9 November 2023
EMA/548921/2023
Human Medicines Division

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

Otezla

apremilast

Procedure no: EMEA/H/C/003746/P46/010

Note

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

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1. Introduction

On 29th August 2023, the MAH submitted a completed paediatric study for Otezla (Apremilast) EMEA/H/C/003746, 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 Clinical Study Report for CC-10004-PPSO-003:A Phase 3, Multi-Center, Randomized, Double- Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Apremilast (CC-10004) in Pediatric Subjects from 6 to less than 18 years of Age with Moderate to Severe Plaque Psoriasis is being submitted as a stand-alone post-authorisation measure (PAM) with no changes to the Otezla product information proposed at this stage.

The above study forms part of clinical measure of the paediatric investigational plan (PIP) for Otezla for the treatment of Psoriasis (PsO) (EMEA- EMEA-000715-PIP03-11-M06).

Directly upon conclusion of this Article 46 procedure and the paediatric Compliance Check, a Type II variation application will be submitted. Dossier preparation for the Type II variation is currently on-going and submission is planned for Nov 2023.

2.2. Information on the pharmaceutical formulation used in the study

In the current study, subjects with baseline weight between 20 to <50 kg received apremilast 20 mg BID or placebo BID and subjects with baseline weight ≥50 kg received apremilast 30 mg BID or placebo BID.Clinical aspects*.*

2.2.1. Introduction

The MAH submitted a final report for one study:

- Clinical Study Report for CC-10004-PPSO-003:

2.2.2. Clinical study

Study CC-10004-PPSO-003 was a phase 3, multicentre, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of apremilast in paediatric subjects with moderate to severe plaque psoriasis. The study included a placebo-controlled treatment phase (weeks 0 to 16), an apremilast extension phase (weeks 16 to 52), and a 14-week observational follow-up phase. In the double-blind, placebo-controlled phase of the study, paediatric subjects were randomized in a 2 (apremilast):1 (placebo)ratio for the first 16 weeks. Subjects 20 to `<50 kg received apremilast 20 mg twice daily (BID) or placebo BID, and subjects ≥ 50 kg received apremilast 30 mg BID or placebo BID. Treatment assignment

was stratified by baseline age group (6 to 11 years or 12 to 17 years). At week 16, subjects in the placebo group were switched to apremilast.

A total of 245 subjects were enrolled (163 subjects were randomized to the apremilast group and 82 subjects were randomized to the placebo group). All 163 subjects (100%)in the apremilast group and 80 subjects (97.6%) in the placebo group received at least 1 dose of investigational product. In the apremilast and placebo groups, 149 subjects (91.4%) and 72 subjects (87.8%), respectively, completed the placebo-controlled phase.

The study met its primary endpoint with an adjusted treatment difference of 21.7% (95% CI: 11.2, 32.1; $p < 0.0001$) between apremilast and placebo in the proportion of paediatric subjects with moderate to severe plaque psoriasis achieving an sPGA response of clear (0) or almost clear (1) at week 16 with at least a 2-point reduction from baseline. Sensitivity analyses confirmed the robustness of the primary analysis results and subgroup analyses showed generally consistent treatment effects in favour of apremilast, including in baseline weight and age subgroups.

The study also met its major secondary endpoint with an adjusted treatment difference of 29.4% (95% CI: 17.8, 40.9; $p < 0.0001$) between apremilast and placebo in the proportion of subjects achieving a PASI-75 response at week 16. Among subjects originally randomized to apremilast who continued with apremilast treatment after week 16, continuous improvements in sPGA and PASI-75 response rates were observed through week 52. Among subjects originally randomized to placebo who were switched to apremilast at week 16, improvements in sPGA and PASI-75 response rates were observed after initiation of apremilast treatment through week 52.

Overall, apremilast 20 or 30 mg was well tolerated in these paediatric subjects. The types of adverse events were similar to those observed in adult subjects. Diarrhea, nausea, abdominal pain, vomiting, and headache were the most frequently reported adverse events. No serious gastrointestinal adverse events were reported during the study. No adverse events of depression were reported during the study. An adverse event of suicidal ideation was reported in the placebo group and none in the apremilast group. The rate of psoriasis flare was lower for apremilast-treated subjects compared with placebo-treated subjects in the placebo-controlled phase. Psoriasis rebound was reported for 4 subjects after apremilast treatment. The subject incidence of adverse events leading to discontinuation was similar for the apremilast and placebo groups. No new safety findings were identified when apremilast was used in paediatric subjects.

3. CHMP overall conclusion and recommendation

Receipt of the completed study report for Study CC-10004-PPSO-003 (20200056) in accordance with Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') is acknowledged. The study report is submitted as a stand-alone post authorization measure. As the applicant is planning to submit a Type II variation application directly upon conclusion of this Article 46 procedure this study will not be further assessed at this point. A full assessment of the study will be conducted as part of the impending variation (Nov 23). Thus no further queries or recommendations for updates to the SmPC are proposed at this time.

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation prior to making any conclusion on product information amendments. The MAH has committed to submit this variation application in November 2023.