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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/P46/021

Note

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

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1. Introduction

On 01 December 2017, the MAH submitted a terminated paediatric study No. 156-13-2076 for Tolvaptan, 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

The MAH stated that Study No. 156-13-2076, entitled "A pilot Phase 3b, multi-centre, randomized, double-blind, placebo-controlled trial of the safety, efficacy, and pharmacokinetics of titrated oral SAMSCA (Tolvaptan) in children and adolescent subjects with euvolemic or hypervolemic hyponatremia", is a part of a paediatric development program.

2.2. Information on the pharmaceutical formulation used in the study<ies>

Oral tolvaptan tablet formulations (3.75 mg, 7.5 mg, 15 mg and 30 mg) and matching placebo are used.

2.3. Clinical aspects

2.3.1. Introduction

The study presented in this procedure (156-13-207) is one of the 3 studies previously included in the PIP for the indication dilutional hyponatraemia resistant to fluid restriction (i.e., euvolaemic and hypervolaemic hyponatraemia).The purpose of this pilot trial was to establish that if this trial design was feasible in a paediatric population and to evaluate the effects of tolvaptan on serum sodium concentration as well as the safety of use of tolvaptan in children and adolescents with euvolemic or hypervolemic hyponatremia secondary to heart failure, hepatocellular disease (including cirrhosis), and syndrome of inappropriate secretion of antidiuretic hormone (SIADH)/other. In addition, blood samples were to be taken to determine tolvaptan pharmacokinetics (PK) specific to a paediatric population, as the absorption, distribution, metabolism, and elimination of drugs in children and adolescents can vary from that of adults.

The PIP also included 2 more paediatric studies as follows:

Study 156-12-205: Multicentre, randomised, double-blind, placebo-controlled trial to evaluate safety, efficacy and pharmacokinetics of tolvaptan in children from 4 weeks to less than 18 years of age with chronic (greater than 48 hours) dilutional hyponatraemia resistant to fluid restriction.

Study 156-11-294: Open-label extension trial to evaluate long-term safety of multiple doses of tolvaptan in children and adolescents with chronic (greater than 48 hours) dilutional hyponatraemia resistant to fluid restriction.

2.3.2. Clinical study

Protocol 156-13-207

Eudra CT No. 2014-001582-27

Protocol Title: A Pilot Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety, Efficacy, and Pharmacokinetics of Titrated Oral SAMSCA (Tolvaptan) in Children and Adolescent Subjects with Euvolemic or Hypervolemic Hyponatremia

Description

Methods

Objective(s)

The primary objective was to evaluate that tolvaptan effectively maintained an increased level of serum sodium in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

The main secondary objective was to evaluate safety of tolvaptan in children and adolescent subjects with euvolemic or hypervolemic hyponatremia.

Study design

Paediatric and adolescent subjects who were diagnosed with euvolemic or hypervolemic hyponatremia (serum sodium < 130 mmol/L) that persisted despite initial standard background therapy (eg, including fluid restriction) were eligible to be screened for participation in this trial. Subjects who demonstrated prior resistance to vasopressin antagonist therapy were to be excluded. All potential subjects must have been deemed by the investigator as likely to benefit from a therapy that would raise serum sodium levels.

Persistent hyponatremia was to be defined as serum sodium assessments < 130 mmol/L documented as present for at least 48 hours. Subjects must have had at least 2 documented serum sodium assessments < 130 mmol/L drawn at least 12 hours apart. These values could have been documented using historical values previously obtained as per standard of care. A third (immediate [STAT]) serum sodium assessment < 130 mmol/L, which was to serve as the baseline value for efficacy endpoints, was to be obtained within 2-4 hours prior to the first dose of investigational medicinal product (IMP). Additional qualification assessments were to be performed as per aetiology of hyponatremia. The first dose of IMP was to be administered upon successful completion of all screening procedures.

Upon successful completion of all screening procedures, eligible subjects were to be randomized to either tolvaptan or matching placebo in a 1:1 ratio for up to 30 (+ 2) days of dosing.

Subjects were required to be in the hospital or a hospital setting during initiation or titration of the IMP dose. Once the subject was maintained on a stable dose of IMP, continued administration could have been done outside of the hospital setting.

After titration was complete, subjects would have returned for visits on a weekly basis until a total of 30 (+ 2) days of treatment were completed. These visits would have occurred in the hospital if the subject was an in-patient or as outpatient visits if the subject had been discharged. Safety follow-up visits were to be performed 72 (± 4) hours, 7 (+ 2) days, and 14 (+ 2) days after the last dose of IMP.

Study population /Sample size

This trial planned to enrol 8 male or female subjects ≥ 4 years of age (or per local Health Authority age restrictions) to < 18 years. No formal sample size calculations were performed

Treatments

Investigational medicinal product was to be administered orally once daily with a dose proportional amount of water.

Subjects were to be administered IMP on an age- and weight-based scale. Titration of IMP doses could occur once daily and would be based on serum sodium levels assessed at 24 (± 4) hours following initiation of therapy and each subsequent dose; titration (up or down) could not occur within 24 (± 4) hours of the previous dose and was to be based on serum sodium assessment obtained > 20 hours post previous dose; a change in serum sodium ≤ 4 mmol/L from baseline was to warrant up-titration, which would have been limited to no more than twice the previous dose.

- Subjects < 4 years of age, or weighing < 10 kg, or who could not safely swallow tablets, were to be excluded until the availability of an alternate formulation.
- Subjects ≥ 4 years of age and weighing ≥ 10 to < 20 kg would have been given a 3.75-mg tablet on Day 1 with possible up-titration to 7.5- and 15-mg doses.
- Subjects weighing 20 to 50 kg, inclusive, would have been given a 7.5-mg tablet on Day 1 with possible up-titration to 15- and 30-mg doses.
- Subjects weighing > 50 kg would have been given a 15-mg tablet on Day 1 with possible up-titration to 30- and 60-mg doses.

Subjects were to continue dosing according to a titration scheme targeting a final serum sodium concentration between 135 and 140 mmol/L. Titration would ideally have achieved a change in serum sodium concentration of at least 4 to 8 mmol/L/24 hours but not exceeded 12 mmol/L/24 hours.

The expected duration for trial participation for each individual subject was approximately 45 days, including 2 screening days, a 30-day treatment period, and follow-up 7 days and 14 days after the last dose.

Outcomes/endpoints

Efficacy:

The average daily area under the curve (AUC) of change from baseline in serum sodium level up to Day 4 within the double-blind treatment period

Secondary Outcome Variables:

Efficacy:

- The key secondary outcome variable was the average daily AUC of changes from baseline at each visit in serum sodium level up to Day 30 within the double-blind treatment period
- Change from baseline in serum sodium concentration at Day 4
- Change from baseline in serum sodium concentration at Day 30

- Percentage of subjects who required rescue therapy or fluid restriction at any time during the double-blind treatment period

Safety:

- Changes from baseline in ALT, AST, and Total Bilirubin
- Clinically significant changes in vital signs
- Incidence of dehydration AEs
- Tanner staging progression score (at 30 days)
- Percentage of subjects with overly rapid correction in serum sodium (≥ 12 mmol/L in 24 hours)

Statistical Methods

The endpoints for this trial were planned to be analysed using descriptive statistics as the population was too small (N = 8) for powered analyses.

Results

After 21 months of open enrolment, no subjects were enrolled therefore the decision to terminate the trial was made. There are no results presented in this submission.

2.3.3. Discussion on clinical aspects

The purpose of this pilot trial was to establish that this trial design was feasible in a pediatric population and to evaluate the effects of tolvaptan on serum sodium concentration as well as the safety of use of tolvaptan in children and adolescents with euvolemic or hypervolemic hyponatremia secondary to heart failure, hepatocellular disease (including cirrhosis), and SIADH/other. After 21 months of open enrolment, no subjects were enrolled; therefore the decision to terminate the trial was made.

3. CHMP overall conclusion and recommendation

Study 156-13-207, which was part of Paediatric Investigational Plan for the indication of dilutional hyponatraemia in children, was terminated early, due to being unable to recruit eligible patients. As such, no clinical data have been submitted in this dossier. Therefore, no assessment on this submission is required. However, the Applicant is reminded to submit the paediatric data of Study 156-08-276 and of Study NCT03255226 when available for review, under the Article No. 46 of the EU Paediatric Regulation

☒ Fulfilled:

No regulatory action required.