EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

VICTRELIS

(boceprevir)

Procedure No. EMEA/H/C/002332/P46/035

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

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

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1. INTRODUCTION

MSD submitted the final data for study P07614 assessing the pharmacokinetics of Boceprevir in Pediatric Subjects with Chronic Hepatitis C Genotype 1 (Phase 1b). This study is part of the Paediatric Investigation Plan EMEA-00583-PIP01-09-M05 and was stopped prematurely in concurrence with FDA and PDCO.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

VICTRELIS is a serine protease inhibitor that has been approved for the treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin in both the United States and the European Union.

Phase I PK study P07614 was started in paediatric patients in accordance with the agreed PIP (PIP Decision P/0043/2013). In the meantime, this study was placed on hold by FDA awaiting the approval of Interferon-free therapies for Hepatitis C with a more positive benefit/risk profile for children. The PDCO informed the MAH in December 2013 that they agree with FDA's position and wanted to grant the MAH a very long deferral for the paediatric program that may ultimately result in a waiver when all oral therapies have been approved. The company has therefore decided to close out study P07614.

To fulfil article 46 requirement, the MAH is submitting the results of a Phase 1 trial evaluating the single dose pharmacokinetics and safety of a pediatric formulation of VICTRELIS in paediatric subjects. No revisions to the product information are proposed.

2.2. Study design and results

As part of the clinical development program in paediatric patients, a phase 1 pharmacokinetic and safety study was performed to evaluate a pediatric formulation of boceprevir prior to the conduct of a Phase 2/3 treatment study in children.

The trial was conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trial was performed.

Design: P07614 was a multicenter, non-randomized, open-label, Phase 1b study in pediatric subjects with Chronic Hepatitis C genotype 1 to determine the pharmacokinetics of boceprevir following single oral dose administration.

This trial was conducted at 12 trial centers: 4 in the US; 1 in Germany; 2 in Poland; 1 in Spain; 2 in Russia and 2 in the UK.

The oldest age cohort of ≥13 to 17 years of age was completed (n=16, 15 analyzed). The trial was terminated prior to enrollment of patients in the two younger age cohorts.

Primary objective: To determine weight based doses of boceprevir for children 3 to 17 years of age.

Hypothese: Single dose boceprevir in children 3 to 17 years of age will be similar in exposure to adults based on assessment of AUC0-∞, i.e., the true GMRs for children at age cohorts of ≥13 to 17 years, ≥7 to <13 years and ≥3 to <7 years vs. adults will be all contained within (0.6-1.40).

The actual dose for each child was calculated by his/her weight obtained at baseline (Day -1) multiplied by 11.4 mg/kg and rounded up or down to the nearest 50 mg, as it is not possible to dose in 1 kg weight increments with powder. Subjects with body weight at baseline greater than 70 kg, regardless of age group, were dosed with the adult dose of 800 mg boceprevir, which was the maximum dose in this study.

Pediatric subjects ranged in weight from 49.4 to 86.9 kg, and received 550-800 mg of boceprevir for a final weight-based dosing of 9.21-11.6 mg/kg.

Pharmacokinetics conclusion were the followings:

1. Statistical comparison of boceprevir PK in pediatric HCV patients (≥ 13 to 17 years old, single-dose pediatric blend formulation, weight-based dosing) with that in healthy adults (single-dose pediatric blend formulation 800 mg, P08075) shows an increase in AUC0-∞ by 17%, Cmax by 24%, and C8hr by 55%. The upper 95% CI for AUC GMR is just outside of the protocol-specified comparability bounds of (0.60, 1.40). The 95% CIs for AUC and Cmax GMRs are within the (0.5, 2.0) bounds of clinical significance in adults.

2. Individual boceprevir concentration-time profiles in pediatric HCV patients (≥ 13 years to 17) following a single, weight-based dose (11.4 mg/kg, max at 800 mg; pediatric blend formulation) were within the range of predicted steady-state boceprevir concentration data in adult HCV patients in prior Phase 3 studies.

3. These results indicate that the boceprevir exposure achieved in pediatric HCV patients following weight-based dosing (11.4 mg/kg, max 800 mg) is comparable to, and not lower than that in adults following 800 mg administration, and support using the weight-based nomogram for dosing of patients in the ≥ 13 to 17 years age range.

Safety data were the followings:

Single doses of the pediatric formulation of boceprevir were generally well tolerated in the ≥ 13 to 17 years (oldest age) cohort. Out of the 16 patients treated, a total of 19 treatment emergent adverse events were reported by 6 subjects overall, of which 6 were considered related to boceprevir. The drug-related adverse events reported were nausea, malaise, hepatic enzyme increased and dysgeusia. There was 1 discontinuation due to an adverse event for a subject who experienced mild nausea due to taste; this subject was discontinued from the study as the subject could not consume the full dose of study drug. All of the adverse events were mild or moderate in intensity. No deaths were reported. One patient reported two serious adverse events (SAEs) (raised liver function tests and elevated ALT) which were separate hospitalizations related to elevated liver function tests, of which 1 was considered possibly related to boceprevir by the investigators (nevertheless, the occurrence of the first event of ALT increased at 24 days post dosing in this single dose study make it doubtful the role of Victrelis).

3. Rapporteur's Overall Conclusion and Recommendation

In accordance with Article 46 of Regulation (EC) n°1901/2006, MSD is submitting the final report for study P07614, a multicenter, non-randomized, open-label, Phase 1b study in pediatric subjects with Chronic Hepatitis C genotype 1 to determine the pharmacokinetics and safety of boceprevir following single oral dose administration.

The study was initially started in July 2012 in accordance with the Victrelis PIP. A total of 16 patients aged ≥13 to 17 years old were included in this study. However, given the shift towards use of IFN-free therapies for hepatitis C, the pediatric program was placed on hold by US and EU regulators waiting for the approval of DAA combination with better efficacy and more favorable safety profile. As a matter of fact, the PDCO has granted in December 2013 a long deferral for the paediatric program that may ultimately result in a waiver when all oral therapies have been approved. The company has appropriately decided to close out study P07614 in January 2014 (before inclusion of the youngest cohort).

The study data have been submitted for regulatory purpose but are of no or poor clinical value since the pediatric clinical development of Victrelis in children is on hold waiting for the approval of DAA combinations. No new safety concern emerged from the submitted data. The final data from study P07614 do not change the benefit/risk for Victrelis in adults and do not mandate any change of the SPC.

Recommendation

☒ Fulfilled – No further action required