Amsterdam, 23 February 2023
EMA/CHMP/57025/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Ronapreve

International non-proprietary name: casirivimab / imdevimab

Procedure no.: EMEA/H/C/005814/P46/017

Marketing authorisation holder (MAH): Roche Registration GmbH

Note

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

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1. Introduction

On 9 December 2022, the MAH submitted completed paediatric study for Ronapreve, in accordance with Article 46 of Regulation (EC) No 1901/2006, 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 2-R10933-10987-COV-2114: Open-label, single dose study to describe the pharmacokinetic profile of casirivimab+imdevimab when administered as treatment in the paediatric population hospitalised due to Covid-19 and to demonstrate that a single intravenous dose of casirivimab+imdevimab was safe and tolerated in these patients, is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Casirivimab and imdevimab drug products are supplied as 120 mg/mL solutions for intravenous (IV) and subcutaneous (SC) administrations. The drug products are preservative-free and non-pyrogenic.

For IV administration, casirivimab and imdevimab must be administered together, after dilution, as a single IV infusion. For SC administration, casirivimab and imdevimab must be administered consecutively by SC injection.

There is no specific paediatric formulation of casirivimab+imdevimab.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 2 - R10933-10987-COV-2114: Open-label, single dose study to describe the pharmacokinetic profile of casirivimab+imdevimab when administered as treatment in the paediatric population hospitalised due to Covid-19 and to demonstrate that a single intravenous dose of casirivimab+imdevimab was safe and tolerated in these patients.

COV-2114 was initiated in the United States (US) on 16 December 2021 (first patient first visit). On 22 December 2021, participant enrolment was paused due to the rapidly increasing prevalence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) BA.1.1.529/BA.1 Omicron variant, against which casirivimab+imdevimab showed diminished in vitro neutralization potency.

2.3.2. Clinical study

Methods

Study participants

Paediatric patients <18 years of age who were hospitalized for COVID-19. For inclusion in the study, patients had to have a SARS-CoV-2 positive antigen or molecular diagnostic test $\leq$ 72 hours prior to study enrolment and symptoms consistent with COVID-19, as determined by the investigator, with onset $\leq$ 14 days before dosing.

Treatments

Participants received a single IV body weight-tiered dose of casirivimab+imdevimab equivalent to a 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) or 8000 mg (4000 mg casirivimab and 4000 mg imdevimab) adult dose (Table 1) according to their oxygenation/mechanical ventilation requirements

☐ A weight-tiered dose equivalent of 2400 mg IV was administered to participants on no supplemental oxygen (O2), or those who were able to maintain O2 saturation >93% on low-flow O2 via nasal cannula, simple face mask, or other similar device.

☐ A weight-tiered dose equivalent of 8000 mg IV was administered to participants wh required:

a) High-intensity O2 therapy without mechanical ventilation, where high-intensity was defined as receiving supplemental O2 delivered by one of the following devices:

– Non-rebreather mask (with an O2 saturation level ≤96% while receiving an O2 flow rate of at least 10 L/min)

– High-flow device (eg, AIRVO or Optiflow) with at least 50% fraction of inspired O2

– Non-invasive ventilator, including continuous positive airway pressure to treat hypoxemia (excluding isolated use for sleep-disordered breathing),

OR

b) Mechanical ventilation

Table 1: Weight-tiered Dose Equivalent of Casirivimab+Imdevimab 8000 mg and 2400 mg IV Doses.

Body Weight	Casirivimab+Imdevimab 8000 mg IV (4000 mg per mAb)	Casirivimab+Imdevimab 2400 mg IV (1200 mg per mAb)
≥40 kg	8000 mg (4000 mg per mAb)	2400 mg (1200 mg per mAb)
≥20 kg to <40 kg	3000 mg (1500 mg per mAb)	900 mg (450 mg per mAb)
≥10 kg to <20 kg	1600 mg (800 mg per mAb)	450 mg (225 mg per mAb)
≥5 kg to <10 kg	700 mg (350 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 kg to <5 kg	400 mg (200 mg per mAb)	120 mg (60 mg per mAb)
≥1.1 kg to <2.5 kg	200 mg (100 mg per mAb)	60 mg (30 mg per mAb)

IV=intravenous; mAb=monoclonal antibody.

Participants were followed-up until Day 169. Assessments were conducted in the hospital prior to discharge and in person at the study site or by phone after discharge

Objective(s) / Outcomes / endpoints

The primary and secondary objectives and endpoints described below are per the protocol. However, as the objectives could not be achieved and none of the hypotheses were evaluable, these were all designated exploratory due to the study's early termination, per the statistical analysis plan.

Table 2: Objectives and endpoints

Objectives	Endpoints
Primary	
• To characterize the concentrations of casirivimab+imdevimab in serum over time • To evaluate the safety and tolerability of casirivimab+imdevimab	• Concentrations of casirivimab+imdevimab in serum over time • The proportion of participants with treatment-emergent serious adverse events (SAEs) through day 29 • The proportion of participants with infusion-related reactions through day 4 • The proportion of participants with hypersensitivity reactions through day 29
Secondary	
• To assess the immunogenicity of casirivimab+imdevimab	• Incidence and titer of anti-drug antibody, and incidence of neutralizing antibodies to casirivimab+imdevimab over time

Sample size

The study planned to enrol at least 40 patients.

Randomisation and blinding (masking)

Not applicable

Results

Baseline data

- ☐ Participant 1(≤5 kg to <10 kg) received 240 mg (the weight-based equivalent of the 2400 mg dose [per Table 1]) IV study treatment (1200 mg per mAb/PK schedule B).
- ☐ Participant 2(≥40 kg) received 8000 mg (the weight-based equivalent of the 8000 mg dose [per Table 1]) IV study treatment (4000 mg per mAb/PK schedule A).

Number analysed

The study planned to enrol at least 40 patients. However, due to early termination of the study, only 2 patients were enrolled across two centres in the US.

Both patients received study treatment and were included in the safety and PK analysis sets. One patient with body weight ≥ 40kg received 8000 mg IV casirivimab+imdevimab and the other with body weight (≤5 kg to <10 kg) received 240 mg IV casirivimab+imdevimab, a weight-tiered dose equivalent of 2400 mg IV. Both patients completed the study.

Pharmacokinetic results

The key clinical pharmacology results are as follows:

- ☐ Maximum concentrations of total casirivimab and total imdevimab were observed immediately following administration of the single IV dose of casirivimab+imdevimab on Day 1.
- ☐ Concentrations declined but remained quantifiable through the final sampling timepoint for each participant (Day 56 for one patient and Day 112 for the other patient).

Immunogenicity

Neither of the two participants in this study developed anti-drug antibodies to casirivimab or imdevimab.

Safety results

Only 1 treatment-emergent adverse event (TEAE) was reported in the study. Participant 1 experienced a TEAE of grade 1 Otitis media 36 days after study treatment, which was considered not related to study treatment. No action was taken with respect to study treatment administration for the event, which resolved after 11 days.

No participant died during the study or experienced a TEAE that led to study treatment withdrawal.

No participant experienced an SAE (Post-text Listing 16.2.4.3) or an AESI (grade ≥2 infusion-related reactions, grade ≥2 hypersensitivity reactions, or MIS-C.

There were no clinically meaningful findings in clinical laboratory values. Although there were abnormal laboratory findings (low and high), these all occurred or were present at the baseline/screening visit, except for an increase in platelets which was not considered clinically significant (427 109/L; normal range: 209 109/L to 405 109/L) in participant 2 on day 29.

There were no abnormal values in vital signs and all measurements were within normal range.

2.3.3. Discussion on clinical aspects

This Phase Ib study in paediatric patients <18 years of age hospitalised with COVID-19 enrolled only 2 patients due to emergence of the BA.1.1.529/BA.1 Omicron variant (which shows diminished in vitro neutralisation susceptibility to casirivimab+imdevimab) and the resultant early termination of the study.

Casirivimab+imdevimab was well tolerated in both patients and there were no new safety observations.

No conclusion on the pharmacokinetics in the patient population can be drawn.

3. CHMP overall conclusion and recommendation

In accordance with Article 46 of Regulation (EC) 1901/2006, the MAH submitted a completed paediatric study for Ronapreve. This Phase Ib study in paediatric patients <18 years of age hospitalised with COVID-19 enrolled only 2 patients due to emergence of the BA.1.1.529/BA.1 Omicron variant (which shows diminished *in vitro* neutralisation susceptibility to casirivimab and imdevimab), and the resultant early termination of the study. Casirivimab and imdevimab was well tolerated in both patients and there were no new safety observations. No conclusion on the pharmacokinetics in the patient population could be drawn.

☒ Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Clinical studies

Treatment of coronavirus disease 2019 (COVID-19)

Product Name: Ronapreve Active substance: casirivimab+imdevimab

Study title	Study number	Date of completion (LPLV)
A Master Protocol assessing the safety, tolerability and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for the treatment of ambulatory patients with Covid-19	R19033-10987-COV-2067	07 June 2022
A phase 1b, open-label, single-dose study assessing the pharmacokinetics, safety, tolerability and efficacy of intravenous anti-spike(s) Sars-CoV-2 monoclonal antibodies (casirivimab+imdevimab) for the treatment of paediatric patients hospitalised due to Covid-19	R10933-10987-COV-2114	09 June 2022

LPLV = Last Patient Last Visit

Prevention of coronavirus disease 2019 (COVID-19)

Study title	Study number	Date of completion (LPLV)
A Phase 3, Randomized, Double-Blind, Placebo-Controlled study assessing the efficacy and safety of anti-spike SARS-CoV-2 monoclonal antibodies in preventing SARS-CoV-2 Infection in household contacts of individuals infected with SARS-CoV-2	R19033-10987-COV-2069	04 October 2021
A Phase 2a, Open-Label study assessing pharmacokinetics, safety, tolerability, And immunogenicity of single-dose subcutaneous antispike(s) SARS-CoV-2 monoclonal antibodies(casirivimab and imdevimab) in high-risk pediatric subjects under 12 years of age	R19033-10987-COV-2121	01 June 2022