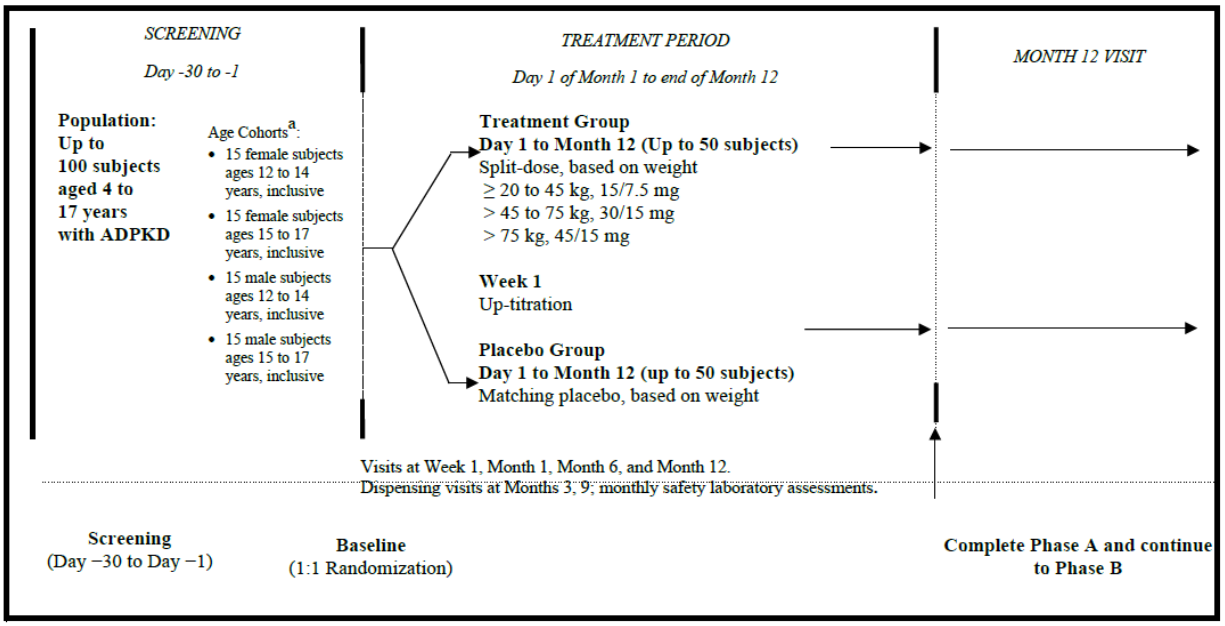
- Female subjects ages 12 to 14 years, inclusive
- Female subjects ages 15 to 17 years, inclusive
- Male subjects ages 12 to 14 years, inclusive
- Male subjects ages 15 to 17 years, inclusive.

Additionally, subjects aged 4 to 11 years were eligible for participation following discussion with the medical monitor who met criteria for entry to be enrolled concurrently during the recruitment period for the target population.

Qualified subjects who completed Phase A were eligible to continue into Phase B. A qualified subject was defined as one who was willing to continue in the trial and who did not have any adverse events (AEs) that would require IMP discontinuation.

Phase B was an open-label phase during which subjects who had completed Phase A of the trial received treatment with tolvaptan for 24 months. The purpose of Phase B was to obtain safety and efficacy data for long-term use of tolvaptan.

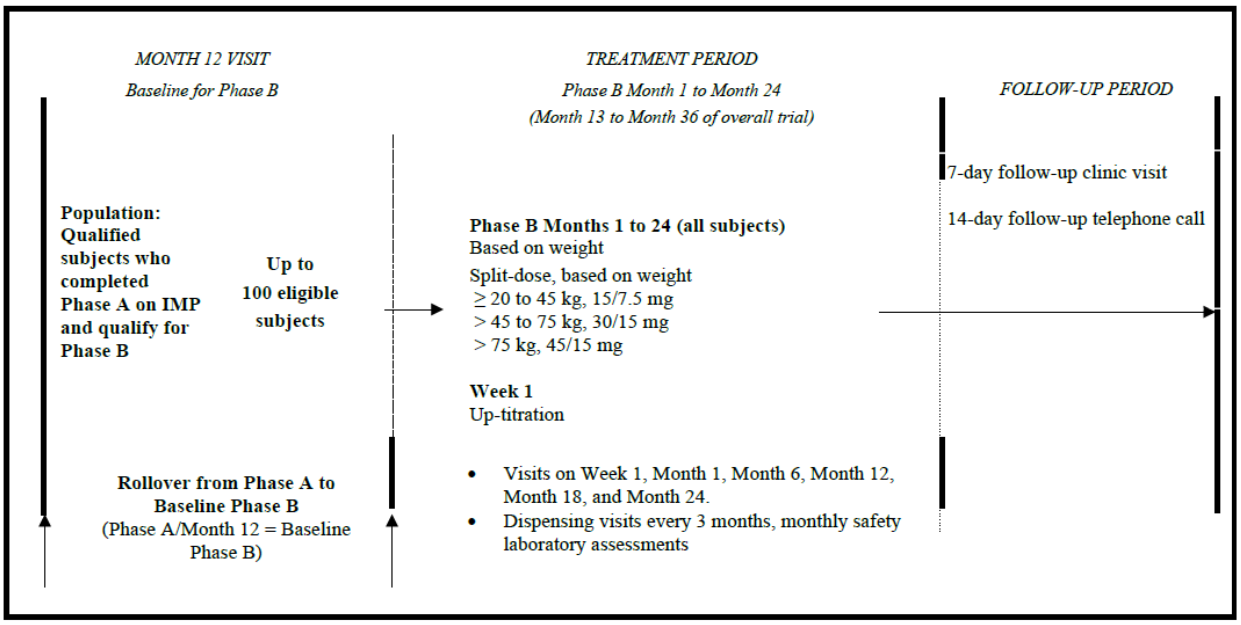
Trial Design Schematic for Phase A



[a]Subjects between the ages of 4 and 11 were eligible for the trial, but were not included in the age cohorts.

Source: Protocol (Section 16.1.1, Figure 3.1-1).

Trial Design Schematic for Phase B



Source: Protocol (Section 16.1.1, Figure 3.1-2).

Study participants

The trial population included male and female subjects aged 12 to 17 years (inclusive), with a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who had at least 10 renal cysts, each of which measured at least 0.5 cm confirmed upon MRI inspection. In accordance with the PIP requirements, the trial also allowed subjects aged 4 to 11 years who met criteria for entry to be enrolled concurrently during the recruitment period for the target population. Subjects who were MRI-naive or under the age of 12 must have had at least 4 cysts (at least 1 cm in size) confirmed by ultrasound prior to MRI inspection.

Inclusion criteria

Table 3.4.2-1	**Inclusion Criteria**
1.	Male and female subjects aged 4 to 17 years (inclusive) with a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which measure at least 0.5 cm, confirmed upon MRI inspection; subjects under the age of 12 years must have at least 4 cysts that are at least 1 cm in size, confirmed by ultrasound.
2.	Weight ≥ 20 kg.
3.	Subjects with eGFR ≥ 60 mL/min/1.73m^2 within 31 days prior to randomization (using the Schwartz formula, eGFR = 0.413 × height [cm] /serum creatinine mg/dL).
4.	Independent in toileting.
5.	Trial-specific written informed consent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws, at screening, prior to the initiation of any protocol required procedures. In addition, the subject must provide age-appropriate informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time.
6.	Ability to swallow a tablet[a].
7.	Ability to commit to remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] or withdrawal are not acceptable methods of contraception) or use two approved methods of birth control during the trial and for 30 days following the last dose of IMP for sexually active females of childbearing potential.

[a]Must also meet Health Authority/Ethics Committee age restrictions on tablet use (if applicable).

Exclusion criteria

Table 3.4.3-1	Exclusion Criteria
1.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
2.	Liver function tests including AST, ALT ≥ 1.5 × ULN.
3.	Nocturnal enuresis.
4.	Need for chronic diuretic use.
5.	Subjects with advanced diabetes (eg, glycosylated hemoglobin [HgbA1c] > 7.5, and/or glycosuria by dipstick, significant proteinuria, retinopathy), evidence of additional significant renal disease(s) (ie, currently active glomerular nephritides), renal cancer, single kidney, or recent (within 6 months of screening) renal surgery or acute kidney injury.
6.	Subjects who have known clinically significant allergic reactions to chemicals with structure similar to tolvaptan (ie benzazepines): benzazepril, conivaptan, fenoldopam mesylate or mirtazapine.
7.	Subjects having disorders in thirst recognition or inability to access fluids.

Table 3.4.3-1	Exclusion Criteria
8.	Subjects who have bladder dysfunction and/or difficulty voiding.
9.	Subjects with critical electrolyte imbalances, as determined by the investigator.
10.	Subjects with or at risk of significant hypovolemia, as determined by investigator.
11.	Subjects with a history of substance abuse (within the last 6 months).
12.	Subjects 12 years of age and older having contraindications to, or interference with MRI assessments (eg, ferro-magnetic prostheses, aneurysm clips, severe claustrophobia).
13.	Subjects taking a vasopressin agonist (eg, desmopressin).
14.	Subjects with a history of persistent noncompliance with antihypertensive or other important medical therapy.
15.	Subjects taking medications or having concomitant illnesses likely to confound endpoint assessments, including taking approved (ie, marketed) therapies for the purpose of affecting PKD cysts such as tolvaptan, vasopressin antagonists, anti-sense RNA therapies, rapamycin, sirolimus, everolimus, or somatostatin analogs (ie, octreotide, sandostatin).
16.	Has any medical condition that, in the opinion of the investigator, could interfere with evaluation of the trial objectives or safety of the subjects.
17.	Is deemed unsuitable for trial participation in the opinion of the investigator.
18.	Subjects who received any investigational agent in a clinical trial within 30 days prior to screening.
19.	Subjects who have a known lactose intolerance.
20.	Subjects who have had cyst reduction surgery within 6 weeks of the screening visit.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PKD = polycystic kidney disease
RNA = ribonucleic acid; ULN = upper limit of normal

Treatments

Tolvaptan was provided as 7.5-, 15-, and 30-mg spray-dried, immediate-release tablets with matching placebo. Tolvaptan was administered as a split-dose, with the first dose taken upon awakening and the second dose taken approximately 8 hours later.

The current tolvaptan tablet formulation is limited to administration to those who can easily swallow a 6 or 8 mm tablet and who weigh ≥ 20 kg.

In Phase A of the trial, subjects were randomized to receive IMP defined as either active tolvaptan or matching placebo for 12 months. Starting doses were based on weight:

- ≥ 20 kg to < 45 kg, 15/7.5 mg tolvaptan split-dose or matching placebo
- ≥ 45 kg to ≤ 75 kg, 30/15 mg tolvaptan split-dose or matching placebo
- > 75 kg, 45/15 mg tolvaptan split-dose or matching placebo.

After 1 week, subjects who tolerated their initial dose up-titrated once from their starting dose:

- ≥ 20 kg to < 45 kg, 30/15 mg tolvaptan split-dose or matching placebo

- ≥ 45 kg to ≤ 75 kg, 45/15 mg tolvaptan split-dose or matching placebo
- > 75 kg, 60/30 mg tolvaptan split-dose or matching placebo

Subjects may have down-titrated at any time during the trial; however, subjects were asked to stay on the highest tolerable dose (by weight group) if possible.

Table 3.2.1-3 Down-titration Steps

Current Dose	Down-titrated Dose
7.5 mg once daily upon awakening	Subject to be withdrawn from IMP
7.5/7.5 mg	7.5 mg once daily upon awakening
15/7.5 mg	7.5/7.5 mg
22.5/15 mg	15/7.5 mg
30/15 mg	22.5/15 mg
45/15 mg	30/15 mg
60/30 mg	45/15 mg

Qualified subjects who have completed Phase A on treatment and continue in Phase B will receive open-label tolvaptan for up to 24 months. In order to preserve the blind in Phase A, subjects will be started at a dose based on their current body weight and after 1 week, they will be asked to up-titrate once from their starting dose. Subjects who wish to lower their dose secondary to tolerance will have their doses adjusted as necessary.

CHMP comment

The study enrolled patients aged 12 to 17 years with a diagnosis of ADPKD. However, the trial also allowed subjects aged 4 to 11 years who met criteria for entry to be enrolled concurrently during the recruitment period for the target population according to the PIP requirements. Patients aged < 12 years must have had at least 4 cysts (at least 1 cm in size) confirmed by ultrasound prior to MRI inspection and this is acceptable as MRI usually requires sedation in younger children. The MAH reports that the current tolvaptan tablet formulation is limited to administration to those who can easily swallow a 6 or 8 mm tablet and who weigh ≥ 20 kg. The study protocol foreseen a questionnaire to be administered during Phase A to all subjects immediately after dosing to assess palatability and the easily to swallow the tablets. Submitted data does not include palatability assessment and if tablets were easy to swallow; this information needs to be provided in case the MAH will apply for an extension of indication.

The study design with 12 months double-blind treatment duration could be considered sufficient to detect the potential benefit of tolvaptan over placebo in a pediatric population and is in accordance with the PIP requirement.

Dosing rationale

Successful treatment of ADPKD appears to require early and constant inhibition of the vasopressin V2 receptor. Maintenance of tolvaptan concentrations for 24 hours produced decreased rates of growth in kidney size in animal models and therefore, subjects are encouraged to take the maximally tolerated dose. The clinical formulation of tolvaptan was optimized to increase bioavailability which necessitates split-dosing to maintain suppression of AVP action across 24 hours. A higher dose is used early in the day, with a lower dose approximately 8 to 9 hours later in order to produce a maximal inhibition on waking, with a gradual fall-off of effect during the night when frequent urination could lead to interruption of sleep. Adult treatment starts with a split-dose regimen of 45 mg in the morning and 15 mg in the afternoon. The child and adolescent subjects to be enrolled in this trial will have well preserved renal function and, therefore, at the adult dose will likely respond with potent diuresis and experience aquaretic-related AEs. The starting dose regimens in this trial are based on the adult starting dose, with

adjustments for body weight. Subjects will be up-titrated to the equivalent of the starting dose used in adult trials at Week 1, and down-titration for tolerability will be allowed. In the pivotal trial for adult subjects with ADPKD (156-04-251), every subject started tolvaptan dosing with the 45/15mg dosing regimen regardless of their weight. When dose is expressed as mg/kg, as shown in Table 2.2-1, the maximum starting dose given to an adult subject was 1.11 mg/kg with the lowest dose being 0.34 mg/kg. This should provide sustained suppression while ameliorating excess aquaretic effects in those with high functioning kidneys. The weight ranges for pediatric subjects were selected so that the maximal starting dose for each weight range was no higher than 67% of the maximal adult dose. The up-titrated morning doses, expressed as mg/kg, are also presented for comparison to the adult trial.

Table 2.2-1 Starting Dose and Up-titrated Doses for Pediatric Subjects Compared to Adults Enrolled in Pivotal Trial 156-04-251

Body Weight (kg)	Starting dose (mg)	Starting dose (mg/kg)	
		maximum	minimum
Adults			
40.6 to 133.6	45	1.11	0.34
Pediatric			
20 to <45	15	0.75	>0.33
45 to 75	30	0.67	0.40
>75	45	0.60	<0.60
Body Weight (kg)	Up-titrated morning dose (mg)	Up-titrated morning dose (mg/kg)	
		maximum	minimum
Adult			
40.6 to 133.6	60	1.48	0.45
Pediatric			
20 to <45	30	1.50	>0.67
45 to 75	45	1.00	0.60
>75	60	0.80	<0.80

Subjects who are unable to tolerate the initial starting dose regimen will be allowed to down-titrate to a dose as low as 7.5 mg once daily. This will allow for the collection of the most information on tolerability, safety, and potentially efficacy as the minimally effective dose of tolvaptan has not been determined. Animal studies indicated a dose response in tolvaptan efficacy with lower doses is still better than placebo. Adults in the pivotal 156-04-251 trial were titrated up in order to maximize inhibition of AVP but efficacy was observed in subjects who down titrated to 45/15 mg and 60/30 mg regimens. In the phase 2 156-04-250 trial, subjects on the fixed regimen of 45/15 mg showed less efficacy when compared to subjects on 60/30 mg; however, both groups showed slower increase in TKV when compared to a matched control group.

CHMP comment

As is already done in TEMPO study with adult dosing, participants received a higher dose early in the day, followed by a lower dose administered approximately 8–9 h later, in order to obtain maximal inhibition on waking and a gradual fall-off of effect during the night, when frequent urination would lead to interruption of sleep. The approach is acceptable.

Objective(s)

The primary objective of the trial was to assess the long-term safety of treatment with tolvaptan in a pediatric and adolescent ADPKD population.

The secondary objective of the trial was to assess the PD, PK, and efficacy of tolvaptan in children and adolescent subjects with ADPKD.

Outcomes/endpoints

The coprimary endpoints were the change from baseline in spot urine osmolality (premorning dose) and specific gravity (premorning dose) after 1 week of daily dosing in Phase A.

The key secondary endpoint was the percent change from Phase A baseline in height-adjusted total kidney volume (htTKV) as measured by magnetic resonance imaging (MRI) at 12 months.

Other secondary endpoints were as follows:

- 24-hour fluid balance prior to Week 1.
- Change from baseline in renal function (estimated glomerular filtration rate [eGFR] by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, and Month 12 in Phase A).
- Change from baseline in renal function (eGFR by Schwartz formula) at each clinic visit (Week 1, Month 1, Month 6, Month 12, Month 18, and Month 24 in Phase B).
- Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 12.
- Percent change in htTKV as measured by MRI from Phase B baseline to Phase B Month 24.
- Pharmacodynamic endpoints of urine volume (including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PK sampling (after at least 1 month on the investigational medicinal product [IMP]).
- Proportions of each Tanner Stage by sex and age compared to normative populations at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B).
- Description of changes from baseline percentiles for height and weight by sex and age at baseline, 6 months, and 12 months during the placebo-controlled phase (Phase A), and every 6 months during the open-label extension phase (Phase B).
- Safety variables (changes from baseline in creatinine, vital signs, laboratory values including liver function tests [LFTs], and rate of aquaretic adverse events [AEs]) in placebo and tolvaptan.

Exploratory endpoints include:

- Percent change in htTKV as measured by MRI from Phase A baseline to Phase B Month 24.
- Change from Phase A baseline in spot urine osmolality (premorning dose) and specific gravity (premorning dose) after 1 month (Phase A only).
- Time to discontinuation due to any reasons in Phase A and Phase B.
- Tolvaptan maximum (peak) plasma concentration (Cmax), minimum plasma concentration (Cmin), time to Cmax (tmax), and area under the concentration-time curve from time zero to 24 hours (AUC0-24h) following dense PK sampling.
- Tolvaptan metabolite concentrations from dense sampling.
- Generic pediatric Quality of Life (QoL) assessments.

- Daytime and nighttime void collection.

For subjects under 12 years of age who have ultrasound assessments, the percent changes for htTKV will also be analyzed.

- Percent change in htTKV as measured by ultrasound from Phase A baseline to Phase A Month 12.
- Percent change in htTKV as measured by ultrasound from Phase A baseline to Phase B Month 24.
- Percent change in htTKV as measured by ultrasound from Phase B baseline to Phase B Month 24.
- Percent change in htTKV as measured by ultrasound from Phase B baseline to Phase B Month 12.

CHMP comment

The choice of the co-primary endpoint is in line with the PIP requirements.

The co-primary endpoints are different to the primary endpoint used in the adult study (TEMPO) in which it was the rate of total kidney volume (TKV) change. As reported in the EPAR (EMA/154879/2015) of tolvaptan MAA in adult population, longitudinal data from the CRISP 2 study published in 2012 suggested a correlation between TKV and total cyst volume, and a correlation of height-corrected TKV and GFR, out to 8 years of follow-up. Measures of renal volume are linked to the progressive development of renal cysts in ADPKD, and correlate with renal function, therefore it is considered an important endpoint. From the other hand it is acknowledged that changes in TKV growth could be difficult to detect in pediatric subjects. However, the percent change from Phase A baseline in height-adjusted total kidney volume (htTKV) was the key secondary endpoint in the current pediatric study and this is acceptable.

Sample size

The target trial population will be at least 60 male and female subjects aged 12 to 17 years (inclusive), with a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which measures at least 0.5 cm confirmed upon magnetic resonance imaging (MRI) inspection.

In accordance with the PIP requirements, the trial will also allow subjects aged 4 to 11 years who meet criteria for entry to be enrolled concurrently during the recruitment period for the target population. It is expected that the trial may enroll approximately 100 subjects.

Subjects who are MRI-naive or under the age of 12 should have at least 4 cysts that are at least 1 cm in size confirmed by ultrasound prior to MRI inspection.

Treatment groups for the required population will be stratified by age and gender in the following age cohorts:

- Female subjects ages 12 to 14 years, inclusive
- Female subjects ages 15 to 17 years, inclusive
- Male subjects ages 12 to 14 years, inclusive
- Male subjects ages 15 to 17 years, inclusive

When > 15 subjects are enrolled in an age cohort, new screening for that age cohort will be closed; subjects concurrently in screening for that age cohort may be enrolled if they meet inclusion/exclusion criteria. When the last subject in the final age cohort for the required population has been achieved, enrollment in the trial will cease.

The trial is also open to children between the ages of 4 to 11 years (inclusive) with ADPKD, who meet the above criteria and who, in the opinion of the investigator, would benefit from treatment. Subjects, aged 4 to 11 years (inclusive), must have an ultrasound to assess renal cysts.

Qualified subjects who complete Phase A on study medication are eligible to participate in Phase B.

Randomisation and blinding (masking)

The blind was not broken for any subjects in **Phase A** prior to the interim snapshot for the sponsor and prior to the final database lock for the trial sites.

Phase B was open-label and blinding procedures were not applicable; however, the trial sites were to remain blinded until completion of the trial or a safety need arose.

Statistical Methods

In general, Phase A baseline measurements of safety variables are defined as their last measurements prior to the randomization for the safety population. Phase B baseline measurements of safety variables are defined as the last measurements prior to the first dose of IMP in Phase B. Safety analysis will be conducted based on the safety population, defined in Section 5.1. Standard safety variables to be analyzed include AEs, change from baseline in creatinine, vital signs, laboratory values including liver function tests (LFTs), and rate of aquaretic AEs. In general, descriptive statistics will be provided for Phase A safety variables and Phase B safety variables as well. Subgroup analysis of key safety endpoints by age cutoff (<12 years vs. ≥ 12 years) will be summarized.

Only descriptive statistics were provided.

No interim analysis was planned before all randomized subjects either completed the Month 12 visit or early terminated in Phase A (the double-blind, placebo-controlled portion of this trial). A snapshot of the database was taken after all subjects in Phase A completed or early terminated; these data were unblinded (but the trial sites remained blinded) and an interim CSR was written to provide early information on safety.

Results

Participant flow

A total of 91 subjects were randomized and took at least 1 dose of IMP in Phase A of the trial. All 91 subjects were included in the safety and primary efficacy analyses for Phase

A. For the purposes of this trial:

- Subjects who were randomized and took IMP through the Month 12 visit in Phase A and completed some or all of the trial visit assessments were defined as Phase A on treatment completers.

- Subjects who were randomized and discontinued IMP prior to the Month 12 visit in Phase A and completed some or all of the trial visit assessments were defined as *Phase A off-treatment completers.*
- Subjects who were randomized, took IMP, but did not complete the Phase A Month 12 visit or the Phase B Month 24 visit were defined as *Trial non-completers.*

A total of 84 (92.3%) subjects completed Phase A. The percentages of on-treatment completers were 91.7% in the tolvaptan group and 90.7% in the placebo group. There was 1 off-treatment completer (2.3%) in the placebo group and none in the tolvaptan group.

A total of 8 (8.8%) subjects discontinued the IMP prior to Month 12 in Phase A: 8.3% of the tolvaptan group and 9.3% of the placebo group.

A total of 81 subjects were enrolled into Phase B and took at least 1 dose of IMP. All 81 subjects were included in the safety analyses for Phase B. Of the 81 subjects, 69 subjects (85.2%) completed Phase B of the trial and 12 subjects (14.8%) discontinued from the trial. Six (7.4%) of the subjects completed Phase B of the trial off-treatment (i.e., these subjects discontinued IMP prior to the Phase B Month 24 visit but continued with trial visit assessments); 3 subjects on prior tolvaptan and prior placebo, respectively.

Recruitment

Trial Initiation Date: 23 Sep 2016

Trial Completion Date: 17 Nov 2021

Baseline data

Demographic and baseline characteristics

Of the 91 randomized subjects in **Phase A,** 25 (27.5%) were < 12 years old, 32 (35.2%) were 12 to 14 years old, and 34 (37.4%) were 15 to 17 years old. Of the 81 treated subjects in Phase B, 23 (28.4%) were < 12 years old, 27 (33.3%) were 12 to 14 years old, and 31 (38.3%) were 15 to 17 years old.

A total of 81 subjects were enrolled in **Phase B** of the trial and took at least 1 dose of IMP. All 81 subjects were included in the safety analyses for Phase B. For this trial:

- Subjects who took IMP through the Month 24 visit in Phase B and completed some or all of the trial visit assessments were defined as On-treatment trial completers.
- Subjects who discontinued IMP prior to the Month 24 visit in Phase B and completed some or all of the trial visit assessments were defined as Off-treatment trial completers.

Of the 81 subjects enrolled in Phase B, 69 (85.2%) completed Phase B. The numbers and percentages of on-treatment completers were 33 (78.6%) in the prior tolvaptan group and 30 (76.9%) in the prior placebo group. There were 3 off-treatment completers in each group: 7.1% of the tolvaptan group and 7.7% of the placebo group. A total of 12 subjects discontinued from the trial in Phase B: 14.3% of the tolvaptan group and 15.4% of the placebo group.

Table 11.2-1 Demographic Characteristics - Phase A Randomized Sample				
Variable		**Tolvaptan (N=48)**	**Placebo (N=43)**	**Total (N=91)**
Age [years]				
	Mean (SD)	12.9 (3.2)	12.8 (2.8)	12.9 (3.0)
	Range	5, 17	6, 17	5, 17
Age Subgroup				
< 12 Years	n (%)	13 (27.1)	12 (27.9)	25 (27.5)
12 to 14 Years	n (%)	17 (35.4)	15 (34.9)	32 (35.2)
15 to 17 Years	n (%)	18 (37.5)	16 (37.2)	34 (37.4)
Gender				
Male	n (%)	27 (56.3)	20 (46.5)	47 (51.6)
Female	n (%)	21 (43.8)	23 (53.5)	44 (48.4)
Race				
White	n (%)	46 (95.8)	42 (97.7)	88 (96.7)
Black or African American	n (%)	0 (0.0)	1 (2.3)	1 (1.1)
American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	n (%)	2 (4.2)	0 (0.0)	2 (2.2)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	n (%)	1 (2.1)	1 (2.3)	2 (2.2)
Not Hispanic or Latino	n (%)	47 (97.9)	42 (97.7)	89 (97.8)
Unknown	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Weight [kg]				
	Mean (SD)	53.8 (16.1)	51.1 (17.6)	52.6 (16.8)
	Range	20.7, 79.0	23.0, 108.2	20.7, 108.2
Height [cm]				
	Mean (SD)	160.5 (18.4)	159.1 (16.0)	159.9 (17.3)
	Range	113.0, 193.0	115.0, 186.0	113.0, 193.0
Body Mass Index (kg/m2)				
	Mean (SD)	20.4 (3.7)	19.6 (4.1)	20.0 (3.9)
	Range	14.2, 28.9	15.0, 34.9	14.2, 34.9

N = number of subjects randomized; n = number of subjects affected, SD = standard deviation.
Note: Percentages are based on the total number of randomized subjects.
Source: CT-1.3.1.1.

Table 11.2-3 Demographic Characteristics - Phase B				
Variable		**Prior Tolvaptan (N=42)**	**Prior Placebo (N=39)**	**Total (N=81)**
Baseline Age in Phase B [years]				
	Mean (SD)	14.3 (3.2)	13.9 (2.9)	14.1 (3.0)
	Range	7, 19	7, 18	7, 19
Age Subgroup				
< 12 Years	n (%)	11 (26.2)	12 (30.8)	23 (28.4)
12 to 14 Years	n (%)	14 (33.3)	13 (33.3)	27 (33.3)
15 to 17 Years	n (%)	17 (40.5)	14 (35.9)	31 (38.3)
Gender				
Male	n (%)	23 (54.8)	18 (46.2)	41 (50.6)
Female	n (%)	19 (45.2)	21 (53.8)	40 (49.4)
Race				
White	n (%)	42 (100.0)	38 (97.4)	80 (98.8)
Black or African American	n (%)	0 (0.0)	1 (2.6)	1 (1.2)
American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	n (%)	1 (2.4)	1 (2.6)	2 (2.5)
Not Hispanic or Latino	n (%)	41 (97.6)	38 (97.4)	79 (97.5)
Unknown	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Weight [kg]				
	Mean (SD)	56.0 (16.1)	54.3 (16.8)	55.2 (16.4)
	Range	22.5, 86.0	25.8, 98.8	22.5, 98.8
Height [cm]				
	Mean (SD)	164.2 (16.9)	161.9 (15.4)	163.1 (16.1)
	Range	120.0, 195.0	122.0, 188.0	120.0, 195.0
Body Mass Index (kg/m^2)				
	Mean (SD)	20.3 (3.6)	20.3 (4.0)	20.3 (3.8)
	Range	14.0, 31.3	15.0, 35.4	14.0, 35.4

Percentages are based on total number of enrolled subjects.
Source: CT-2.3.1.1.

In terms of **ADPKD medical history,** which was taken at the time of Phase A enrollment, the age at diagnosis was 5.2 years of age in the tolvaptan group and 7.7 years of age in the placebo group. For the majority of subjects, their diagnosis was made as part of asymptomatic screening (66.7% in the tolvaptan group, 46.5% in the placebo group). Mean TKV was 286.1 mL in the tolvaptan group and 393.3 mL in the placebo group.

Table 2.5.4.4-3 ADPKD Medical History (Diagnosis) - Phase A Randomized Sample		
	Tolvaptan (N=48)	**Placebo (N=43)**
Diagnosis age (years)		
N	48	43
Mean (SD)	5.2 (5.2)	7.7 (5.4)
Range	0, 17	0, 16
Genetic testing done?, n (%)		
Yes	14 (29.2)	13 (30.2)
No	34 (70.8)	30 (69.8)
If genetic testing done, specific gene, n (%):[a]		
ADPKD-1	2 (14.3)	1 (7.7)
ADPKD-2	0 (0.0)	0 (0.0)
C.7209+2t>c	0 (0.0)	1 (7.7)
C.3914-3923del (exon15)	0 (0.0)	1 (7.7)
C.829c>t	1 (7.1)	0 (0.0)
C.1412c>a	0 (0.0)	1 (7.7)
C.1830 g>a (p.ala610ala)	1 (7.1)	0 (0.0)
C-2674 mutation	0 (0.0)	1 (7.7)
C.8311g>a (p.glu2771lys) in eterozigosi (esone 23)	0 (0.0)	1 (7.7)
C.6544c>t (p.gin2182ter) in eterozigosi	0 (0.0)	0 (0.0)
C.3236_3236dela (p.asp1079fs) esone 14 del gene PKD1; c.6749c>t (p.thr2250met) esone 15	1 (7.1)	0 (0.0)
Mutatie c.2674 (exon11)	1 (7.1)	0 (0.0)
C.1321_1322ins13 (p.gly441alafsx82) heterozygous, exon 6	0 (0.0)	1 (7.7)
C.7345dup at exon18	0 (0.0)	1 (7.7)
C.10719dupap.(gly3574argfs*53	0 (0.0)	1 (7.7)
Tsc2/PKDi contiguous gene deletion	0 (0.0)	0 (0.0)

Table 2.5.4.4-3 ADPKD Medical History (Diagnosis) - Phase A Randomized Sample		
	Tolvaptan (N=48)	Placebo (N=43)
C.9398-2a	1 (7.1)	0 (0.0)
C.4835c>t(p.thr1612met) und c.6684c>g (p.tyr2228*)	0 (0.0)	1 (7.7)
Ivs4+1g>a	0 (0.0)	1 (7.7)
P.s1352n (c.4055c>a) and p.s2372f (c.7115c>t)	1 (7.1)	0 (0.0)
C.8301_8302delcg (p.arg2767fs53)	1 (7.1)	0 (0.0)
C.9395c>t (p.ser3132leu)	0 (0.0)	1 (7.7)
C.10748delg (p.gly3853alafs2) esone 36	0 (0.0)	1 (7.7)
13 beats per dilatation	1 (7.1)	0 (0.0)
Mosaic for PKD1/tsc2 deletion	1 (7.1)	0 (0.0)
No further information	0 (0.0)	0 (0.0)
Unknown	3 (21.4)	0 (0.0)
Aware of family history before diagnosis?, n (%)		
Yes	43 (89.6)	39 (90.7)
No	5 (10.4)	4 (9.3)
Diagnosis, n (%)		
A consequence of ADPKD symptoms	6 (12.5)	17 (39.5)
Incidental (due to tests unrelated to ADPKD or its symptoms)	10 (20.8)	5 (11.6)
Part of asymptomatic screening (no prior ADPKD symptoms)	32 (66.7)	20 (46.5)
Diagnosis due to, n (%):[b]		
Hypertension	1 (16.7)	2 (11.8)
Kidney pain (flank/abdominal)	0 (0.0)	3 (17.6)
Hematuria	1 (16.7)	1 (5.9)
Urinary tract infection	2 (33.3)	0 (0.0)
Hypertension,kidney pain (flank/abdominal)	0 (0.0)	1 (5.9)
Hypertension,hematuria	0 (0.0)	0 (0.0)
CKD (father and grandfather)	0 (0.0)	0 (0.0)
Kidney transplantation (grandfather)	0 (0.0)	0 (0.0)
Kidney transplantation (father)	0 (0.0)	0 (0.0)
Uncle in hemodialysis, father ADPKD (good kidney function)	0 (0.0)	0 (0.0)
Hypertension,proteinuria	0 (0.0)	1 (5.9)
Hypertension,kidney pain (flank/abdominal),urinary tract infection	0 (0.0)	1 (5.9)
Palpable kidneys	0 (0.0)	0 (0.0)
Cystic kidneys	0 (0.0)	1 (5.9)
Abnormal US	0 (0.0)	2 (11.8)
Prenatal abnormal US	1 (16.7)	2 (11.8)
Family history - screening US	0 (0.0)	1 (5.9)
Jaundice	0 (0.0)	1 (5.9)
Kidney pain (flank/abdominal), urinary tract infection, dysuria and frequency	0 (0.0)	1 (5.9)
Kidney pain (flank/abdominal), urinary tract infection, pulsating headaches	1 (16.7)	0 (0.0)
Polyuria	1 (16.7)	0 (0.0)
Urinary tract infection, tuberous sclerosis	1 (16.7)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Initial diagnosis confirmed by, n (%)		
DNA test	6 (12.5)	9 (20.9)
Radiographic	41 (85.4)	34 (79.1)

Table 2.5.4.4-3 ADPKD Medical History (Diagnosis) - Phase A Randomized Sample		
	Tolvaptan (N=48)	Placebo (N=43)
Other	0 (0.0)	0 (0.0)
Unknown	1 (2.1)	0 (0.0)
Total kidney volume (mL)		
N	21	13
Mean (SD)	286.1 (110.7)	393.3 (226.0)
Range	131, 583	56, 912
Other blood-related family with PKD, n (%)		
Yes	43 (89.6)	39 (90.7)
No	4 (8.3)	4 (9.3)
Unknown	1 (2.1)	0 (0.0)

CKD = chronic kidney disease; DNA = deoxyribonucleic acid; PKD = polycystic kidney disease; US = ultrasound.

[a]Denominator is the number of subjects who answered yes to genetic testing done.

[b]Percentages are based on the number of subjects who answered diagnosis was a consequence of ADPKD symptoms.

Source: CSR 156-12-298 CT-1.3.2.1.

CHMP comment

Demographic characteristics are well balanced between tolvaptan and placebo both in phase A and phase B. The most represented age group was 15 to17 years (37.5% and 37.2% in phase A and 40.5% and 35.9% in phase B) and almost all patients were white (95.8% and 97.7% in phase A and 100% and 97.4% in phase B). The overall mean age was 12.9 years (range: 5 - 17 years) and the mean body mass index (BMI) was 20.0 kg/m2 (range: 14.2 - 34.9 kg/m2).

Even if a diagnosis of ADPKD as defined by the presence of family history and/or genetic criteria (AND who had at least 10 renal cysts) was required by inclusion criteria, only a low number of subjects had a genetic testing done (29,2 % in tolvaptan group vs 30.2% in plb group), of which only 2 patients (14.3%) in the study group were ADPKD-1 positive. The majority of patients were aware of a positive family history before diagnosis (89.6% in tolva vs 90.7% in plb), however it is not clear if patients without a family history had a genetic diagnosis. This information should be included in case the MAH will apply for an extension of indication

Overall, the mean total kidney volume was higher in the placebo group (393.3 mL) than in tolva group (286.1 mL) suggesting a possible more advanced disease in this group of patients, even though the low number of patients (13 in plb group) makes difficult to draw firm conclusion.

Number analysed

Three analysis sets were defined for the efficacy and safety analyses in this trial:

- The randomized analysis set consists of all subjects who were randomized in the trial.
- The full analysis set (FAS) for Phase A consists of all subjects who were randomized to a treatment group, received at least 1 dose of the IMP, and had both a Phase A baseline and at least 1 postbaseline efficacy evaluation. These subjects were analyzed according to the treatment group to which they were randomized. The FAS for Phase B consists of all subjects who enrolled to Phase B, received at least 1 dose of the IMP, and had both a baseline and at least 1 postbaseline efficacy evaluation in Phase B. The FAS, which is based on an intent-to-treat principle, is the primary analysis set for efficacy analyses on the primary/key secondary endpoints and other secondary endpoints.

The safety analysis set consists of all subjects who were administered at least 1 dose of IMP. The safety dataset is being used for the safety analyses.

Efficacy results

Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints were the **changes from baseline in spot urine osmolality** and in **specific gravity** after 1 week of daily dosing in Phase A of the trial. The mean change from baseline in spot urine osmolality (premorning dose) after 1 week of daily dosing in Phase A was substantially greater in the tolvaptan group (−386 mOsm/kg, from 635 to 250 mOsm/kg) versus the placebo group (−93 mOsm/kg, from 646 to 553 mOsm/kg) (Table 2.5.4.6-1, below). These findings were consistent across age groups and for each sex.

Table 2.5.4.6-1 Coprimary Analysis of Change From Phase A Baseline in Spot Urine Osmolality (Premorning Dose) (mOsm/kg), Full Analysis Set

	Tolvaptan		Placebo	
Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)
Baseline	48	635 (252)	43	646 (250)
Week 1 Phase A	48	-386 (284)	42	-93 (332)
Month 1 Phase A	48	-360 (242)	43	-47 (318)

[a]Baseline is the last available predose evaluation.

[b]For the baseline visit, n is the total number of treated subjects with a baseline evaluation. For postdose visits, n is the total number of treated subjects with both baseline and postdose evaluations at the specific visit.

Source: CSR 156-12-298 CT-1.5.1.1.

ST-1.1
Co-Primary Analysis of Change from Phase A Baseline in Spot Urine Osmolality (mOsm/kg) by Age Groups
Full Analysis Set (FAS)

AGE GROUP (YEARS OLD)	VISIT[1]	TREATMENT	n[2]	MEAN	MEDIAN	SD	MIN	MAX	CHANGE FROM BASELINE: BASELINE n[3]	BASELINE MEAN	CHANGE FROM BASELINE MEAN	CHANGE FROM BASELINE MEDIAN	CHANGE FROM BASELINE SD	CHANGE FROM BASELINE MIN	CHANGE FROM BASELINE MAX
12 to 14	BASELINE	TOLVAPTAN	17	688	690	297	175	1174							
		PLACEBO	15	572	617	234	164	884							
		TOTAL	32	634	651	272	164	1174							
	WEEK 1 PHASE A	TOLVAPTAN	17	229	228	134	52	514	17	688	-459	-502	310	-970	46
		PLACEBO	15	529	555	203	207	770	15	572	-43	-8	275	-607	424
		TOTAL	32	370	302	226	52	770	32	634	-264	-209	358	-970	424
	MONTH 1 PHASE A	TOLVAPTAN	17	222	194	127	60	446	17	688	-466	-463	303	-912	168
		PLACEBO	15	592	617	285	171	999	15	572	20	32	288	-532	607
		TOTAL	32	396	319	283	60	999	32	634	-238	-274	382	-912	607
15 to 17	BASELINE	TOLVAPTAN	18	572	607	241	143	1063							
		PLACEBO	16	712	801	283	71	1013							
		TOTAL	34	638	667	267	71	1063							
	WEEK 1 PHASE A	TOLVAPTAN	18	195	186	86	72	378	18	572	-378	-394	270	-860	226
		PLACEBO	16	572	599	284	151	1045	16	712	-140	-150	391	-672	974
		TOTAL	34	372	253	277	72	1045	34	638	-266	-306	349	-860	974
	MONTH 1 PHASE A	TOLVAPTAN	18	263	272	160	51	622	18	572	-309	-295	184	-585	-29
		PLACEBO	16	635	721	334	114	1072	16	712	-77	-73	365	-663	942
		TOTAL	34	438	317	316	51	1072	34	638	-200	-184	303	-663	942

The mean change from baseline in **specific gravity** (premorning dose) after 1 week of daily dosing in Phase A was greater in the tolvaptan group (−0.009, from 1.017 to 1.008) versus the placebo group (−0.002, from 1.017 to 1.015) (Table 2.5.4.6 2, below). The same trend was seen at 1 month. These findings were consistent across age groups and for each sex.

Table 2.5.4.6-2	Coprimary Analysis of Change From Phase A Baseline in Specific Gravity (Premorning Dose), Full Analysis Set			
	Tolvaptan		Placebo	
Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)
Baseline	48	1.017 (0.006)	43	1.017 (0.006)
Week 1 Phase A	48	-0.009 (0.007)	41	-0.002 (0.008)
Month 1 Phase A	48	-0.009 (0.006)	43	0.000 (0.009)

[a]Baseline is the last available predose evaluation.

[b]For the baseline visit, n is the total number of treated subjects with a baseline evaluation. For postdose visits, n is the total number of treated subjects with both baseline and postdose evaluations at the specific visit.

Source: CSR 156-12-298 CT-1.5.1.2.

ST-1.2
Co-Primary Analysis of Change from Phase A Baseline in Specific Gravity by Age Groups
Full Analysis Set (FAS)

AGE GROUP (YEARS OLD)	VISIT[1]	TREATMENT	n[2]	MEAN	MEDIAN	SD	MIN	MAX	CHANGE FROM BASELINE: BASELINE n[3]	BASELINE MEAN	CHANGE MEAN	CHANGE MEDIAN	CHANGE SD	CHANGE MIN	CHANGE MAX
12 to 14	BASELINE	TOLVAPTAN	17	1.018	1.019	0.007	1.007	1.030							
		PLACEBO	15	1.016	1.016	0.005	1.005	1.023							
		TOTAL	32	1.017	1.017	0.006	1.005	1.030							
	WEEK 1 PHASE A	TOLVAPTAN	17	1.008	1.008	0.003	1.004	1.016	17	1.018	-0.010	-0.011	0.008	-0.023	0.001
		PLACEBO	14	1.014	1.016	0.005	1.006	1.021	14	1.016	-0.001	-0.001	0.007	-0.014	0.013
		TOTAL	31	1.011	1.010	0.005	1.004	1.021	31	1.017	-0.006	-0.004	0.009	-0.023	0.013
	MONTH 1 PHASE A	TOLVAPTAN	17	1.007	1.007	0.003	1.003	1.014	17	1.018	-0.011	-0.011	0.007	-0.023	0.005
		PLACEBO	15	1.016	1.017	0.007	1.006	1.028	15	1.016	0.000	0.001	0.008	-0.013	0.014
		TOTAL	32	1.011	1.009	0.007	1.003	1.028	32	1.017	-0.006	-0.005	0.009	-0.023	0.014
15 to 17	BASELINE	TOLVAPTAN	18	1.016	1.017	0.006	1.004	1.031							
		PLACEBO	16	1.017	1.021	0.008	1.004	1.025							
		TOTAL	34	1.016	1.017	0.007	1.004	1.031							
	WEEK 1 PHASE A	TOLVAPTAN	18	1.007	1.007	0.002	1.004	1.010	18	1.016	-0.009	-0.009	0.007	-0.024	0.006
		PLACEBO	16	1.015	1.016	0.007	1.005	1.029	16	1.017	-0.002	-0.003	0.010	-0.016	0.025
		TOTAL	34	1.011	1.008	0.006	1.004	1.029	34	1.016	-0.006	-0.008	0.009	-0.024	0.025
	MONTH 1 PHASE A	TOLVAPTAN	18	1.008	1.008	0.004	1.003	1.016	18	1.016	-0.008	-0.007	0.005	-0.016	-0.001
		PLACEBO	16	1.018	1.018	0.009	1.005	1.030	16	1.017	0.001	-0.001	0.011	-0.016	0.025
		TOTAL	34	1.013	1.010	0.008	1.003	1.030	34	1.016	-0.004	-0.005	0.009	-0.016	0.025

***CHMP* comment**

A greater change from baseline in spot urine osmolality as well as in specific gravity at 1 week, was observed in tolvaptan group than in placebo group and this is reassuring. Moreover, these changes are maintained up to 1 month from baseline. Results from the co-primary endpoints seem to suggest that tolvaptan is effective in reducing urine osmolality and in increasing the output of water, as could be expected from its mechanism of action (inhibition of V2 receptor). Therefore, these endpoints indicates that tolvaptan can inhibit the V2 receptor also in the pediatric population in a similar manner than in adults. However, even if recent studies seem to support the link between vasopressin V2R signalling and renal disease progression in ADPKD (Devuys O., 2016), these results need to be translated in a clinical effect, in particular in a reduction of clinical progression. Moreover, the study lack of a statistical analysis and therefore these results could be only considered as descriptive.

The mean change in spot urine osmolality from baseline across age groups was slightly lower in patients from 15-17 years (-378 mOsm/kg at week 1 and 295 at month 1) compared to patients from 12-14 years (-459 mOsm/kg at week 1 and -466 mOsm/kg at month 1), with a similar trend also for change from baseline in specific gravity. Moreover, a greater change of spot urine osmolality was observed in the placebo arm of patients aged 15-17, suggesting a minor effect of tolvaptan over placebo in this age group. Furthermore, no data results on co-primary endpoints have been provided in patients younger

than 12 years which should be provided or otherwise this lack should be justified in case the MAH will apply for an extension of indication

Key Secondary Endpoint

The mean percent change from baseline to 12 months in htTKV (as measured by MRI) for subjects 12 to 17 years old was smaller in the tolvaptan group (2.28%) versus the placebo group (6.11%) in Phase A (Table 2.5.4.7 1). One subject in the tolvaptan group was enrolled with a concomitant diagnosis of tuberous sclerosis and therefore had a notably larger kidney size when compared with the other subjects. When htTKV was assessed without the inclusion of this subject, the trend favoring tolvaptan remained intact: without this subject, the mean percent change from baseline to 12 months in htTKV (as measured by MRI) for subjects 12 to 17 years old was also smaller in the tolvaptan group (2.84%) versus the placebo group (6.11%).

Table 0-1 Key Secondary Analysis of Percent Change in htTKV (By MRI) From Phase A Baseline to Month 12 in Phase A (%), Full Analysis Set

	Tolvaptan		Placebo	
Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)
Baseline (mL/cm)	30	3.49 (4.29)	27	2.66 (0.79)
Month 12 Phase A (%)	30	2.28 (8.75)	27	6.11 (7.48)

a Baseline is the last available predose evaluation.

bFor the baseline visit, n is the total number of treated subjects with a baseline evaluation. For the postdose visit, n is the total number of treated subjects with both baseline and postdose evaluations at the specific visit

When analyzed by subgroup, the mean percent change from baseline to 12 months in htTKV as measured by MRI was also consistently smaller in the tolvaptan group versus the placebo group for each age group and for each sex in Phase A (Table 2.5.4.7-2).

Table 0-2 Subgroup Analysis of Percent Change in htTKV (By MRI) From Phase A Baseline to Month 12 in Phase A (%), Full Analysis Set

			Tolvaptan		Placebo	
Category	Subgroup	Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)
Age	12 to 14 Years	Baseline (mL/cm)	14	2.35 (0.61)	12	2.21 (0.58)
		Month 12 Phase A (%)	14	4.15 (7.61)	12	10.23 (8.90)
	15 to 17 Years	Baseline (mL/cm)	16	4.49 (5.74)	15	3.02 (0.76)
		Month 12 Phase A (%)	16	0.65 (9.58)	15	2.81 (3.92)
Gender	Male	Baseline (mL/cm)	14	3.96 (6.20)	12	2.82 (0.79)
		Month 12 Phase A (%)	14	0.69 (9.07)	12	4.18 (6.80)
	Female	Baseline (mL/cm)	16	3.08 (1.36)	15	2.53 (0.80)
		Month 12 Phase A (%)	16	3.68 (8.50)	15	7.65 (7.86)

a Baseline is the last available predose evaluation.

b For the baseline visit, n is the total number of treated subjects with a baseline evaluation. For the postdose visit, n is the total number of treated subjects with both baseline and postdose evaluations at the specific visit.

***CHMP* comment**

A smaller mean percent change from baseline to 12 months in htTKV (as measured by MRI) for subjects 12 to 17 years old was observed in the tolvaptan group (2.28%) versus the placebo group (6.11%) in Phase A. The results seem to be in line with those of the adult studies. A difference with placebo in

change from baseline to 12 months in htTKV was constant by age groups, even though with more limited results in patients aged 15 to 17 Years.

Height- adjusted TKV (htTKV) on MRI is at present the most established imaging surrogate parameter for monitoring disease progression in adult with ADPKD and TKV was the one used as primary endpoint in TEMPO study supporting tolvaptan authorization in adult population. Despite the scarce knowledges relating to the htTKV value in pediatric population, it is reported in literature that the vast majority of children with ADPKD maintained normal kidney function despite progressive structural kidney disease, thus emphasizing the great importance of total kidney volume (TKV) as a measurable outcome of early disease progression and the primary focus of therapeutic intervention in the pediatric ADPKD population (*M. A. Cadnapaphornchai, 2017*). Unfortunately, even if the difficulties in doing MRI mainly in younger and/or non-cooperative children who require sedation are acknowledged, it was noted that only data from 57 patients were provided, limiting the robustness of these results in support of the co-primary endpoints. However, data from ultrasound evaluation in 9 patients < 12 years old have been provided, which seem to be no sufficiently supportive (see below among other secondary endpoints).

Other Secondary Endpoints

The mean 24-hour fluid balance for all subjects prior to Week 1 in Phase A was 31 mL in the tolvaptan group versus 241 mL in the placebo group, and in Phase B was 138 mL in the prior tolvaptan group versus 207 mL for the prior placebo group prior to Week 1.

The mean change in renal function (eGFR by Schwartz formula) from baseline to 12 months in Phase A was −1.4 mL/min/1.73 m2 in the tolvaptan group versus −0.9 mL/min/1.73 m2 in the placebo group. To account for the known acute hemodynamic effects of tolvaptan, a supplemental analysis was done to determine the change in eGFR using Week 1 as a baseline in Phase A. In this analysis, the mean change in renal function (eGFR by Schwartz formula) from Week 1 to 12 months in Phase A was 2.6 versus −3.2 mL/min/1.73 m2 in the tolvaptan versus placebo groups, respectively. This analysis indicates that, after accounting for hemodynamic effects, the placebo group experienced more loss of eGFR over 12 months than the tolvaptan group.

Age subgroup analyses of the mean change in renal function (eGFR by Schwartz formula) from baseline to 12 months in Phase A had similar results, except in the 15 to 17 year old subgroup, where the change was similar between treatment groups. For subjects 12 to 17 years old, the mean change in renal function from Week 1 to 12 months in Phase A was −0.1 versus −3.5 mL/min/1.73 m2 in the tolvaptan versus placebo groups, respectively. The mean change in this time period was 1.5 vs. −1.8 mL/min/1.73 m2 for males and −5.5 versus −0.2 mL/min/1.73 m2 for females in the tolvaptan and placebo groups, respectively.

Table 11.4.1.2.2.2-3 Subgroup Analysis of Change From Baseline in Renal Function (eGFR by Schwartz formula) at Each Clinic Visit (Week 1, Month 1, Month 6, and Month 12 in Phase A), Full Analysis Set

			Tolvaptan		Placebo	
Category	Subgroup	Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)
Age	< 12 Years	Baseline	13	102.6 (25.6)	12	97.7 (19.3)
		Week 1 Phase A	12	-3.8 (11.7)	11	3.9 (12.3)
		Month 1 Phase A	13	-5.3 (15.9)	12	2.7 (11.2)
		Month 6 Phase A	13	2.6 (19.6)	12	4.3 (7.5)
		Month 12 Phase A	13	4.7 (16.5)	12	2.6 (8.3)
	12 to 14 Years	Baseline	17	106.2 (17.4)	15	103.7 (10.8)
		Week 1 Phase A	16	-6.0 (11.1)	15	1.5 (9.2)
		Month 1 Phase A	16	0.8 (11.4)	15	-1.6 (9.1)
		Month 6 Phase A	14	-0.6 (12.0)	15	-3.4 (6.8)
		Month 12 Phase A	14	-6.1 (17.6)	13	-2.2 (7.7)
	15 to 17 Years	Baseline	18	89.1 (11.3)	16	98.0 (15.2)
		Week 1 Phase A	16	-4.6 (8.9)	16	-0.2 (6.5)
		Month 1 Phase A	16	-3.1 (9.4)	16	-1.2 (7.7)
		Month 6 Phase A	17	-2.0 (9.1)	14	-2.6 (11.2)
		Month 12 Phase A	16	-2.2 (8.8)	15	-2.5 (9.0)
Gender	Male	Baseline	27	92.8 (16.5)	20	94.9 (13.2)
		Week 1 Phase A	25	-3.5 (9.7)	19	-0.2 (9.1)
		Month 1 Phase A	26	-0.5 (11.8)	20	-1.2 (7.2)
		Month 6 Phase A	25	0.9 (14.8)	20	-0.7 (9.2)
		Month 12 Phase A	25	1.5 (13.7)	18	-1.8 (8.0)
	Female	Baseline	21	106.5 (20.5)	23	104.3 (15.4)
		Week 1 Phase A	19	-6.8 (11.1)	23	2.8 (9.2)
		Month 1 Phase A	19	-4.9 (12.7)	23	0.5 (10.8)
		Month 6 Phase A	19	-1.6 (12.2)	21	-1.0 (9.4)
		Month 12 Phase A	18	-5.5 (15.8)	22	-0.2 (9.0)

[a]Baseline is the last available predose evaluation.

[b]For the baseline visit, n is the total number of treated subjects with a baseline evaluation. For postdose visits, n is the total number of treated subjects with both baseline and postdose evaluations at the specific visit.

In Phase B, the mean change from baseline to 24 months in renal function (eGFR by Schwartz formula) was greater in the prior placebo group versus the tolvaptan group (−10.3 versus −5.2 mL/min/1.73 m2), due to hemodynamic effects. In subgroup analyses of the same time period, mean renal function changes showed similar differences between treatment groups for each age group. The mean change in this time period for male subjects was also greater in the prior placebo group versus the prior tolvaptan group for both male and female subjects (−11.4 versus −6.8 mL/min/1.73 m2 in male subjects, and −9.4 versus −3.1 mL/min/1.73 m2 in female subjects, respectively).

The mean percent change from Phase A baseline to 24 months in Phase B in htTKV (as measured by MRI) was consistently less in the prior tolvaptan group versus the prior placebo group in subjects 15 to 17 years old and in both females and males. The reverse was found in subjects 12 to 14 years old at 12 and 24 months: the mean change from baseline in htTKV was less in the prior placebo group versus the prior tolvaptan group.

In Phase B, the mean percent change in htTKV (measured by MRI) from **Phase B baseline to 12 and 24 months** was less in the prior placebo group (3.09% and 7.35%, respectively) versus the prior tolvaptan group (7.68% and 13.55%, respectively). A similar result was seen in subgroup analyses for

each sex and age group, except for subjects 15 to 17 years old at 24 months, for whom the change was similar in both the prior placebo and prior tolvaptan groups.

Table 11.4.1.2.2.4-1 Percent Change in htTKV as Measured by MRI From Phase B Baseline to Month 12 and Month 24 in Phase B (%), Full Analysis Set

	Prior Tolvaptan		Prior Placebo		Total	
Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)	n[b]	Mean (SD)
Baseline - Phase B (mL/cm)	26	3.42 (3.92)	23	2.76 (0.75)	49	3.11 (2.90)
Month 12 Phase B (%)	26	7.68 (9.67)	23	3.09 (8.97)	49	5.53 (9.54)
Month 24 Phase B (%)	24	13.55 (12.88)	21	7.35 (9.57)	45	10.66 (11.75)

[a]Baseline is the last evaluation prior to the first dose in Phase B.

[b]For baseline visit, n is the total number of treated subjects with a baseline evaluation. For postdose visit, n is the total number of treated subjects with both baseline and postdose evaluation at the specific visit.

No notable differences in **Tanner Staging progression** compared to normative populations were found between the two treatment groups at any time point in either Phase A or B, nor in the age and sex groups. The mean change in growth percentiles for height and weight from baseline to 12 months in Phase A was 1 in the tolvaptan group and −4 in the placebo group. In Phase B, the mean change in this endpoint was 3 in the prior tolvaptan group versus 4 in the prior placebo group at 12 months, and 0 in the prior tolvaptan group versus 5 in the prior placebo group at 24 months.

Time to discontinue to any reason

Table 11.4.1.3.3-1 Time to Discontinuation Due to Any Reason, Phase A Safety Sample

	Days					
Treatment	n	Mean	Median	SD	Min	Max
Tolvaptan	4	134.0	147.5	54.1	62	179
Placebo	3	262.0	290.0	59.2	194	302

Max = maximum; min = minimum.

Health-related quality of life (HrQoL) showed a sustained improvement with tolvaptan treatment across core domains and stable fatigue scores in Phase A, indicating a low level of disease and treatment burden as well as a high level of functioning. In Phase B, subjects in the prior placebo group generally improved to similar levels reported by subjects in the prior tolvaptan group. Both groups showed improved HrQoL scores compared to baseline during the treatment period.

Percent Change in htTKV as Measured by Ultrasound for Subjects Under 12 Years Old

Table 11.4.1.3.6-1 Summary of Percent Change in htTKV From Baseline to Month 12 in Phase A, as Measured by Ultrasound - Full Analysis Set

	Tolvaptan		Placebo	
Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)
Baseline (mL/cm)	9	1.73 (0.72)	6	2.84 (1.68)
Month 12 Phase A (%)	9	20.42 (68.32)	6	16.27 (24.12)

[a]Baseline is the last available predose evaluation.

[b]For the baseline visit, n is the total number of treated subjects with a baseline evaluation. For the postdose visit, n is the total number of treated subjects with both baseline and postdose evaluations at the specific visit.

Table 11.4.1.3.6-2 Percent Change in htTKV From Phase B Baseline to Month 24 in Phase B, as Measured by Ultrasound (%), Full Analysis Set

	Prior Tolvaptan		Prior Placebo		Total	
Visit[a]	n[b]	Mean (SD)	n[b]	Mean (SD)	n[b]	Mean (SD)
Baseline - Phase B (mL/cm)	9	1.94 (0.93)	7	2.96 (1.98)	16	2.39 (1.52)
Month 12 Phase B (%)	9	-3.00 (20.99)	7	-2.33 (29.57)	16	-2.71 (24.19)
Month 24 Phase B (%)	9	1.09 (26.62)	7	1.28 (20.97)	16	1.17 (23.53)

[a]Baseline is the last evaluation prior to the first dose in Phase B.

[b]For baseline visit, n is the total number of treated subjects with a baseline evaluation. For postdose visit, n is the total number of treated subjects with both baseline and postdose evaluation at the specific visit.

CHMP comment

A number of other secondary endpoints have been explored. Overall, they seem to be in line with co-primary and key secondary endpoints. The mean change in renal function (**eGFR** by Schwartz formula) showed a difference between tolvaptan group and placebo when analyzed from week 1 to month 12 due to the hemodynamic effect. However, no difference between tolvaptan and placebo group in the mean change in renal function was observed in 15 to 17 years age group, while the change was more evident in females.

The mean percent change from Phase A baseline in htTKV as measured by ultrasound (for subjects < 12 years old) at 12 months is slightly greater in the tolvaptan group (20.42%) than in the placebo group (16.27%) from baseline to month 12 in Phase A. Therefore change of htTKV measured by ultrasound seems to be not consistent with that of htTKV as measured by MRI in older patients arising further uncertainties on the evaluation of TKV in children mainly in younger. This aspect needs to be well justified at the time of submission of data for the extension of indication. Pharmacokinetic and pharmacodynamic data

Among the secondary endpoints there were PD endpoints such as urine volume (including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PK sampling (after at least 1 month on the investigational medicinal product [IMP]).
Other endpoints included tolvaptan PK parameters following dense PK sampling
The PK/PD analysis foreseen dense sampling in a subset of subjects.

Sampling

A subset of 20 subjects in the 12 to 17 year-old age group had dense PK and PD sampling conducted at selected sites after at least 1 month of IMP treatment. Samples were collected predose (within 15 minutes prior to the morning dose), 1, 2, 4, 8 (within 15 minutes prior to the afternoon dose), 12, and 24 hours post the morning dose. These subjects will be hospitalized the evening prior to the scheduled PK sampling (typically a Friday evening) and discharged after the 24 hour PK sample collection (typically Sunday morning).

For dense PK sampling, tolvaptan concentrations will be analyzed by noncompartmental methods. Concentrations will be summarized with descriptive statistics by total daily dose of tolvaptan and time point. Pharmacokinetic parameters will be summarized with descriptive statistics by total daily dose of tolvaptan. No subjects or data were excluded from the dense PK/PD analysis.

The DM-4103 metabolite has a half-life of approximately 180 hours and, consequently, is a good marker of long-term compliance with dosing.

Bioanalytical report

Plasma samples were analyzed for tolvaptan (OPC-41061) and its metabolites, DM-4103 and DM-4107, using a validated high-performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS). Tolvaptan, metabolites, and the internal standard OPC-41100 were extracted from human plasma containing sodium heparin as an anticoagulant using solid phase extraction. The method was validated for concentrations ranging from 5.00 to 1000 ng/mL for tolvaptan, 12.5 to 12500 ng/mL for DM-4103, and 12.5 to 2500 ng/mL for DM-4107.

Result of ISR	76.7% of samples (23/30) were within the criteria for OPC-41061 93.3% of samples (28/30) were within the criteria for DM-4103 83.3% of samples (25/30) were within the criteria for DM-4107	
Maximum sample storage duration prior to analysis (including ISR)	1026 days *	
Actual sample storage conditions	-70°C	

*All samples (except for sample #27 for incurred sample re-analysis) were analyzed within the determined storage stability period for 1025 days at a nominal temperature of -70°C.

A total of 276 samples were analyzed for OPC-41061 and DM-4107. A total of 275 samples were analyzed for DM-4103.

Pharmacokinetic results

Subjects included in the dense PK sampling are the following:

PKT-1: Individual and Summary Demographic Characteristics for Subjects with Dense PK/PD Sampling

Tolvaptan Subjects Subject ID	Dose (mg)	Age (y)	Weight (kg)	Serum Creatinine (mg/dL)	eGFR (mL/min/1.73m²)	Sex	Race
[redacted]	22.5	[redacted]	[redacted]	0.83	83.10	[redacted]	White
	37.5			0.88	81.19		White
	37.5			0.94	76.89		White
	37.5			0.54	126.96		White
	45			0.57	108.68		White
	45			1.10	72.46		White
	45			0.74	96.55		White
	60			0.71	95.40		White
	60			0.79	94.62		White
	60			0.78	91.60		White
	60			1.07	71.02		White
	60			0.86	80.68		White
N	—	12	12	12	12	12	12
Median	—	16.0	62.7	0.84	87.35	Males 7 (58%)	White 12 (100.0%)
Mean	—	15.5	61.9	0.83	89.93	Females 5 (42%)	
SD	—	1.4	10.8	0.18	16.13		
%CV	—	9.3	17.5	22.0	17.9		
Minimum	—	12	33.0	0.53	71.02		
Maximum	—	17	71.2	1.10	126.96		

SOURCE: ADPC analysis dataset

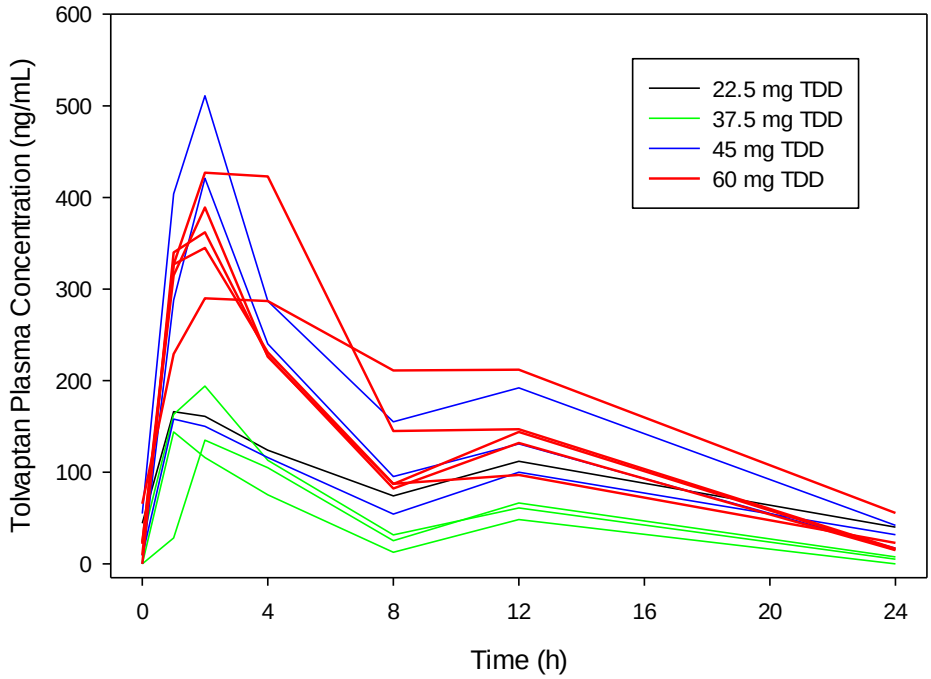
PKT-1: Individual and Summary Demographic Characteristics for Subjects with Dense PK/PD Sampling

Placebo Subjects Subject ID	Dose (mg)	Age (y)	Weight (kg)	Serum Creatinine (mg/dL)	eGFR (mL/min/1.73m²)	Sex	Race
[redacted]	45	[redacted]	[redacted]	0.76	88.03	[redacted]	White
	45			0.59	114.80		White
	60			0.69	101.16		White
	60			0.67	107.26		White
	60			0.61	114.42		White
	60			0.66	112.64		White
	60			0.79	89.92		White
	90			1.02	75.21		White
N	—	8	8	8	8	8	8
Median	—	15.0	59.0	0.73	104.21	Males 6 (75%)	White 8 (100.0%)
Mean	—	14.6	60.3	0.76	100.43	Females 2 (25%)	
SD	—	1.2	10.1	0.13	14.63		
%CV	—	8.1	16.7	17.1	14.6		
Minimum	—	12	44.0	0.60	75.21		
Maximum	—	16	79.0	1.02	114.8		

SOURCE: ADPC analysis dataset

Tolvaptan plasma concentrations over time for individual subjects in the dense PK/PD sampling subset at the four total daily doses (TDD) are shown in figure below.

Individual Subject Tolvaptan Plasma Concentrations Following Tolvaptan Split-dose Regimens in Subjects With ADPKD, 12 to 17 Years Old



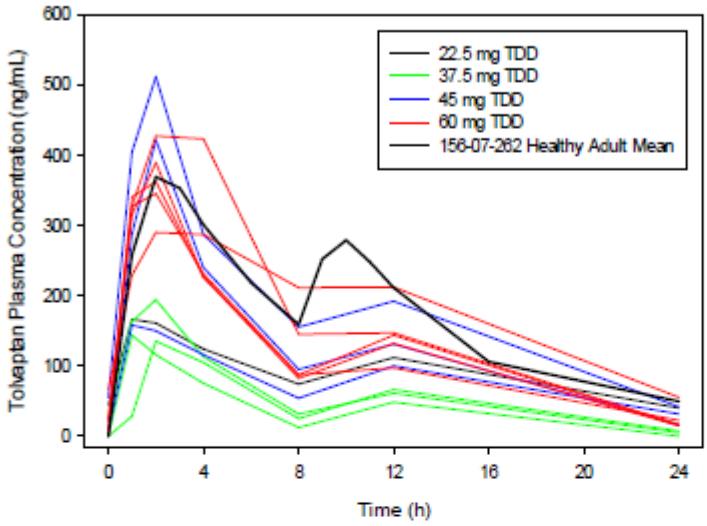
Note: Lower limit of quantitation of tolvaptan is 5.00 ng/mL.
The TDD split-dose regimens were as follows: 22.5 mg (15/7.5), 37.5 mg (22.5/15), 45 mg (30/15), and 60 mg (45/15).
Source: CSR 156-12-298 PKT-2.1 through PKT-2.4.

The same plot with overlay of mean tolvaptan concentrations following tolvaptan administered as a TDD of 60 mg to healthy adult subjects is presented in PKF-1, Panel A.

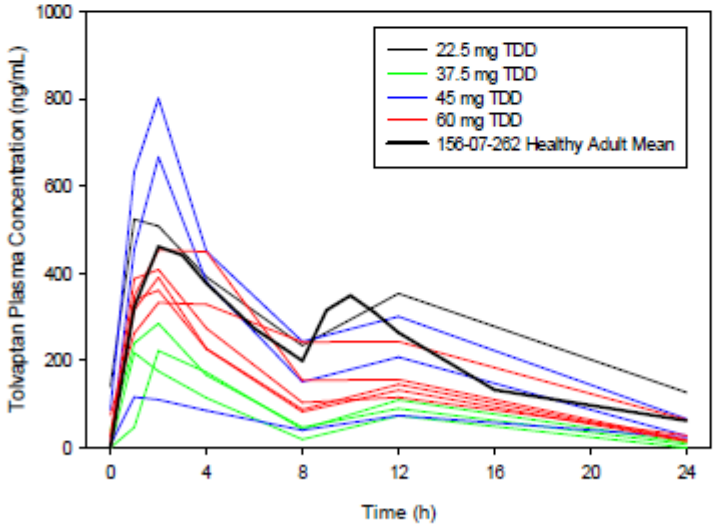
A composite plot of the concentration-time curves normalized to a 1 mg/kg TDD for each subject and overlaid with mean healthy subject concentrations normalized to a 1 mg/kg TDD is presented in PKF-1, Panel B.

PKF- 1 Individual Tolvaptan Plasma Concentrations During Dense PK/PD Sampling Period (Panel A) and Normalized to a 1 mg/kg Dose (Panel B)

A



B



Note: Overlaid on Panel A are mean tolvaptan plasma concentrations following a 45 mg/15 mg split-dose regimen given to 18 healthy adult subjects (CSR 156-07-262, PKT-2). Panel B presents the same concentrations normalized to a 1 mg/kg dose for each subject or the mean of adult subjects in 156-07-262 trial; for the adult data, the dose was 60 mg and the mean body weight of all subjects was 75 kg (CSR 156-07-262, PKT-1).
Source: PKT-1, PKT-2.1 to PKT-2.4

Intersubject variability of tolvaptan plasma concentrations was large even after normalization of doses to a 1 mg/kg TDD.

Table 0-3	Mean (SD) Tolvaptan Plasma Pharmacokinetic Parameters Following Tolvaptan Split-dose Regimens in Subjects With ADPKD, 12 to 17 Years Old			
Parameters	**Tolvaptan Total Daily Doses**			
	22.5 mg (n=1)	**37.5 mg (n=3)**	**45 mg (n=3)**	**60 mg (n=5)**
C_{max} (ng/mL)	166	158 (31.8)	363 (183)	363 (51.1)
t_{max} (h)[a]	1.00	2.02 (1.00-2.17)	2.00 (1.00-2.00)	2.00 (2.00-2.02)
C_{min} (ng/mL)	40.0	1.69 (2.92)	16.9 (22.2)	20.5 (21.1)
AUC_{0-24h} (h·ng/mL)	2220	1320 (175)[b]	3190 (1250)	3510 (705)

AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours; C_{max} = Maximum (peak) plasma concentration; C_{min} = Minimum plasma concentration; SD = standard deviation; t_{max} = time to maximum (peak) plasma concentration.
Note: Split-dose regimens were as follows: 22.5 mg (15/7.5), 37.5 mg (22.5/15), 45 mg (30/15), and 60 mg (45/15).
[a]Values are median (range).
[b]n = 2.
Source: CSR 156-12-298 PKT-3.1 through PKT-3.4.

DM-4103 has a long half-life, approximately 180 hours, making DM-4103 concentrations a good marker of compliance because concentrations accumulate, up to 30 µg/mL in adults dosed with tolvaptan 120 mg daily. Steady-state concentrations following 60 mg daily are rarely below 1 µg/mL. Therefore, subjects with consistent concentrations below this level yet reporting daily dosing at 60 mg/day or higher would be considered noncompliant with their reported dosing. If expected concentrations were 500 ng/mL, as might be observed following a 37.5-mg daily dose, subjects with concentrations near or less than the LLOQ (12.5 ng/mL) would have discontinued IMP about 5 weeks previously. DM-4103 concentrations at Week 1 and Month 1 were consistent with reported dosing for all subjects with an evaluable sample. At Month 6, 1 of 42 subjects (2.4%) with a PK sample was not compliant with reported dosing. At Month 12, 5 additional subjects (for a total of 6 out of 40 subjects [15%]) had DM-4103 concentrations ranging from 0 to < 140 ng/mL (PKT-4), indicating noncompliance with reported dosing and limited to no dosing within the previous weeks.

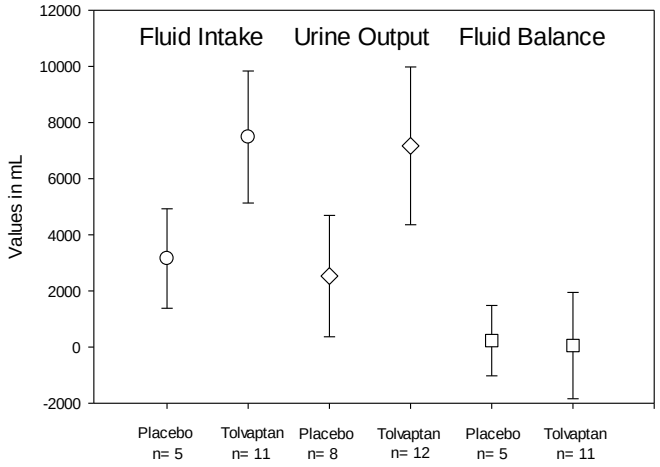
Pharmacodynamics Results

The pharmacodynamic analysis includes:

- Urine osmolality and specific gravity
- 24-hour fluid balance
- Serum sodium, creatinine, and osmolality
- Urine volume and urine sodium, creatinine, and osmolality
- Fluid intake
- Palatability and acceptability of tolvaptan formulation

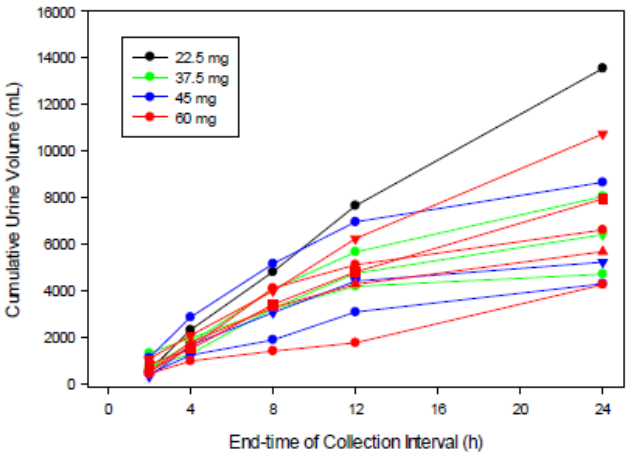
Fluid intake and urine output were higher in the tolvaptan group, which is not surprising given tolvaptan's aquaretic effects. Subjects appeared to maintain a neutral fluid balance, as fluid balance was close to zero over 24 hours.

Mean (SD) Fluid Intake, Urine Output, and Fluid Balance for 0 to 24 Hours for Tolvaptan- and Placebo-treated Subjects During Dense PK/PD Sampling

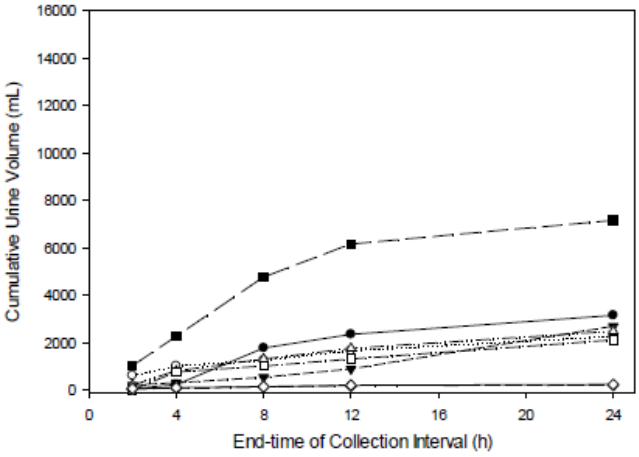


PKF- 2 Individual Cumulative Urine Volume During Dense PK/PD Sampling Period

A) Tolvaptan-treated subjects



B) Placebo-treated subjects

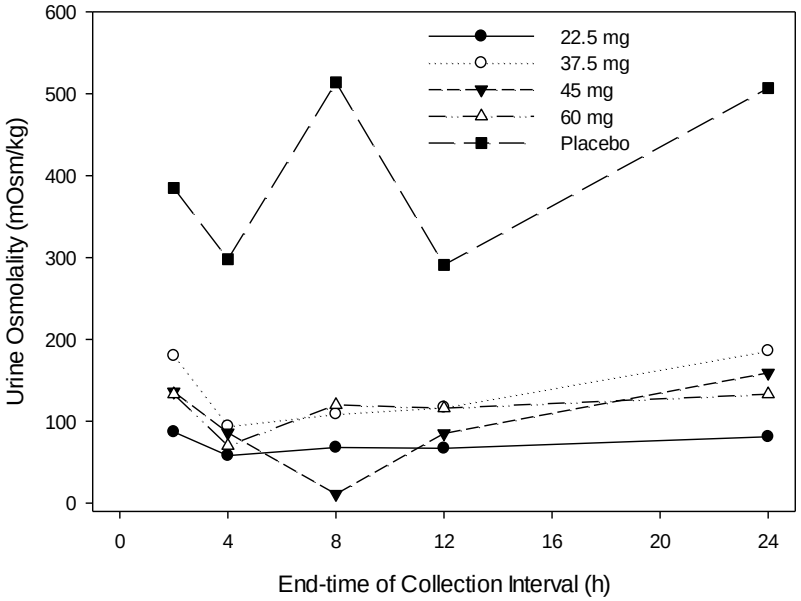


Source: adpd analysis dataset

Source: CSR 156-12-298 CT-1.6.4.1.

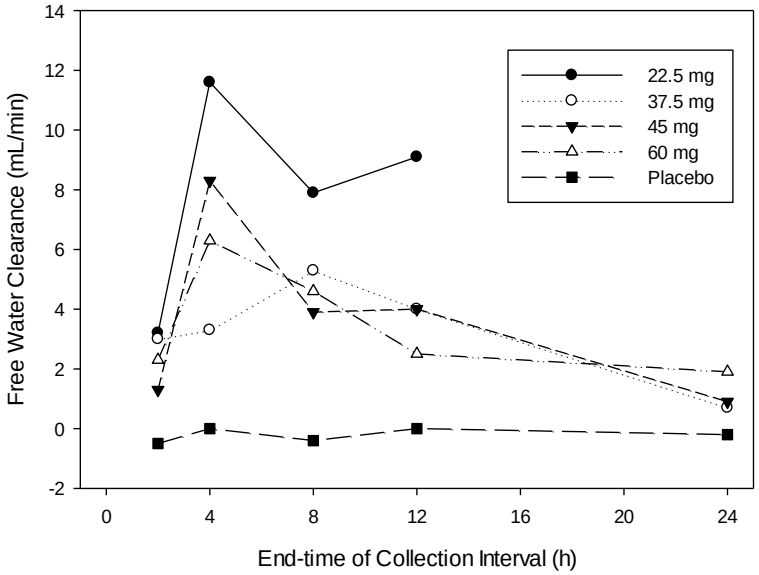
In addition to increasing urine output, tolvaptan administration produced decreases in urine osmolality and increases in free water clearance, indicating target engagement at the V2 receptor for the 24-hour dosing interval in all subjects, despite the range of doses being taken.

Median Urine Osmolality by Collection Interval and Dose for Tolvaptan- and Placebo-treated Subjects During Dense PK/PD Sampling



Note: n = 8 for placebo, n = 1 for 22.5 mg, n = 3 for 37.5 and 45 mg, and n = 5 for 60 mg TDD.
Source: CSR 156-12-298 CT-1.6.4.3.

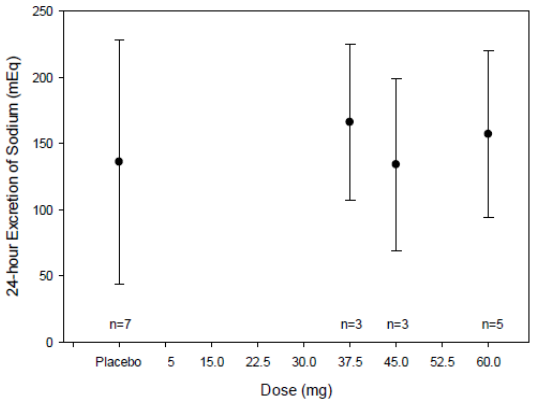
Median Free Water Clearance by Collection Interval and Dose for Tolvaptan- and Placebo-treated Subjects During Dense PK/PD Sampling



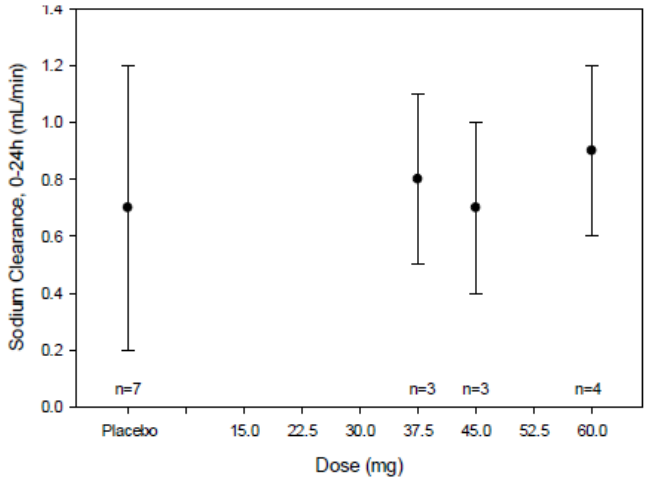
Note: n = 8 for placebo, n = 1 for 22.5 mg, n = 3 for 37.5 and 45 mg, and n = 5 for 60 mg TDD.
Source: CSR 156-12-298 CT-1.6.4.2.

As expected, excretion of sodium and sodium and creatinine clearances were not changed by tolvaptan administration.

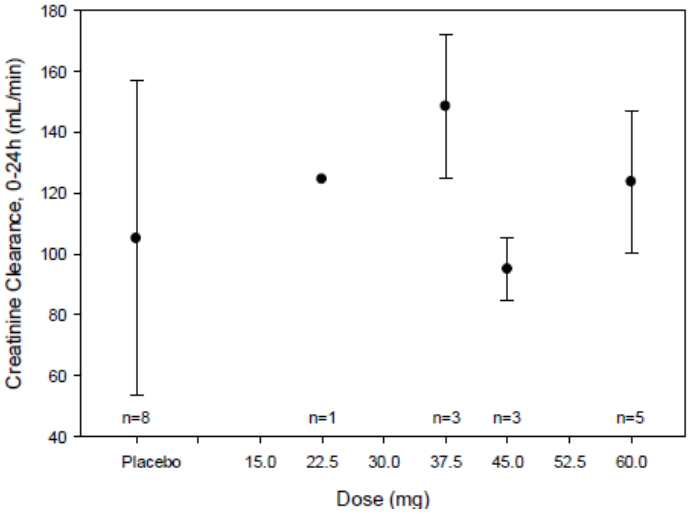
Mean (SD) Urine Sodium Excretion for 0 to 24 Hours by Dose for Tolvaptan- and Placebo-treated Subjects During Dense PK/PD Sampling



Mean (SD) Sodium Clearance for 0 to 24 Hours by Dose for Tolvaptan- and Placebo-treated Subjects During Dense PK/PD Sampling



Mean (SD) Creatinine Clearance for 0 to 24 Hours by Dose for Tolvaptan- and Placebo-treated Subjects During Dense PK/PD Sampling



Serum sodium and osmolality concentrations fluctuated during the day, predose and 24-hour postdose concentrations were similar.

After a review of the data, PK/PD correlations were not explored. Subjects participating in the dense PK/PD sampling took tolvaptan daily doses ranging from 22.5 mg to 60 mg. Even after normalizing concentrations to a 1 mg/kg dose, concentrations were highly variable (PKF-1, Panel B), but all tolvaptan doses reduced urine osmolality to the same extent during the 24-hour sampling period. Intersubject variability in urine output following tolvaptan dosing was high with 24-hour urine volumes ranging from 4245 to 13550 mL, with no obvious dose-response relationship.

MAH's conclusions

For subjects participating in the dense PK/PD sampling:

- Intersubject variability of tolvaptan plasma concentrations was large even after normalization of doses.
- Tolvaptan administration produced increases in free water clearance and urine output with decreases in urine osmolality, indicating target engagement at the V2 receptor.
- Subjects appeared to be maintaining their fluid balance, as fluid balance for 24 hours was close to zero and serum sodium and osmolality were similar at predose and 24 hours postdose.
- As expected, excretion of sodium and sodium clearance was not changed by tolvaptan administration.
- PK/PD correlations were not performed, as visual inspection of intersubject variability in PD responses indicated no obvious dose response.

CHMP comment

The study samples were analysed for determination of tolvaptan, DM-4103 and DM-4107 using HPLC-MS/MS according to a mentioned validation report dated 2015; however, this validation report is not included in the current dossier. All samples were analysed in the LTS range and were within the established calibration range. Twenty subjects of 12-17 years of age (12 in treatment arm and 8 in placebo arm) were included in a subset of patient with dense PK/PD sampling conducted after 1 month of treatment at predose, 1, 2, 4, 8, 12, and 24 hours post the morning dose. No subjects below 12 years of age had dense PK sampling.

The doses administered to these 12 patients at 1 month after the start of treatment were 22.5 mg (15/7.5 mg, N=1), 37.5 mg (22.5/15 mg, N=3), 45 mg (30/15 mg, N=3) and 60 mg (45/15 mg, N=5).

According to the selected tolvaptan dose based on weight, subjects $\geq$ 45 kg to $\leq$ 75 kg were administered with a starting dose of 30/15 mg tolvaptan; if tolerated, the starting dose was followed by, after 1 week, a dose of 45/15 mg. Six subjects (out of 12 treated with tolvaptan) weighting between 55 kg and 71.2 kg, at 1 month of treatment, had a down-titration at the starting dose (2 subjects remained on 45 mg) or less than the starting dose (e.g. one subject weighing approximately 70 kg, should have taken a final dose of 60 mg, whereas they took 22.5 mg). The reasons why a high percentage of patients downgraded to a lower dose of that foreseen after 1 month are not clear since overall seems to suggest it could be inadequate (safety concerns?). In case the MAH will apply for an extension of indication clarification is expected.

The PK analysis showed that the median Tmax was reached after 2 hours for all morning doses except for 22.5 mg dose that however was administered to only one subject. The Tmax after the afternoon doses, according to the provided figure, seems to be delayed (about 4 h). The median Cmax seems not increase with increasing dose, the median AUC0-24h although similar between doses, showed a very high variability, presumably due to the low number of patients. The metabolites DM-4103 and DM-4107 were also determined in samples. DM-4103 was used to check the compliance to the treatment, with 6

out of 40 subjects (of which 2 in dense PK sampling) non-compliant. The MAH provides individual plasma concentrations during dense PK/PD sampling period in paediatrics overlaid with mean tolvaptan plasma concentrations in healthy adults following a 45 mg/15 mg split-dose regimen, normalised by dose. It is noted that in paediatric patients dosed with 45 mg (30/15 mg, N=3) and 60 mg (45/15 mg, N=5) after one month of treatment, showed Cmax values higher than in adults after the morning dose. Therefore, an adequate definition and a comprehensive discussion of the selected dose, including the starting one, is expected in case the MAH will apply for an extension of indication.

In subjects with dense PD sampling, urine osmolality and specific gravity, 24-hours fluid balance, serum sodium, creatinine and osmolality, urine volume and urine sodium, were determined.

The urine osmolality decrease in all dose groups, urine volume and free water clearance increase in all groups, 24-hours fluid balance remain unchanged, sodium excretion and clearance did not change; no clear trend between dose groups is observed for serum sodium, creatinine and osmolality and the creatinine clearance. These results have no clear relationship with administered doses and can only confirm the aquaretic effect of tolvaptan due to its mechanism of action.

Among the PD analysis, the protocol foreseen the palatability and acceptability of tolvaptan formulation; however, no data is provided.

Safety results

Extent of Exposure

All 91 randomized subjects in **Phase A** received at least 1 dose of IMP and were included in the safety analyses. Exposure up to 361 to 390 days was achieved in 33 of 48 subjects (68.8%) in the tolvaptan group and 29 of 43 subjects (67.4%) in the placebo group. The average daily dose during that time was 40.4 mg in the tolvaptan group and 52.6 mg in the placebo group.

For subjects 12 to 17 years old, 12 subjects were on a modal TDD of 45 mg tolvaptan while 13 subjects were on a modal TDD of 37.5 or 60 mg tolvaptan at 12 months. For subjects < 12 years old, 4 subjects were on a modal TDD of 22.5 mg tolvaptan and 4 subjects were on a modal TDD of 15 mg tolvaptan at 12 months.

All 81 enrolled subjects in **Phase B** received at least 1 dose of IMP and were included in the safety analyses. Exposure up to 691 to 720 days was achieved in 21 of 42 subjects (50.0%) in the prior tolvaptan group and 19 of 39 subjects (48.7%) in the prior placebo group. The average daily dose during that time was 37.5 mg in the prior tolvaptan group and 38.7 mg in the prior placebo group.

CHMP comment

More than half of patients achieved a 1 year of exposure both in tolvaptan and placebo group. The average daily dose was different among age groups, and this is expected. However, it was noted that modal TDD was different among patients within the same age group, with the majority of patient of 12 to 17 years as well as < 12 years taking 45 mg of modal TDD in tolvaptan group. However, the number of patients taking different TDD seem to be balanced within the group. In phase B almost 50% of patients achieved up to 720 days of exposure and the average daily dose remained 37.5 mg in the prior tolvaptan group.

See comment above regarding the dose.

Adverse events

Overall, a total of 526 treatment-emergent adverse events (TEAEs) were reported for 86 of 91 subjects (94.5%) during Phase A of the trial (see table below).

Table 12.2.1-1 Adverse Events (All Causalities), Phase A Safety Sample

	Tolvaptan (N=48)	Placebo (N=43)
Number of	**n (%)[a]**	**n (%)[a]**
Subjects treated	48 (100.0)	43 (100.0)
Subject days of drug exposure	16502	15060
Subjects with adverse events	45 (93.8)	42 (97.7)
Adverse events	344	307
Subjects with treatment-emergent adverse events	44 (91.7)	42 (97.7)
Treatment-emergent adverse events[b]	289	237
Subjects with serious treatment-emergent adverse events	1 (2.1)	6 (14.0)
Subjects with non-serious treatment-emergent adverse events	44 (91.7)	42 (97.7)
Subjects with severe treatment-emergent adverse events	1 (2.1)	2 (4.7)
Subjects discontinued investigational medicinal product due to adverse events	1 (2.1)	1 (2.3)
Deaths	0 (0.0)	0 (0.0)

[a]Percentages are based on the number of subjects treated.

[b]Treatment-emergent adverse event is defined as an adverse event that started after trial drug treatment; or if the event was continuous from baseline and was serious, trial drug related, or resulted in death, discontinuation, interruption, or reduction of trial therapy. Multiple occurrences of treatment-emergent adverse events are counted once per Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Overall, a total of 613 TEAEs were reported for 77 of 81 subjects (95.1%) during **Phase B** of the trial (CT-2.8.1.1). The incidence of TEAEs was lower in the prior tolvaptan group (38 subjects [90.5%]) than in the prior placebo group (39 subjects [100.0%]) (Table 12.2.1-2). Serious TEAEs were reported in 7 subjects in the prior tolvaptan group and 8 subjects in the placebo group, while discontinuations due to AEs were reported in 3 subjects in the prior placebo group only. There were no deaths reported in this trial.

Table 12.2.2.1-1 Treatment-emergent Adverse Events With an Incidence of at Least 5% in Any Treatment Group by System Organ Class and MedDRA Preferred Term, Phase A Safety Sample		
	Tolvaptan (N=48)	**Placebo (N=43)**
System Organ Class Adverse Event (MedDRA Preferred Term)	**n (%)**	**n (%)**
Ear and Labyrinth Disorders		
Ear Pain	3 (6.3)	2 (4.7)
Gastrointestinal Disorders		
Abdominal Pain	6 (12.5)	3 (7.0)
Abdominal Pain Upper	5 (10.4)	4 (9.3)
Constipation	5 (10.4)	1 (2.3)
Diarrhoea	3 (6.3)	7 (16.3)
Nausea	3 (6.3)	7 (16.3)
Vomiting	7 (14.6)	10 (23.3)
General Disorders and Administration Site Conditions		
Asthenia	0 (0.0)	3 (7.0)
Fatigue	4 (8.3)	3 (7.0)
Pyrexia	4 (8.3)	3 (7.0)
Thirst	7 (14.6)	2 (4.7)
Immune System Disorders		
Seasonal Allergy	4 (8.3)	1 (2.3)
Infections and Infestations		
Bronchitis	3 (6.3)	1 (2.3)
Ear Infection	1 (2.1)	4 (9.3)
Nasopharyngitis	10 (20.8)	14 (32.6)
Pharyngitis	4 (8.3)	0 (0.0)
Rhinitis	3 (6.3)	3 (7.0)
Upper Respiratory Tract Infection	4 (8.3)	2 (4.7)
Viral Infection	3 (6.3)	1 (2.3)
Investigations		
Blood Creatinine Increased	9 (18.8)	2 (4.7)
Metabolism and Nutrition Disorders		
Decreased Appetite	4 (8.3)	2 (4.7)
Polydipsia	5 (10.4)	1 (2.3)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	4 (8.3)	5 (11.6)
Pain in Extremity	0 (0.0)	6 (14.0)

Nervous System Disorders		
Dizziness	3 (6.3)	5 (11.6)
Headache	16 (33.3)	21 (48.8)
Migraine	2 (4.2)	3 (7.0)
Renal and Urinary Disorders		
Nocturia	7 (14.6)	3 (7.0)
Pollakiuria	9 (18.8)	0 (0.0)
Polyuria	13 (27.1)	2 (4.7)
Renal Pain	2 (4.2)	3 (7.0)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (14.6)	5 (11.6)
Epistaxis	3 (6.3)	0 (0.0)
Oropharyngeal Pain	4 (8.3)	6 (14.0)
Vascular Disorders		
Hypertension	4 (8.3)	1 (2.3)
Orthostatic Hypotension	5 (10.4)	0 (0.0)

The incidence of **aquaretic TEAEs** (Medical Dictionary for Regulatory Activities [MedDRA] preferred terms of dry mouth, thirst, polydipsia, nocturia, pollakiuria, and polyuria) in Phase A was higher in the tolvaptan group (31 of 48 subjects [64.6%]) than in the placebo group (7 of 43 subjects [16.3%]) (Table 12.2.2.1-2). The most frequently reported aquaretic TEAEs in the tolvaptan group were polyuria (27.1% tolvaptan versus 4.7% placebo) and pollakiuria (18.8% tolvaptan versus 0.0% placebo).

The incidence of **dehydration-related TEAEs** (including all preferred terms under the dehydration standardised MedDRA queries [SMQ] that were reported in this trial) in Phase A was higher in the tolvaptan group (17 of 48 subjects [35.4%]) than in the placebo group (6 of 43 subjects [14.0%]) (Table 12.2.2.1-3). The most frequently reported dehydration-related TEAEs in the tolvaptan group were thirst (14.6% tolvaptan versus 4.7% placebo) and orthostatic hypotension (10.4% tolvaptan versus 0.0% placebo).

Related Treatment-emergent Adverse Events

The most frequently reported TEAEs (occurring in at least 10% of subjects in the tolvaptan group and at a higher incidence than the placebo group) assessed by the investigator as related to the IMP in Phase A were as follows:

- Polyuria (27.1% tolvaptan versus 2.3% placebo)
- Pollakiuria (18.8% tolvaptan versus 0.0% placebo)
- Blood creatinine increased (16.7% tolvaptan versus 2.3% placebo)
- Nocturia (14.6% tolvaptan versus 7.0% placebo)
- Thirst (12.5% tolvaptan versus 2.3% placebo)
- Headache (10.4% tolvaptan versus 4.7% placebo)
- Polydipsia (10.4% tolvaptan versus 2.3% placebo)

The most frequently reported TEAE (occurring in at least 10% of subjects overall) assessed by the investigator as related to the IMP in Phase B were as follows:

- Blood creatinine increased (14.3% prior tolvaptan versus 12.8% prior placebo)
- Headache (4.8% prior tolvaptan versus 17.9% prior placebo)

- Polyuria (4.8% prior tolvaptan versus 33.3% prior placebo)

CHMP comment

A similar rate of patients with TEAE were reported in tolvaptan and placebo group in phase A (91.7% and 97.7%, respectively). They were all no serious TEAEs, except for 1 patient in tolvaptan group and 6 patients in placebo group who experienced serious TEAEs. Discontinuations due to AEs were reported in 1 subject in each treatment group, while no deaths were reported in this study.

In phase B of the trial the incidence of TEAEs was lower in the prior tolvaptan group (38 subjects [90.5%]) than in the prior placebo group (39 subjects [100.0%]), as well as serious TEAEs (16.7% vs 20.5%).

The most frequently reported TEAEs which occurred more frequently in at **least 10%** of subjects in the tolvaptan group than in the placebo group in Phase A were: **polyuria** (27.1% tolvaptan versus 4.7% placebo), Blood creatinine increased (18.8% vs 4.7%), **pollakiuria** (18.8% vs 0.0%), cough (14.6% vs 11.6%), **nocturia** (14.6% vs 7.0%), **thirst** (14.6% vs 4.7%), abdominal pain (12.5% vs 7.0%), constipation (10.4% vs 2.3%), orthostatic hypotension (10.4% vs 0.0% placebo), polydipsia (10.4% vs 2.3%), abdominal pain upper (10.4% vs 9.3%). The incidence of aquaretic TEAEs and dehydration-related TEAEs was higher in the tolvaptan group than in the placebo group (64.4% vs 16.3% and 35.4% vs 14%). These AEs are expected due to the mechanism of action of the drug and to the known safety profile in adult patients and are reflected in the SmPC, however they are considered of concern in a pediatric population, mainly in younger patients, more sensitive to acquaretic AEs. Moreover, most of these AEs are also the more frequently TEAEs **related** to study drug. However, it was noted that in phase B of the trial they are reduced in tolvaptan group ad increased in placebo group, maybe due to titration in the early stage.

This trial had a small number of subjects and no formal subgroup analyses were performed for the TEAEs in the trial.

Deaths and other serious adverse events

No **deaths** occurred during the trial

In **Phase A** of the trial there was 1 subject in the tolvaptan group who had a serious TEAE of **viral pericarditis** which the investigator assessed as moderate severity and not related to tolvaptan. The subject was admitted to the hospital with symptoms of chest pain, dizziness, and suspected endocarditis. No corrective treatments were administered, and the event resolved after 8 days.

There were 6 subjects in the placebo group who had serious TEAEs: 1 subject had a hand fracture and ulna fracture, 1 subject had hematuria and renal pain, 1 subject had an intentional overdose and intentional self-injury, and 1 subject each had petit mal epilepsy, pelvic pain, and hypertensive crisis. None of the serious TEAEs reported in both treatment groups were assessed by the investigator as related to the IMP.

In **Phase B** of the trial there were 7 subjects in the prior tolvaptan group who had serious TEAEs (see table below).

Table 12.3.1.2-2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and MedDRA Preferred Term, Phase B Safety Sample			
	Prior Tolvaptan (N=42)	Prior Placebo (N=39)	Total (N=81)
System Organ Class Adverse Event (MedDRA Preferred Term)	n (%)	n (%)	n (%)
Any TEAE			
Subjects with any Serious Adverse Event[a]	7 (16.7)	8 (20.5)	15 (18.5)
Gastrointestinal Disorders			
Abdominal Pain	1 (2.4)	1 (2.6)	2 (2.5)
Colitis Ulcerative	1 (2.4)	0 (0.0)	1 (1.2)
Pancreatitis Acute	1 (2.4)	0 (0.0)	1 (1.2)
Immune System Disorders			
Anaphylactic Reaction	1 (2.4)	0 (0.0)	1 (1.2)
Infections and Infestations			
Arthritis Bacterial	0 (0.0)	1 (2.6)	1 (1.2)
COVID-19	2 (4.8)	0 (0.0)	2 (2.5)
Injury, Poisoning and Procedural Complications			
Expired Product Administered	0 (0.0)	1 (2.6)	1 (1.2)
Investigations			
Alanine Aminotransferase Increased	1 (2.4)	1 (2.6)	2 (2.5)
Aspartate Aminotransferase Increased	0 (0.0)	2 (5.1)	2 (2.5)
Heart Rate Increased	0 (0.0)	1 (2.6)	1 (1.2)
SARS-COV-2 Test Positive	1 (2.4)	1 (2.6)	2 (2.5)
Psychiatric Disorders			
Eating Disorder	0 (0.0)	1 (2.6)	1 (1.2)
Renal and Urinary Disorders			
Renal Impairment	1 (2.4)	1 (2.6)	2 (2.5)

The event of **ulcerative colitis** was assessed by the investigator as severe and not related to tolvaptan. The subject was admitted to the hospital with abdominal pain and increased frequency of blood in the stool. As a result of this event, dosing of tolvaptan was interrupted. Corrective treatments included methylprednisone and the event resolved after 7 days.

One serious TEAE of ALT increased in 1 subject and serious TEAEs of ALT and AST increased in 1 subject were all assessed by the investigator as related to the IMP

CHMP comment

Overall, the frequency of serious TEAEs was lower in the tolvaptan group both in Phase A and B. Serious adverse events were reported in 1 patient in phase A in tolvaptan group (viral pericarditis) which was considerate moderate in intensity and not related by the investigator and in 7 patients in phase B in prior tolvaptan group of which the event of ulcerative colitis was reported as not related by the investigator. One serious TEAE of ALT increased in 1 subject and serious TEAEs of ALT and AST increased in 1 subject were all assessed by the investigator as related to the IMP.

. No death was reported in this trial.

AEs leading to discontinuation

One subject in the tolvaptan group discontinued IMP due to pollakiuria and 1 subject in the placebo group discontinued IMP due to dizziness, both in Phase A. Both events were assessed by the investigator as moderate severity and as related to the IMP.

Three subjects in Phase B discontinued IMP due to eating disorder, polyuria, and liver

function test increased. All events were assessed by the investigator as moderate severity and the event of polyuria was assessed as related to the IMP.

AEs of special interest (AESI)

There were no adverse events of special interest (AESI) reported during the trial.

For the 5 hepatic standardised MedDRA queries (SMQs; cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; noninfectious hepatitis; liver-related investigations, signs, and symptoms; and liver-related coagulation and bleeding disturbances), in Phase A there was 1 TEAE of increased blood bilirubin in the placebo group. In Phase B in the prior tolvaptan group there were 5 subjects with TEAEs: 3 TEAEs of increased ALT, 1 TEAE of increased AST, and 1 TEAE of increased hepatic enzymes; in the prior placebo group there were 6 subjects with TEAEs: 3 TEAEs of increased AST, 2 TEAEs of increased LFT, and 1 TEAE each of increased ALT, increased blood bilirubin, and increased hepatic enzyme, respectively. Six subjects spontaneously recovered without intervention, in 4 subjects treatment was interrupted, and in 1 subject treatment was withdrawn (withdrawal was not related to hepatic AEs).

Pregnancy

There were no pregnancies reported during the trial

Laboratory Values

Changes from baseline were observed for various **serum chemistry** and **hematology** parameters; however, none of the changes were considered to be clinically meaningful.

Any shifts from the normal limits at baseline to outside of the reference limits (low or high) at postbaseline evaluations for clinical laboratory parameters were not considered to be clinically meaningful.

Changes from baseline were observed for erythrocytes and leukocytes in **urinalysis** however, none of the changes were considered to be clinically meaningful.

There were no cases of drug-induced liver injury **(DILI)** in either phase of the trial.

There were no subjects who experienced elevated transaminases and no potentially clinically significant (PCS) elevations in hepatic laboratory data were reported during Phase A of the trial. Four subjects experienced PCS elevations in **hepatic laboratory** data during Phase B of the trial, including **3 serious AEs** (1 prior tolvaptan subject and 2 prior placebo subjects) and 1 AE leading to discontinuation (prior placebo subject). The 4 PCS elevations in hepatic laboratory data were reviewed independently by hepatic adjudication committee and considered unlikely related to tolvaptan.

In **Phase A**, PCS increases in creatinine occurred in 4 subjects in the tolvaptan group and in no subjects in the placebo group. In addition, the following PCS laboratory test results were reported: 2 placebo

subjects had a decrease in neutrophils, 1 placebo subject had a decrease in glucose, and 1 tolvaptan subject had an increase in potassium.

In **Phase B**, PCS increases in **creatinine** occurred in 3 subjects in the prior tolvaptan group and in 3 subjects in the prior placebo group. In addition, the following PCS laboratory test results were reported: 3 subjects (2 prior tolvaptan and 1 prior placebo) had a decrease in neutrophils, 1 prior tolvaptan subject had an increase in triglycerides and 3 prior placebo subjects each had an increase in sodium and potassium and a decrease in glucose.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Changes from baseline were observed for vital sign parameters throughout the trial; however, the changes were not considered to be clinically meaningful, with the exception of the TEAEs noted below.

The incidence of PCS vital signs was similar between the treatment groups. For both phases the most frequently reported finding was diastolic blood pressure (DBP) $\leq$ 80 mmHg and decrease from baseline $\geq$ 15 mmHg, which in Phase A occurred in 6 of 48 subjects (12.5%) in the tolvaptan group and 8 of 43 subjects (18.6%) in the placebo group, and in Phase B occurred in 7 of 42 subjects (16.7%) in the prior tolvaptan group and 5 of 39 subjects (12.8%) in the prior placebo group.

The following TEAEs related to vital signs were reported during Phase A of the trial (with a system organ class of investigations or vascular disorders):

- Orthostatic hypotension (10.4% tolvaptan versus 0.0% placebo)
- Hypertension (8.3% tolvaptan versus 2.3% placebo)
- Hypotension (4.2% tolvaptan versus 2.3% placebo)
- Weight decreased (4.2% tolvaptan versus 2.3% placebo)
- Peripheral coldness (2.1% tolvaptan versus 0.0% placebo)
- Hypertensive crisis (0.0% tolvaptan versus 2.3% placebo)

The following TEAEs related to vital signs were reported during Phase B of the trial (with a system organ class of investigations or vascular disorders):

- Hypertension (9.5% prior tolvaptan versus 5.1% prior placebo)
- Orthostatic hypotension (7.1% prior tolvaptan versus 7.7% prior placebo)
- Hypotension (4.8% prior tolvaptan versus 7.7% prior placebo)
- Body temperature increased (2.4% prior tolvaptan versus 0.0% prior placebo)
- Heart rate decreased (2.4% prior tolvaptan versus 0.0% prior placebo)
- Heart rate increased (2.4% prior tolvaptan versus 2.6% prior placebo)
- Weight decreased (2.4% prior tolvaptan versus 12.8% prior placebo)
- Peripheral coldness (0.0% prior tolvaptan versus 2.6% prior placebo)

CHMP comment

Overall, changes of laboratory values were reported as no clinically meaningful by the MAH. The 4 PCS elevations in **hepatic laboratory** occurred both in prior tolvaptan (1 serious AE) and in prior placebo

subjects, were considered unlikely related to tolvaptan by hepatic adjudication committee. However, due to the known hepatic toxicity of tolvaptan coming from adult's studies, the correlation with study drug cannot be completely excluded also in the pediatric population and it is considered of concern. No cases of DILI meeting Hy's Law laboratory criteria occurred.

An imbalance in PCS increase of **creatinine** was reported in favour of placebo group in phase A of the trial (4 subjects vs 0, respectively). In phase B of the trial it was reported in 3 subjects both in tolvaptan and in placebo group. I addition, blood creatinine increase was also reported as one of the most common related-TEAEs (16.7% tolvaptan versus 2.3% placebo in phase A and 14.3% prior tolvaptan versus 12.8% prior placebo in phase B). In the MAH's opinion, it can be considered a known, reversible, and expected effect secondary to the hemodinamic effect of the drug.

Moreover, 3 subjects (2 prior tolvaptan and 1 prior placebo) had a decrease in neutrophils, 1 prior tolvaptan subject had an increase in triglycerides, and 3 prior placebo subjects each had an increase in sodium and potassium and a decrease in glucose.

A number of TEAEs related to vital signs were reported in phase A and were more frequent in tolvaptan group than in placebo group (Orthostatic hypotension, Hypertension, Hypotension, Weight decreased and Peripheral coldness). Most of them could be related to dehydration. A diastolic blood pressure (DBP) $\leq$ 80 mmHg and decrease from baseline $\geq$ 15 mmHg was the most frequently reported finding which occurred in both treatment groups and in a higher rate in subjects in the prior tolvaptan group (16.7%) than in prior placebo group (12.8%).

2.2.3. Discussion on clinical aspects

For this Article 46 procedure, the MAH submitted the final report for study **156-12-298**, a Phase 3b, Two-part, Multicenter, One Year Randomized, Double-blind, Placebo-controlled Trial of the Safety, Pharmacokinetics, Tolerability, and Efficacy of Tolvaptan followed by a Two Year Open-label Extension in Child.

Study design

The trial comprised 2 phases: **Phase A:** 12 months, randomized, double-blind, placebo-controlled phase to compare tolvaptan with placebo. It was open to subjects between the ages of 4 and 17 years, inclusive. Additionally, in accordance with the PIP requirements subjects aged 4 to 11 years were eligible for participation following discussion with the medical monitor who met criteria for entry to be enrolled concurrently during the recruitment period for the target population. Qualified subjects who completed Phase A were eligible to continue into **Phase B,** an open-label phase during which subjects who had completed Phase A of the trial received treatment with tolvaptan for 24 months in order to obtain safety and efficacy data for long-term use of tolvaptan in children and adolescent subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

The study design with 12 months double-blind treatment duration could be considered sufficient to detect the potential benefit of tolvaptan over placebo in a pediatric population and is in accordance with the PIP requirement. However, it is of note that only descriptive statistics were provided and therefore no firm conclusion can be drawn on efficacy of tolvaptan in pediatric population.

The diagnosis of ADPKD was defined by the presence of family history and/or genetic criteria AND who had at least 10 renal cysts, each of which measured at least 0.5 cm confirmed upon MRI inspection. Subjects who were MRI-naive or under the age of 12 must have had at least 4 cysts (at least 1 cm in

size) confirmed by ultrasound prior to MRI inspection and this could be considered acceptable as MRI usually requires sedation in younger children.

As is already done in TEMPO study with adult dosing, participants received a higher dose early in the day, followed by a lower dose administered approximately 8–9 h later, in order to obtain maximal inhibition on waking and a gradual fall-off of effect during the night, when frequent urination would lead to interruption of sleep and this is acceptable. The study protocol foreseen a questionnaire to be administered during Phase A to all subjects immediately after dosing to assess palatability and the easily to swallow the tablets. Unfortunately, no data is provided on this topic, although, in case the MAH will apply for an extension of indication, it could be important to know if there were patients who did not managed to take tablets as well as if tablets has been crushed prior the administration.

Endpoints

The **coprimary endpoints** were the change from baseline in spot urine osmolality (premorning dose) and specific gravity (premorning dose) after 1 week of daily dosing in Phase A.

The key secondary endpoint was the percent change from Phase A baseline in height-adjusted total kidney volume (htTKV) as measured by magnetic resonance imaging (MRI) at 12 months.

A number of other secondary and exploratory endpoints were used.

The choice of the co-primary endpoint is in line with the PIP requirements, but different to the primary endpoint used in the adult study (TEMPO) in which it was the rate of total kidney volume (TKV) change, which is considered an important endpoint considering that measures of renal volume seem to be linked to the progressive development of renal cysts in ADPKD, and correlate with renal function. From the other hand it is acknowledged that changes in TKV growth could be difficult to detect in pediatric subjects. However, the percent change from Phase A baseline in height-adjusted total kidney volume (htTKV) was the **key secondary endpoint** in the current pediatric study which could be considered as supportive.

Demographic characteristics were well balanced between tolvaptan and placebo. A low number of subjects had a genetic testing done (29,2 % in tolvaptan group vs 30.2% in plb group), of which only 2 patients (14.3%) in the study group were ADPKD-1 positive. The majority of patients were aware of a positive family history before diagnosis (89.6% in tolva vs 90.7% in plb). However, it is not clear if patients without a family history had a genetic diagnosis.

Overall, the mean total kidney volume was higher in the placebo group (393.3 mL) than in tolvaptan group (286.1 mL) suggesting a possible more advanced disease in this group of patients that could be a bias, even though the low number of patients (13 in plb group) limits any firm conclusion.

Efficacy

A greater change from baseline in **spot urine osmolality** as well as in **specific gravity** at 1 week was observed in tolvaptan group than in placebo group and was maintained up to 1 month from baseline and this is reassuring. Results from the co-primary endpoints suggest that tolvaptan is effective in reducing urine osmolality and in increasing the output of water, as could be expected from its mechanism of action (inhibition of V2 receptor). Therefore, these endpoints indicates that tolvaptan can inhibit the V2 receptor also in the pediatric population in a similar manner than in adults. However, even if recent studies seem to support the link between vasopressin V2R signaling and renal disease progression in ADPKD (Devuys O., 2016), these results need to be translated in a clinical effect, in particular in a reduction of clinical progression. Moreover, the study lack of a statistical analysis and therefore these results could be only considered as descriptive. Moreover, a greater change of spot urine osmolality was observed in the placebo arm of patients aged 15-17, suggesting a minor effect of tolvaptan over placebo in this age group. A possible reason of such imbalance in results of co-primary endpoints in patients younger than

12 years should be provided or otherwise this lack should be justified in case the MAH will apply for an extension of indication.

A smaller mean percent change from baseline to 12 months **in htTKV** (as measured by MRI) for subjects 12 to 17 years old was observed in the tolvaptan group (2.28%) versus the placebo group (6.11%) in Phase A. The results seem to be in line with those of the adult studies.

Height- adjusted TKV (htTKV) on MRI is at present the most established imaging surrogate parameter for monitoring disease progression in adult with ADPKD and TKV was the one used as primary endpoint in TEMPO study supporting tolvaptan authorization in adult population. Despite the scarce knowledges relating to the htTKV value in pediatric population, it is reported in literature that the vast majority of children with ADPKD maintained normal kidney function despite progressive structural kidney disease, thus emphasizing the great importance of total kidney volume (TKV) as a measurable outcome of early disease progression and the primary focus of therapeutic intervention in the pediatric ADPKD population (M. A. Cadnapaphornchai, 2017).

Even if difficulties in doing MRI mainly in younger and/or non-cooperative children who require sedation are acknowledged, only data from 57 patients were provided, limiting the robustness of these results in support of the co-primary endpoints. Data from ultrasound evaluation in 9 patients < 12 years old have been provided, which seem to be no sufficiently supportive.

A number of other secondary endpoints have been explored. Overall, they seem to be in line with co-primary and key secondary endpoints. The mean change in renal function (eGFR by Schwartz formula) showed a difference between tolvaptan group and placebo when analyzed from week 1 to month 12 due to the hemodynamic effect. However, no difference between tolvaptan and placebo group in the mean change in renal function was observed in 15 to 17 years age group, while the change was more evident in females.

Among the secondary endpoints there were PD endpoints such as urine volume (including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PK sampling (after at least 1 month).

Other endpoints included tolvaptan PK parameters following dense PK sampling

A high percentage of patients downgraded to a lower dose of that foreseen after 1 month this could suggest occurrence of safety concerns or in any case raises doubts on the adequateness of the starting dose. The reasons that lead to downgrade the dose should be provided in case the MAH will apply for an extension of indication.

Moreover, in paediatric patients dosed with 45 mg (30/15 mg, N=3) and 60 mg (45/15 mg, N=5) after one month of treatment, showed Cmax values higher than in adults after the morning dose. Therefore, an adequate definition and a comprehensive discussion of the selected dose, including the starting one, is expected in case the MAH will apply for an extension of indication.

Safety

Overall, the safety profile of tolvaptan seems to be in line with that observed in adults (with the exception of cough) and associated with its aquaretic properties. The most frequently reported TEAEs in the tolvaptan group than in the placebo group in phase A were: polyuria (27.1% tolvaptan versus 4.7% placebo), Blood creatinine increased (18.8% vs 4.7%), pollakiuria (18.8% vs 0.0%), cough (14.6% vs 11.6%), nocturia (14.6% vs 7.0%), thirst (14.6% vs 4.7%), abdominal pain (12.5% vs 7.0%), constipation (10.4% vs 2.3%), orthostatic hypotension (10.4% vs 0.0% placebo), polydipsia (10.4% vs 2.3%), abdominal pain upper (10.4% vs 9.3%). The incidence of aquaretic TEAEs and dehydration-

related TEAEs was higher in the tolvaptan group than in the placebo group (64.4% vs 16.3% and 35.4% vs 14%). These AEs are expected due to the mechanism of action of the drug and to the known safety profile in adult patients and are reflected in the SmPC, however they are considered of concern in a pediatric population, mainly in younger patients, more sensitive to acquaretic AEs.

The frequency of serious TEAEs was lower in the tolvaptan group both in Phase A and B. Serious adverse events were reported in 1 patient in phase A in tolvaptan group **(viral pericarditis)** which was considered moderate in intensity and not related by the investigator and in 7 patients in phase B in prior tolvaptan group of which the event of ulcerative colitis was reported as not related by the investigator. However, no information on seriousness and relationship with study drug were reported about the other serious adverse events in phase B. No death was reported in this trial.

In phase A, only one subject in the tolvaptan group discontinued IMP due to pollakiuria and the event was assessed by the investigator as moderate in severity and as related to the IMP. Three subjects in Phase B discontinued IMP due to eating disorder, polyuria, and liver function test increased. All events were assessed by the investigator as moderate severity and the event of polyuria was assessed as related to the IMP.

Changes of laboratory values were reported as no clinically meaningful by the MAH. No cases of DILI meeting Hy's Law laboratory criteria occurred. 4 PCS elevations in **hepatic laboratory** occurred both in prior tolvaptan (1 serious AE) and in prior placebo subjects, were considered unlikely related to tolvaptan by hepatic adjudication committee. One serious TEAE of ALT increased in 1 subject and serious TEAEs of ALT and AST increased in 1 subject were all assessed by the investigator as related to the IM. Therefore, considering the known hepatic toxicity of tolvaptan coming from adult's studies, the correlation with study drug cannot be excluded also in the pediatric population and it is considered of concern in such population.

An imbalance in PCS increase of **creatinine** was reported in favour of placebo group in phase A of the trial (4 subjects vs 0, respectively). In phase B of the trial it was reported in 3 subjects both in tolvaptan and in placebo group. In addition, blood creatinine increase was also reported as one of the most common related-TEAEs (16.7% tolvaptan versus 2.3% placebo in phase A and 14.3% prior tolvaptan versus 12.8% prior placebo in phase B). In the MAH's opinion, it can be considered a known, reversible, and expected effect secondary to the haemodynamic effect of the drug. Moreover, 3 subjects (2 prior tolvaptan and 1 prior placebo) had a decrease in neutrophils, 1 prior tolvaptan subject had an increase in triglycerides, and 3 prior placebo subjects each had an increase in sodium and potassium and a decrease in glucose.

A number of TEAEs related to vital signs were reported in phase A and were more frequent in tolvaptan group than in placebo group (Orthostatic hypotension, Hypertension, Hypotension, Weight decreased and Peripheral coldness). Most of them, such as orthostatic hypotension, could be related to dehydration and may be secondary to inadequate fluid intake to replace fluid loss. However, these effects could be less tolerated in children and also more harmful. A diastolic blood pressure (DBP) ≤ 80 mmHg and decrease from baseline ≥ 15 mmHg was the most frequently reported finding which occurred in both treatment groups and in a higher rate in subjects in the prior tolvaptan group (16.7%) than in prior placebo group (12.8%).

The MAH proposes no adjustments of the SmPC.

3. CHMP overall conclusion and recommendation

Study results indicate that tolvaptan is able to inhibit the V2 receptor also in the paediatric population in a similar manner than in adult one with potential beneficial effects. However, the limited sample size, the lack of a formal statistical analysis limit the robustness of the conclusion. Importantly, study results do not allow an adequate definition of the dose, this is expected to be addressed in case the MAH will decide to submit these data in the context of a variation. The safety profile seems to be similar to that of the adults (with few new signals like cough) and characterized mostly by aquaretic properties and their relative effects, such as orthostatic hypotension, which may be less tolerated by a paediatric population and also more harmful. Moreover, hepatic toxicity is also of concern in a paediatric population.

☒ Fulfilled:

No regulatory action required.