Amsterdam, 23 February 2023
EMA/CHMP/57024/2023
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/P46/016

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 7 December 2022, the MAH submitted a 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 R10933-10987-COV-2067 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 is a stand-alone study.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for:

- R10933-10987-COV-2067 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 is a part of a clinical development program.

COV-2067 was initiated on 16 June 2020 (first patient first visit). Results from the study have previously been reported.

The present report (COV-2067 Primary Analysis CSR Addendum 3, hereinafter referred to as 'COV-2067 CSR Addendum 3') describes the results of the primary analyses for Phase 3 Cohort 2 (N=206; <18 years of age and not pregnant at randomization).

Due to decreased in vitro neutralization activity of casirivimab+imdevimab against the Omicron variant BA.1.1.529/BA.1, paediatric studies including paediatric cohorts in COV-2067 were paused in December 2021 and subsequently terminated in June 2022.

2.2.2. Clinical study

Methods

Study participants

Table 1: Summary of Study Cohorts at Randomisation

Phase	SARS-CoV-2 Infection	COVID-19 Symptoms	Age	Pregnancy at Randomization Allowed?	Cohort Designation[2]
1	Yes	Yes	≥18	No	Symptomatic
2	Yes	Yes	≥18	No	Symptomatic
2	Yes	No	≥18	No	Asymptomatic
3	Yes	Yes	≥18	No[1]	Cohort 1
3	Yes	Yes	<18	No	Cohort 2
3	Yes	Yes	All	Yes	Cohort 3

[1] Pregnant participants were allowed in cohort 1 until cohort 3 was added in protocol amendment 7. Pregnant participants enrolled in cohort 1 were reclassified such that cohort 3 includes all participants who were pregnant at randomization.
[2] All cohorts who were enrolled are provided for context, however, only results from phase 3 cohort 1 (long COVID study analysis only), phase 3 cohort 2, and phase 3 cohort 3 are presented in the body of this report.

Paediatric patients were enrolled in Phase 3 Cohort 2 (<18 years of age and not pregnant at randomization). One patient <18 years old pregnant at randomization was also enrolled in Phase 3

Cohort 3. Phase 3 Cohort 2 is part of the approved Paediatric Investigation Plan (PIPs) for casirivimab and imdevimab.

Treatments

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 as the existing formulation including excipients are suitable for paediatric use.

Participants in Phase 3 Cohort 2 were initially randomized 1:1:1 to a single IV dose of casirivimab+imdevimab 1200 mg (or body weight equivalent), casirivimab+imdevimab 2400 mg (or body weight equivalent), or placebo, with the casirivimab+imdevimab dose adjusted according to body weight as shown in Table 2. Placebo was discontinued per independent data monitoring committee (IDMC) recommendation from 24 February 2021; thus, participants were subsequently randomized 1:1 to a single IV dose of casirivimab+imdevimab 1200 mg (or body weight equivalent) or 2400 mg (or body weight equivalent). The 2400 mg arm was later dropped with the implementation of Protocol Amendment 10 (approved 16 Aug 2021), after which all participants enrolling into Cohort 2 were assigned to the 1200 mg dose level (or body weight equivalent).

Table 2: COV-2067: Casirivimab+Imdevimab Dose Equivalent for Patients Aged ≤18 Years by Body Weight Group

Body Weight Group	Dose Equivalent for 1200 mg IV Dose (600 mg per mAb)	Dose Equivalent for 2400 mg IV Dose (1200 mg per mAb)
≥40 kg	1200 mg (600 mg per mAb)	2400 mg (1200 mg per mAb)
≥20 kg to < 40 kg	450 mg (225 mg per mAb)	900 mg (450 mg per mAb)
≥ 10 kg to < 20 kg	224 mg (112 mg per mAb)	450 mg (225 mg per mAb)
≥ 5 to <10 kg	120 mg (60 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 to <5 kg	60 mg (30 mg per mAb)	120 mg (60 mg per mAb)
<2.5 kg	30 mg (15 mg per mAb)	60 mg (30 mg per mAb)

mAb = monoclonal antibody.

Objective(s) / Outcomes / endpoints

For all study participants, details of COVID-19-related medically-attended visits (defined as hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) were collected throughout the study up to Day 29, with collection occurring minimally on a weekly basis.

Phase 3 participants (regardless of cohort) were followed to Day 169 (end of study) for longer-term safety assessment.

Safety collection was targeted to avoid imposing significant additional burden on an already overstrained healthcare system during the pandemic. The targeted safety collection for participants <18 years of age included serious adverse events (SAEs) up to Day 169, adverse events of special interest (Grade $\geq$ 2 hypersensitivity reactions up to Day 29, Grade $\geq$ 2 infusion-related reactions up to Day 4, and any adverse event [AE] that led to a medically-attended visit regardless of relatedness to COVID-19 up to Day 29), and Grade 3 and 4 AEs up to Day 29.

Sample size

Enrolment in casirivimab+imdevimab paediatric studies was paused in December 2021 and subsequently terminated in June 2022 due to the emergence of the B.1.1.529/BA.1 SARS-CoV-2 (Omicron) variant, against which casirivimab+imdevimab shows diminished in vitro neutralization potency. As a result, the agreed PIPs for casirivimab (EMEA-002964-PIP01-21-M02) and imdevimab

(EMEA-002965-PIP01-21-M02) were modified to align the required numbers of treated patients with the status of enrolment prior to the enrolment pause and subsequent early termination of the study.

For COV-2067 Phase 3 Cohort 2 (PIP Study #1), the minimum number of paediatric patients evaluable for the primary analysis receiving weight-based doses equivalent to the 1200 mg IV adult dose levels was reduced from 44 patients to 35 patients. At the time enrolment to Phase 3 Cohort 2 was paused, the applicant had recruited more patients than required in the higher body weight groups and fewer than required in the lower body weight groups, with no patients below 2.5 kg.

Table 3: Casirivimab and Imdevimab PIP Study #1: Minimum Number of Patients by Paediatric Body Weight Subset

Original PIP	Modified PIP
At least 44 patients from birth to less than 18 years of age evaluable for the primary analysis in Cohort 2, receiving weight-based doses equivalent to the 1200mg IV adult dose levels, of whom: • 14 patients ≥ 40 kg BW • 10 patients ≥ 20 kg to <40 kg BW • 10 patients ≥ 10 kg to <20 kg BW • 4 patients ≥ 5 kg to <10 kg BW • 4 patients ≥ 2.5 kg to <5 kg BW • 2 patients < 2.5 kg BW	At least 35 patients from birth to less than 18 years of age evaluable for the primary analysis in Cohort 2, receiving weight-based doses equivalent to the 1200mg IV adult dose levels, of whom at least: • 14 patients ≥ 40 kg BW • 10 patients ≥ 20 kg to <40 kg BW • 11 patients ≥ 5 kg to <20 kg BW • no minimum number for <10 kg BW

BW = body weight; PIP = paediatric investigational plan.

Results

Participant flow

A total of 206 non-pregnant paediatric outpatients <18 years of age with symptomatic COVID-19 and at least one risk factor for developing severe disease were randomized to Phase 3 Cohort 2, of whom 2 patients (1.0%) were randomized to placebo, 129 patients (62.6%) were randomized to casirivimab+imdevimab 1200 mg, and 75 patients (36.4%) were randomized to casirivimab+imdevimab 2400 mg. The majority of patients were randomized to casirivimab+imdevimab 1200 mg due to discontinuation of the placebo arm per IDMC recommendation on 24 February 2021 and dropping of the 2400 mg dose level upon implementation of Protocol Amendment 10.

Of the 206 randomized patients, 202 patients (98.1%) received treatment and 190 patients (90.2%) completed the study. Discontinuations were higher in the casirivimab+imdevimab 2400 mg group (10/75 patients [13.3%]) than in the 1200 mg group (6/129 patients [4.7%]). Most discontinuations were either lost to follow-up or subject decision. No patient discontinued the study due to an AE. Results were similar regardless of whether patients were <12 or ≥ 12 years of age.

All 202 patients who received treatment were included in the safety analysis set (SAF): N=2 for the placebo group, N=129 for the 1200 mg group, and N=71 for the 2400 mg group.

Baseline data

In the overall Phase 3 Cohort 2 mFAS, the median age was 11 years (range 0-17 years), with approximately half of the patients <12 years of age (98 patients [51.0%]) and the other half ≥ 12 years (94 patients [49.0%]). More males (108 patients [56.3%]) were enrolled than females (84 patients [43.8%]), and most patients (167 patients [87.0%]) were White. The majority had a body weight ≥ 40 kg (129 patients [67.2%]); the remaining patients had a body weight 20 to <40 kg (48 patients [25.0%]), 10 to <20 kg (13 patients [6.8%]), or <10 kg (2 patients [1.0%]). Most patients (150 patients [78.1%]) were seronegative at baseline.

Number analysed

A total of 206 non-pregnant paediatric outpatients <18 years of age with symptomatic COVID-19 and at least one risk factor for developing severe disease were randomized to Phase 3 Cohort 2. Of the 206 randomized patients, 202 patients (98.1%) received treatment and 190 patients (90.2%) completed the study.

All 202 patients who received treatment were included in the safety analysis set (SAF): N=2 for the placebo group, N=129 for the 1200 mg group, and N=71 for the 2400 mg group. Consistent with prior analyses in adult participants, efficacy analyses in Phase 3 Cohort 2 focused on those patients whose baseline nasopharyngeal samples were RT-qPCR positive for SARS-CoV-2 (mFAS: N=1 for the placebo group, N=121 for the 1200 mg group, and N=70 for the 2400 mg group).

Efficacy results

Overall, for participants in the cohort 2 mFAS, >99% of whom were treated with casirivimab+imdevimab, key clinical assessments showed no deaths, no COVID-19-related hospitalizations, low rates of COVID-19-related medically attended-visits, and a median time to symptoms resolution of 7 or 8 days. When compared to similar assessments in casirivimab+imdevimab-treated adult participants in the phase 3 cohort 1 mFAS (Primary Analysis CSR), the results in the paediatric population were generally more favourable.

Endpoints Evaluating COVID-19-related Hospitalization or All-cause Death

There were no deaths in cohort 2 and no participant experienced a COVID-19-related hospitalization through day 29 (Phase 3 Cohort 2).

Endpoints Evaluating COVID-19-related Medically Attended Visits (MAV)

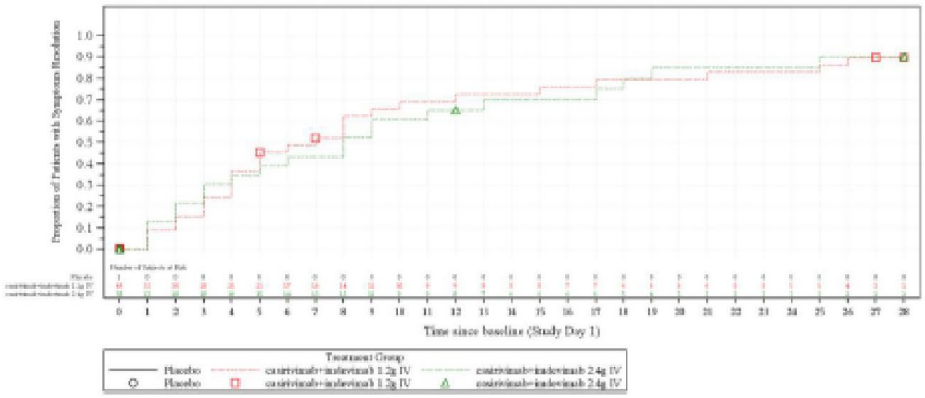
There were only 3 participants in cohort 2 who experienced a COVID-19-related MAV through day 29, 2 in the 1200 mg group and 1 in the 2400 mg group. One participant in the 1200 mg group had an ER visit and 2 participants (one in the 1200 mg group, one in the 2400 mg group) had a physician office/telemedicine visit.

Time to Resolution of Symptoms Consistent with COVID-19

Time to COVID-19 symptoms resolution was defined for all participants who had a total symptoms raw score of more than 3 at baseline as the time from treatment assignment to the first day during which the participant scored 0 on all symptoms except fatigue, headache, and cough which could be mild/moderate or none.

The median time to symptoms resolution following administration of casirivimab+imdevimab was 7 days for the 1200 mg group and 8 days for the 2400 mg group. Results were generally consistent across subgroups of participants defined by baseline serologic status and viral load.

Figure 1: Kaplan Meier Curve for Time to Resolution of Symptoms Consistent with COVID-19 (Phase 3 Cohort 2 Paediatric Participants ≥12 years of age, mFAS)



Abbreviations: COVID-19 = Coronavirus Disease 2019; IV=intravenous; mFAS=modified full analysis set.
Source: Phase 3 Cohort 2 PTF 14.2.4.1M

The curve shows a similar time course of improvement for both doses, indicative of the absence of a dose response.

Safety results

Only targeted treatment-emergent adverse events (TEAEs [SAEs and AESIs]) were required to be reported in this study. TEAEs outside of the required categories were voluntarily reported for some participants by some sites; these events were retained in the database and are summarized in the overview tables.

It is important to note that while the small number of participants in cohorts 2 and 3 who received placebo precludes the ability to make any meaningful comparisons between casirivimab+imdevimab and placebo groups for these vulnerable populations, the safety profile observed for participants treated with casirivimab+imdevimab in cohorts 2 and 3 is consistent with the known safety profile for non-pregnant, adult participants in cohort 1, with no new safety signals having been identified.

Phase 3 Cohort 2 (<18 Years Old, not Pregnant at Randomisation)

Summary of Adverse Events

Targeted TEAEs required to be reported for participants in phase 3 cohort 2 included SAEs up to day 169, grade 3/4 TEAEs up to day 29, and AESIs of grade ≥2 IRRs up to day 4, grade ≥2 hypersensitivity reactions up to day 29, and any TEAE that lead to a MAV (regardless of COVID-19-relatedness) up to day 29.

For phase 3 cohort 2 participants who received at least 1 dose or part of a dose of study drug (N=202; all having at least 1 risk factor for severe COVID-19 per protocol), an overview of reported TEAEs, including TEAEs that were voluntarily reported for some participants outside of the required TEAE reporting.

Consistent with the absence of any dose effect, AE categories were generally balanced across the casirivimab+imdevimab 1200 mg and 2400 mg treatment groups, with minor discrepancies, when observed, likely driven by the small sample size. Across all treatment groups, only 2 participants (1%) in cohort 2 experienced a grade ≥2 hypersensitivity reaction (1 participant in the 1200 mg group) or IRR through day 4 (1 participant in the 2400 mg group). Moreover, there were no TEAEs leading to death, withdrawal from the study, or study infusion interruption; 1 TEAE (the aforementioned hypersensitivity reaction in the 1200 mg group) led to study infusion discontinuation. No participant in phase 3 cohort 2 experienced a fatal event.

Serious Adverse Events

The incidence of SAEs in cohort 2 was low overall. There were a total of 4 SAEs that occurred amongst 3 participants (1.5%), all of whom were in the 1200 mg group.

An evaluation of SAEs reported by time to onset, up to day 29 and from day 30 until the last available timepoint, did not show any specific safety trends: 2 SAEs occurred up to day 29 (Metapneumovirus pneumonia and Urinary retention) and 2 SAEs occurred after day 29 (Suicidal ideation and Respiratory distress). None of the SAEs were considered related to study drug and all were confounded by the participant's concurrent clinical condition/medical history.

No participant in phase 3 cohort 2 withdrew from the study or had an infusion interruption due to a TEAE. However, 1 participant in the 1200 mg group experienced a TEAE that led to infusion discontinuation and did not receive the full dose of study drug. The participant had a grade 2 event of Urticaria that was considered an AESI (grade ≥2 hypersensitivity reactions).

Adverse Events of Special Interest

Throughout the study, treatment-emergent AESI (serious and nonserious) were defined as:

- Grade ≥2 infusion-related reactions (IRRs), up to study day 4
- Grade ≥2 hypersensitivity reactions, up to study day 29
- Any TEAE that led to a MAV, up to day 29*

**Note: After PA 7, TEAEs that led to a MAV were collected up to day 29 as AESIs to inform MAV narratives. Those that were considered COVID-19-related are not described in this section as they are primarily captured in the Efficacy section.*

One participant in the 2400 mg group experienced a grade 2 infusion-related reaction of pyrexia that was reported on day 1 and resolved on the next day. One participant in the 1200 mg group experienced a grade 2 hypersensitivity reaction that was reported on day 1 during study infusion prompting discontinuation of study drug; the event resolved the same day.

Thirteen participants (6.5%) experienced TEAEs that led to a MAV through day 29. Only 2 of these TEAEs were related to COVID-19. Non-COVID-19-related TEAEs that led to a MAV included Conjunctivitis, Crohn's disease, Gastroenteritis, Injury, Metapneumovirus pneumonia, Otitis externa, Pyrexia (2 events), Sinusitis, Tonsilitis, Urinary retention, and Vomiting. All but 1 event of Pyrexia were considered not related to study drug.

Grade 3 or 4 Adverse Events

Two participants (both in the 1200 mg group) experienced a total of 3 grade 3 or 4 TEAEs up to day 29. One participant experienced 2 grade 3 TEAEs (aminotransferase increase). Another experienced 1 grade 4 TEAE (non-COVID-19 pneumonia). None of the TEAEs were considered related to study drug.

Clinical Laboratory Evaluation

Overall, no clinically meaningful trends in laboratory parameters were noted in the treatment groups. Findings were generally similar between dose groups with minor differences, when observed, likely driven by the relatively small sample sizes. For each laboratory category, the potentially clinically significant values (PCSVs) observed were not considered clinically significant and were considered related to COVID-19 disease and its associated complications in participants with multiple concurrent medical conditions.

Table 4: Overview of TEARs from Day 1 to Day 169 (Phase 3 Cohort 2 Paediatric Participants, SAF)

	Placebo (N=2)	R10933+R10987 1.2g IV (N=129)	R10933+R10987 2.4g IV (N=71)	R10933+R10987 Combined (N=200)
Total number of TEAE[1]	1	84	37	121
Total number of grade 3 or 4 TEAE	0	12	0	12
Total number of TE SAE	0	4	0	4
Total number of TE AESI	0	12	5	17
Total number of TE serious AESI	0	2	0	2
Patients with any TEAE	1 (50.0%)	23 (17.8%)	12 (16.9%)	35 (17.5%)
Patients with any grade 3 or 4 TEAE	0	3 (2.3%)	0	3 (1.5%)
Patients with any TE SAE	0	3 (2.3%)	0	3 (1.5%)
Patients with any TE AESI	0	10 (7.8%)	5 (7.0%)	15 (7.5%)
Patients with any TE serious AESI	0	2 (1.6%)	0	2 (1.0%)
Patients with at least one TE AESI of infusion related reaction (grade ≥2), through day 4[2]	0	0	1 (1.4%)	1 (0.5%)
Patients with at least one TE AESI of hypersensitivity reaction (grade ≥2), through day 4	0	1 (0.8%)	0	1 (0.5%)
Patients with at least one TE AESI of hypersensitivity reaction (grade ≥2), through day 29	0	1 (0.8%)	0	1 (0.5%)
Patients with TE AESI of event that led to a MAV, through day 29	0	9 (7.0%)	4 (5.6%)	13 (6.5%)
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to withdrawal from the study	0	0	0	0
Patients with any TEAE leading to study infusion interruption[3]	0	0	0	0
Patients with any TEAE leading to study infusion discontinuation[4]	0	1 (0.8%)	0	1 (0.5%)

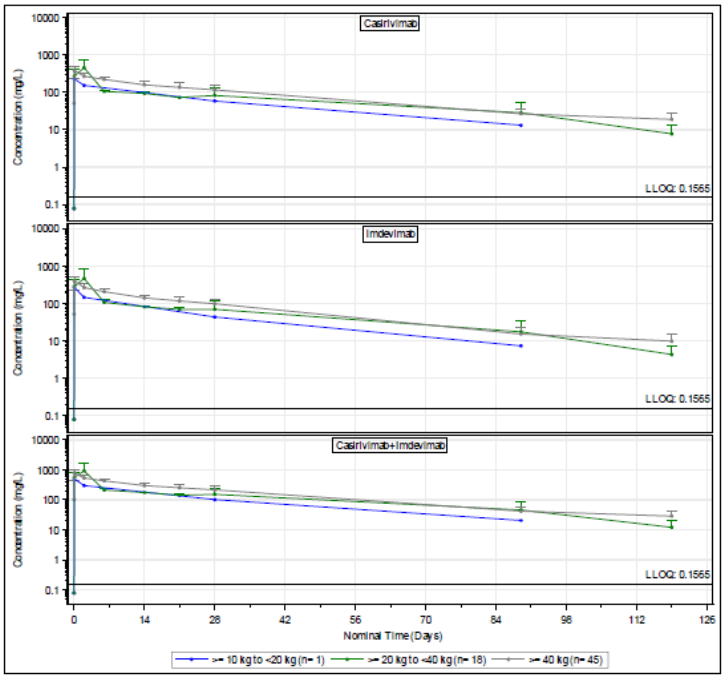
Abbreviation: TE=treatment-emergent; TEAE=treatment-emergent adverse event; AESI=adverse event of special interest; MAV=medically-attended visit; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SAF=safety analysis set.
Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period which is from the time of study drug administration to the last study visit.
MedDRA (Version 25.0) coding dictionary applied.
[1] TEAEs collected include TE SAEs, AESIs and grade 3/4TEAEs, as well as ad-hoc/voluntarily reported TEAEs by some sites.
[2] TEAEs deemed treatment-related as per investigator assessment.
[3] Infusion interruption: the administration of the infusion was interrupted before being completed, but subsequently was re-started and the full planned dose was administered.
[4] Infusion discontinuation: the administration of the infusion was stopped before being completed, and the full planned dose was not administered

Results Clinical Pharmacology

Based on phase 3 Cohort 2 (age <18 years, not pregnant at randomization)

As one result in paediatric outpatients with symptomatic COVID-19 and at least one risk factor for developing severe COVID-19, casirivimab and imdevimab concentrations in serum displayed linear and dose proportional pharmacokinetics, as expected based on the mode of action and results from PK observations in the adult population. Serum concentrations achieved across different body weight groups by selection of different body-weight equivalent doses are regarded comparable.

Figure 2: Mean (+SD) Concentrations of Total Casirivimab, Total Imdevimab, and Total Casirivimab+Imdevimab Combined in Serum by Nominal Time, Treatment Group, and Body Weight Tier in Ambulatory Patients <18 Years of Age with COVID-19 (Study R10933-10987-COV-2067, Phase 3, Cohort 2, 2400 mg Dose Group, Log-Scaled [PKAS])

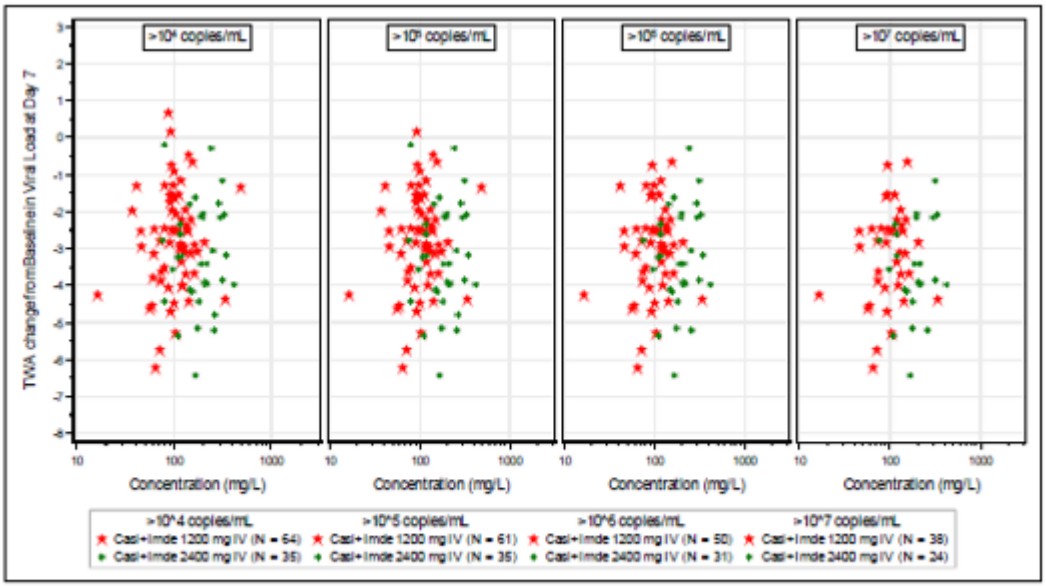


n = Number of participants
Note: Concentrations below the LLOQ were set to LLOQ/2. Participants <18 years of age were administered the body weight equivalent (BWE) of the casirivimab+imdevimab 1200 mg or 2400 mg adult dose.
Source: Appendix 16.1.14 Figure 2

Concentrations of casirivimab and imdevimab at end of infusion and Day 28 in pediatric participants were within the range of concentrations observed in Phase 3 Cohort 1 adult participants at end of infusion and Day 28.

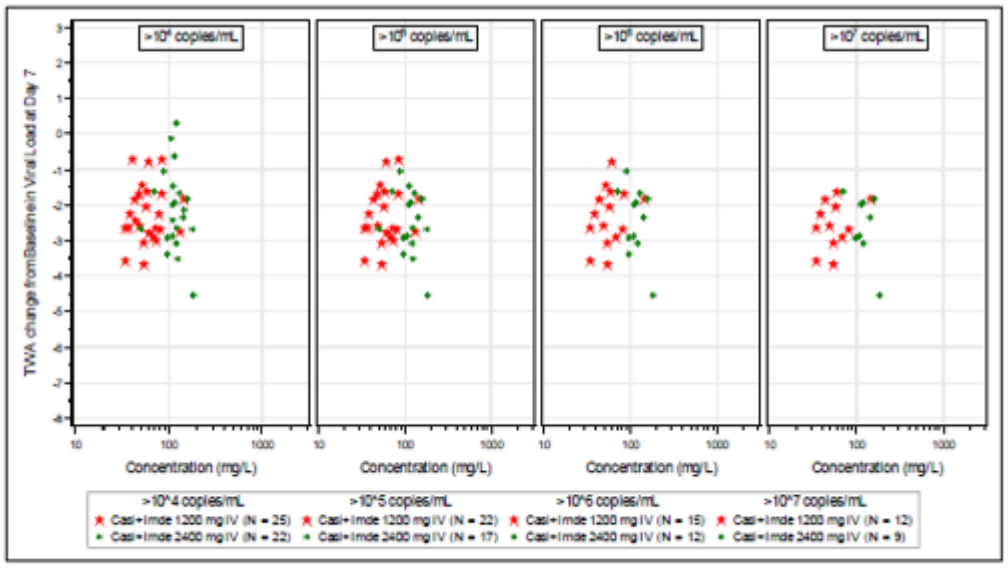
No exposure-response (change in viral load or time-weighted average change in viral load from baseline to Day 7) relationship was observed across different viral load categories over the dose range investigated was observed, as expected from previously collected data.

Figure 3: Scatter Plot of Time-Weighted Average Change from Baseline in Viral Load (log10 copies/mL) from Day 1 Through Day 7 vs Log-Scaled C28 of Total Casirivimab+Imdevimab Combined in Serum by Baseline Viral Load Category in Symptomatic Ambulatory Patients <18 Years of Age with COVID-19 (Study R10933-10987-COV-2067, Phase 3, Cohorts 2 [mCRSERAS])



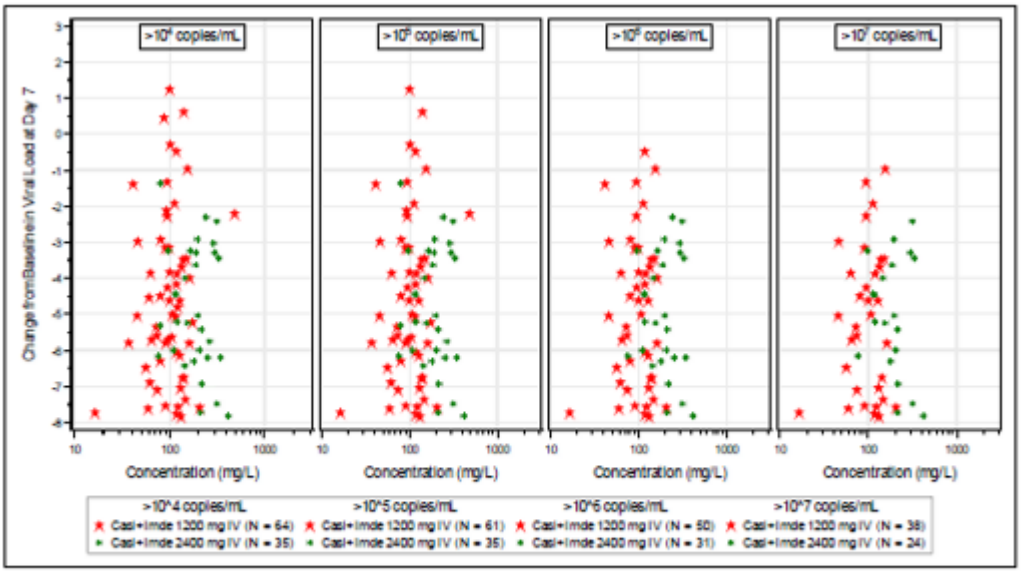
N = Number of patients. mCRSERAS = CR-Seronegative mFAS
Note: BLQs were set to LLOQ/2. Participants <18 years of age were administered the body weight equivalent of casirivimab+imdevimab 1200 mg or 2400 mg.

Figure 4: Scatter Plot of Time-Weighted Average Change from Baseline in Viral Load (log10 copies/mL) from Day 1 Through Day 7 vs Log-Scaled C28 of Total Casirivimab+Imdevimab Combined in Serum by Baseline Viral Load Category in Pregnant Patients with COVID-19 (Study R10933-10987-COV-2067, Phase 3, Cohorts 2 [CR-FAS])



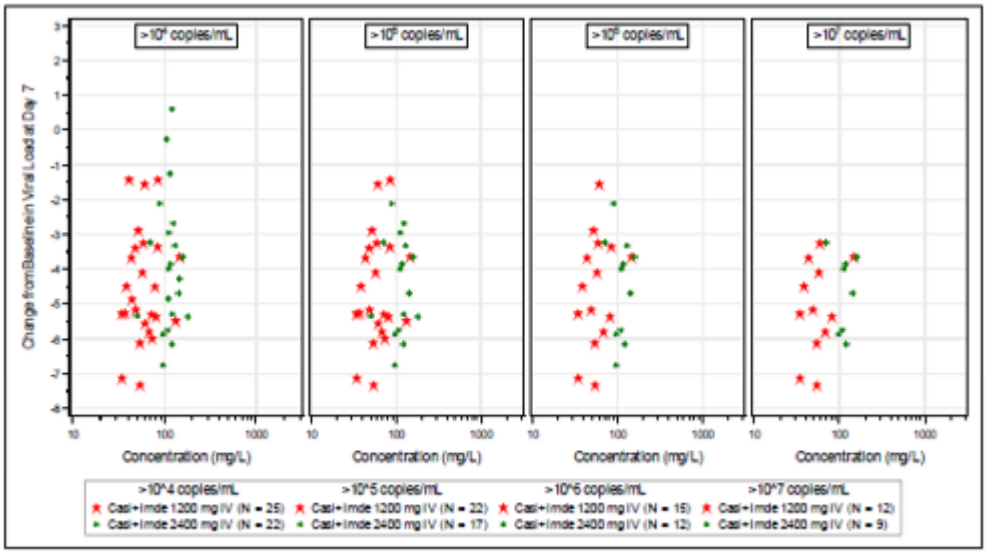
N = Number of patients
Note: BLQs were set to LLOQ/2

Figure 5: Scatter Plot of Change in Viral Load (log10 copies/mL from Baseline to Day 7 vs Log-Scaled C28 of Total Casirivimab+Imdevimab Combined in Serum by Baseline Viral Load Category in Symptomatic Ambulatory Patients <18 Years of Age with COVID-19 (Study R10933-10987-COV-2067, Phase 3, Cohorts 2 [mCRSERAS])



N = Number of patients; mCRSERAS = CR-Seronegative mFAS
Note: BLQs were set to LLOQ/2. Participants <18 years of age were administered the body weight equivalent of casirivimab+imdevimab 1200 mg or 2400 mg.

Figure 6: Scatter Plot of Change in Viral Load (log10 copies/mL from Baseline to Day 7 vs Log-Scaled C28 of Total Casirivimab+Imdevimab Combined in Serum by Baseline Viral Load Category in Pregnant Patients <18 Years of Age with COVID-19 (Study R10933-10987-COV-2067, Phase 3, Cohorts 3 [CR-FAS])



N = Number of patients
Note: BLQs were set to LLOQ/2

There was a low incidence of treatment-emergent ADA in the paediatric cohort (1/187 [0.5%]), in consistency with observations previously reported for non-pregnant adult participants. The single participant with a positive ADA response was negative for NAb against casirivimab but positive for NAb against imdevimab. The casirivimab and imdevimab concentrations in this participant were not notably different from concentrations in patients who did not develop ADAs to casirivimab and imdevimab.

2.2.3. Discussion on clinical aspects

Due to decreased in vitro neutralisation activity of casirivimab+imdevimab against the Omicron variant BA.1.1.529/BA.1, paediatric studies including paediatric cohorts in COV-2067 were paused in December 2021 and finally terminated in June 2022. The relevance and adequacy of an update of the product information for inclusion of paediatric patients weighing > 10 kg for treatment with casirivimab+imdevimab is currently hampered by epidemiological situation.

Results from clinical pharmacology are overall in line with those observed previously in the adult populations. No new safety risks have been identified.

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. Results from clinical pharmacology were overall in line with those observed previously in the adult populations. No new safety risks were identified.

☒ **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