Amsterdam, 23 February 2023
EMA/CHMP/57023/2023
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/P46/015

Marketing authorisation holder (MAH): Roche Registration GmbH

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

An agency of the European Union

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

1. Introduction

On 30 November 2002, 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 R1093310987-COV-2121 A Phase 2a, Open-Label Study Assessing Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Single-Dose Subcutaneous Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (Casirivimab and Imdevimab) in High-Risk Paediatric Subjects Under 12 Years of Age 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 nonpyrogenic.

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:

- R1093310987-COV-2121 A Phase 2a, Open-Label Study Assessing Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Single-Dose Subcutaneous Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies (Casirivimab and Imdevimab) in High-Risk Paediatric Subjects Under 12 Years of Age.

The study was initiated in the United States (US) on 13 September 2021 (first patient first visit) when the dominant circulating variant of SARS-CoV-2 was Delta. On 23 December 2021, participant enrolment was paused due to the rapidly increasing prevalence of the SARS-CoV-2 B.1.1.529/BA.1 Omicron variant, against which casirivimab+imdevimab showed diminished in vitro neutralization potency. The participants who had been enrolled prior to the pause date were followed according to the protocol. Enrolment was not restarted, and the study was officially terminated on 28 June 2022. As a result of the early termination, only 7 participants were enrolled in the study.

2.3.2. Clinical study

Methods

Study participants

Enrolled in this study were participants <12 years old who were not infected with SARS-CoV-2 but were at high risk to develop severe COVID-19 if they became infected.

Key inclusion criteria

- ☐ Was <12 years of age and ≥3 kg to <40 kg at the time parental/guardian consent was signed
- ☐ Had at least 1 risk factor for developing severe COVID-19 if they became infected

Treatments

Participants received a single dose of casirivimab+imdevimab, that was the body weight dose equivalent to the 1200 mg adult dose (600 mg of casirivimab and 600 mg of imdevimab) administered as 1 to 4 SC injections based on body weight.

Table 1: Weight-Tiered Dosing of Casirivimab+Imdevimab.

Dose Group	Weight-Tiered Dose Group	Total Dose (mg)	Route of Administration	Total Number of Injections	Total Volume (mL) of Injection[8]
A1	≥20 kg to <40 kg	792 (396 per mAb)	SC[3, 7]	4	6.6 (3.3 per mAb)
A2	≥10 kg to <20 kg	408 (204 per mAb)	SC[3, 7]	2 or 4[4]	3.4 (1.7 per mAb)
B1	≥5 kg to <10 kg[1]	144 (72 per mAb)	SC[7]	1 or 2[5]	1.2 (0.6 per mAb)
B2	≥3 kg to <5 kg[2]	96 (48 per mAb)	SC[7]	1	0.8 (0.4 per mAb)

eCRF = electronic Case Report Form; mAb=monoclonal antibody; SC=subcutaneous

[1] Participants between 5 and 10 kg were not to receive an injection containing more than 1.25 mL.

[2] Participants <5 kg were not to receive an injection containing more than 1 mL.

[3] For SC injection, investigators could use an infusion pump containing the combined volume with both mAbs. This could improve tolerability through administration of a single injection.

[4] Study intervention could be administered as 2 injections (1.7 mL of casirivimab and 1.7 mL of imdevimab) or 4 injections (0.8 mL of casirivimab, 0.9 mL of casirivimab, 0.8 mL of imdevimab, and 0.9 mL of imdevimab).

[5] Study intervention could be administered as 1 injection (1.2 mL total) or as 2 injections (0.6 mL of casirivimab and 0.6 mL of imdevimab).

[6] The total volume of study treatment per syringe and the number of injections were recorded in the eCRF.

[7] In the original protocol, subjects <10 kg were to receive study drug by intramuscular administration. However, from Amendment 1, all subjects were to receive study drug by SC administration, including those <10 kg body weight. No participants received intramuscular administration.

Source: COV 2121 Abbreviated CSR, Table 2.

Objective(s) / Outcomes / endpoints

Table 2: Objectives and endpoints

Only endpoints analyzed in the study are provided in the table below (see Section 3.7.2).

Objectives	Endpoints
Primary	
• To characterize the concentrations of casirivimab and imdevimab in serum over time after a single subcutaneous (SC) administration	• Concentrations of casirivimab and imdevimab in serum over time
Secondary	
• To assess the safety and tolerability of SC single administration of casirivimab+imdevimab	• Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of especial interest (AESI), and severity of TEAEs, through end of study
• To assess the occurrence of grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions in participants treated with SC doses of casirivimab+imdevimab	• Grade ≥3 injection site reactions and grade ≥3 hypersensitivity reactions through day 4
• To assess the immunogenicity of casirivimab and imdevimab	• Immunogenicity as measured by anti-drug antibodies (ADA) and neutralizing antibodies (Nab) to casirivimab and imdevimab over time
Exploratory	
• To assess the occurrence of COVID-19 during the study	
• To assess the occurrence of COVID-19-related medically-attended visits during the study	

Participants were followed-up for PK and safety tests until Day 169.

Sample size

The study planned to enrol at least 24 participants (12 in Group A and 12 in Group B). However, due to the early termination, the study only enrolled 7 participants across 3 centres in the US. All 7 participants were enrolled into Group A (≥10 kg to <40 kg); no participants were enrolled into Group B (≥3 kg to <10 kg). Participants in Group A (≥10 kg to <40 kg) were subsequently divided into two groups for analysis: Group A (≥20 kg to <40 kg), which included 2 participants, and Group A2 (≥10 kg to <20 kg), which included 5 participants.

Results

Participant flow

Table 3: Participant Disposition, All Enrolled Participants.

	Group A1 ≥20kg to <40kg (N=2)	Group A2 ≥10kg to <20kg (N=5)	Total (N=7)
Participants screened (signed informed consent form)			7
Screen failure	0	0	0
Participants enrolled	2 (28.6%)	5 (71.4%)	7 (100%)
Participants treated	2 (28.6%)	5 (71.4%)	7 (100%)
Participants discontinued from study	0	1 (14.3%)	1 (14.3%)
Reason for Study Discontinuation			
Lost to Follow-Up	0	1 (14.3%)	1 (14.3%)
Source: PTT 14.1.1.2, 14.1.1.3; PTL 16.2.1.1, 16.2.4.1			

Baseline data

All participants in the study were ≥ 1 years old (range 1 to 11 years). The majority were female (5 participants [71.4%]) and White (6 participants [85.7%]).

Number analysed

All participants received study treatment and were included in the safety analysis set One (14.3%) participant discontinued the study early (at Week 9) due to being lost to follow-up.

Safety results

Five participants experienced 12 TEAEs, all non-serious (grade 1-2).

Table 4: Treatment-emergent Adverse Events by Primary System Organ Class and Preferred Term, SAF.

Primary System Organ Class Preferred Term	Group A1 ≥20 kg to <40 kg (N=2)	Group A2 ≥10 kg to <20 kg (N=5)	Total (N=7)
Participants with at least one TEAE	**2 (100%)**	**3 (60.0%)**	**5 (71.4%)**
Infections and infestations	**2 (100%)**	**2 (40.0%)**	**4 (57.1%)**
COVID-19	1 (50.0%)	2 (40.0%)	3 (42.9%)
Gastroenteritis	0	1 (20.0%)	1 (14.3%)
Pneumonia viral	1 (50.0%)	0	1 (14.3%)
Upper respiratory tract infection	1 (50.0%)	0	1 (14.3%)
Respiratory, thoracic and mediastinal disorders	**1 (50.0%)**	**2 (40.0%)**	**3 (42.9%)**
Cough	1 (50.0%)	1 (20.0%)	2 (28.6%)
Cough variant asthma	0	1 (20.0%)	1 (14.3%)
Rhinorrhoea	1 (50.0%)	0	1 (14.3%)
Nervous system disorders	**0**	**1 (20.0%)**	**1 (14.3%)**
Headache	0	1 (20.0%)	1 (14.3%)

Abbreviations: COVID-19, coronavirus disease 2019; SAF, safety analysis set; TEAE, treatment-emergent adverse event
A participant who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A participant who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
System organ class and preferred term sorted by decreasing frequency of the total group.
Source: PTT 14.3.2.1

One event each of Pneumonia viral, Gastroenteritis, Cough and Cough variant asthma were grade 2; all other events were grade 1.

None of the participants experienced grade ≥3 TEAEs, AESIs, treatment-related TEAEs, or SAEs. None of the participants either discontinued the study due to a TEAE, died during the study, or experienced any hypersensitivity reactions or any injection site reactions.

No clinically meaningful findings in clinical laboratory values or vital signs measurements were reported.

Pharmacokinetics results

The concentrations of casirivimab and imdevimab following a single SC dose of casirivimab+imdevimab based on body weight tier are linear and characterized by an initial absorption phase followed by a linear terminal elimination phase.

Maximum concentrations of casirivimab and imdevimab were achieved approximately 3 to 7 days following SC administration, although 1 participant in the ≥10 kg to <20 kg body weight tier exhibited peak concentration at 28 days post-dose. Concentrations remained quantifiable for all participants through the last sampling time point which ranged from 11 to 175 days post-dose. The mean concentration-time profiles of casirivimab and imdevimab are similar between the ≥10 kg to <20 kg tier and the ≥20 kg to <40 kg tier). This suggests that tiered weight-based dosing achieves similar exposures across the body weight range of ≥10 kg to <40 kg.

Immunogenicity results

None of the 7 participants in this study developed anti-drug antibodies to casirivimab or imdevimab.

2.3.3. Discussion on clinical aspects

The scope of this study was evaluating the pharmacokinetics, safety, tolerability, and immunogenicity of a single-dose subcutaneous Casirivimab and Imdevimab in high-risk paediatric subjects under 12 years of age.

Enrolment was paused after 4 months due to the rapidly increasing prevalence of the SARS-CoV-2 B.1.1.529/BA.1 Omicron variant, against which casirivimab+imdevimab showed diminished in vitro

neutralisation potency. The participants who had been enrolled prior to the pause date were followed according to the protocol. Enrolment was not restarted. As a result of the early termination, only 7 participants were enrolled in the study.

Eligible were participants <12 years old and with a weight of ≥3 kg to <40 kg who were not infected with SARS-CoV-2 but were at high risk to develop severe COVID-19 if they became infected.

The study planned to enrol at least 24 participants (12 participants ≥10 kg to <40 kg (Group A) and 12 participants ≥3 kg to <10 kg (Group B). However due to the early termination of the study only 7 participants were enrolled, all participants were > 1 years old (range 1 to 11 years).

The concentrations of total casirivimab and imdevimab following a single SC dose of casirivimab+imdevimab based on body weight tier are linear and characterised by an initial absorption phase followed by a linear terminal elimination phase. Maximum concentrations of total casirivimab and total imdevimab were typically achieved approximately 3 to 7 days following SC administration. The mean concentration-time profiles of casirivimab and imdevimab are similar between the ≥10 kg to <20 kg tier and the ≥20 kg to <40 kg tier). This suggests that tiered weight-based dosing achieves similar exposures across the body weight range of ≥10 kg to <40 kg. Following single 1200 mg dose SC administration, the casirivimab and imdevimab serum concentrations reported in this study are higher than in the adult population from study R10933-10987-COV-2069. No data in participants < 1 year of age are available.

Efficacy of casirivimab+imdevimab in the paediatric population has to be determined in the paediatric population, however that is currently hampered by epidemiological situation i.e. diminished efficacy in the currently circulating variants. In addition, collected confirmatory PK data to support an envisaged bridging approach are not deemed conclusive.

No changes to the product information are proposed.

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. The scope of this study was evaluating the pharmacokinetics, safety, tolerability, and immunogenicity of a single-dose subcutaneous Casirivimab and Imdevimab in high-risk paediatric subjects under 12 years of age. Seven (7) participants were enrolled, all participants were > 1 year old (range 1 to 11 years). Following single 1200 mg dose subcutaneous administration, the casirivimab and imdevimab serum concentrations reported in this study were higher than in the adult population from study R10933-10987-COV-2069. None of the 7 participants in this study developed anti-drug antibodies to casirivimab or imdevimab. The safety profile reported was acceptable. Treatment-emergent Adverse Events were mild or moderate. Efficacy of casirivimab and imdevimab in the paediatric population under 12 years of age still has to be determined, however that is currently hampered by the epidemiological situation. At this point in time no changes to the product information are proposed.

☒ 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