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Human Medicines Evaluation Division

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

## Samsca

tolvaptan

Procedure no: EMEA/H/C/000980/P46/022

## Note

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

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# 1. Introduction

On 19/1/2018, the MAH submitted the final study reports of two paediatric trials for Samsca, 156-08-276 and 156-11-294, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

Tolvaptan is currently approved and marketed in the European Union (EU) for the treatment of adults with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) as well as for autosomal dominant polycystic kidney disease (ADPKD).

Tolvaptan is approved in the United States (US) and Australia for treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and SIADH.

This submission contains the final study reports of two paediatric trials, 156-08-276 and 156-11-294. Both clinical trials were designed and conducted to fulfil the paediatric regulatory requirements of the European medicines Agency (EMA) (Trial 156-11-294) and the US Food and Drug Administration (FDA) (Trial 156-08-276). These two trials were prematurely terminated due to issues with subject enrolment and recruitment and not due to safety reasons.

For Samsca, in October 2017, EMA Paediatric Committee (PDCO) granted a waiver for the dilutional hyponatremia indication pertaining to the trials in the Paediatric Investigation Plan (PIP) (*EMEA-001231-PIP02-13-M05).* Before the waiver was granted, trial 156-11294 was a PIP requirement with objective of long term safety follow up of children with hyponatraemia who have previously participated in tolvaptan trials, including US phase 3b trial 156-08-276.

A joint clinical overview was submitted to discuss the results of both paediatric clinical trials.

## *2.2. Information on the pharmaceutical formulation used in the studies*

Tolvaptan was supplied or planned to be supplied as 3.75 mg, 7.5 mg, 15 mg and 30 mg spray-dried tablets with a dose-proportional amount of water for both studies and additionally as a 1 mg/mL (0.1% w/v) syrup suspension for trial 156-08-276.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted final reports for Trial 156-08-276 and Trial 156-11-294.

## 2.3.2. Clinical studies

**156-08-276**

**Description**

A Phase 3b, multicenter, open-label, randomized withdrawal trial of the effects of titrated oral SAMSCA (Tolvaptan) on serum sodium, pharmacokinetics, and safety in children and adolescent subjects hospitalized with euvolemic or hypervolemic hyponatremia.

## Methods

***Objective***

The objectives of this trial were to evaluate that tolvaptan effectively and safely increases and maintains serum sodium concentrations and to evaluate the pharmacokinetics of tolvaptan and the effect on fluid balance in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

***Study design***

This trial was an open-label, multicentre, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children and adolescent subjects hospitalized with euvolemic or hypervolemic hyponatremia (serum sodium < 130 mEq/L) that was persistent despite initial standard background therapy including fluid restriction and excluding a vasopressin antagonist.

After screening, all subjects underwent a treatment phase (2 to 5 days of tolvaptan treatment) and then a follow-up phase post-randomization of 14 days. During Treatment Phase A, subjects received tolvaptan once daily on Days 1 and 2. If the serum sodium level did not increase at least 4 mEq/L by Day 2, treatment was extended one additional day (to Day 2a). On Day 2a, subjects achieving an increase in serum sodium of ≥ 4 mEq/L were defined as responders, and subjects not achieving a ≥ 4 mEq/L increase in serum sodium were defined as non-responders. Subjects who were responders continued to Treatment Phase B (Randomization Phase) on Day 3, and were randomized to either the Early Withdrawal group (not receiving additional tolvaptan on Days 3 or 4) or the Late Withdrawal group (continuing tolvaptan treatment for Days 3 and 4). Randomization included stratification by age (< 10 years of age and ≥ 10 to < 18 years of age), serum sodium response (≤ 7 and > 7 mEq/L), and underlying aetiology of hyponatremia.

Subjects randomized to Early Withdrawal were monitored for any interventions needed to maintain appropriate serum sodium levels. Where sodium levels declined by ≥ 4 mEq/L, or where the overall clinical condition warranted further intervention to increase serum sodium levels, subjects were treated per the investigator's preferred standard of care. Any intervention, including fluid restriction, during the first 48 hours of the Early Withdrawal phase was defined as rescue therapy, and subject data was censored thereafter.

Subjects who were non-responders during Phase A were not randomized in Phase B but were treated per the investigator's discretion, either continuing tolvaptan for 2 additional days, or discontinuing

tolvaptan and receiving the investigator's preferred standard of care for Days 3 and 4. Serum sodium was measured in all subjects at 8, 12 and 24 hours post-first dose, and every 12 (± 4) hours through the end of Treatment Phase B. Additional sampling was conducted for safety assessments on Day 1 at 4 to 6 (-1 to + 0.25) hours post-dose and 18 (± 1) hours post-dose; this sodium safety assessment was repeated at 6 (- 1 to + 0.25) and 18 hours (± 1) post-dose each day for the remainder of titration.

During Phase C (Follow-up Phase), subjects were monitored and treated per the investigator's preferred standard of care up to an additional 3 days after the last tolvaptan dose. Serum sodium was also measured 72 (± 4) hours and 7 (+ 1) days post-last dose. A final safety follow-up telephone contact/visit was performed 14 (+ 2) days post-last dose. Pharmacokinetic samples were obtained on Day 1 and Day 2 in Phase A and for tolvaptan-treated subjects at 24 and 48 hours post-randomization in Phase B. Hospitalization was required during initiation and up-titration of tolvaptan. When a subject was in the withdrawal phase, or not expected to receive a higher tolvaptan dose, administration could continue outside of the hospital setting.

***Study population /Sample size***

Up to 100 male and female subjects were planned for inclusion; recruitment efforts focused on major paediatric referral centres at up to 50 sites globally.

Inclusion criteria required the presence of chronic (> 48 hours) dilutional hyponatremia associated with heart failure, hepatocellular disease including cirrhosis, or syndrome of inappropriate antidiuretic hormone excretion in subjects with the potential to benefit from tolvaptan treatment.

Key inclusion criteria included: male and female subjects ≥ 4 weeks (or ≥ 44 weeks adjusted gestational age) to < 18 years old; hospitalization with euvolemic or hypervolemic hyponatremia persisting despite initial standard background therapy (including fluid restriction and excluding a vasopressin antagonist); and persistent euvolemic or hypervolemic hyponatremia (present for at least 48 hours).

Exclusion criteria included subjects with acute hyponatremia, or hyponatremia expected to resolve spontaneously. Subjects with impaired ability to sense or communicate thirst were required to be more closely monitored in hospital or were excluded. Other exclusion criteria included: evidence of hypovolemia or intravascular volume depletion; serum sodium < 120 mEq/L with or without associated neurologic impairment; use or anticipated use during the trial of potent cytochrome P450 (CYP) 3A4 inhibitors in subjects ≤ 12 kg or moderate CYP3A4 inhibitors in subjects < 6 kg; lack of free access to water or without Intensive Care Unit-level fluid monitoring and management; history or current diagnosis of nephrotic syndrome; hyperkalemia; estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2; acute kidney injury; severe or acute neurological symptoms requiring other intervention; previous treatment for hyponatremia with hypertonic saline, urea, lithium, demeclocycline, conivaptan or tolvaptan within 4 days of qualifying serum sodium assessments, or other treatments to increase serum sodium concurrent with dosing of trial medication; anuria or urinary outflow obstruction unless catheterized during the trial; history of drug or medication abuse within 3 months prior to screening or current alcohol abuse; history of hypersensitivity and/or idiosyncratic reaction to benzazepine or benzazepine derivatives; psychogenic polydipsia; uncontrolled diabetes mellitus; screening liver function values > 3 × upper limit of normal; subjects with deficient coagulation; cirrhosis, and with any of the following: major gastrointestinal bleed within the past 6 months, evidence of active bleeding, platelet count < 50,000/μL, or use of concomitant medications known to increase bleeding risk; hyponatremia secondary to medication that could safely be

withdrawn; hyponatremia more appropriately corrected with alternative therapies; currently pregnant or breastfeeding; any medical condition that could interfere with evaluation of trial objectives or subject safety, or any unsuitability for trial participation; participation in another investigational drug trial within 30 days without prior sponsor approval; subjects weighing < 3 kg; subjects unable to swallow tablets if the suspension formulation was unavailable; subjects requiring the suspension formulation but having hereditary fructose intolerance.

***Treatments***

The first dose of trial 156-08-276 medication was administered upon successful completion of screening procedures. Subjects underwent a treatment phase of 2 to 5 days, and a follow-up phase post-randomization of 14 days.

***Outcomes/endpoints***

*Efficacy:*

- Primary efficacy endpoint: for subjects with serum sodium increases of ≥ 4 mEq/L (ie, responders), change in serum sodium concentration from Day 2 (or 2a) at the end of Treatment Phase A to the end of Treatment Phase B for Early compared to Late Withdrawal groups

- Secondary efficacy endpoint for all subjects was change from baseline in serum sodium concentration at the end of Day 2 (or 2a) in Treatment Phase A

- Exploratory endpoints were assessed in non-responders continuing tolvaptan therapy by change from baseline in serum sodium concentration at the end of Treatment Phase B compared to the end of Treatment Phase A. In addition, in all subjects, 24-hour excretion of sodium and creatinine and urine osmolality were obtained on Days 1 and 2; and 24-hour sodium clearance was obtained on Day 1.

Quality of life assessments were also planned.

*Pharmacokinetics/Pharmacodynamics:*

- On Day 1 in Treatment Phase A, tolvaptan maximum (peak) plasma concentration (Cmax), time to maximum (peak) plasma concentration (tmax), and area under the concentration-time curve from time zero to 24 hours (AUC0-24h)

- Fluid intake, urine output, and fluid balance (intake minus output) every 6 hours on Days 1 and 2 in Treatment Phase A.

*Safety Outcome Variables:*

- Percentage of subjects with an overly rapid increase in serum sodium (≥ 12 mEq/L in 24 hours after first dose); percentage of subjects requiring rescue therapy during Phase A and Phase B; change in serum sodium from 24 hours post-last dose to 7 days post-last dose; percentage of subjects requiring fluid restriction during Phase A and Phase B; and vital signs, blood pressure, clinical laboratory tests, body weight, and neurological examinations.

***Statistical Methods***

A total of 70 randomized subjects would provide 90% power to detect a treatment difference of 4 mEq/L (mmol/L) change in serum sodium from the end of Treatment Phase A to end of Treatment Phase B, using a 2-sided alpha of 0.05.

## Results

***Recruitment/ Number analysed***

5 subjects were screen failures, and 9 were screened successfully, met inclusion criteria and were enrolled and treated, with 7 completing the trial and two discontinued. 9 subjects were analysed for safety and efficacy. Responders eligible for Phase B included one subject who was 39 weeks of age, 2 were 3 years, one was 8 years, and one was 10 years of age. All were White except one 3-year-old African-American subject and the 10-year-old subject was of Hispanic ethnicity. All 5 responders completed the trial. 2 non-responders completed the trial; two subjects discontinued the trial due to AEs (Phase A Early Terminators), one due to haemorrhage at the medical device site (left ventricular assist device [LVAD]), and one due to increased faecal volume.

***Efficacy results***

For the primary efficacy endpoint of increase in serum sodium, 9 subjects achieved the target ≥ 4 mEq/L increase in serum sodium during Treatment Phase A, and permitting randomization into Phase B (2 into the Late Withdrawal group and 3 to Early Withdrawal). At 7 days post-last dose, 1 subject in the Late Withdrawal and 1 subject in the Early Withdrawal groups achieved serum sodium levels > 135 mEq/L to fall within the normal reference range for serum sodium values. There was no incidence of serum sodium level ≥ 145 mEq/L and no incidence of overly rapid rise in serum sodium level (i.e., ≥ 8 mEq/L in 8 hours or ≥ 12 mEq/L in 24 hours). Serum sodium level exceeded the lower limit reference range in 2 of the 5 responders (1 subject in the Early Withdrawal Phase at 7 days after the last dose, and 1 in the Late Withdrawal Phase) where serum sodium level was at or above the lower limit range at 12 of the 15 measured time-points. One subject in the Standard of Care group, considered a non-responder, continued to receive tolvaptan titrated doses but had been initially under-dosed, noted as a protocol deviation. All subjects were compliant with trial medication dosing. Protocol deviations relating to dose occurred in 1 subject in the non-responders group who continued to receive tolvaptan treatment at a lower than prescribed dose.

CHMP's comments:

Only 9 subjects were enrolled and achieved the target serum sodium increase in phase A. 5 of them were considered responders to tolvaptan treatment. The trial was prematurely terminated due to low recruitment. Due to the extremely low number of paediatric patients recruited no conclusion on tolvaptan's efficacy in this trial can be drawn.

***Safety results***

8 out of the 9 subjects reported AEs.

One subject each in the Early Withdrawal and Late Withdrawal groups experienced mild diarrhoea considered related to study medication, each resolving without change in dose. No deaths occurred during the trial. The SAEs included one incidence each of the following: worsening chronic diarrhoea, catheter site extravasation, bleeding at device site, and faecal volume increase. Two AEs that were also SAEs (the case of bleeding at device site, and the case of faecal volume increase) resulted in discontinuation; faecal volume increase was also related to Study drug.

Due to the small number of subjects enrolled, no comparison of tolvaptan concentrations between adults and children was conducted.

CHMP's comments:

The trial was terminated due to enrolment issues and not due to safety reasons. No new safety signals were identified.

**156-11-294**

**Description**

A Phase 3b, multicentre, extension follow-up trial to evaluate the long-term safety of children and adolescent subjects with euvolemic or hypervolemic hyponatremia who have previously participated in a trial of titrated oral SAMSCA.

## Methods

***Objective***

The objective of this trial was to provide 6 months of safety follow-up for children and adolescents with dilutional hyponatremia who had previously participated in tolvaptan trials including trial 156-08-276, and to assess the efficacy of tolvaptan in increasing serum sodium for those subjects who received optional continuing tolvaptan treatment of variable duration (up to 6 months).

***Study design***

This trial consisted of a 6-month safety follow-up trial and an embedded optional tolvaptan treatment trial for eligible subjects. The duration of tolvaptan treatment in trial 156-11-294 was case-specific and could have consisted of 1 or more treatment cycles.

Patients were to be followed (at a clinical trial site and/or through telephone calls), regardless of the need for treatment for hyponatremia, to assess the long-term safety of tolvaptan. There was no screening phase.

***Study population /Sample size***

Approximately 100 male or female subjects were planned to be enrolled in this trial. Eligible subjects were subjects who enrolled in a previous tolvaptan paediatric trial for hyponatremia; There were no exclusion criteria for entry into the core safety follow up component of this trial.

***Outcomes/endpoints***

Trial safety endpoints included:

- Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mEq/L [mmol/L]) in 24 hours after the first dose at introduction or reintroduction of tolvaptan

- Changes from baseline in ALT, AST, BT, and creatinine for subjects on tolvaptan

- Frequency of AE reports (including cases of dehydration)

- Changes from baseline in growth percentiles by visit for body height and weight

- Tanner Staging progression score (at 6 months)

Pharmacokinetics for optional tolvaptan treatment component

Primary efficacy endpoint: Change from baseline in serum sodium while tolvaptan was being administered

**Results**

***Recruitment/ Number analysed***

A total of 3 subjects were enrolled in this trial (after approximately 18 months of open enrolment), but no subjects received optional investigational medicinal product (IMP). No major protocol deviations were reported during the trial.

1 subject was ⩾ 4 weeks to < 4 years of age, 1 subject ⩾ 4 to < 8 years of age, and 1 subject ⩾ 8 to < 12 years of age. Two subjects were female; Two subjects were White and 1 subject was Hispanic or Latino. The mean (SD) weight for subjects in the trial was 26.5 (11.9) kg, and the mean (SD) height was 111.3 (24.8) cm. The mean body mass index was 21.3 kg/m2. 2 subjects were classified as hypervolemic secondary to heart failure and 1 subject was classified as euvolemic secondary to pseudohypoparathyroidism. 2 subjects had heart failure and 1 subject had syndrome of inappropriate secretion of antidiuretic hormone (SIADH)/other. No subjects had an underlying aetiology of hepatocellular disease.

The most common medical history events reported were cardiac failure and hepatomegaly, each occurring in 2 trial subjects. All trial subjects were using 1 or more medications prior to or during the trial. The most common concomitant medications taken prior to start of the trial were acetylsalicylic acid, enoxaparin, and furosemide, each of which were taken by 2 subjects. All other concomitant medications taken prior to the start of the trial and during the trial period were taken by 1 subject. In all subjects, > 30 days had passed since the last visit of the previous tolvaptan trial (156-08-276). One subject reported at least one new episode of hyponatremia since the last visit of the previous trial; this subject received previous treatment (fluid restriction and tolvaptan) for the last episode of hyponatremia.

***Efficacy results***

Due to the early trial termination status and the small subject population, planned efficacy analyses could not be performed in this trial. Mean scores for PedsQL GCS were only obtained in 1 subject and were analysed following the Core Safety Month 6. The change from baseline in PedsQL GCS total score was -3.5. The change from baseline in PedsQL GCS physical health summary score was 12.5 (n = 1), and the change from baseline in PedsQL GCS psychosocial health summary score was -13.5 (n = 1). Mean scores for PedsQL QoL MFS were also only obtained in 1 subject and were analysed following the Core Safety Month 6. The change from baseline in PedsQL QoL MFS total score was 9.7.

***Safety results***

No subject received IMP during this trial. All 3 subjects were included in the analysis of safety. Overall, 2 subjects experienced at least 1 AE during the trial. 11 events were reported between the 2 subjects.

Subjects experienced AEs from the system organ classes of general disorders and administration site conditions (1 subject) and infections and infestations (2 subjects). Most of all AEs were considered moderate or severe. Only 1 subject reported SAEs (enterovirus infection, pyrexia, rhinovirus infection, and urosepsis) during the trial, all considered not related to tolvaptan. No deaths due to AEs were reported. No subjects discontinued IMP due to AEs. No potentially clinically significant laboratory test result abnormalities were reported in any subject.

CHMP's comments:

3 subjects completed the 6-month core safety study follow-up. No adverse event was considered related to treatment.

The trial was terminated due to low subject enrolment. No new safety signals are identified from these 3 subjects that completed the trial.

# 3. CHMP's overall conclusion and recommendation

The MAH submitted the study reports of trials 156-08-276 and 156-11-294.

Trial 156-08-276 was an open-label, multicentre, multiple-dose, randomized withdrawal, parallel-group trial of tolvaptan in children hospitalized with euvolemic or hypervolemic hyponatremia that was persistent despite initial standard background therapy. Only 9 subjects were enrolled in this trial. No efficacy conclusions can be drawn due to the low number of paediatric patients recruited.

Trial 156-11-294 was a 6-month extension follow-up trial to evaluate the long-term safety of children with dilutional hyponatremia who had previously participated in tolvaptan trials, including trial 156-08-276. No subjects received IMP.

Both trials were terminated due to low recruitment of patients. The trials' termination was not due to safety reasons. No safety signals emerged from these two trials.

The results of these trials do not influence the benefit-risk ratio of Samsca. No further action is required.

## ☒ Fulfilled:

No regulatory action required.