30 January 2025
EMA/CHMP/104963/2025
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Ronapreve

International non-proprietary name: casirivimab / imdevimab

Procedure No. EMEA/H/C/005814/II/0017

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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List of abbreviations

ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
COV-2067	R10933-10987-COV-2067
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DLP	data lock point
EEA	European Economic Area
ER	emergency room
EU	European Union
FAS	Full Analysis Set
IDMC	independent data monitoring committee
IgG1	immunoglobulin G1
IRR	infusion-related reactions
IV	intravenous
mAb	monoclonal antibody
MAV	medically-attended visit
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PBRER	Periodic Benefit-Risk Evaluation Report
PCSV	potentially clinically significant value
PIP	Paediatric Investigation Plan
PSUR	Periodic Safety Update Report
RBC	red blood cells
RoW	Rest of World
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 14 February 2024 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of paediatric patients from 2 to less than 12 years old, weighing at least 10kg, who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 for Ronapreve, based on final results from study COV-2067; this was a seamless, adaptive, Phase 3, randomized, double-blinded, placebo-controlled, multi-center study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate COVID-19. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0300/2022 and P/0343/2022 on the agreement of paediatric investigation plans (PIPs).

At the time of submission of the application, the PIPs were completed.

The PDCO issued an opinion on compliance for the PIPs P/0300/2022 and P/0343/2022.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Jayne Crowe

Timetable	Actual dates
Submission date	14 February 2024
Start of procedure	2 March 2024
CHMP Rapporteur Assessment Report	30 April 2024
CHMP Co-Rapporteur Assessment Report	3 May 2024
PRAC Rapporteur Assessment Report	3 May 2024
PRAC members comments	7 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	21 May 2024
Updated CHMP Rapporteurs Joint Assessment Report	27 May 2024
Request for supplementary information (RSI)	30 May 2024
CHMP Rapporteur Assessment Report	29 October 2024
PRAC Rapporteur Assessment Report	15 October 2024
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	31 October 2024
CHMP members comments	04 November 2024
Updated CHMP Rapporteur Assessment Report	23 January 2025
Opinion	30 January 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

COVID-19 is a disease caused by SARS-CoV-2, a novel RNA betacoronavirus initially identified from patients experiencing atypical pneumonia in Wuhan City, China (Zhu et al. 2020). COVID-19 was designated by the World Health Organization (WHO) as a global pandemic and public health emergency of international concern between March 2020 and May 2023. Since March 2020, over 772 million confirmed cases and approximately 7 million deaths worldwide have been reported to the WHO (WHO, 2024), with surges of infections continuing to occur across the world.

The global risk of symptomatic infection remains high despite evidence of reducing risks to society through high population-level immunity from infection and/or vaccination and even when newly circulating SARS-CoV-2 variants do not appear to be associated with increased severity. A recent report by the European Centre for Disease Prevention and Control (ECDC) highlighted the ongoing impact of COVID-19 in Europe where, since the peak of COVID-19 infections following the emergence of Omicron BA.1, there have been periodic waves of infection associated with Omicron sub-lineages approximately every 2–3 months. Although the peaks reported for cases, hospitalisations, intensive

care unit admission, and deaths have shown a downward trend, each wave has disproportionately affected those older than 65 years and those with underlying comorbidities (ECDC, 2023). Furthermore, individuals who did not show a good immune response after vaccination and who have not received updated booster vaccinations are more likely to be susceptible to reinfection and severe disease. Therefore, therapeutics for COVID-19 treatment and prevention continue to remain important for the management of mild, moderate, and severe disease.

Claimed therapeutic indication

With this Type II variation, the MAH proposes to extend the already approved treatment indication in adults and children older than 12 years of age for patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, to paediatric patients 2 years of age and older, who weigh at least 10 kg.

Epidemiology and risk factors, screening tools/prevention

In the United States during the Omicron BA.1 wave of infections in early 2022, the hospitalisation rate peaked at 7.6 per 100,000 people in children (<18 years old) compared with 43.0 per 100,000 people in adults (≥18 years old). In children <12 years of age, the peak hospitalisation rate increased with decreasing age: 3.0 per 100,000 people in 5- to 11-year-olds, 7.6 per 100,000 in 1- to 4-year-olds, and 57.5 per 100,000 people in children aged less than 1 year (CDC, 2023d). During this period, COVID-19 was one of the leading causes of death in children, likely reflecting the number of children infected during the Omicron BA.1 wave (Flaxman et al., 2023). Rates of COVID-19-related hospitalisation and death since the Omicron BA.1 wave have been lower, which could reflect the increase in proportion of children with SARS-CoV-2 antibodies from prior infection and COVID-19 vaccination.

As in adults, children with certain underlying comorbidities are at a higher risk of COVID-19-related hospitalisation and severe outcomes compared to those without underlying comorbidities (Harwood et al., 2022). Comorbidities associated with an increased risk in children include, but are not limited to, cardiac disease, neurologic disorders, chronic lung disease, chronic kidney disease, endocrine disorders such as diabetes and obesity, and immunocompromised status. The risk is even higher in those with multiple comorbid conditions. These patient groups are the highest priority for vaccination and should be considered for COVID-19 treatment if they become infected.

COVID-19 vaccines continue to be the first line of protection against COVID-19-related hospitalisation (and severe outcomes) in children at increased risk of severe disease. In the EU, mRNA COVID-19 vaccines have been approved in children as young as 6 months of age for both primary series and booster vaccinations, including those that have been adapted to the recently circulating SARS-CoV-2 strains.

Biologic features / Aetiology and pathogenesis

SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike glycoprotein to angiotensin converting enzyme 2 (ACE2) on the surface of host cells. The receptor binding domain of the spike glycoprotein is, consequently, the main target for neutralising antibodies.

Clinical presentation, diagnosis and stage/prognosis

Infection with SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illness, ranging from a mild upper respiratory tract infection to severe acute respiratory distress syndrome and multiple organ failure (Wiersinga et al., 2020). The majority of patients with SARS-CoV-2 infection exhibit relatively mild to moderate symptoms or are asymptomatic (Hu et al., 2020; Oran and Topol, 2020), suggesting that most cases can be managed in an outpatient setting. However, for some patients, the SARS-CoV-2 infection leads to hypoxemia and other serious respiratory conditions that require hospitalisation and can be fatal (Guan et al., 2020; Richardson et al., 2020; Wu and McGoogan, 2020). Infection is more likely to lead to hospitalisation and severe disease among patients with pre-existing risk factors or comorbidities, such as older age, obesity, diabetes mellitus, cardiovascular disease, chronic lung disease, and immunocompromised status (CDC 2023c; Lighter et al., 2020).

There is also a subset of patients who recover from the acute SARS-CoV-2 infection but experience persistent symptoms such as fatigue with bodily pain or mood swings, cognitive problems, and ongoing respiratory problems. This has been defined as post-COVID condition (also known as long COVID), which occurs beyond 3 months from the initial SARS-CoV-2 infection, with symptoms lasting for at least 2 months with no other explanation (WHO, 2021). Literature reviews have estimated the prevalence of post-COVID condition to be at least 10% and potentially as high as 50% during the pre-Omicron period (Davis et al., 2023; ECDC, 2022).

COVID-19 in Paediatric Patients

Children usually develop asymptomatic or mild disease, often with upper respiratory symptoms. However, similar to adults, children who develop severe COVID-19 may require hospitalisation and oxygen support, have severe pneumonia, and/or have signs of severe respiratory distress.

Multi-system inflammatory syndrome in children (MIS-C) is a rare but serious condition that requires treatment in hospital. MIS-C associated with SARS-CoV-2 infection is a severe delayed hyperinflammatory condition in children and adolescents occurring 2-6 weeks after antecedent SARS-CoV-2 infection. The clinical criteria for diagnosis include fever, laboratory evidence of systemic inflammation (C-reactive protein $\geq$ 30 mg/dL), severity that requires hospitalisation or results in death, and new-onset manifestations in at least 2 categories (i.e. cardiac, shock, hematologic, gastrointestinal, dermatologic) (CDC, 2023b). The prevalence of these cases peaked during the Delta wave of SARS-CoV-2 infections and has since subsided to relatively low levels with the Omicron variant (CDC, 2023a; McCrindle et al., 2023). This could be due to more children becoming immune via infection and/or COVID-19 vaccination, or a lower hyperinflammatory response with the Omicron variant.

In a systematic review and meta-analysis, the prevalence of one or more post-COVID conditions in children was 25%, with the most common symptoms being mood symptoms (16.5%), fatigue (9.7%), and sleep disorders (8.4%) (Lopez-Leon et al., 2022). Many of the studies included in the review did not discriminate between children <12 years old and adolescents, where there is bias in younger children who cannot express emotional and functional status as part of symptom evaluation.

Management

There are currently no therapeutic options for the treatment of COVID-19 in children weighing <40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe

COVID-19 (table below). Veklury (remdesivir) is indicated for the treatment of adult and paediatric patients, but only for those weighing at least 40 kg, whilst Evusheld (tixagevimab and cilgavimab) and Xevudy (sotrovimab) are indicated for the treatment of adults and adolescents aged 12 years and over and weighing at least 40 kg. Paxlovid (nirmatrelvir and ritonavir) and Regkirona (regdanvimab) are only indicated for the treatment of COVID-19 in adults. Veklury (remdesivir), Paxlovid (nirmatrelvir and ritonavir), and Regkirona (regdanvimab) have ongoing Paediatric Investigation Plans (PIP)s.

Table 1. Overview of Treatments other than Casirivimab+Imdevimab Currently Authorised in the EU to Treat COVID-19 in Patients who do not require Supplemental Oxygen

Treatment	Indication	Status
Monoclonal antibody treatments		
EVUSHELD (tixagevimab and cilgavimab)	• Treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	MA granted 25/03/2022
Xevudy (sotrovimab)	• Treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	MA granted 17/12/2021
Regkirona (regdanvimab)	• Treatment of adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	MA granted 12/11/2021; ongoing PIP
Antiviral treatments		
Paxlovid (nirmatrelvir and ritonavir)	• Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19	Conditional MA granted 28/01/2022, converted to full MA on 27/01/2023; ongoing PIP
Veklury (remdesivir)	• Treatment of COVID-19 in adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	Conditional MA granted 03/07/2020, converted to full MA on 08/08/2022; ongoing PIP

MA = marketing authorization; PIP = paediatric investigational plan.
Source: EMA, 2023.

None of the already approved monoclonal antibody treatments are effective against the SARS-CoV-2 variants of concern currently in circulation. On the other hand, there may be other factors that limit the use of the antiviral medications.

Should future circulating variants be susceptible to casirivimab+imdevimab, Ronapreve would present a viable treatment option for paediatric patients who are at high risk of progressing to severe COVID-19.

2.1.2. About the product

Casirivimab and imdevimab are two human, high affinity, IgG1 mAbs that bind to non-overlapping epitopes on the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. These mAbs are non-competing with one another, exhibit potent neutralisation, and can bind simultaneously to the S protein RBD.

When co-administered as combination therapy, casirivimab+imdevimab treatment neutralises SARS-CoV-2 in cell culture, minimises the likelihood of viral escape due to genetic mutations, and prevents and treats infection in animal models. There is compelling evidence across the clinical development program that this antibody combination has an acceptable safety profile and is an effective antiviral option, against susceptible viral variants, to prevent and treat COVID-19 in an outpatient setting.

Ronapreve is currently indicated for:

- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result.
- Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

The approved dosage for adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen is 1200 mg casirivimab+imdevimab (600 mg of casirivimab and 600 mg of imdevimab) administered as a single IV infusion or by subcutaneous (SC) injection.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Regulatory agency guidance was sought from the European Medicines Agency [EMA]/ Committee for Medicinal Products for Human Use [CHMP] and incorporated into the paediatric development program as appropriate. Interactions with the Agency included a scientific advice consultation as well as review of the PIPs:

- Scientific advice on the design of the paediatric cohort in Study COV-2067 was received on 30 November 2020 (EMA/SA/0000048369) with a focus on the paediatric dosing strategy, sample size, and endpoints.
- The initial PIPs for casirivimab (EMEA 002964 PIP01-21) and imdevimab (EMEA 002965-PIP01-21) were approved by the Paediatric Committee (PDCO) on 16 August 2021. The PIPs included 4 clinical studies (2 treatment studies and 2 prevention studies) and 3 modelling and simulation studies.
- The first PIP modifications for casirivimab (EMEA 002964 PIP01-21-M01) and imdevimab (EMEA 002965-PIP01-21-M01) were approved by the PDCO on 3 February 2022. The modifications adjusted the doses for COV-2114 in hospitalised patients and the route of administration for uninfected subjects weighing less than 10 kg in COV-2121.
- The second PIP modifications for casirivimab (EMEA 002964 PIP01-21-M02) and imdevimab (EMEA 002965-PIP01-21-M02) were approved by the PDCO on 10 August 2022. The PIPs 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 studies resulting from the

emergence of the B.1.1.529/BA.1 SARS-CoV-2 (Omicron) variant, against which casirivimab+imdevimab shows diminished *in vitro* neutralisation potency.

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, with no changes where the minimum sample size had already been met. At the time enrolment to Phase 3 Cohort 2 was paused; the MAH 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.

The other treatment study, COV-2114, was deleted from the PIPs due to limited study enrolment prior to the Omicron-related enrolment pause (only 2 patients were enrolled).

- The final CSRs for the PIP studies were submitted to the EMA as Article 46 post-authorisation measures.

2.1.4. General comments on compliance with GCP

All clinical trials contributing to the current submission were submitted previously with the appropriate documentation relating to GCP compliance.

2.2. Non-clinical aspects

2.2.1. Introduction

An overview of non-clinical studies is available for casirivimab and imdevimab individually, as well as Ronapreve (the invented name for the combination casirivimab+imdevimab therapy accepted by the EMA; formerly referred to as REGN-COV2), and has been previously presented and reviewed. The submitted non-clinical overview addendum includes additional information elaborated in the context of the primary pharmacodynamics study updated (R10933-PH-20091-SR-01V10), investigating *in vitro*, the ability of casirivimab, imdevimab, and casirivimab+imdevimab to neutralise virus through blockade of viral entry into cells. These updates have already been assessed in procedure EMEA/H/C/PSUSA/00010963/202307. Accordingly, the MAH is submitting this Type II variation to update Section 5.1 of the SmPC with the adopted data. In addition, the MAH has removed the country of origin in Tables 6 and 7 of the SmPC to align with the WHO variant names as the variant identifier.

2.2.2. Pharmacology

PRIMARY PHARMACODYNAMICS – *IN VITRO* PHARMACOLOGY

Antibody Resistance Profiles

In vitro neutralisation studies were performed using pVSV-SARS-CoV-2-S pseudoparticles to evaluate the ability of casirivimab (REGN10933), imdevimab (REGN10987), and Ronapreve to neutralise putative escape mutants identified *in vitro* under antibody pressure with anti-S protein mAbs, as well as S protein variants identified from preclinical animal studies, clinical trials, and publicly available sources of SARS-CoV-2 in circulation.

Results demonstrated that the majority of single mutations that reduced neutralisation potency (IC50) of either casirivimab or imdevimab did not reduce neutralisation potency of Ronapreve with the exception of S371F, S371L, E406Q, E406W, N440D, K444T, V445F, N487D, P499S, and T500A.

Ronapreve retained neutralisation potency against full sequences or key S protein residues of the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.427/B.1.429), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), and Mu (B.1.621) variants. However, casirivimab+imdevimab was not active (i.e., activity below the lower limit of quantitation) against the Omicron BA.1, BA.1.1, BA.3, BA.4.6, BQ.1, BQ.1.1, XBB lineages. Some activity, albeit reduced, of Ronapreve and imdevimab monotherapy was demonstrated against the full S protein sequence of the Omicron BA.2, BA.2.12.1, BA.2.75 and BA.4/BA.5 lineages (325-, 275-, 881- and 201-fold reduction of Ronapreve activity compared with the reference strain, respectively). A loss of neutralisation activity was observed for casirivimab monotherapy against the full S protein sequences of these Omicron lineages.

2.2.3. Pharmacokinetics

No new information was submitted.

2.2.4. Toxicology

No new information was submitted.

2.2.5. Ecotoxicity/environmental risk assessment

No new information was submitted.

2.2.6. Discussion on non-clinical aspects

The *in vitro* neutralisation results presented above, taken together with the results from non-clinical i*n vitro* and *in vivo* studies previously assessed, are supportive of the use of Ronapreve for the prevention and treatment of patients infected with susceptible SARS-CoV-2 variants.

2.2.7. Conclusion on the non-clinical aspects

The submitted non-clinical data includes additional information elaborated in the context of the updated (R10933-PH-20091-SR-01V10) primary pharmacodynamics study investigating *in vitro* the ability of casirivimab, imdevimab, and casirivimab+imdevimab to neutralise virus through blockade of viral entry into cells. These updates were previously assessed in procedure EMEA/H/C/PSUSA/00010963/202307.

There is no need to re-assess the already accepted data. The related updates in Section 5.1 of the SmPC are accepted. The non-clinical package is considered acceptable. These data are not a specific requisite to extend use down to children 2 years of age and 10 kg body weight.

This application does not lead to a significant increase in environmental exposure to casirivimab+imdevimab.

2.3. Clinical aspects

2.3.1. Introduction

Table 2. Overview of Paediatric Treatment Investigations

PIP Study	Description	Report	Report Submission Status
Treatment Studies			
Study 1 (COV-2067 Phase 3 Cohort 2)	Adaptive Phase 1/2/3, randomized, double-blind, placebo-controlled study to assess the PK, safety and tolerability of a single IV dose of cas+im in paediatric outpatients (and adults) at risk of severe COVID-19	COV-2067 Primary Analysis CSR Addendum 3 (LPLV 7 June 2022)	Procedure EMEA/H/C/005814/P46/016 (eCTD sequence 0044) Submitted: 07 Dec 2022 Approved: 23 Feb 2023
Study 2 (COV-2114) [a]	Phase 1b open-label study to assess the PK, tolerability and safety of a single IV dose of cas+im in paediatric patients from birth to <18 years of age who were hospitalized for COVID-19	COV-2114 Abbreviated CSR (LPLV 9 June 2022)	Procedure EMEA/H/C/005814/P46/017 (eCTD sequence 0045) Submitted: 09 Dec 2022 Approved: 23 Feb 2023
Prevention Studies			
Study 5 (COV-2069)	Phase 3 randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of a single SC dose of cas+im in asymptomatic adolescent (and adult) household contacts of the first known household member infected with SARS-CoV-2	COV-2069 Primary Analysis CSR Addendum 2 (LPLV 4 Oct 2021)	Procedure EMEA/H/C/005814/P46/005 (eCTD sequence 0021) Submitted: 31 Mar 2022 Approved: 10 Nov 2022
Study 6 (COV-2121)	Phase 2a open-label study to assess the PK, tolerability and safety of a single SC dose of cas+im in paediatric subjects from birth to <12 years of age at high risk of developing severe COVID-19 if they became infected	COV-2121 Abbreviated CSR (LPLV 1 June 2022)	Procedure EMEA/H/C/005814/P46/015 (eCTD sequence 0043) Submitted: 30 Nov 2022 Approved: 23 Feb 2023
Modelling and Simulation Studies			
Study 3 (modeling and simulation)	PopPK model for dosing prediction and confirmation of the IV and SC routes of administration in paediatric subjects from birth to <18 years of age	PopPK report (R10933-PK-23020-SR-01V1)	Procedure EMEA/H/C/005814/P46/018 (eCTD sequence 0053) Submitted: 31 Mar 2023 Approved: 23 June 2023
Study 4 (extrapolation – treatment)	PK bridging and extrapolation of safety and efficacy to support use of a single IV dose of cas+im for the treatment of COVID-19 from adults to paediatric patients from birth to <18 years of age		
Study 7 (extrapolation – prevention)	PK bridging and extrapolation of safety and efficacy to support use of a single SC dose of cas+im for the prevention of COVID-19 from adults to paediatric subjects from birth to <18 years of age		

cas+im = casirivimab+imdevimab; CSR = clinical study report; LPLV = last participant last visit; PIP = paediatric investigational plan; PopPK = population PK.

[a] COV-2114 was removed from the agreed PIPs due to limited study enrollment prior to the Omicron-related enrolment pause (only 2 patients were enrolled).

The claimed indication of the current submission is supported by clinical pharmacology and immunogenicity data from Phase 3 Cohort 2 of Study COV-and on popPK analyses of data from paediatric (birth to <18 years) and adult participants pooled from 6 studies (COV-2066, COV-2067, COV-2069, COV-20145, COV-2114, COV-2121).

The efficacy evaluation for paediatric patients based on clinical and virologic efficacy data from Phase 3 Cohort 2 of Study COV-2067 is included in the submission. The data are considered supportive.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

All clinical trials contributing to the current submission were submitted previously with the appropriate documentation relating to GCP compliance.

2.3.2. Pharmacokinetics

This section presents the clinical pharmacology data to support the use of Ronapreve for the treatment of Coronavirus Disease 2019 in children aged 2 years and older weighing at least 10 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Data to support the indication

The treatment indication in high-risk adolescent outpatients from ≥12 to <18 years of age with body weight ≥40 kg was previously supported by clinical pharmacology data and extrapolation of adult safety and efficacy data. The PK, PD and safety data supporting the treatment of paediatric patients (≥2 years of age and body weight ≥ 10 kg) with casirivimab+imdevimab are derived from the paediatric data within the COV-2067 study (Phase 3 Cohort 2), PK modelling and an extrapolation approach involving an assessment of similarity in the PK, PK/PD (viral load reduction), and PK/efficacy (medically attended visits [MAVs] including hospitalisations and deaths) relationships between paediatric patients <18 years of age and adults in study COV-2067.

The modified paediatric investigation plans (PIPs) for casirivimab (EMEA-002964-PIP01-21-M02) and imdevimab (EMEA-002965-PIP01-21-M02) contain three clinical studies (Studies 1, 5, and 6) and three modelling and simulation studies (Studies 3, 4, and 7) in which paediatric pharmacokinetic (PK) data were collected and analysed, respectively (see table above).

- Phase 3 Cohort 2 of the pivotal study COV-2067

The PK evaluation for the treatment of COVID-19 in paediatric patients (from birth to <12 years of age) draws upon data derived from Phase 3 Cohort 2 of the pivotal study COV-2067. Primary objective was to characterise the concentrations of Ronapreve in serum over time, secondary objective was to assess the immunogenicity. Supporting PK data are provided from five additional adult and paediatric studies for the purpose of popPK modelling in both the adult and paediatric populations.

Table 3. Clinical Studies Used to Support Pharmacokinetic Evaluation of Casirivimab+Imdevimab in Paediatrics

Study Number	Phase	Title/Design	Treatment Groups	Dosage Form	Population	PK and ADA Samples
COV–2066	1/2/3	A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Hospitalized Patients With COVID-19	Casirivimab+imdevimab IV 2400 mg single dose or placebo Casirivimab+imdevimab IV 8000 mg single dose or placebo	IV 1-hour infusion	Hospitalized adult patients infected with SARS-CoV-2	**PK samples** Phase 1: pre-dose, post-dose[a], Days 3, 5, 7, 15 and 29. When applicable, at discharge before Day 29. Phase 2/3: pre-dose, post-dose, Day 15, Day 29. When applicable, at discharge before Day 29. **ADA samples** Phase 1: pre-dose, at discharge before Day 29, on Days 29 and 57 over the hospitalization/post-discharge period, and at EOS on Day 169 Phases 2 and 3: pre-dose, at discharge before Day 29, and on Day 29 in the hospitalization/post-discharge period
COV–2067	1/2/3	Adaptive, Randomized, Double-blind, Placebo-controlled Study Assessing the Safety, Tolerability, and Efficacy of Anti-Spike(s) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19	Adults: Casirivimab+imdevimab 1200 mg IV or placebo Casirivimab+imdevimab 2400 mg IV or placebo Casirivimab+imdevimab 8000 mg IV or placebo Paediatrics (Phase 3 Cohort 2) Treatment groups for paediatrics are presented in Table 3	IV 1-hour infusion	Adult and paediatric outpatients with COVID-19	**PK samples** Phase 1: pre-dose, post-dose[a], Days 3, 5, 7, 15 and 29. When applicable, at discharge before Day 29. Phase 2: pre-dose, post-dose[a] and Day 29. Phase 3 (patients ≥18 years)[b]: pre-dose, post-dose[a], Days 29 and 120 Phase 3 (patients <18 years): pre-dose, post-dose[a], Days 3, 7, 15, 22, 29, 90 and 120 **ADA samples** Phase 1 and 2: pre-dose, Day 29 Phase 3 (patients ≥18 years): pre-dose, Days 29 and 120 Phase 3 (patients <18 years)[b, c]: pre-dose, post-dose[a], Days 3, 7, 15, 22, 29, 90 and 120
COV–2069	3	A 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	Casirivimab+imdevimab 1200 mg SC or placebo Treatment groups for paediatrics are presented in Table 3	SC injection	Adults and paediatrics with household contact exposure to individuals with SARS-CoV-2 infection	**PK samples** Adult/Adolescents: Sentinel group: pre-dose, Days 2, 4, 8, 15, 22, 29, 57, 85, 113, 141, 169, 197, 225 and early termination visit when applicable. Safety group: pre-dose, Days 29, 57, 113, 169, 225 and early termination visit when applicable **ADA samples** pre-dose, Day 29, 113 and 225
COV–20145	2	A Randomized, Double-blind, Placebo-controlled Study Assessing the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Outpatients with SARS-CoV-2 Infection	Casirivimab+imdevimab IV 2400, 1200, 600 or 300 mg single dose or placebo Casirivimab+imdevimab SC 1200 or 600 mg single dose or placebo	IV 1-hour infusion or SC injection	Adult outpatients with COVID-19	**PK samples** Pre-dose, post-dose[a], Days 3, 5, 7 and 120 **ADA samples** pre-dose, and Day 120

Study Number	Phase	Title/Design	Treatment Groups	Dosage Form	Population	PK and ADA Samples
COV–2114	1b	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 Hospitalized Due to COVID-19	Single IV body weight-based dose equivalent to casirivimab+imdevimab 2400 mg or 8000 mg IV adult dose (Table 3)	IV 1-hour infusion	Hospitalized paediatric patients with COVID-19	**PK samples** Pre-dose, post-dose[a], Days 7, 29, 57 and 113 **ADA samples** [b] pre-dose, Day 29, 56 and 113
COV–2121	2a	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	Single SC body weight-based dose equivalent to casirivimab+imdevimab 1200 mg SC adult dose (Table 3)	SC injection	High-risk paediatric subjects	**PK samples** Pre-dose, Days 2, 4, 8, 15, 29, 57, 85 and 113 **ADA samples** [b] pre-dose, Day 29 and 85

ADA = anti-drug antibody; COVID-19 = Coronavirus disease 2019; IV = intravenous; PK = pharmacokinetic; Q4W = every 4 weeks; SC = subcutaneous; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

[a] For IV, within 60 minutes after the end of infusion; for SC, at least 60 minutes after study drug administration.

[b] Patients were randomly assigned to a blood sample collection schedule.

[c] In patients <12 years in COV-2067, immunogenicity was analyzed only in pre-dose and Day 29 PK-ADA samples.

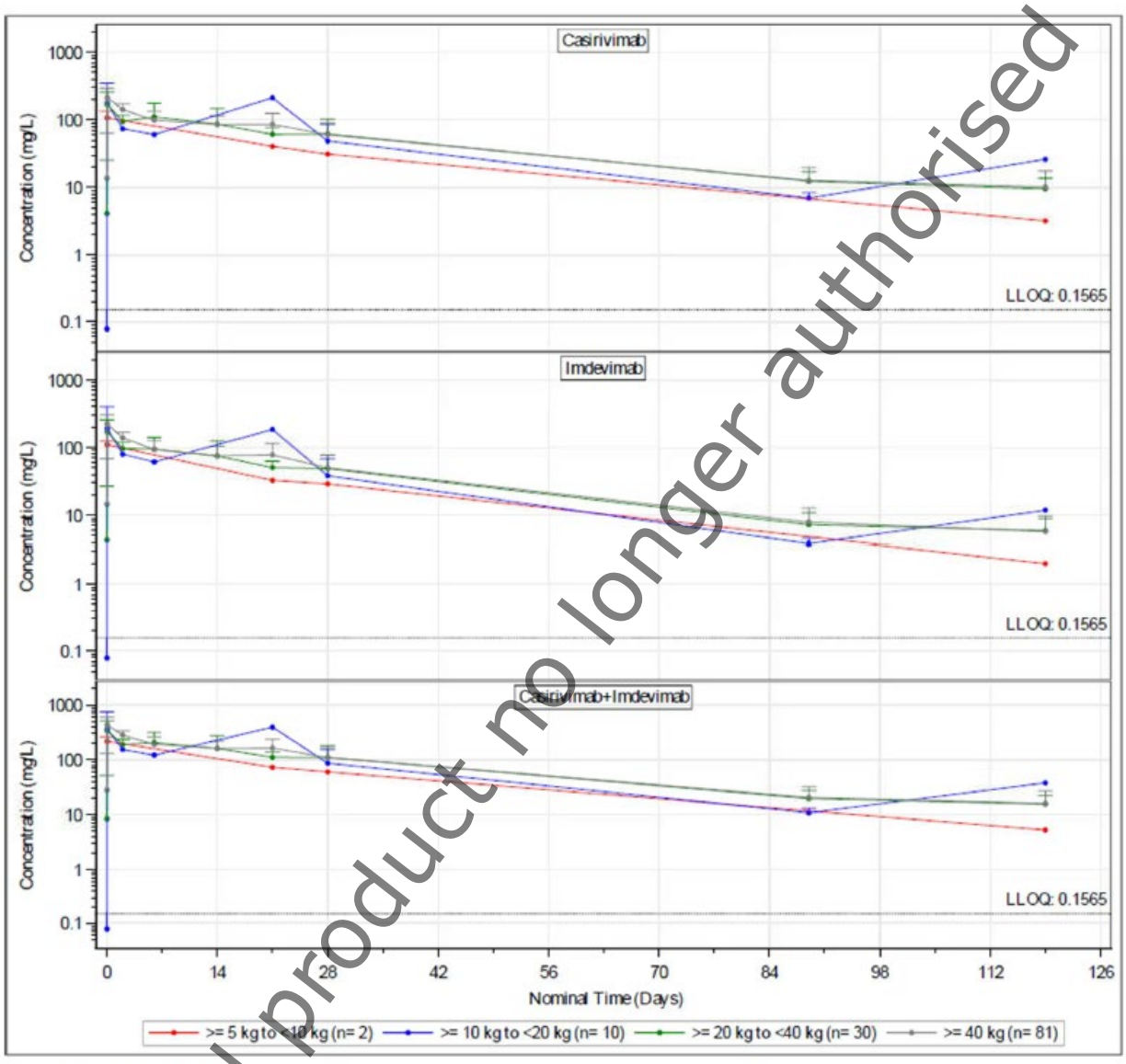
Table 4. Treatment Groups for Paediatric Subjects in Studies COV-2067, 2069, 2114, and 2121 based on Body Weight-based Dose Equivalent to Casirivimab+Imdevimab 1200 or 2400 mg IV or 1200 mg SC

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)	Dose Equivalent for 1200 mg SC Dose (600 mg per mAb)
≥40 kg	1200 mg IV (600 mg per mAb)	2400 mg IV (1200 mg per mAb)	1200 mg SC (600 mg per mAb)
≥20 kg to <40 kg	450 mg IV (225 mg per mAb)	900 mg IV (450 mg per mAb)	792 mg SC (396 mg per mAb)
≥10 kg to <20 kg	224 mg IV (112 mg per mAb)	450 mg IV (225 mg per mAb)	408 mg SC (204 mg per mAb)
≥5 kg to <10 kg	120 mg IV (60 mg per mAb)	240 mg IV (120 mg per mAb)	144 mg SC (72 per mAb)

IV = intravenous; mAb = monoclonal antibody; SC = subcutaneous.

The concentrations of total casirivimab, total imdevimab, and total casirivimab+imdevimab combined are summarised descriptively by nominal sampling time and treatment group.

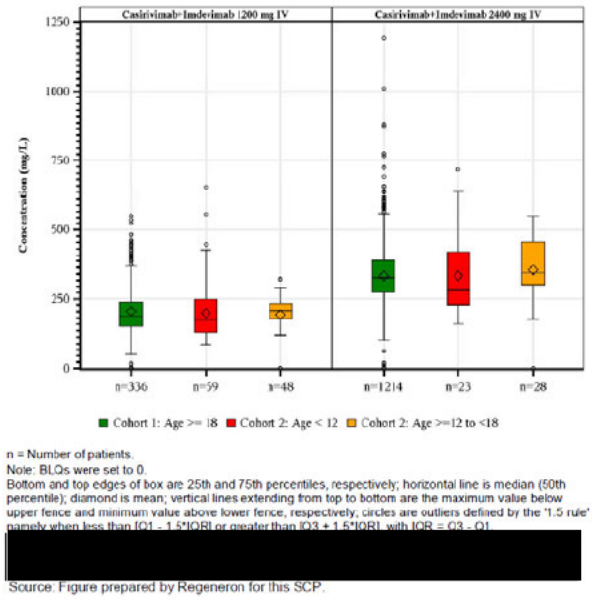
Figure 1. Mean (+SD) Concentrations of Total Casirivimab, Total Imdevimab, and Total Casirivimab+Imdevimab Combined in Serum by Nominal Time, Treatment Group, and Body Weight Tier in Outpatients <18 Years of Age with COVID-19 (COV-2067 Phase 3 Cohort 2, 1200 mg IV Dose Group, Log-Scaled [PKAS])



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.

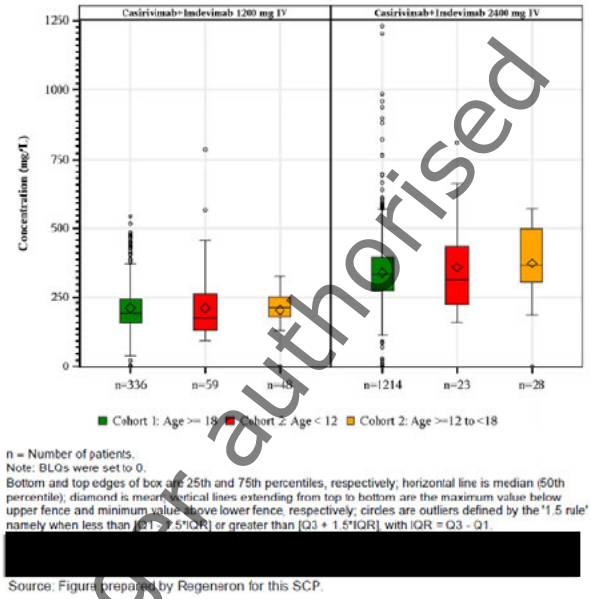
Figure 2. Boxplot of Concentrations of Total Casirivimab (left) and Imdevimab (right) in Serum at End of Infusion in Paediatric and Adult Outpatients with COVID-19 by Age Group and Treatment Group (COV-2067, Phase 3 Cohort 1 and Phase 3 Cohort 2 [PKAS])



n = Number of patients.
Note: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; horizontal line is median (50th percentile); diamond is mean; vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence, respectively; circles are outliers defined by the "1.5 rule" namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

[redacted]

Source: Figure prepared by Regeneron for this SCP.

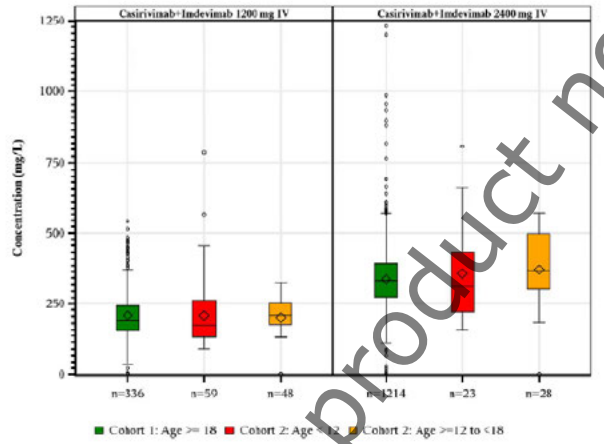


n = Number of patients.
Note: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; horizontal line is median (50th percentile); diamond is mean; vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence, respectively; circles are outliers defined by the "1.5 rule" namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

[redacted]

Source: Figure prepared by Regeneron for this SCP.

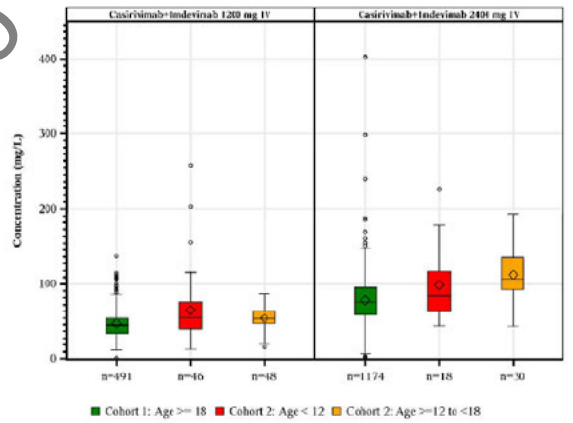
Figure 3. Boxplot of Concentrations of Total Imdevimab (left) and Casirivimab (right) in Serum at End of Infusion in Paediatric and Adult Outpatients with COVID-19 by Age and Treatment Group (COV-2067, Phase 3 Cohort 1 and Phase 3 Cohort 2 [PKAS])



n = Number of patients.
Note: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; horizontal line is median (50th percentile); diamond is mean; vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence, respectively; circles are outliers defined by the "1.5 rule" namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

[redacted]

Source: Figure prepared by Regeneron for this SCP.



n = Number of patients.
Note: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; horizontal line is median (50th percentile); diamond is mean; vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence, respectively; circles are outliers defined by the "1.5 rule" namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

[redacted]

Source: Figure prepared by Regeneron for this SCP.

Non-compartmental analysis was not conducted in the paediatric cohort but was instead investigated by popPK analyses.

The tables below provide an overview of the number of adult and paediatric subjects included in the updated model popPK analysis sets by study and antibody, and a stratified overview on included and available PK data in paediatrics.

Table 5. Summary of Subjects included in the Updated Model Population PK Analysis Sets for Casirivimab and Imdevimab

Study	All Subjects		Paediatric Subjects	
	Casirivimab	Imdevimab	Casirivimab	Imdevimab
COV–2066	1303	1302	-	-
COV–2067	4304	4303	145	145
COV–2069	286	284	72	71
COV–20145	967	967	-	-
COV–2114	1	1	1	1
COV–2121	7	7	7	7
Overall	6868	6864	225	224

Studies COV–2066 and COV–20145 did not include paediatric subjects.

Table 6. Summary of Paediatric Subjects and Quantifiable Samples included in the Population PK Analysis for Casirivimab and Imdevimab by Age Category and Study

Study	Baseline Age Category (Years)	Casirivimab		Imdevimab	
		Number of Subjects	Number of Quantifiable Samples	Number of Subjects	Number of Quantifiable Samples
COV–2067	<1	1	2	1	2
	≥ 1 - <2	1	3	1	3
	≥ 2 - <5	6	17	6	17
	≥ 5 - <9	19	58	19	58
	≥ 9 - <12	42	126	42	126
	≥ 12 - <18	76	240	76	240
COV–2069	≥ 12 - <18	72	185	71	171
COV–2114	≥ 1 - <2	1	3	1	3
COV–2121	≥ 1 - <2	1	2	1	2
	≥ 2 - <5	3	14	3	14
	≥ 5 - <9	2	8	2	8
	≥ 9 - <12	1	4	1	4
Overall	**Overall**	**225**	**662**	**224**	**648**

Table 7. Summary of Paediatric Subjects and Quantifiable Samples included in the Population PK Analysis for Casirivimab and Imdevimab by Body Weight Group and Study

Study	Baseline Weight Category (kg)	Casirivimab		Imdevimab	
		Number of Subjects	Number of Quantifiable Samples	Number of Subjects	Number of Quantifiable Samples
COV–2067	≥5 to <10	2	5	2	5
	≥10 to <20	9	22	9	22
	≥20 to <40	33	99	33	99
	≥40	101	320	101	320
COV–2069	≥20 to <40	1	3	1	3
	≥40	71	182	70	168
COV–2114	≥5 to <10	1	3	1	3
COV–2121	≥10 to <20	5	20	5	20
	≥20 to <40	2	8	2	8
Overall	**Overall**	**225**	**662**	**224**	**648**

- Pop PK analysis

Pop PK analysis has been conducted based on pooled data as indicated above in order to characterise PK profiles across populations, to evaluate covariates in the paediatric population, support the extrapolation approach (efficacy and safety) based on achieving matching exposures between the two populations, and the determination of flat doses for paediatric weight bands.

A previously developed model was updated (PIP Study 3) including PK data from two additional paediatric studies: COV-2114 (hospitalised patients below 18 years of age) and COV-2121 (high-risk paediatric subjects below 12 years of age). The paediatric data from COV-2114 and COV-2121 were pooled with final adult data from the initial studies (COV-2066, COV-2067, COV-2069, and COV-20145), as well as final paediatric data from COV-2067 and COV-2069.

For both the casirivimab (n = 6868) and imdevimab (n = 6864) pooled popPK analysis sets, the majority of participants were adults (96.7%) and there were approximately equal numbers of males and females. Most of the study participants were White (approximately 81.2%), 7.0% were Black, and 3.5% were Asian. The median age was 45 years (range 0–98 years), median baseline body weight (BMI) was 81.6 kg (range 8.6-235 kg), and median body mass index was 28.4 kg/m2 (range 4.2–74.2 kg/m2).

For paediatric subjects, the median age was 13 years (range 0-17 years), the median baseline body weight was 58.3 kg (range: 8.6-157 kg), and the median BMI was 21.8 kg/m2 (range: 12.2-47.8 kg/m2).

Table 8. Casirivimab Final Population Pharmacokinetic Parameter Estimates and Bootstrapped Confidence Intervals

Parameter (Units)	Estimate	%RSE	Bootstrap Median (2.5th, 97.5th percentiles)
CL: Clearance (L/day)	0.1753	0.9224	0.1752 (0.1727, 0.1785)
Vc: Central Volume of Distribution (L)	3.849	1.129	3.846 (3.775, 3.923)
Q: Intercompartmental Clearance (L/day)	0.5954	4.044	0.5949 (0.555, 0.6417)
Vp: Peripheral Volume of Distribution (L)	3.274	1.727	3.273 (3.203, 3.348)
KA: Absorption Rate Constant (1/day)	0.2621	8.558	0.2622 (0.2251, 0.3054)
F1: Bioavailability	0.6897	1.472	0.689 (0.6636, 0.7125)
Weight on CL	0.7954	2.429	0.7955 (0.7507, 0.8423)
Weight on Vc	0.5636	5.264	0.5619 (0.5164, 0.6044)
Weight on Q	0.5518	24.03	0.5477 (0.2532, 0.8172)
Weight on Vp	0.6315	7.647	0.6355 (0.543, 0.721)
Albumin on CL	-0.9052	4.542	-0.9067 (-0.9991, -0.8057)
Female on CL	-0.05647	16.31	-0.05615 (-0.07747, -0.03752)
Black Race on CL	0.1019	17.19	0.101 (0.06246, 0.1463)
Mild Hepatic Impairment on CL	0.05663	22.55	0.05609 (0.0344, 0.08167)
High Flow Oxygen Supply on CL	0.2667	14.16	0.2657 (0.1686, 0.3838)
Hospitalization Status on CL	0.2997	7.861	0.2968 (0.2431, 0.3486)
C-reactive Protein on CL (COV-2066 & COV-2067 only)	0.02560	17.36	0.02564 (0.01654, 0.03368)
IL-8 on CL (COV-2066 only)	0.09332	15.76	0.09021 (0.05464, 0.1266)
Albumin on Vc	-0.1925	28.11	-0.1972 (-0.3106, -0.09313)
Female on Vc	-0.1238	9.459	-0.1237 (-0.1447, -0.101)
Hospitalization Status on Vc	0.1171	21.43	0.1149 (0.07729, 0.1616)
Positive Serostatus on CL	0.07408	14.32	0.07513 (0.05483, 0.09354)
Bioavailability for Paediatrics	0.8768	4.940	0.874 (0.8174, 0.9341)

Parameter (Units)	Estimate	%RSE	Bootstrap Median (2.5th, 97.5th percentiles)
Residual Variability	32.12	0.1591	31.97 (29.16,34.88)
IIV in CL (%CV)	21.18	1.565	21.3 (19.49,22.67)
IIV in Vc (%CV)	31.84	0.4428	31.39 (25.83,37.88)
IIV in Q (%CV)	75.59	2.588	74.74 (65.13,84.52)
IIV in KA (%CV)	115.1	2.674	114.9 (91.99,135.7)
Objective Function	-10,678.350		

CI = Confidence interval; RSE = Relative standard error; IIV = Inter-individual variability; IL-8 = Interleukin-8; KA = absorption rate constant.
Note: Covariates are time-varying unless otherwise noted.

Table 9. Imdevimab Final Population Pharmacokinetic Parameter Estimates and Bootstrapped Confidence Intervals

Parameter (Units)	Estimate	%RSE	Bootstrap Median (2.5th, 97.5th percentiles)
CL: Clearance (L/day)	0.2193	0.8787	0.2199 (0.2159, 0.2238)
Vc: Central Volume of Distribution (L)	3.870	1.080	3.874 (3.8, 3.946)
Q: Intercompartmental Clearance (L/day)	0.5307	3.571	0.5115 (0.4647, 0.5646)
Vp: Peripheral Volume of Distribution (L)	3.377	1.648	3.381 (3.305, 3.464)
KA: Absorption Rate Constant (1/day)	0.2515	8.441	0.2514 (0.2173, 0.2976)
F1: Bioavailability	0.6864	1.601	0.688 (0.662, 0.7142)
Weight on CL	0.7583	2.466	0.7529 (0.7035, 0.7944)
Weight on Vc	0.5660	4.922	0.5583 (0.5107, 0.6072)
Weight on Q	0.5853	20.19	0.533 (0.2528, 0.7941)
Weight on Vp	0.6247	8.002	0.6193 (0.5235, 0.7072)
Albumin on CL	-0.8787	4.152	-0.8795 (-0.9744, -0.787)
Female on CL	-0.06838	12.53	-0.07086 (-0.08747, -0.05066)
Black Race on CL	0.09415	17.98	0.09685 (0.05846, 0.1463)
Mild Hepatic Impairment on CL	0.06234	19.70	0.0621 (0.03777, 0.08708)
High Flow Oxygen Supply on CL	0.3106	11.57	0.3039 (0.196, 0.4112)
Hospitalization Status on CL	0.2316	8.813	0.2235 (0.1858, 0.2683)
C-reactive Protein on CL (COV-2066 & COV-2067 only)	0.02583	15.92	0.02628 (0.01795, 0.03565)
Albumin on Vc	-0.3409	11.95	-0.3471 (-0.4246, -0.2746)
Female on Vc	-0.1197	10.03	-0.1181 (-0.141, -0.09474)
Positive Serostatus on CL	0.07206	14.11	0.0737 (0.05415, 0.09271)
Bioavailability for Paediatrics	0.8522	5.514	0.8438 (0.78, 0.9053)
Residual Variability	32.34	0.1883	32.9 (29.64, 35.97)
IIV in CL (%CV)	21.04	1.460	22.39 (20.1, 24.99)
IIV in Vc (%CV)	32.28	0.4346	30.66 (24.24, 38.05)
IIV in Q (%CV)	69.85	2.500	61.95 (0.0233, 78.05)
IIV in KA (%CV)	112.9	2.583	111.8 (89.33, 132.5)
Objective Function	-9565.86		

CI = Confidence interval; IIV = Inter-individual variability; RSE = Relative standard error
Note: Covariates are time-varying unless otherwise noted.

Pop PK evaluation /predictivity

Absorption

The product is intended for intravenous use, this section is therefore not applicable.

Distribution

Based on post-hoc predictions utilising individual empirical Bayesian estimates (EBEs) of PK parameters, using the final PK model handed in, the mean total volume of distribution (combined central [Vc] and peripheral [Vp] volumes) in paediatric outpatients was estimated to be 5.526 L for casirivimab and 5.592 L for imdevimab. Estimated values for distribution were lower compared to adult outpatients, where the mean total volume of distribution was 7.093 L for casirivimab and 7.232 L for imdevimab.

Elimination

Typically for mabs, the metabolism of casirivimab and imdevimab is expected to be limited to proteolytic catabolism to small peptides and individual amino acids.

Based on post-hoc model-based predictions utilising individual EBEs of PK parameters, the mean terminal half-life and clearance in paediatric outpatients were estimated to be 34.4 days and 0.126 L/day, respectively, for casirivimab and 28.2 days and 0.157 L/day, respectively, for imdevimab. The clearance rates in paediatric outpatients were lower compared to those in adult outpatients, with mean clearances of 0.182 L/day for casirivimab and 0.226 L/day for imdevimab. Conversely, the half-lives in paediatric outpatients were longer compared to those in adult outpatients, with a mean half-life of 30.3 days for casirivimab and 25.7 days for imdevimab.

Due to sparse sampling, no non-compartmental PK analysis has been conducted, against which these results could be compared. The observed time course does not indicate a clear difference in terminal half-live compared to subjects weighing at least 40 kg (Figure 1).

Dose proportionality and time dependencies

Figures 2 and 3 indicate an overall linear increase in exposure over the dose range 1200 mg and 2400 mg in paediatrics, including age cohort 2 (below 12 years of age). As the administration is by single dose given IV, no accumulation is expected.

Special populations

- Simulations of Casirivimab+Imdevimab to Inform IV Dose Selection for Paediatrics (‹12 years of age and ‹ 40 kg)

PopPK modeling results based on pooled data suggest that the weight-tiered IV dose levels used in the paediatric cohort of Study COV-2067 would result in unmatched exposures as compared to those in adult outpatients treated with the equivalent 1200 mg IV dose. Following a weight-tiered IV dose of 120 mg (<10 kg), 224 mg (≥10 kg to <20 kg) and 450 mg (≥20 kg to <40 kg), exposures (AUCd28 and C28) to casirivimab and imdevimab were generally predicted to be lower across the body weight groups compared to those in adults receiving a 1200 mg IV dose (Figure 4). Stochastic simulations were performed to identify near optimal weighttiered IV doses that would provide casirivimab and

imdevimab simulated but untested exposures in paediatric subjects similar to SARS-CoV-2 infected adult outpatients receiving a single 1200 mg IV dose of casirivimab+imdevimab (Table 10 below). This potentially optimised proposal would lead to the following simulated exposure of both mabs in comparison with adults as expressed in Figure 5.

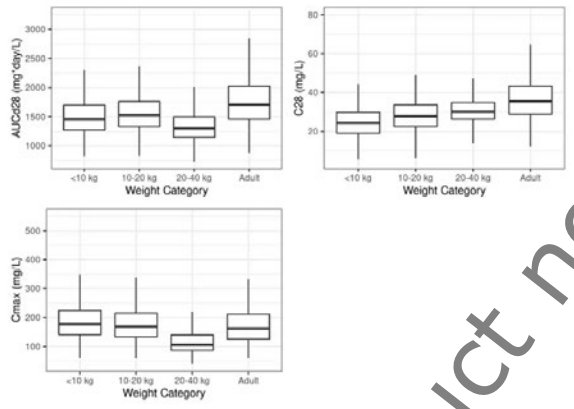
Table 10. Recommended Casirivimab+Imdevimab IV Doses for Each Weight Group in Paediatrics <18 Years of Age used for Simulations.

Body Weight Group	Dose Equivalent for Adult 1200 mg IV Dose (600 mg per mAb)
≥40 kg	1200 mg IV (600 mg per mAb)
≥20 kg to <40 kg	650 mg IV (325 mg per mAb)
≥10 kg to <20 kg	250 mg IV (125 mg per mAb)
≥5 kg to <10 kg [a]	150 mg IV (75 mg per mAb)

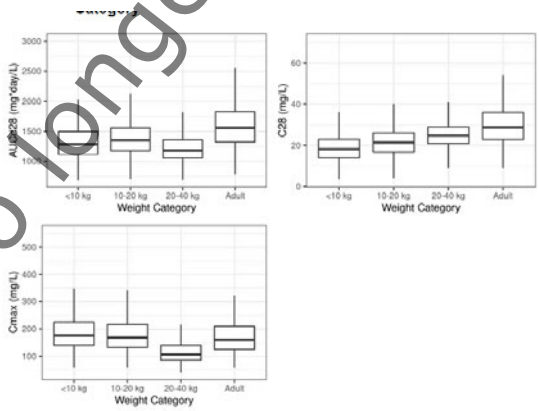
IV = intravenous; mAb = monoclonal antibody.

[a] Due to limited enrollment in patients weighing less than 10 kg where maturation processes can influence pharmacokinetics, extrapolation of safety and efficacy data from adults based on comparable exposures was considered insufficient for this body weight group.

Figure 4. Simulated Casirivimab (left) and Imdevimab (right) Exposures Following Single IV Dose of 1200 mg Casirivimab+Imdevimab or Body Weight Equivalent Dose Evaluated in Clinical Trials in Outpatients by Weight Category

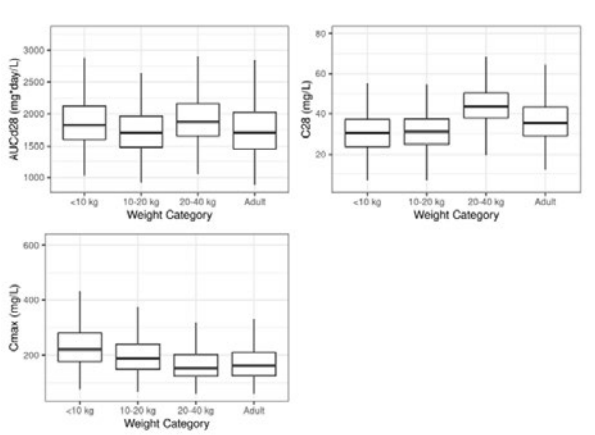


AUC_{d28} = area under the concentration time curve for 28-day interval after dosing; C_{28} = concentration on Day 28 after single dose; C_{max} = maximum (peak) concentration for a 28-day interval following dosing; IV = intravenous.
Body weight equivalent dose: 120 mg IV for <10 kg; 224 mg IV for ≥10 to <20 kg; 450 mg IV for ≥20 to < 40 kg; 1200 mg IV for adults (≥40 kg).
Source: R10933-PK-23020-SR-01V1 Addendum (Figure 1)



AUC_{d28} = area under the concentration time curve for 28-day interval after dosing; C_{28} = concentration on Day 28 after single dose; C_{max} = maximum (peak) concentration for a 28-day interval following dosing; IV = intravenous.
Body weight equivalent dose: 120 mg IV for <10 kg; 224 mg IV for ≥10 to <20 kg; 450 mg IV for ≥20 to <40 kg; 1200 mg IV for adults (≥40 kg).
Source: R10933-PK-23020-SR-01V1 Addendum (Figure 2).

Figure 5. Simulated Casirivimab (left) and imdevimab (right) Exposures Following a Single IV Dose of 1200 mg (600 mg per mAb) or Recommended Body Weight Equivalent Dose in Outpatients by Weight Category

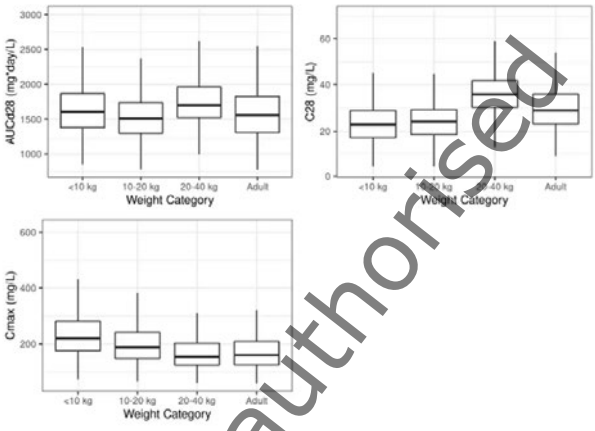


AUC_{d28} = area under the concentration time curve for 28-day interval after dosing; C_{28} = concentration on Day 28 after single dose; C_{max} = maximum (peak) concentration for a 28-day interval following dosing; IV = intravenous; mAb = monoclonal antibody

Body weight equivalent dose: 150 mg IV for <10 kg [a]; 250 mg IV for ≥10 to <20 kg; 650 mg IV for ≥20 to <40 kg; 1200 mg IV for adults (≥40 kg).

[a] Due to limited enrollment in patients weighing less than 10 kg where maturation processes can influence pharmacokinetics, extrapolation of safety and efficacy data from adults based on comparable exposures was considered insufficient for this body weight group.

Source: R10933-PK-23020-SR-01V1 Addendum (Figure 3).



AUC_{d28} = area under the concentration time curve for 28-day interval after dosing; C_{28} = concentration on Day 28 after single dose; C_{max} = maximum (peak) concentration for a 28-day interval following dosing; IV = intravenous; mAb = monoclonal antibody.

Body weight equivalent dose: 150 mg IV for <10 kg [a]; 250 mg IV for ≥10 to <20 kg; 650 mg IV for ≥20 to <40 kg; 1200 mg IV for adults (≥40 kg).

[a] Due to limited enrollment in patients weighing less than 10 kg where maturation processes can influence pharmacokinetics, extrapolation of safety and efficacy data from adults based on comparable exposures was considered insufficient for this body weight group.

Source: R10933-PK-23020-SR-01V1 Addendum (Figure 4).

Observed data from subjects between 20 and 40 kg are more in line with PK observed for subjects at least 40 kg. Thus, it cannot be ruled out that there are uncertainties and correlations of covariates and/or characterisation of weight affects accounting for this mismatch. Of note, neither the tested simulated nor the "optimised" simulated regimen did match convincingly well with the adult comparators.

2.3.3. Pharmacodynamics

Mechanism of action

Casirivimab+imdevimab is a combination of two neutralising immunoglobulin G1 (IgG1) recombinant human monoclonal antibodies directed against different, non-overlapping epitopes in the spike (S) protein receptor binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Primary and secondary pharmacology

The PD evaluation for the treatment of COVID-19 in paediatric patients (from birth to <12 years of age) is based on viral load data from Phase 3 Cohort 2 of pivotal study COV-2067 (see Section 5.4 – Clinical Efficacy).

Immunogenicity

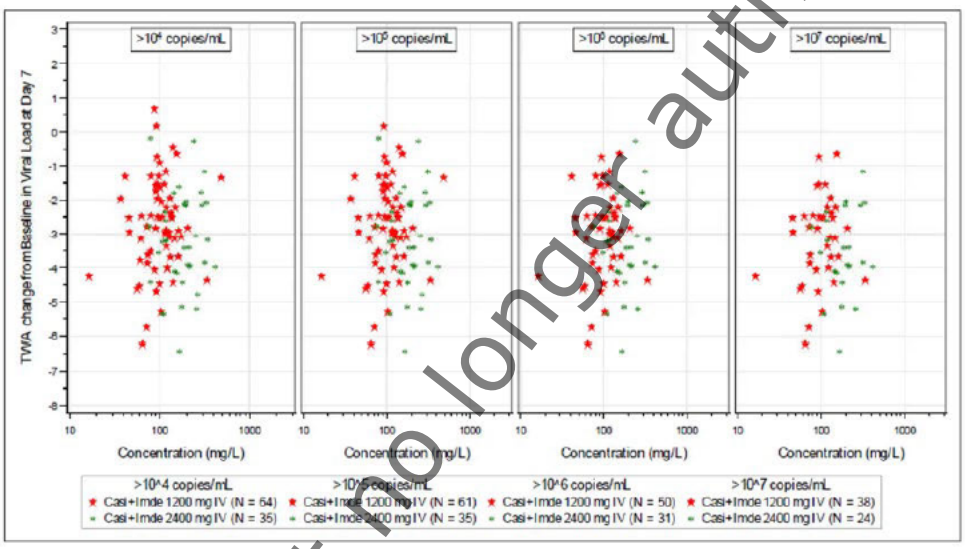
ADA dataset from Phase 3 Cohort 2 was limited with only a single participant positive to ADA against casirivimab and imdevimab. One paediatric participant below 12 years of age who received active treatment (1/123; 0.8%) had low titer treatment-emergent ADA for casirivimab and imdevimab, and was negative for Nab against casirivimab but positive for Nab against imdevimab.

2.3.4. PK/PD modelling

- Concentration-response analysis of viral load

No relationship between C28 of total casirivimab+imdevimab combined in serum and the time-weighted average change from baseline in viral load from Day 1 through Day 7 was observed across different baseline viral load categories (>104 copies/mL, >105 copies/mL, >106 copies/mL, >107 copies/mL) in the paediatric participants over the tested dose range.

Figure 6. 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 Outpatients <18 Years of Age with COVID-19 (Study COV-2067 Phase 3 Cohort 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.

[redacted]

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology data to support the use of Ronapreve for the treatment of COVID-19 in children aged 2 years and older weighing at least 10 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 together with the proposed extrapolation concept is discussed.

Ronapreve is currently approved in the EU for both the treatment of COVID-19 and prophylaxis against SARS-CoV-2 infection for adults and adolescents (12 years of age and older weighing at least 40 kg). The authorised dosage of casirivimab+imdevimab is 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) administered via intravenous (IV) infusion or subcutaneous (SC) injection for both treatment of COVID-19 in patients who do not require supplemental oxygen and prophylaxis against SARS-CoV-2 infection. The clinical pharmacology development program for casirivimab+imdevimab in adults and adolescents was presented and assessed in the initial marketing authorisation (EMEA/H/C/005814). Data were discussed and the posology was assessed based on the original COVID-19 strains present at time of development. Since then, epitopes in the spike (S) protein receptor binding domain underwent mutations and as a result, Ronapreve is not considered efficacious

against the variants currently in circulation. Consequently, enrolment in the paediatric studies was paused in December 2021 and terminated in June 2022. Data and extrapolation are discussed based on the very unlikely condition that re-mutation to the original strains would occur, and the binding behaviour would be shown to be similar to the former conditions.

Formerly agreed PIPs for casirivimab and imdevimab were modified to align the required numbers of treated patients with the status of enrolment prior to the enrolment issues and early termination of the studies. The justification for the extrapolation approach is based on several key scientific assumptions: morbidity and mortality results from SARS-CoV-2 infection and COVID-19 stems from the extent of the viral infection; viral burden reduction should lead to clinical benefit; the same viral pathogen, equally effects children and adults; the ability to contract the infection and routes of infection, as well as the characteristics of the viral infection (e.g. viral distribution, burden and infection course), are similar between adults and children; and it is anticipated that treatment with casirivimab+imdevimab will result in a similar reduction in viral burden across the adult and paediatric populations, ultimately leading to comparable clinical benefits.

It has been reported that COVID-19 disease severity is generally milder in children compared to adults, and children are at lower risk of experiencing severe outcomes such as hospitalisation, mechanical ventilation and mortality. Nevertheless, according to the MAH, the extrapolation for efficacy and, of note, also for safety, are based on an adequate characterisation of PK parameters aiming at the dosing strategy (flat dosing per weight bin, based on pop PK) that ensures paediatric exposures match those achieved in adults in terms of comparable target concentrations in the lung epithelial lining fluid, approximating the effective *in vitro* concentration required for 99% neutralisation of SARS-CoV-2 (original strains).

The modified agreed PIPs for casirivimab (EMEA-002964-PIP01-21-M02) and imdevimab (EMEA-002965-PIP01-21-M02) contain three clinical studies (Studies 1, 5, and 6) and three modelling and simulation studies (Studies 3, 4, and 7) in which paediatric pharmacokinetic (PK) data were collected following 120 mg, 224 mg, and 450 mg per increasing body weight bin, and were analysed, respectively, to assess the similarity in the PK, PK/PD (viral load reduction), and PK/efficacy (medically attended visits [MAVs] including hospitalisations and deaths) relationships between paediatric patients <18 years of age and adults in study COV-2067. Formally, the agreed reduced sample sizes were adequately reached.

As both mabs have been shown to follow a comparable linear PK, as expected when targeting an exogeneous target, the pharmacokinetics was found to be well characterised, especially in not severely ill subjects and patients throughout the former assessment of Ronapreve. Body weight was found to have the most influential impact on PK, thus selecting flat doses by weight bin is in general agreeable also for the paediatric population including children aged 2 years and older weighing at least 10 kg.

Subjects included in COV-2067 received 120 mg, 224 mg, and 450 mg per increasing body weight bin, starting from 5-10 kg of weight, whereas 150 mg, 250 mg, and 650 mg are the recommended doses based on pop PK.

PK observed following the doses selected for Cohort 2 (COV-2067) was initially not deemed plausible following a single dose treatment (sigmoidal shape observed for the treatment group 10-20 kg, this might be attributed to the low sample size (N=9), however, d21 concentration is in the range of the EOI value, and deemed not plausible.

The MAH was asked about the seemingly missing report R10933-10987-COV-2067-CP-01V3 and the Simulation Report (R10933-PK-23020-SR-01V1) and its Addendum. The MAH clarified that the reports were indeed submitted in December 2022, March 2023 and February 2024 respectively. Several concerns were raised in regard to the pop PK model and the proposal of increased single IV dose

derived from this model. The observed PK data seemed to suggest, that there was no need to increase the single IV dose, in particular that from 450 mg to 650 mg, as proposed on the bases of pop PK simulations. Similarly, the time-course was deemed highly similar compared with that observed for paediatric patients weighing more than 40 kg (targeted exposure range), in contrast to the simulated exposure. The population PK model that was used to select the increased dosing regimen was not well documented and reported. The report handed in indicated an inadequate reflection of weight and covariate selection. Further, no model diagnostics or plots to show an adequate predictive performance could be found to show a good characterisation of PK in paediatrics in particular for children aged 2 years and older weighing at least 10 kg, and to support the dosing proposal that would result in recommended dosing of clinically not tested doses (high impact). Therefore, it was assessed that the Model-predicted PK deviated to far from the observed PK and partly contradicted similarities of PK amongst subpopulations.

Furthermore, PK/PD characterisation in terms of viral load was regarded as no conclusive bridge to the clinical endpoint. In addition, there was no conclusive dose-response relationship identified that clearly guided dose selection during clinical development Ronapreve is indicated for. Thus, as the description and characterisation of PK (following the applied and modified regimen) was not considered adequate, this affected the justification of the extrapolation concept – especially in supporting the similarity in exposure between populations - and the B/R was not deemed to be positive. To address these criticisms the MAH provided and updated pop PK report. The updated model changed the arbitrary set age cut-offs and changed from fixed to estimated allometric exponents. The abandoning of the age based cut-offs lead to overall more reliable model fit for all weight groups. As the fixed allometric exponents in under 6 year olds as inconsistent and did not improve model fit the estimation of allometric exponents for all weight groups can be supported. Additionally, the previous model included certain covariates that were considered not relevant. The updated model reanalysed covariates and excluded hospitalisation status, oxygen supply, and inflammatory biomarkers as not significant or potentially confounding covariates. The retained covariates body weight (BW), albumin (ALB), sex, Black race and mild hepatic impairment (HEPIMP) on CL; BW, ALB, and sex on Vc were similar to previous models and the resulting model is considered to more robustly describe weight and covariate effects. To evaluate model fit and adequate predictive performance, the MAH provided additional diagnostic plots including prediction-corrected visual predictive checks and diagnostic plots by weight tiers and treatment groups. Apart from a slight under prediction of certain exposures, the model was able to describe the admittedly limited paediatric data reasonably well. As such the models ability to describe the similarity of exposure between adults and paediatric patients older than 2 years and weighing at least 10 could be supported. Furthermore, the MAH presented simulations for higher proposed doses for paediatric patients aged >2 years and weighing more than 10 mg. The model showed generally lower exposures for the weight groups <10 kg, 10-20 kg and 20-40 kg when given the originally intended doses of 120 mg, 224 mg and 450 mg respectively. The MAH conducted further simulations, adjusting flat doses for these lower weight groups to reach similar exposures as found in paediatric patients with weight over 40 kg or adult patients. These simulations were carried out for the adult dose equivalents of 600 mg and 1200mg per antibody. The resulting flat dose proposals for these paediatric patients in the weight groups 10-20 kg and 20-40 kg corresponding to the 600mg per antibody adult dose were 155 mg, 270 mg. For the 1200mg per antibody dose, the simulated doses for these groups were 310 mg and 540 mg per antibody. The 95th percentiles resulting simulated exposures did not reach simulated exposures in adults following a 2400 mg IV dose. Additional simulations of adult doses of up to 8000 mg per antibody were also presented. Taken together the MAH's proposal of an increase in flat doses for paediatric patients older than 2 years and above the weight of 10 kg could be agreed to as the modelling substantiates an increased similarity of exposure between adult and paediatric patient following the simulated dose increases, while not leading to additional safety concerns.

Potential changes in reference to raised concerns were not deemed necessary.

2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology was assessed based on the very unlikely situation of re-mutation of the COVID-19 virus back to surface proteins, that are of the same structure, and to which both antibodies, casirimab and imdevimab, need to be shown to have the same affinity, compared to the original program that led to MAA.

One major objection was initially raised concerning the adequacy of PK characterisation, the proposed more intense dosing regimen and deviations observed from the assumptions laid down in the corresponding PIPs.

The MAH discussed the observed trends in underprediction observed in paediatrics weight cohorts sufficiently. Overall, it could be agreed that the updated pop PK model shows an overall acceptable predictive power to support the selected doses to achieve exposure similarity. This conclusion has been supported by simulations of exposure following the dose as administered in the clinical paediatric studies, as well as following the proposed recommended dosing.

It is further agreed that the higher proposed dose levels in children are not considered to be of major concern given the high selectivity of these monoclonal antibodies to an exogeneous target and their established safety/tolerability profiles at doses up to 8 g IV in adults.

2.4. Clinical efficacy

The efficacy evaluation for paediatric patients is based on clinical and virologic efficacy data from Phase 3 Cohort 2 of Study COV-2067. While the focus is on efficacy data from patients <12 years of age, the data are presented by age (<12 years and ≥ 12 to < 18 years) and, as a subgroup analysis, by body weight (<40 kg and ≥ 40 kg).

Figure 7. Summary of Studies Contributing to the Efficacy Evaluation of Casirivimab+Imdevimab Treatment in Paediatric Patients with COVID-19 (figure taken from Clinical Overview 1.1; p 8)

Study No (Phase)	Study Design	Population	Number of Patients	Dose, Route, and Regimen	CSR
COV-2067 (Phase 3 Cohort 2 only)	Adaptive Phase 1/2/3, randomized, double-blind, placebo-controlled, multi-center master protocol to evaluate the efficacy, safety, and tolerability of cas+im combination therapy in outpatients with COVID-19.	Non-pregnant paediatric outpatients <18 years of age with laboratory-confirmed symptomatic COVID-19 and at least one risk factor for developing severe disease	Phase 3 Cohort 2: 206 patients <18 years (104 patients <12 years, 102 patients ≥ 12 years)	Phase 3 Cohort 2 [a]: Single dose (weight-tiered dose equivalent) of: • cas+im 1200 mg IV (129 patients) • cas+im 2400 mg IV (75 patients) • placebo IV (2 patients)	COV-2067 CSR Addendum 3 Phase 3 Cohort 2: LPLV = 07 Jun 2022 DBL =12 July 2022

cas+im = casirivimab+imdevimab; CSR = clinical study report; DBL = database lock; LPLV = last patient last visit; PA = protocol amendment.

[a] Placebo was discontinued per independent data monitoring committee (IDMC) recommendation from 25 February 2021 onwards. The 2400 mg arm was later discontinued with the implementation of PA9 Global/PA10 US (date of issue 16 Aug 2021), after which all participants enrolling into Cohort 2 were assigned to the 1200 mg dose level (or body weight equivalent).

Study COV-2067 was a seamless, adaptive Phase 1/2/3, randomised, double-blinded, placebo-controlled, multi-centre study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate COVID-19. Phases 1 and 2 focused on the safety and virologic efficacy of casirivimab+imdevimab, while the aim of Phase 3 was to assess the clinical efficacy and safety.

The study utilised an adaptive master protocol design to maximise the efficiency of identifying early signs of efficacy, allow for the potential to study multiple therapeutic combinations, and avoid the use of ineffective dose levels in patients with COVID-19.

On 23 December 2021, enrolment in COV-2067 and the other paediatric studies was paused by the MAH due to the emergence of the B.1.1.529/BA.1 SARS-CoV-2 (Omicron) variant and Omicron subvariants, against which casirivimab+imdevimab shows diminished *in vitro* neutralisation potency. As a result, the agreed PIPs for casirivimab and imdevimab 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 studies (Section 1.5). The other treatment study, COV-2114, was removed from the PIPs since only 2 patients had been enrolled at the time.

Study COV-2067 was terminated on 07 June 2022 (following the last patient last visit) due to the sustained loss of efficacy of casirivimab+imdevimab. At the time of termination, a total of 206 non-pregnant paediatric patients had been randomised to treatment in Phase 3 Cohort 2.

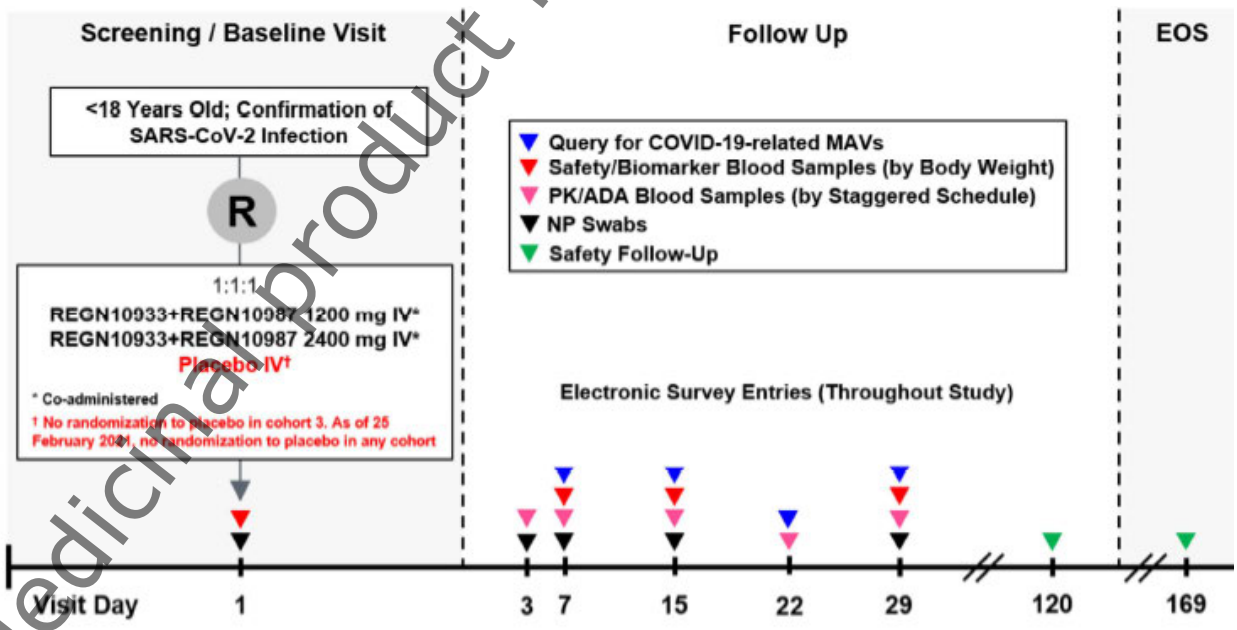
Study 2067 was assessed previously in the context of the initial marketing authorisation. The efficacy data for the entire Phase 3 Cohort 2 (<18 years of age, not pregnant at randomisation) were also assessed previously.

2.4.1. Main study

R10987-10933-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 (Study COV-2067)

Methods

COV-2067: Overview of Study Design for Phase 3 Cohort 2 and Phase 3 Cohort 3 Prior to Protocol Amendment 9 Global/10 US (Patients <18 Years)



The 2400 mg IV arm was discontinued with PA 9 Global/PA 10 US.
ADA = anti-drug antibody; EOS = end of study; IV = intravenous; MAV = medically-attended visit; NP = nasopharyngeal; PK = pharmacokinetic; R = randomization; REGN10933+REGN10987 = casirivimab+imdevimab; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Study participants

Patients eligible for participation in Phase 3 Cohort 2 had to have symptomatic COVID-19 at baseline (onset of COVID-19 symptoms within ≤ 7 days of randomisation).

The key eligibility criteria for Phase 3 Cohort 2 were as follows:

- <18 years of age and not pregnant at randomisation
- Outpatient (non-hospitalised with oxygen saturation ≥93% on room air)
- Positive diagnostic test for SARS-CoV-2 infection within ≤72 hours of randomisation
- Onset of COVID-19 symptoms within ≤7 days of randomisation (symptoms were determined by the investigator)
- No prior, current, or planned future use of COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IV immunoglobulin, systemic corticosteroids, or treatments for COVID-19 (investigational, authorised, or approved)
- At least one risk factor for developing severe COVID-19:
    - Obesity, defined as body mass index (BMI) ≥ 95th percentile for age and sex based on Centres for Disease Control and Prevention (CDC) growth charts (≥ 2 years only)
    - Cardiovascular disease, including hypertension
    - Chronic lung disease, including asthma
    - Type 1 or type 2 diabetes mellitus
    - Chronic kidney disease, including those on dialysis
    - Chronic liver disease
    - Immunosuppressed
    - Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19.

Treatments

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 randomised 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 the table below. Placebo was discontinued per independent data monitoring committee (IDMC) recommendation from 24 February 2021; thus, participants were subsequently randomised 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).

Summary of Casirivimab+Imdevimab IV Doses for Paediatric Patients <18 Years by Body Weight Group (COV-2067, Phase 3 Cohort 2)

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 kg to <10 kg	120 mg (60 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 kg 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)

IV = intravenous; mAb = monoclonal antibody.

Objectives / outcomes/endpoints

The primary objective of Study COV-2067 Phase 3 Cohort 2 was to evaluate the safety and tolerability of casirivimab+imdevimab compared to placebo.

All efficacy objectives and endpoints for Phase 3 Cohort 2 were secondary. The efficacy objectives were:

- to evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo using various measures of COVID-19-related MAVs, including COVID-19-related hospitalisations or all cause death, and
- to describe the virologic effects of casirivimab+imdevimab compared to placebo.

The efficacy endpoints presented in current submission are restricted to the key endpoints shown in below.

Overview of Key Efficacy Endpoints Presented in this Summary of Clinical Efficacy for Paediatric Patients (COV-2067 Phase 3 Cohort 2)

Endpoint	Definition	Assessment Time Points	Analysis Methods
Clinical Efficacy			
Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death	COVID-19 related hospitalizations were identified from information collected in the 'Medically-attended Visit' form of the CRF. All-cause death was defined as death from any cause, including AEs, progression/recurrence of disease, and 'other'.	Pre-dose through Day 29 [a]	Summarized descriptively. 95% CI estimated using Clopper Pearson method.
Proportion of patients with ≥1 COVID-19-related MAV or all-cause death	MAV was defined as hospitalization, ER visit, urgent care center, or outpatient/physician office/telemedicine visit, with the primary reason for the visit being COVID-19. Patients with multiple types of event were counted using the worst level event (decreasing order): all-cause death, hospitalization, ER, urgent care, physician office visit/telemedicine.	Pre-dose through Day 29 [a]	Summarized descriptively. 95% CI estimated using Clopper Pearson method.
Virologic Efficacy			
Time-weighted average change from baseline in viral load from Day 1 to Day 7	Viral load in RT-qPCR NP swab samples (log_{10} copies/mL)	Pre-dose and Day 7	Summarized descriptively with mean (SD), median, Q1:Q3, and min:max. Baseline defined as the last non-missing value measured prior to dosing.

Endpoint	Definition	Assessment Time Points	Analysis Methods
Virologic Efficacy cont.			
Change from baseline in viral load at each visit through Day 29	Viral load in RT-qPCR NP swab samples (log_{10} copies/mL)	Pre-dose and Days 3, 7, 15 and 29	Actual value, change from baseline, and percent change from baseline are summarized descriptively with mean (SD), median, Q1:Q3, and min:max. Baseline defined as the last non-missing value measured prior to dosing.

AE = adverse event; COVID-19 = Coronavirus disease 2019; CRF = Case Report Form; ER = emergency room; MAV = medically-attended visit; NP = nasopharyngeal; Q1:Q3: first quartile and third quartile; RT-qPCR = reverse transcription quantitative polymerase chain reaction; SD = standard deviation; SE-C19 = Self-reported Symptom Evolution of COVID-19.

[a] Queried at in-person visits or via phone.

Sample size

The study originally planned to enrol up to approximately 180 paediatric patients in Phase 3 Cohort 2. This was intended to allow approximately 52 patients to receive each dose of study drug available at the time Phase 3 Cohort 2 enrolment began (body weight equivalent of 1200 mg, 2400 mg, or placebo), which was considered adequate to describe the drug concentrations over time.

Regulatory commitments in the US required enrolment of at least 10 patients per treatment group <10 kg and 10 patients per treatment group between 10 kg and <40 kg.

To facilitate sufficient enrolment to satisfy these commitments, the sample size for Phase 3 Cohort 2 was increased (as of COV-2067 PA 10 Global/PA 11 US) to approximately 240 patients.

The sample size requirements by body weight category were also addressed in the EU PIPs.

COV-2067 Phase 3 Cohort 2: Minimum Number of Patients by Paediatric Body Weight Subset

Initial PIPs [a]	Final PIPs [b]
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.
[a] EMEA 002964 PIP01-21 (casirivimab) and EMEA 002965-PIP01-21 (imdevimab).
[b] EMEA 002964 PIP01-21-M02 (casirivimab) and EMEA 002965-PIP01-21-M02 (imdevimab).

Efficacy Analysis Population

Consistent with prior analyses in adult participants, all efficacy analyses for Phase 3 Cohort 2 are based on the modified full analysis set (mFAS). The mFAS includes all randomised patients whose baseline nasopharyngeal swab sample was positive for SARS-CoV-2 by reverse transcription quantitative polymerase chain reaction (RT-qPCR) and is based on the treatment allocated (as randomised).

If pre-dose results from the qualitative test were missing, the result from a post-dose sample could be used to determine the qualitative PCR status at baseline provided the sample was collected within 2 hours after starting the study drug infusion.

Randomisation

Paediatric patients in Phase 3 Cohort 2 were randomised 1:1:1 to receive a single IV dose of casirivimab+imdevimab 1200 mg (or weight-adjusted equivalent), casirivimab+imdevimab 2400 mg (or weight-adjusted equivalent), or placebo.

The placebo arm was discontinued for all cohorts per independent data monitoring committee (IDMC) recommendation from 25 February 2021 onwards; thus, participants in Phase 3 Cohort 2 were subsequently randomised 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 IV arm was later discontinued with the implementation of PA9 Global/PA10 US (protocol dated 16 August 2021), whereby all participants enrolled into Phase 3 Cohort 2 were assigned to a single IV dose of 1200 mg casirivimab+imdevimab (or body weight equivalent) to maximise data collection at that dose level. Thus, treatment assignment to patients enrolled under PA9 Global/PA10 US and later was open label.

Blinding (masking)

For patients enrolled prior to PA 9 Global/PA 10 US, the study patients, principal investigators, and study site personnel (except for the unblinded pharmacist at each site responsible for preparation of the drug infusion solution for IV administration) remained blinded to all randomisation assignments throughout the study. As of PA 9 Global/PA 10 US, the study consisted of a single arm and blinding was no longer applicable.

Statistical methods

All efficacy analyses for Phase 3 Cohort 2 were descriptive. No hypothesis testing was performed.

Changes in Planned Efficacy Analyses and Post-hoc Analyses

There were no changes to the planned efficacy analyses for Phase 3 Cohort 2 prior to or following unblinding or database lock.

Since the purpose of this Type 2 variation is to extend the treatment indication for patients who do not require supplemental oxygen to include paediatric patients from 2 to <12 years of age weighing at least 10 kg, the following post-hoc analyses were performed specifically for this SCE:

- Time-weighted average change from baseline in nasopharyngeal sample viral load (log10 copies/mL) from Day 1 to Day 7 in patients aged <12 years and patients ≥ 12 to <18 years and by body weight subgroups.
- Change from baseline in nasopharyngeal sample viral load at each visit through Day 29 in patients aged <12 years and patients ≥ 12 to <18 years (Section 2.1.4.2.2) and by body weight subgroups.

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 randomised to COV-2067 Phase 3 Cohort 2, of whom 2 patients (1.0%) were randomised to placebo, 129 patients (62.6%) were randomised to casirivimab+imdevimab 1200 mg IV (or body weight-tiered dose equivalent), and 75 patients (36.4%) were randomised to casirivimab+imdevimab 2400 mg IV (or body weight-tiered dose equivalent). Most patients were randomised to casirivimab+imdevimab 1200 mg IV due to discontinuation of the placebo arm per IDMC recommendation from 25 February 2021 onwards and discontinuation of the 2400 mg IV dose level upon implementation of PA 9 Global/PA 10 US.

Of the 206 randomised patients, 202 patients (98.1%) received treatment and 190 patients (92.2%) completed the study.

Discontinuations were higher in the casirivimab+imdevimab 2400 mg IV arm (10/75 patients [13.3%]) than in the 1200 mg IV arm (6/129 patients [4.7%]). Most discontinuations were either due to loss to follow-up or subject decision. No patient discontinued the study due to an adverse event.

Approximately half of the 206 randomised patients were aged <12 years (104 patients) and the other half were aged ≥ 12 to <18 years (102 patients). When comparing the disposition in the two age groups, the proportion of patients who discontinued the study prematurely was higher in the <12 years age group (10/104 [9.6%]) than in the older age group (6/102 [5.9%]); however, the absolute numbers in both treatment groups were low and the difference between the groups was due to more patients being lost to follow-up rather than due to an efficacy or safety concern

Summary of Patient Disposition for Paediatric Patients < 12 Years of Age (COV-2067 Phase 3 Cohort 2, FAS)

Age Category: <12

	Placebo (N=0)	R10933+R10987 1.2g IV (N=71)	R10933+R10987 2.4g IV (N=33)	R10933+R10987 Combined (N=104)	Total (N=104)
Randomized patients	0	71 (100%)	33 (100%)	104 (100%)	104 (100%)
Randomized patients but not treated	0	0	2 (6.1%)	2 (1.9%)	2 (1.9%)
Patients who completed the study	0	66 (93.0%)	28 (84.8%)	94 (90.4%)	94 (90.4%)
Patients who discontinued the study	0	5 (7.0%)	5 (15.2%)	10 (9.6%)	10 (9.6%)
Reasons for study discontinuation					
Adverse Event	0	0	0	0	0
Pregnancy	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0
Physician Decision	0	0	1 (3.0%)	1 (1.0%)	1 (1.0%)
Sponsor Request	0	0	0	0	0
Death	0	0	0	0	0
Lost To Follow-Up	0	4 (5.6%)	3 (9.1%)	7 (6.7%)	7 (6.7%)
Subject Decision	0	1 (1.4%)	1 (3.0%)	2 (1.9%)	2 (1.9%)

Patients with a body weight <40 kg received the body weight dose equivalent (Table 3).
Source: COV-2067 Addendum 3 CSR, Post-text Table 14.1.1.2A.

Summary of Patient Disposition for Paediatric Patients 12 to < 18 Years of Age (COV-2067 Phase 3Cohort 2, FAS)

Age Category: >=12

	Placebo (N=2)	R10933+R10987 1.2g IV (N=58)	R10933+R10987 2.4g IV (N=42)	R10933+R10987 Combined (N=100)	Total (N=102)
Randomized patients	2 (100%)	58 (100%)	42 (100%)	100 (100%)	102 (100%)
Randomized patients but not treated	0	1	2 (4.8%)	2 (2.0%)	2 (2.0%)
Patients who completed the study	2 (100%)	57 (98.3%)	37 (88.1%)	94 (94.0%)	96 (94.1%)
Patients who discontinued the study	0	1 (1.7%)	5 (11.9%)	6 (6.0%)	6 (5.9%)
Reasons for study discontinuation					
Adverse Event	0	0	0	0	0
Pregnancy	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0
Physician Decision	0	0	0	0	0
Sponsor Request	0	0	1 (2.4%)	1 (1.0%)	1 (1.0%)
Death	0	0	0	0	0
Lost To Follow-Up	0	1 (1.7%)	1 (2.4%)	2 (2.0%)	2 (2.0%)
Subject Decision	0	0	3 (7.1%)	3 (3.0%)	3 (2.9%)

[redacted]

Source: COV-2067 Addendum 3 CSR, Post-text Table 14.1.1.2A.
Patients with a body weight <40 kg received the body weight dose equivalent (Table 3).

Conduct of the study

The protocol underwent 10 amendments globally and 11 amendments in the US; the extra amendment in the US was primarily to incorporate an analysis of long COVID-19 (Protocol Amendment [PA] 9 US), which was only conducted at US sites. Thus, PA 9 Global corresponds to PA 10 US and PA 10 Global corresponds to PA 11 US. Paediatric patients were enrolled from PA 6.

Table 11. Overview of Protocol Amendments in Study COV-2067

Protocol Amendment	Date of Issue
Amendment 10 Global/11 US	3 December 2021
Amendment 9 Global/10 US	16 August 2021
Amendment 9 US	14 July 2021
Amendment 8	12 March 2021
Amendment 7	18 December 2020
Amendment 6	14 November 2020
Amendment 5	8 August 2020
Amendment 4	11 July 2020
Amendment 3	4 July 2020
Amendment 2	19 June 2020
Amendment 1	3 June 2020
Original protocol	29 May 2020

The placebo arm was discontinued for all cohorts per independent data monitoring committee (IDMC) recommendation from 25 February 2021 onwards. The 2400 mg IV arm was later discontinued with the implementation of PA 9 Global/PA 10 US, whereby all participants enrolled into Phase 3 Cohort 2 were assigned to a single IV dose of 1200 mg casirivimab+imdevimab (or body weight equivalent) Thus, treatment assignment to patients enrolled under PA9 Global/PA10 US and later were open label.

On 23 December 2021, enrolment in COV-2067 and the other paediatric studies was paused by the MAH due to the emergence of the B.1.1.529/BA.1 SARS-CoV-2 (Omicron) variant and Omicron subvariants, against which casirivimab+imdevimab shows diminished *in vitro* neutralisation potency. Study COV-2067 was terminated on 07 June 2022 (following the last patient last visit) due to the sustained loss of efficacy of casirivimab+imdevimab.

Baseline data

The median age in the overall Phase 3 Cohort 2 mFAS was 11 years (range 0-17 years), with 98 patients (51.0%) <12 years of age and 94 patients (49.0%) ≥ 12 years. Most patients were enrolled in the United States (187 patients [97.4%]), with the remainder in Mexico. More males (108 patients [56.3%]) were enrolled than females (84 patients [43.8%]), and patients were most commonly White (167 patients [87.0%]) and Hispanic or Latino (120 patients [62.5%]). The mean (SD) body weight was 55.7 (29.0) kg, with the majority having a body weight ≥ 40 kg (129 patients [67.2%]). A total of 48 patients [25.0%] had a body weight between 20 to <40 kg, 13 patients [6.8%] had a body weight from 10 to <20 kg, and 2 patients [1.0%] had a body weight <10 kg.

Among the 98 patients aged <12 years, the median age was 9.5 years (range 0-11 years), 52 (53.1%) patients were male, and 83 (84.7%) patients were White. The majority of patients aged <12 years had a body weight <40 kg (62 patients [63.3%]), with most patients in the 20 to <40 kg category. The mean (SD) body weight in patients aged <12 years was 38.5 (20.9) kg (Phase 3 Cohort 2 Post-text Table 14.1.2.1MA).

For the 94 patients aged ≥ 12 years, the median age was 14.5 years (range 12-17 years), 56 (59.6%) patients were male, and 84 (89.4%) patients were White. All except one patient aged ≥ 12 years had a body weight ≥ 40 kg (93/94 patients [98.9%]). The mean (SD) body weight in patients ☐ 12 years was 73.8 (25.0) kg.

Baseline Disease Characteristics

In the overall Phase 3 Cohort 2 mFAS, the median time from symptom onset to randomisation was 3.0 days (range: 0 to 7 days), 191/192 (99.5%) patients had a positive RT-qPCR result at baseline, and more patients were seronegative (150/192 patients [78.1%]) than seropositive (30/192 patients [15.6%]). One patient with a missing

RT-qPCR result at baseline had a positive result for a post-baseline sample collected within 2 hours after starting the study drug infusion. The mean (SD) viral load in nasopharyngeal swabs measured at the central lab was 6.85 (1.734) log10 copies/mL.

Among patients aged <12 years, the median time from symptom onset to randomisation was 2.5 days (range: 0 to 6 days), 97/98 (99.0%) patients had a positive RT-qPCR result at baseline, and most patients were seronegative (79/98 patients [80.6%]). In patients with a positive RT-qPCR result at baseline, the mean viral load in nasopharyngeal swabs measured at the central lab was 6.81 (1.867) log10 copies/mL ().

Baseline disease characteristics for patients aged ≥ 12 years were similar to those of patients aged <12 years. Among patients aged ≥ 12 years, the median time from symptom onset to randomisation was 3.0 days (range: 0 to 7 days), all 94 patients had a positive RT-qPCR result at baseline, and most patients were seronegative (71/94 patients [75.5%]). The mean viral load in nasopharyngeal swabs measured at the central lab was 6.90 (1.594) log10 copies/mL.

Numbers analysed

The full analysis set (FAS) includes all 206 randomised patients, grouped as randomised, while the safety analysis set (SAF) includes all 202 patients who received treatment, grouped as treated.

Consistent with prior analyses in adult participants, the efficacy analyses for Phase 3 Cohort 2 are based on the mFAS, which includes the 192 patients whose baseline nasopharyngeal samples were RT-qPCR positive for SARS-CoV-2, grouped as randomised. The mFAS includes 98 patients aged <12 years and 94 patients ≥ 12 to <18 years.

By body weight, the mFAS includes 63 patients with a body weight <40 kg and 129 patients with a body weight ≥ 40 kg. All except one patient in the <40 kg subgroup was <12 years of age.

Summary of Analysis Sets (COV-2067 Phase 3 Cohort 2, FAS)

	Placebo	Casirivimab+Imdevimab		Total
		1200 mg IV	2400 mg IV	
All patients <18 years of age				
No. of patients:				
FAS [a]	2	129	75	206
mFAS [b]	1	121	70	192
SAF [c]	2	129	71	202
Patients <12 years of age [d]				
No. of patients:				
FAS [a]	0	71	33	104
mFAS [b]	0	68	30	98
SAF [c]	0	71	31	102
Patients ≥12 to <18 years of age				
No. of patients:				
FAS [a]	2	58	42	102
mFAS [b]	1	53	40	94
SAF [c]	2	58	40	100
Patients <40 kg [d]				
No. of patients:				
FAS [a]	0	45	22	67
mFAS [b]	0	43	20	63
SAF [c]	0	45	21	66
Patients ≥40 kg [d]				
No. of patients:				
FAS [a]	2	84	51	137
mFAS [b]	1	78	50	129
SAF [c]	2	84	50	136

FAS = full analysis set; IV = intravenous; mFAS = modified full analysis set; NP=nasopharyngeal; RT-qPCR=reverse transcription quantitative polymerase chain reaction; SAF = safety analysis set.

[a] The FAS includes all randomized patients, based on the treatment allocated (as randomized).

[b] The mFAS includes all randomized patients with positive RT-qPCR in NP swab samples at randomization, based on the treatment allocated (as randomized). If pre-dose results from the qualitative test were missing, results from post-dose sample could be used to determine the qualitative PCR status at baseline provided the sample was collected within 2 hours after starting the study drug infusion.

[c] The SAF includes all randomized patients who received any study drug, based on the treatment received (as treated). Determination of 'as treated' was based on the actual study drug received on Day 1.

[d] Patients with a body weight <40 kg received the body weight dose equivalent (Table 3).

Source: COV-2067 CSR Addendum 3, Table 15.

Outcomes and estimation

The primary objective of Study COV-2067 Phase 3 Cohort 2 was to evaluate the safety and tolerability of casirivimab+imdevimab compared to placebo. Thus, there were no primary efficacy endpoints.

The efficacy endpoints presented in this submission are restricted to the key endpoints:

Clinical efficacy

- Proportion of patients with ≥1 COVID-19-related hospitalisation or all-cause death

- Proportion of patients with ≥1 COVID-19-related MAV or all-cause death

Virologic efficacy

- Time-weighted average change from baseline in viral load from Day 1 to Day 7
- Change from baseline in viral load at each visit through Day 29

While the focus of the efficacy evaluation for the proposed indication expansion is on data from patients <12 years, the data from Phase 3 Cohort 2 are presented by age (<12 years and ≥ 12 to <18 years) and, as a subgroup analysis, by body weight.

The clinical and virologic efficacy analyses 4 were repeated for the following body weight subgroups using the mFAS:

- Weight category 1 (<10 kg, 10 kg to <20 kg, 20 kg to <40 kg, ≥ 40 kg)
- Weight category 2 (<40 kg, ≥ 40 kg).

While the body weight subgroups were predetermined for the purpose of safety analyses, the efficacy subgroup analyses by body weight were not predetermined.

Clinical efficacy

COVID-19-related Hospitalisation or All-cause Death

No patients in the overall COV-2067 Phase 3 Cohort 2 mFAS, and therefore no patients aged <12 years, had a COVID-19-related hospitalisation or all-cause death through Day 29

COVID-19-related medically attended visits

Two patients aged <12 years in the Phase 3 Cohort 2 mFAS had a COVID-19-related MAV through Day 29 (2/98 patients [2.0%]). One patient had an emergency room visit on Day 2 and the other had an outpatient/physician office/telemedicine visit on Day 28. Both MAVs occurred in the 1200 mg IV arm.

One patient aged ≥12 years had a COVID-19-related MAV through Day 29 (1/94 patients [1.1%]). The patient was in the 2400 mg IV arm and had an outpatient/physician office/telemedicine visit on Day 29.

Overall, 3/192 (1.6%) paediatric patients in the COV-2067 Phase 3 Cohort 2 mFAS had a COVID-19-related MAV through Day 29: 2/121 (1.7%) patients in the 1200 mg IV arm and 1/70 (1.4%) patient in the 2400 mg IV arm. The one patient who received placebo did not have a COVID-related MAV.

Virologic efficacy

Time-weighted average change from baseline in nasopharyngeal sample viral load through Day 7

The viral load in nasopharyngeal samples decreased rapidly and similarly in the 1200 mg and 2400 mg IV arms as shown by the mean (SD) time-weighted average change from baseline in viral load through Day 7 (1200 mg IV = -2.65 (1.474) log10 copies/mL; 2400 mg IV = -2.57 (1.607) log10 copies/mL).

In patients aged <12 years, the mean (SD) time-weighted average daily change from baseline viral load through Day 7 in patients who received casirivimab+imdevimab was -2.65 (1.474) log10 copies/mL in the 1200 mg IV arm and -2.57 (1.607) log10 copies/mL in the 2400 mg IV arm. Corresponding mean (SD) values for patients aged ≥ 12 to < 18 years were -2.30 (1.325) and -3.15 (1.296) log10 copies/mL, respectively.

Time-weighted average change from baseline in viral load through Day 7 in paediatric patients by age group (COV-2067 Phase 3 Cohort 2, mFAS).

	<12 Years			≥ 12 to <18 Years		
		Casirivimab+Imdevimab [a]			Casirivimab+Imdevimab	
	Placebo (N=0)	1200 mg IV (N=68)	2400 mg IV (N=30)	Placebo (N=1)	1200 mg IV (N=53)	2400 mg IV (N=40)
BL viral shedding (log10 copies/mL)						
n	0	68	29	1	53	40
Mean (SD)		6.69 (1.854)	7.07 (1.905)	4.50 (.)	6.68 (1.402)	7.25 (1.759)
Median		6.97	7.36	4.50	6.91	7.46
Q1 : Q3		5.51 : 7.96	5.40 : 8.82	4.50 : 4.50	5.82 : 7.47	6.13 : 8.67
Min : Max		2.6 : 10.3	2.9 : 9.5	4.5 : 4.5	3.3 : 9.2	2.9 : 9.8
TWA change from BL in viral load through Day 3 (log_{10} copies/mL)						
n	0	59	19	0	50	35
Mean (SD)		-1.06 (0.868)	-1.12 (0.896)		-1.01 (0.886)	-1.50 (0.935)
Median		-1.18	-0.93		-0.90	-1.36
Q1 : Q3		-1.62 : -0.48	-1.60 : -0.49		-1.43 : -0.37	-2.20 : -0.99
Min : Max		-3.2 : 1.0	-2.9 : 0.3		-4.3 : 0.5	-3.2 : 0.5
TWA change from BL in viral load through Day 7 (log_{10} copies/mL)						
n	0	64	23	1	53	39
Mean (SD)		-2.65 (1.474)	-2.57 (1.607)	-0.97 (.)	-2.30 (1.325)	-3.15 (1.296)
Median		-2.69	-2.61	-0.97	-2.38	-3.19
Q1 : Q3		-3.73 : -1.85	-3.68 : -1.13	-0.97 : -0.97	-2.94 : -1.30	-3.98 : -2.12
Min : Max		-5.7 : 1.2	-5.4 : -0.2	-1.0 : -1.0	-6.2 : 0.7	-6.4 : -0.3

BL = baseline; IV = intravenous; max = maximum; mFAS = modified full analysis set; min = minimum; n = number of subjects within a specified category; Q1 : Q3 = first quartile and third quartile; TWA = time-weighted average; SD = standard deviation.

Baseline is defined as the last non-missing value measured prior to dosing.

mFAS Cohort 2 includes all randomized patients with positive RT-qPCR in NP swab samples at randomization.

[a] Patients with a body weight <40 kg the body weight dose equivalent (Table 3).

Change from baseline in nasopharyngeal sample viral load through Day 29

The median change from baseline in nasopharyngeal sample viral load was similar in the two casirivimab+imdevimab treatment arms of the Phase 3 Cohort 2 mFAS at all post baseline timepoints up to Day 29 for patients <12 years as well as for patients ≥ 12 to <18 years.

In patients aged <12 years, the median baseline nasopharyngeal sample viral load was 6.97 log10 copies/mL in the 1200 mg IV arm and 7.36 log10 copies/mL in the 2400 mg IV arm. Following treatment with casirivimab+imdevimab, the median change from baseline in viral load was -2.36 and -1.86 log10 copies/mL, respectively, at Day 3, and -5.04 and -5.58 log10 copies/mL, respectively, at Day 7. The median viral load was 0.00 log10 copies/mL from Day 7 onwards in the 1200 mg IV arm and from Day 15 onwards in the 2400 mg IV arm.

In patients aged ≥ 12 to < 18 years, the median baseline nasopharyngeal sample viral load was 6.91 log10 copies/mL in the 1200 mg IV casirivimab+imdevimab treatment arm and 7.46 log10 copies/mL in the 2400 mg IV arm. Similar to the younger age group, the median change from baseline in viral load following treatment with casirivimab+imdevimab was -1.80 and -2.71 log10 copies/mL, respectively, at Day 3, and -4.02 and -5.20 log10 copies/mL, respectively, at Day 7. The one placebo participant had a baseline viral load of 4.50 log10 copies/mL; data are not available for Day 3 but the median change from baseline was -1.95 log10 copies/mL at Day 7. Across all three treatment arms for patients aged ≥ 12 years, the median viral load was 0.00 log10 copies/mL from Day 15 onwards.

Change from baseline in viral load through Day 29 in paediatric patients by age group (COV-2067 Phase 3 Cohort 2, mFAS)

	<12 Years			≥ 12 to <18 Years		
		Casirivimab+Imdevimab [a]			Casirivimab+Imdevimab	
	Placebo (N=0)	1200 mg IV (N=68)	2400 mg IV (N=30)	Placebo (N=1)	1200 mg IV (N=53)	2400 mg IV (N=40)
BL viral shedding (log_{10} copies/mL)						
n	0	68	29	1	53	40
Median viral load		6.97	7.36	4.50	6.91	7.46
Q1 : Q3		5.51 : 7.96	5.40 : 8.82	4.50 : 4.50	5.82 : 7.47	6.13 : 8.67
Day 3 (log_{10} copies/mL)						
n	0	59	19	0	50	35
Median viral load		4.91	5.09		4.93	4.70
Q1 : Q3		3.61 : 6.04	4.17 : 6.32		3.68 : 6.25	3.66 : 6.23
Median change from BL		-2.36	-1.86		-1.80	-2.71
Q1 : Q3		-3.24 : -0.96	-3.20 : -0.99		-2.85 : -0.75	-4.41 : -1.97
Day 7 (log_{10} copies/mL)						
n	0	63	20	1	53	39
Median viral load		0.00	1.28	2.55	3.24	2.55
Q1 : Q3		0.00 : 3.16	0.00 : 3.61	2.55 : 2.55	0.00 : 4.71	0.00 : 4.00
Median change from BL		-5.04	-5.58	-1.95	-4.02	-5.20
Q1 : Q3		-7.05 : -3.24	-6.78 : -3.28	-1.95 : -1.95	-5.79 : -2.42	-6.42 : -3.29

	<12 Years			≥ 12 to <18 Years		
		Casirivimab+Imdevimab [a]			Casirivimab+Imdevimab	
	Placebo (N=0)	1200 mg IV (N=68)	2400 mg IV (N=30)	Placebo (N=1)	1200 mg IV (N=53)	2400 mg IV (N=40)
Day 15 (log_{10} copies/mL)						
n	0	63	21	1	52	37
Median viral load		0.00	0.00	0.00	0.00	0.00
Q1 : Q3		0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Median change from BL		-6.56	-7.36	-4.50	-6.12	-6.92
Q1 : Q3		-7.83 : -4.72	-8.72 : -5.40	-4.50 : -4.50	-7.35 : -5.12	-8.58 : -5.84
Day 29 (log_{10} copies/mL)						
n	0	58	21	1	53	36
Median viral load		0.00	0.00	0.00	0.00	0.00
Q1 : Q3		0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Median change from BL		-6.97	-7.36	-4.50	-6.72	-6.76
Q1 : Q3		-8.06 : -5.36	-8.72 : -5.75	-4.50 : -4.50	-7.39 : -5.79	-8.62 : -6.06

BL = baseline; IV = intravenous; max = maximum; mFAS = modified full analysis set; min = minimum; n = number of subjects within a specified category; Q1 : Q3 = first quartile and third quartile; SD = standard deviation.
Baseline is defined as the last non-missing value measured prior to dosing.
mFAS Cohort 2 includes all randomized patients with positive RT-qPCR in NP swab samples at randomization.
[a] Patients with a body weight <40 kg received the body weight dose equivalent (Table 3).
Source: COV-2067 Phase 3 Cohort 2 Additional Outputs 1, Table 2.3.2MA.

Virologic efficacy by body weight time-weighted average change from baseline in nasopharyngeal sample viral load through Day 7

In patients with a body weight <40 kg, the mean (SD) time-weighted average daily change from baseline in viral load through to Day 7 in patients who received casirivimab+imdevimab was -2.41 (1.586) log10 copies/mL in the 1200 mg IV arm and -2.65 (1.477) log10 copies/mL in the 2400 mg IV arm. Corresponding mean (SD) values for patients with a body weight ≥40 kg were -2.53 (1.328) and -3.03 (1.425) log10 copies/mL, respectively.

Figure 8. Time-weighted average change from baseline in viral Load through Day 7 in paediatric patients by body weight group (COV-2067 Phase 3 Cohort 2, mFAS) (figure taken from Summary Clinical Efficacy 2.1.5. 2.1; p 35-36)

	<40 kg			≥ 40 kg		
		Casirivimab+Imdevimab [a]			Casirivimab+Imdevimab [a]	
	Placebo (N=0)	1200 mg IV (N=43)	2400 mg IV (N=20)	Placebo (N=1)	1200 mg IV (N=78)	2400 mg IV (N=50)
BL viral shedding (log10 copies/mL)						
n	0	43	19	1	78	50
Mean (SD)		6.45 (2.021)	7.11 (1.902)	4.50 (.)	6.82 (1.428)	7.20 (1.793)
Median		6.58	7.36	4.50	7.07	7.46
Q1 : Q3		4.96 : 8.06	5.40 : 8.82	4.50 : 4.50	5.82 : 7.73	6.03 : 8.76
Min : Max		2.6 : 10.3	2.9 : 9.8	4.5 : 4.5	3.3 : 9.6	2.9 : 9.8
TWA change from BL in viral load through Day 3 (log_{10} copies/mL)						
n	0	35	11	0	74	43
Mean (SD)		-1.03 (0.964)	-1.22 (0.908)		-1.04 (0.833)	-1.40 (0.943)
Median		-1.18	-1.12		-0.98	-1.35
Q1 : Q3		-1.64 : -0.25	-2.34 : -0.61		-1.47 : -0.49	-2.15 : -0.84
Min : Max		-3.2 : 1.0	-2.6 : 0.3		-4.3 : 0.9	-3.2 : 0.5
TWA change from BL in viral load through Day 7 (log_{10} copies/mL)						
n	0	39	15	1	78	47
Mean (SD)		-2.41 (1.586)	-2.65 (1.477)	-0.97 (.)	-2.53 (1.328)	-3.03 (1.425)
Median		-2.17	-2.77	-0.97	-2.65	-3.17
Q1 : Q3		-3.77 : -1.63	-3.68 : -1.26	-0.97 : -0.97	-3.21 : -1.54	-3.98 : -2.05
Min : Max		-5.7 : 1.2	-5.4 : -0.2	-1.0 : -1.0	-6.2 : 0.7	-6.4 : -0.2

BL = baseline; IV = intravenous; max = maximum; mFAS = modified full analysis set; min = minimum; n = number of subjects within a specified category; Q1 : Q3 = first quartile and third quartile; TWA = time-weighted average; SD = standard deviation;.
Baseline is defined as the last non-missing value measured prior to dosing.
mFAS Cohort 2 includes all randomized patients with positive RT-qPCR in NP swab samples at randomization.
[a] Patients with a body weight <40 kg received the body weight dose equivalent (Table 3).
Source: COV-2067 Phase 3 Cohort 2 Additional Outputs 1, Table 2.3.1MW2.

Change from baseline in nasopharyngeal sample viral load through Day 29

Analysis of the data for patients who received casirivimab+imdevimab with a body weight <40 kg by narrower body weight categories (<10 kg, 10 to <20 kg, and 20 to <40 kg) did not identify any notable differences in the median change from baseline in viral load through Day 29. However, the low number of patients in these body weight categories, particularly the <10 kg (n = 2; both received 1200 mg IV) and 10 to <20 kg (n = 13; n = 12 received 1200 mg IV) categories, limits interpretation of the results and identification of any meaningful differences between the 1200 mg and 2400 mg casirivimab+imdevimab arms.

Change from baseline in Viral Load through Day 29 in Paediatric Patients by Body Weight Group (COV-2067 Phase 3 Cohort 2, mFAS)

	<40 kg			≥ 40 kg		
		Casirivimab+Imdevimab [a]			Casirivimab+Imdevimab [a]	
	Placebo (N=0)	1200 mg IV (N=43)	2400 mg IV (N=20)	Placebo (N=1)	1200 mg IV (N=78)	2400 mg IV (N=50)
BL viral shedding (log_{10} copies/mL)						
n	0	43	19	1	78	50
Median viral load		6.58	7.36	4.50	7.07	7.46
Q1 : Q3		4.96 : 8.06	5.40 : 8.82	4.50 : 4.50	5.82 : 7.73	6.03 : 8.76
Day 3 (log_{10} copies/mL)						
n	0	35	11	0	74	43
Median viral load		5.09	5.09		4.86	4.70
Q1 : Q3		3.48 : 6.13	4.17 : 6.40		3.74 : 6.24	3.66 : 6.23
Median change from BL		-2.36	-2.25		-1.96	-2.69
Q1 : Q3		-3.29 : -0.50	-4.68 : -1.21		-2.94 : -0.98	-4.29 : -1.68
Day 7 (log_{10} copies/mL)						
n	0	38	14	1	78	45
Median viral load		0.00	1.28	2.55	2.90	2.55
Q1 : Q3		0.00 : 3.45	0.00 : 4.35	2.55 : 2.55	0.00 : 4.27	0.00 : 3.60
Median change from BL		-4.66	-5.42	-1.95	-4.70	-5.24
Q1 : Q3		-6.29 : -2.97	-6.90 : -2.93	-1.95 : -1.95	-6.29 : -2.92	-6.42 : -3.64
Day 15 (log_{10} copies/mL)						
n	0	38	13	1	77	45
Median viral load		0.00	0.00	0.00	0.00	0.00
Q1 : Q3		0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Median change from BL		-5.86	-7.36	-4.50	-6.69	-6.92
Q1 : Q3		-7.61 : -3.57	-8.39 : -5.80	-4.50 : -4.50	-7.54 : -5.35	-8.65 : -5.31
Day 29 (log_{10} copies/mL)						
n	0	35	15	1	76	42
Median viral load		0.00	0.00	0.00	0.00	0.00
Q1 : Q3		0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00	0.00 : 0.00
Median change from BL		-6.56	-7.36	-4.50	-6.95	-7.07
Q1 : Q3		-8.06 : -4.72	-8.72 : -5.40	-4.50 : -4.50	-7.58 : -5.79	-8.65 : -6.03

BL = baseline; IV = intravenous; max = maximum; mFAS = modified full analysis set; min = minimum; n = number of subjects within a specified category; Q1 : Q3 = first quartile and third quartile; SD = standard deviation.
Baseline is defined as the last non-missing value measured prior to dosing.
mFAS Cohort 2 includes all randomized patients with positive RT-qPCR in NP swab samples at randomization.
[a] Patients with a body weight <40 kg received the body weight dose equivalent (Table 3).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of efficacy for trial COV-2067 (Phase 3 Cohort 2)

Title: 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

Study identifier	Protocol number: R10933-10987-COV-2067 (hereinafter referred to as 'COV-2067') EudraCT number:2020-003690-21 NCT number: NCT04425629	
Design	Adaptive, Phase 1/2/3, randomised, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy for the treatment of outpatients with COVID-19. The application is based on efficacy data from Phase 3 Cohort 2 only (<18 years old, not pregnant at randomisation) with a focus on patients aged <12 years and patients with a body weight <40 kg to extend the treatment indication for patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19 to include paediatric patients aged at least 2 years and weighing at least 10 kg. Participants in Phase 3 Cohort 2 were initially randomised 1:1:1 to a single intravenous (IV) dose of casirivimab+imdevimab 1200 mg (or body weight equivalent), casirivimab+imdevimab 2400 mg (or body weight equivalent), or placebo. The placebo arm was discontinued per independent data monitoring committee (IDMC) recommendation from 25 February 2021 onwards, while the 2400 mg IV arm was discontinued with the implementation of protocol amendment (PA) 9 Global/PA 10 United States (date of issue 16 August 2021). Thus, the majority of the 206 randomised patients were randomised to the 1200 mg IV arm: 129 patients to the 1200 mg IV arm, 75 patients to the 2400 mg IV arm, and 2 patients to placebo. Of the 206 randomised patients, 202 patients (98.1%) received treatment and 190 patients (92.2%) completed the study. Discontinuations were higher in the 2400 mg IV arm (10/75 patients [13.3%]) than in the 1200 mg IV arm (6/129 patients [4.7%]). Most discontinuations were due to either loss to follow-up or subject decision; no patient discontinued the study due to an adverse event. The primary objectives of Phase 3 Cohort 2 were to evaluate the safety and tolerability of casirivimab+imdevimab compared to placebo and to further characterise the concentrations of casirivimab and imdevimab in serum over time. Efficacy was assessed up to Day 29. All efficacy objectives and endpoints for Phase 3 Cohort 2 were secondary and all efficacy analyses were descriptive.	
	Duration of main phase:	29 days (for efficacy)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	No formal hypothesis testing		
Treatments groups	Cas+Im 1200 mg IV		Single IV dose of 1200 mg casirivimab+imdevimab or body weight equivalent (N = 129 for all randomised patients <18 years; N = 71 for age <12 years; N = 45 for body weight <40 kg)
	Cas+Im 2400 mg IV		Single IV dose of 2400 mg casirivimab+imdevimab or body weight equivalent (N = 75 for all randomised patients <18 years; N = 33 for age <12 years; N = 22 for body weight <40 kg)
	Placebo		Single IV dose of placebo (N = 2 for all randomised patients <18 years; N = 0 for age <12 years; N = 0 for body weight <40 kg)
Endpoints and definitions	Secondary endpoint (clinical efficacy)	COVID-19 hospitalisation or all-cause death	Proportion of patients with at least one COVID-19-related hospitalisation or all-cause death through Day 29
	Secondary endpoint (clinical efficacy)	COVID-19 MAV	Proportion of patients with at least one COVID-19-related medically-attended visit (MAV) through Day 29. A MAV was defined as hospitalisation, ER visit, urgent care center, or outpatient/physician office/telemedicine visit, with the primary reason for the visit being COVID-19.
	Secondary endpoint (virologic efficacy)	TWA change from BL in viral load	Time-weighted average (TWA) change from baseline in viral load (log10 copies/mL) from Day 1 to Day 7, as measured by RT-qPCR in nasopharyngeal (NP) swab samples
	Secondary endpoint (virologic efficacy)	Change from BL in viral load	Change from baseline in viral load (log10 copies/mL) at each visit up to Day 29, as measured by RT-qPCR in NP swab samples
Database lock	12 July 2022		
Results and Analysis			
Analysis description	**Secondary Analysis (Clinical Efficacy)**		
Analysis population and time point description	Phase 3 Cohort 2 modified full analysis set (mFAS) (age <12 years): All randomised patients aged <12 years whose baseline NP swab sample was positive for SARS-CoV-2 by RT qPCR. Based on the treatment allocated. Timepoint: up to 29 days after randomisation		

Descriptive statistics	Treatment group	Placebo	Cas+Im 1200 mg IV	Cas+Im 2400 mg IV
	Number of subjects	0	68	30
	COVID-19 hospitalisation or all-cause death, n (%)	-	0/68	0/30
	COVID-19 MAV, n (%)	-	2/68 (2.9%)	0/30

Notes	This was a subgroup analysis. The COVID-19-related MAVs through Day 29 were an emergency room visit on Day 2 and an outpatient/physician office/telemedicine visit on Day 28. Results for patients aged ≥ 12 to <18 years and <18 years are consistent with those of patients aged <12 years.			
Analysis population and time point description	Phase 3 Cohort 2 mFAS (body weight <40 kg): All randomised patients with a body weight <40 kg whose baseline NP swab sample was positive for SARS-CoV-2 by RT qPCR. Based on the treatment allocated. Timepoint: up to 29 days after randomisation			
Descriptive statistics	Treatment group	Placebo	Cas+Im 1200 mg IV	Cas+Im 2400 mg IV
	Number of subjects	0	43	20
	COVID-19 hospitalisation or all-cause death, n (%)	-	0/43	0/20
	COVID-19 MAV, n (%)	-	2/43 (4.7%)	0/20
Notes	This was a subgroup analysis. The COVID-19-related MAVs through Day 29 were an emergency room visit on Day 2 and an outpatient/physician office/telemedicine visit on Day 28. Results for patients with a body weight ≥ 40 kg are consistent with those of patients with a body weight <40 kg.			
Analysis description	**Secondary Analysis (Virologic Efficacy)**			
Analysis population and time point description	Phase 3 Cohort 2 mFAS (aged <12 years): All randomised patients aged <12 years whose baseline NP swab sample was positive for SARS-CoV-2 by RT qPCR. Based on the treatment allocated. Timepoint: up to 7 (TWA change from BL) or 29 (change from BL) days after randomisation			
Descriptive statistics and estimate variability	Treatment group	Placebo	Cas+Im 1200 mg IV	Cas+Im 2400 mg IV
	Number of subjects	0	68	30
	TWA change from BL in viral load through Day 7 (log10 copies/mL) Day 7 n Mean (SD)	 - -	 64 -2.65 (1.474)	 23 -2.57 (1.607)
	Change from BL in viral load through Day 29 (log10 copies/mL) Day 3 n Median Q1 : Q3 Day 7 n Median Q1 : Q3 Day 15	 - - - - - -	 59 -2.36 -3.24 : -0.96 63 -5.04 -7.05 : -3.24	 19 -1.86 -3.20 : -0.99 20 -5.58 -6.78 : -3.28

	n	-	63	21
	Median	-	-6.56	-7.36
	Q1 : Q3	-	-7.83 : -4.72	-8.72 : -5.40
	Day 29			
	n	-	58	21
	Median	-	-6.97	-7.36
	Q1 : Q3	-	-8.06 : -5.36	-8.72 : -5.75
Notes	The viral load in NP samples decreased rapidly and similarly in the 1200 mg and 2400 mg IV arms as shown by the TWA change from baseline in viral load through Day 7 and the change from baseline in viral load through Day 29. Results for patients aged ≥ 12 to <18 years and <18 years are consistent with those of patients aged <12 years.			
Analysis population and time point description	Phase 3 Cohort 2 mFAS (body weight <40 kg): All randomised patients with a body weight <40 kg whose baseline NP swab sample was positive for SARS-CoV-2 by RT qPCR. Based on the treatment allocated. Timepoint: up to 7 (TWA change from BL) or 29 (change from BL) days after randomisation			
Descriptive statistics and estimate variability	Treatment group	Placebo	Cas+Im 1200 mg IV	Cas+Im 2400 mg IV
	Number of subjects	0	43	20
	TWA change from BL in viral load through Day 7 (log10 copies/mL)			
	Day 7			
	n	-	39	15
	Mean (SD)	-	-2.41 (1.586)	-2.65 (1.477)
	Change from BL in viral load through Day 29 (log10 copies/mL)			
	Day 3			
	n	-	35	11
	Median	-	-2.36	-2.25
	Q1 : Q3	-	-3.29 : -0.50	-4.68 : -1.21
	Day 7			
	n	-	38	14
	Median	-	-4.66	-5.42
	Q1 : Q3	-	-6.29 : -2.97	-6.90 : -2.93
	Day 15			
	n	-	38	13
	Median	-	-5.86	-7.36
	Q1 : Q3	-	-7.61 : -3.57	-8.39 : -5.80
	Day 29			
	n	-	35	15
	Median	-	-6.56	-7.36
	Q1 : Q3	-	-8.06 : -4.72	-8.72 : -5.40

Notes	The viral load in NP samples decreased rapidly and similarly in the 1200 mg and 2400 mg IV arms as shown by the TWA change from baseline in viral load through Day 7 and the change from baseline in viral load through Day 29. Results for patients with a body weight ≥40 kg are consistent with those of patients with a body weight <40 kg.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study COV-2067 was an adaptive, phase 1/2/3, randomised, double-blinded, placebo controlled master protocol to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy for the treatment of COVID-19 in adult outpatients with SARS. Phases 1 and 2 focused on the safety and virologic efficacy of casirivimab+imdevimab, while the primary aim of Phase 3 was to assess the safety and clinical efficacy in adults and safety and PK in paediatrics. The approval of casirivimab+imdevimab for the treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19 was primarily supported by this pivotal study.

Non-hospitalised patients who have a positive diagnostic test for SARSCoV-2 were enrolled in the study. Cohort 1 (≥ 18 years of age) of the Phase 3 part was the relevant population to support the claimed indication in context of the marketing authorisation. The data of Cohort 2 (patients < 18 years of age) and Cohort 3 (pregnant at randomisation as well as asymptomatic patients (Phase 1/2) are not included in this submission and were reported already earlier in the context of the P46 procedure.

Eligible for participation in Phase 3 Cohort 2 were patients 18 years of age and not pregnant at randomisation who had symptomatic COVID-19 at baseline (onset of COVID-19 symptoms within 7 days of randomisation) and at least one risk factor for developing severe COVID. The further inclusion / exclusion criteria were the same as for the other Phase 3 cohorts.

Participants initially randomised 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. Placebo was discontinued per IDMC recommendation from 24 February 2021; thus, participants were subsequently randomised 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).

The primary objective of Study COV-2067 Phase 3 Cohort 2 was to evaluate the safety and tolerability of casirivimab+imdevimab compared to placebo. However, since the placebo was discontinued per from 24 February 2021 all efficacy analyses for Phase 3 Cohort 2 were descriptive. No hypothesis testing was performed.

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.

In context of the initial marketing authorisation, the CHMP concluded with regard to the design of study COV-2067: "*it is evident through the changes to the ongoing study that uncertainty was high at*

the initial planning stage and the trial underwent repeated refinement in light of accumulating information in an adaptive design approach" and finally accepted the design. With regard to the Cohort 2 the uncertainties and flaws of the study design are even more pronounced.

Results

While the focus is on the efficacy data from patients <12 years of age, the data are presented in the SCE by age (<12 years and ≥ 12 to < 18 years) and, as a subgroup analysis, by body weight (<40 kg and ≥40 kg).

Clinical efficacy

No patients in the overall COV-2067 Phase 3 Cohort 2 mFAS, and therefore no patients aged <12 years, had a COVID-19-related hospitalisation or all-cause death through Day 29

COVID-19-related medically attended visits

Two patients aged <12 years in the Phase 3 Cohort 2 mFAS had a COVID-19-related MAV through Day 29 (2/98 patients [2.0%]). One patient had an emergency room visit on Day 2 and the other had an outpatient/physician office/telemedicine visit on Day 28. Both MAVs occurred in the 1200 mg IV arm.

One patient aged >12 years had a COVID-19-related MAV through Day 29 (1/94 patients [1.1%]). The patient was in the 2400 mg IV arm and had an outpatient/physician office/telemedicine visit on Day 29.

Overall, 3/192 (1.6%) paediatric patients in the COV-2067 Phase 3 Cohort 2 (2 patients <12 year and 1 patient aged >12) had a COVID-19-related MAV through Day 29: 2/121 (1.7%) patients in the 1200 mg IV arm and 1/70 (1.4%) patient in the 2400 mg IV arm. The one patient who received placebo did not have a COVID-related MAV.

Virological efficacy

The viral load in nasopharyngeal samples decreased rapidly and similarly in the 1200 mg and 2400 mg IV arms as shown by the mean (SD) time-weighted average change from baseline in viral load through Day 7 (1200 mg IV = -2.65 (1.474) log10 copies/mL; 2400 mg IV = -2.57 (1.607) log10 copies/mL).

Subgroup analysis of the virologic efficacy data by body weight group for patients in the overall Phase 3 Cohort 2 mFAS who received casirivimab+imdevimab did not identify any differences in response between patients with a body weight <40 kg (n=63) and those with a body weight ≥ 40 kg (n=128).

2.4.3. Conclusions on the clinical efficacy

The clinical efficacy indicated that in paediatric patients aged <12 years and/or weighing <40 kg in Study COV-2067 (Phase 3 Cohort 2), there were no COVID-19-related hospitalisations or deaths and the viral load in nasopharyngeal samples decreased rapidly and similarly following treatment with a single IV dose of 1200 mg or 2400 mg casirivimab+imdevimab. No difference in response between the 1200 mg IV and 2400 mg IV doses was observed. All efficacy analyses for Phase 3 Cohort 2 were descriptive. No hypothesis testing was performed, the data are considered supportive and are not considered basis of the regulatory decision. This decision could be based on the pharmacological / extrapolation data.

Moreover, the conclusion made in the P46 procedure is still valid: 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 this procedure for inclusion of paediatric

patients weighing > 10 kg for treatment with casirivimab+imdevimab is currently hampered by epidemiological situation.

For further discussion please see the Benefit/Risk section.

2.5. Clinical safety

Introduction

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 summarised in the overview tables.

Patient exposure

All 202 paediatric patients in Phase 3 Cohort 2 of COV-2067 who received treatment were included in the safety analysis set (SAF), grouped as treated: n=2 for the placebo group, n=129 for the 1200 mg IV group, and n=71 for the 2400 mg IV group (2.7.4 SCS, Section 1.3.1). With the exception of 2 patients who received casirivimab+imdevimab (one <12 years and the other ≥ 12 to <18 years), all patients received the total planned IV dose.

Adverse events

Overview of Treatment-Emergent Adverse Events in Paediatric Participants aged <18 Years up to Day 29 (COV-2067 Phase 3 Cohort 2, SAF)

	Placebo (N = 2)	Casirivimab+Imdevimab		
		1200 mg IV (N=129)	2400 mg IV (N=71)	Combined Doses (N=200)
Total number of TEAEs [a]	0	31	26	57
Total number of Grade 3 or 4 TEAEs	0	3	0	3
Total number of TE SAEs	0	2 [e]	0	2 [e]
Total number of TE AESIs	0	12	5	17
Total number of TE serious AESIs	0	2	0	2
No. (%) of patients with any TEAE	0	17 (13.2%)	10 (14.1%)	27 (13.5%)
No. (%) of patients with any Grade 3 or 4 TEAE	0	2 (1.6%)	0	2 (1.0%)
No. (%) of patients with any TE SAE	0	2 (1.6%) [e]	0	2 (1.0%) [e]
No. (%) of patients with any TE AESI	0	10 (7.8%)	5 (7.0%)	15 (7.5%)
Grade ≥ 2 IRR through Day 4 [b]	0	0	1 (1.4%)	1 (0.5%)
Grade ≥ 2 hypersensitivity reaction through Day 4	0	1 (0.8%)	0	1 (0.5%)
Grade ≥ 2 hypersensitivity reaction through Day 29	0	1 (0.8%)	0	1 (0.5%)
Event that led to a MAV through Day 29	0	9 (7.0%)	4 (5.6%)	13 (6.5%)
No. (%) of patients with any serious TE AESI	0	2 (1.6%)	0	2 (1.0%)
Serious Grade ≥ 2 IRR through Day 4 [b]	0	0	0	0
Serious Grade ≥ 2 hypersensitivity reaction through Day 29	0	0	0	0
Serious event that led to a MAV through Day 29	0	2 (1.6%)	0	2 (1.0%)
No. (%) of patients with any TEAE leading to death	0	0	0	0
No. (%) of patients with any TEAE leading to study withdrawal	0	0	0	0
No. (%) of patients with any TEAE leading to infusion interruption [c]	0	0	0	0
No. (%) of patients with any TEAE leading to infusion discontinuation [d]	0	1 (0.8%)	0	1 (0.5%)

AESI=adverse event of special interest; MAV=medically-attended visit (includes physician's office visit, telemedicine, urgent care visit, hospitalization, or emergency room visit for COVID-19); MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

TEAEs 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.

[a] TEAEs collected include TE SAEs, AESIs and Grade 3/4 TEAEs, as well as ad hoc/voluntarily reported TEAEs by some sites.

[b] TEAEs deemed treatment-related as per investigator assessment.

[c] Infusion interruption: the administration of the infusion was interrupted before being completed, but subsequently was re-started and the full planned dose was administered.

[d] Infusion discontinuation: the administration of the infusion was stopped before being completed, and the full planned dose was not administered.

[e] Two additional SAEs were reported between Day 30 and Day 169; Grade 3 respiratory distress in a patient <12 years (onset Day 146) and Grade 2 suicidal ideation in a patient ≥ 12 years (onset Day 56); both patients were in the 1200 mg IV arm. The patient with the respiratory distress SAE had previously experienced an SAE of metapneumovirus pneumonia with onset on Day 23 (see COV 2067 CSR Addendum 3, Section 5.2.1.1.3 and Phase 3 Cohort 2 Post-text Listing 14.4.2.1.2S).

Source: COV 2067 CSR Addendum 3, Post text Table 14.4.1.1S1.

Among the 102 patients in the COV-2067 Phase 3 Cohort 2 SAF aged <12 years, 16 (15.7%) patients experienced a total of 34 TEAEs up to Day 29. The majority of events were non-serious and Grade 1-2. Only 2 (2.0%) patients experienced a TE SAE up to Day 29.

Among the 98 patients aged ≥ 12 years who received casirivimab+imdevimab, 11 (11.2%) patients experienced a total of 23 TEAEs up to Day 29. No patients experienced a TESAE up to Day 29, although one patient experienced a TESAE after Day 29 (Grade 2 suicidal ideation [onset Day 56]).

Serious adverse event/deaths/other significant events

No deaths were reported in Phase 3 Cohort 2.

Two patients aged <12 years experienced a TESAE up to Day 29 (2/102 patients [2.0%]). A 1-year-old patient experienced Grade 4 metapneumovirus pneumonia with onset on Day 23 and an 11-year-old patient experienced Grade 1 urinary retention with onset on Day 2. In addition, the patient with

the metapneumovirus pneumonia event had one additional TESAE of Grade 3 respiratory distress with onset after Day 29 (onset Day 146).

In the ≥ 12 years age group, no patients experienced a TE SAE up to Day 29. However, one 12-year-old patient experienced a Grade 2 TE SAE of suicidal ideation with onset on Day 56 (1/98 patients [1.0%]).

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 of urticaria that was reported on day 1 during study infusion prompting discontinuation of study drug; the event resolved the same day. Both participants were < 12 years of age.

Thirteen participants (6.5%) (5 patients ≥ 12 years) 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 of Alanine aminotransferase increased and Aspartate aminotransferase increased. Another experienced 1 grade 4 TEAE of Metapneumovirus pneumonia). None of the TEAEs were considered related to study drug.

Laboratory findings

No clinically meaningful trends in laboratory parameters were noted in patients aged <12 years or patients aged ≥ 12 to <18 years who received casirivimab+imdevimab. Findings were generally similar between dose groups with minor differences, when observed, likely driven by the relatively small sample sizes. Although some potentially clinically significant values (PCSVs) were reported, none were considered clinically significant as all PCSVs were attributed to COVID-19 infection and its associated complications in participants with multiple concurrent medical conditions.

Vital signs

No clinically meaningful changes from baseline or clinically relevant PCSVs in vital signs (systolic and diastolic blood pressure, oxygen saturation, heart [pulse] rate, respiratory rate, and temperature) were noted in patients aged <12 years or patients aged ≥12 to <18 years who received casirivimab+imdevimab.

Discontinuation due to adverse events

One patient aged <12 years experienced a TEAE that led to infusion interruption. The 3-year-old patient in the 1200 mg IV arm experienced a Grade 2 event of urticaria on Day 1 during the infusion of casirivimab+imdevimab.

The patient did not receive the full dose of study drug but remained in the study.

No patients aged <12 years experienced a TEAE that led to infusion discontinuation.

Analysis by body weight

Although the overall TEAE incidence was higher in patients with a body weight <40 kg (13/66 [19.7%]) than in patients with a body weight ≥ 40 kg (14/134 [10.4%]), review of the data did not identify any new safety signals for casirivimab+imdevimab treatment for either of the body weight groups. Within the two body weight groups, the TEAE categories were generally balanced across the casirivimab+imdevimab 1200 mg and 2400 mg IV treatment arms, with minor discrepancies in incidence, when observed, likely driven by the small sample sizes.

Analysis of the AE data for patients with a body weight <40 kg (n = 66) by narrower body weight categories (<10 kg, 10 to <20 kg, and 20 to <40 kg) did not identify any notable differences in the AE profile. However, the low number of patients in these body weight categories, particularly the <10 kg (n = 2) and 10 to <20 kg (n = 14) categories, limits interpretation of the results and identification of any meaningful differences between the 1200 mg and 2400 mg casirivimab+imdevimab arms or between the different bodyweight groups.

2.5.1. Discussion on clinical safety

The data were submitted and assessed previously in the context of the EMEA/H/C/005814/P46/016.

In the context of this submission the marketing authorisation holder provided an analysis of 2 different age groups i.e. < 12 years of age and ≥ 12 years of age.

Among the 102 patients, in the COV-2067 Phase 3 Cohort 2 SAF aged <12 years, 16 (15.7%) patients experienced a total of 34 TEAEs up to Day 29. The majority of events were non-serious and Grade 1-2. Only 2 (2.0%) patients experienced a TESAE up to Day 29.

Among the 98 patients aged > 12 years who received casirivimab+imdevimab, 11 (11.2%) patients experienced a total of 23 TEAEs up to Day 29. No patients experienced a TESAE up to Day 29.

One participant in the 2400 mg group experienced a grade 2 infusion-related reaction and one participant in the 1200 mg group experienced a grade 2 hypersensitivity reaction. Both participants were < 12 years of age.

No dose response was observed. The TEAE categories were generally balanced across the casirivimab+imdevimab 1200 mg and 2400 mg IV treatment arms, with minor discrepancies in

incidence, when observed, likely driven by the small sample sizes. Analysis of the data for patients by bodyweight, was limited by the low number of patients in low <40 weight category, particularly the <10 kg (n = 2) and 10 to <20 kg (n = 14) categories.

Due to the small number of participants in cohorts 2 who received placebo any meaningful comparisons between casirivimab+imdevimab and placebo groups for the paediatric population is not possible.

It can be concluded that the safety profile observed for participants treated with casirivimab+imdevimab in cohort 2 is consistent with the known safety profile for non-pregnant, adult participants in cohort 1, with no new safety signals having been identified.

2.5.2. Conclusions on clinical safety

The safety profile observed for participants treated with casirivimab+imdevimab in cohort 2 is consistent with the known safety profile for non-pregnant, adult participants in cohort 1.

No new safety signals having been identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 4.1 with this application. The main proposed RMP changes were the following:

- **Part I**: Table 1 (Product Overview) aligned with the updates from the Summary of Product Characteristics.
- **Part II, SI.1:** Addition of epidemiology data for paediatric patients and update of adult patient epidemiology since the previous RMP.
- **Part II, SIII:** Addition of exposure information for paediatric patients in Study COV-2067 Phase 3 Cohort 2.
- **Part II, SV.1 and Annex 7:** Updated to incorporate new post-authorisation data from most recent Periodic Benefit-Risk Evaluation Report (PBRER) (Report No. 1123568; Data Lock Point [DLP]: 18 July 2023). The cumulative patient exposure per region has been moved to Annex 7.
- **Annex 7:** New literature references added.
- **Annex 8**: Updated to reflect the changes to this RMP.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

The Safety Concern "Use in pregnancy" was removed as missing information in procedure EMEA/H/C/005814/II/0015. Considering the data in the safety specification, the summary of safety concerns table is considered appropriate.

Pharmacovigilance plan

No changes to the Pharmacovigilance plan have been proposed in this procedure, which is acceptable. The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

2.7. Update of the Product information

As a consequence of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are being updated to extend the indication of treatment for Ronapreve of paediatric patients from 2 to less than 12 years old, weighing at least 10 kg, who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19.This is based on final results from study COV-2067; this was a seamless, adaptive, phase 3, randomised, double-blinded, placebo-controlled, multi-center study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate COVID-19.The Package Leaflet is updated in accordance. A revised RMP version 4.1 has also been approved.

Changes are also made to the PI of both strengths to bring it in line with the current QRD template version 10.4, Annex of the excipient's guideline.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A first user consultation was carried out by a contractor during the marketing authorisation in November 2021. Furthermore, a single round of testing was performed in May 2022 and the assessment was favourable.

According to the readability guideline additional consultations with target patient groups should be performed in case that significant changes are implemented during regulatory procedures.

With regard to the scope of the extension to include paediatric information for the treatment of infants from 2 years of age to children below 12 years of age, weighting at least 10 kg bodyweight, who do not require oxygen and who are at increased risk of progression to severe COVID-19 for Ronapreve, based on clinical studies results, the following sections of the SmPC were adapted:

Section 4.1 ("therapeutic indication"), 4.2 ("Posology and method of administration"), 4.8 ("Undesirable effects"), 5.1 ("Pharmacodynamic properties"), 5.2 ("Pharmacokinetic properties"), 6.6 ("Special precautions for disposal and other handling"). These amendments are related to the various strengths Ronapreve 300 mg + 300 mg (casirivimab plus imdevimab) and 120 mg/ml + 120 mg/ml solution for injection/infusion.

The changes proposed in the SmPC will be reflected in the following sections of the package leaflet: section 1 "What Ronapreve is", section 2 "What you need to know before you are given Ronapreve" and section 3 "How Ronapreve is given to you". These changes proposed by the MAH are minor and will not affect the key safety information. The readability is not negatively affected due to similar structure, similar descriptions and terminology. Therefore, neither a full user testing nor an abridged testing is necessary.

Nevertheless, for the next variation the MAH is requested to provide an overview of all changes implemented in the PI during the life cycle, due to the fact that via this variation an update of the warning and precautions section is requested related to the updated annex of the excipient's guideline.

The Package Leaflet is updated in accordance.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ronapreve (casirivimab+imdevimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is a disease caused by SARS-CoV-2, a novel RNA betacoronavirus.

Children usually develop asymptomatic or mild disease, often with upper respiratory symptoms. However, similar to adults, children who develop severe COVID-19 may require hospitalisation and oxygen support, have severe pneumonia, and/or have signs of severe respiratory distress.

3.1.2. Available therapies and unmet medical need

There are currently no therapeutic options for the treatment of COVID-19 in children weighing <40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. Veklury (remdesivir) is indicated for the treatment of adult and paediatric patients, but only for those weighing at least 40 kg, whilst Evusheld (tixagevimab and cilgavimab) and Xevudy (sotrovimab) are indicated for the treatment of adults and adolescents aged 12 years and over and weighing at least 40 kg. Paxlovid (nirmatrelvir and ritonavir) and Regkirona (regdanvimab) are only indicated for the treatment of COVID-19 in adults.

3.1.3. Main clinical studies

The efficacy evaluation for paediatric patients is based on clinical and virologic efficacy data from Phase 3 Cohort 2 of Study COV-2067. While the focus is on efficacy data from patients <12 years of age, the data are presented by age (<12 years and ≥ 12 to < 18 years) and, as a subgroup analysis, by body weight (<40 kg and ≥ 40 kg).

Study COV-2067 was a seamless, adaptive Phase 1/2/3, randomised, double-blinded, placebo-controlled, multi-centre study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate COVID-19. Phases 1 and 2 focused on the safety and virologic efficacy of casirivimab+imdevimab, while the aim of Phase 3 was to assess the clinical efficacy and safety.

The study utilised an adaptive master protocol design to maximise the efficiency of identifying early signs of efficacy, allow for the potential to study multiple therapeutic combinations, and avoid the use of ineffective dose levels in patients with COVID-19.

Since casirivimab+imdevimab shows diminished *in vitro* neutralisation potency for the B.1.1.529/BA.1 SARS-CoV-2 (Omicron) variant and Omicron subvariants the was paused in December 2021 and was terminated in June 2022 (following the last patient last visit) due to the sustained loss of efficacy of casirivimab+imdevimab against the variants currently in circulation.

Participants in Phase 3 Cohort 2 were initially randomised 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. Placebo was discontinued February 2021; thus, participants were subsequently randomised 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 (Protocol Amendment 10).

3.2. Favourable effects

No patients in the overall COV-2067 Phase 3 Cohort 2 mFAS, and therefore no patients aged <12 years, had a COVID-19-related hospitalisation or all-cause death through Day 29.

Overall, 3/192 (1.6%) paediatric patients in the COV-2067 Phase 3 Cohort 2 (2 patients <12 year and 1 patient aged >12) had a COVID-19-related MAV through Day 29: 2/121 (1.7%) patients in the 1200 mg IV arm and 1/70 (1.4%) patient in the 2400 mg IV arm. The one patient who received placebo did not have a COVID-related MAV.

The viral load in nasopharyngeal samples decreased rapidly and similarly in the 1200 mg and 2400 mg IV arms as shown by the mean (SD) time-weighted average change from baseline in viral load through Day 7 (1200 mg IV = -2.65 (1.474) log10 copies/mL; 2400 mg IV = -2.57 (1.607) log10 copies/mL).

Subgroup analysis of the virologic efficacy data by body weight group for patients in the overall Phase 3 Cohort 2 mFAS who received casirivimab+imdevimab did not identify any differences in response between patients with a body weight <40 kg (n=63) and those with a body weight ≥ 40 kg (n=128).

3.3. Uncertainties and limitations about favourable effects

It should be noted that the sample size was limited. In addition, all efficacy analyses for Phase 3 Cohort 2 were descriptive and no hypothesis testing all endpoints was performed.

Therefore, the data are considered supportive and are not considered to be the basis for the regulatory decision. The decision is mainly based on the pharmacological / extrapolation data.

The decision is mainly based on the PK considerations and modelling aiming at supporting the similarity of exposure between adult and paediatric populations. The extrapolation concept of exposure similarity has been agreed previously. Several analyses, model update and simulations have been provided to enhance the credibility in pop PK modelling and PK characterisation in paediatric subjects aged 2 years and older weighing at least 10 kg. These addressed allometric scaling and aimed at justifying the weight-tiered dosing regimen. Observed trends in underprediction observed in paediatrics weight cohorts were discussed. Overall, it could be agreed that the updated model shows an acceptable predictive power to support the selected doses to achieve exposure similarity between populations to expect comparable favourable effects. This conclusion has been supported by simulations of exposure following the dose as administered in the clinical paediatric studies, as well as following the proposed recommended dosing.

Given the sparseness of PK data for model building and validation, a certain degree of uncertainty is remaining. However, the potentially higher proposed dose levels in children are not considered to be of major concern given the high selectivity of these monoclonal antibodies to an exogeneous target and their established safety/tolerability profiles at doses up to 8 g IV in adults (see Sections 3.4 and 3.5).

Moreover, 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. Finally, the relevance and adequacy of this procedure for inclusion of paediatric patients weighing > 10 kg for treatment with casirivimab+imdevimab is currently hampered by epidemiological situation since Ronapreve has no activity against the variants currently in circulation.

The currently approved indication already states that Ronapreve should be used in accordance with official recommendations where available and based on information on the activity of casirivimab and imdevimab against presently circulating viral variants.

3.4. Unfavourable effects

In the context of this submission, the marketing authorisation holder provided an analysis of 2 different age groups i.e. < 12 years of age and ≥ 12 years of age.

Among the 102 patients, in the COV-2067 Phase 3 Cohort 2 SAF aged <12 years, 16 (15.7%) patients experienced a total of 34 TEAEs up to Day 29. The majority of events were non-serious and Grade 1-2. Only 2 (2.0%) patients experienced a TESAE up to Day 29.

Among the 98 patients aged > 12 years who received casirivimab+imdevimab, 11 (11.2%) patients experienced a total of 23 TEAEs up to Day 29. No patients experienced a TESAE up to Day 29.

One participant in the 2400 mg group experienced a grade 2 infusion-related reaction and one participant in the 1200 mg group experienced a grade 2 hypersensitivity reaction. Both participants were < 12 years of age.

No dose response was observed. The TEAE categories were generally balanced across the casirivimab+imdevimab 1200 mg and 2400 mg IV treatment arms, with minor discrepancies in incidence, when observed, likely driven by the small sample sizes.

It can be concluded that the safety profile observed for participants treated with casirivimab+imdevimab in cohort 2 is consistent with the known safety profile for non-pregnant, adult participants in cohort 1, with no new safety signals having been identified.

3.5. Uncertainties and limitations about unfavourable effects

As indicated before the sample size was limited. Analysis of the data for patients by bodyweight, was limited by the low number of patients in low <40 weight category, particularly the <10 kg (n = 2) and 10 to <20 kg (n = 14) categories.

Due to the small number of participants in cohorts 2 who received placebo any meaningful comparisons between casirivimab+imdevimab and placebo groups for the paediatric population is not possible.

3.6. Effects Table

Table 13. Effects Table for Ronapreve, treatment of children < 12 years of age data cut-off.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
COVID-19 hospitalisation or all-cause death	Proportion of patients with at least one COVID 19-related hospitalisation or all cause death through Day 29	N	Cas+Im 1200 mg IV: 0/68 Cas+Im 2400 mg IV: 0/30	0	Placebo arm dropped after 2 patients, open design, small sample size, all results descriptive	COV-2067 Phase 3
COVID-19 MAV	Proportion of patients with at least one COVID 19-related medically-attended visit (MAV) through Day 29. A MAV was defined as hospitalisation, ER visit, urgent care center, or outpatient/physician office/telemedicine visit, with the primary reason for the visit being COVID-19.		Cas+Im 1200 mg IV: 2/68 (2.9%) Cas+Im 2400 mg IV: 0/30	-	No placebo, open design, small sample size, all results descriptive	COV-2067 Phase 3
TWA change	TWA change from BL in viral load through Day 7 (log10 copies/mL)	N Mean (SD)	Cas+Im 1200 mg IV: 64 -2.65 (1.474) Cas+Im 2400 mg IV: 23 -2.57 (1.607)	-	No placebo, open design, small sample size, all results descriptive	COV-2067 Phase 3
Unfavourable Effects						
IRR		n	2	N/A	Small sample size,	COV-2067

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					no control group	Phase 3

Abbreviations:
TWA: Time-weighted average
IRR: infusion related reaction
Notes: The efficacy data are provided for Phase 3 Cohort 2 modified full analysis set (mFAS) (age <12 years).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The clinical efficacy data indicated that in paediatric patients aged <12 years and/or weighing <40 kg in Study COV-2067 (Phase 3 Cohort 2), there were no COVID-19-related hospitalisations or deaths and the viral load in nasopharyngeal samples decreased rapidly and similarly following treatment with a single IV dose of 1200 mg or 2400 mg casirivimab+imdevimab.

All efficacy analyses for Phase 3 Cohort 2 were descriptive. No hypothesis testing was performed, therefore the data is considered supportive and not considered basis of the regulatory decision. This decision is mainly based on the pharmacological / extrapolation data.

As formally agreed in the corresponding PIPs, PK characterisation and model-based description is considered adequate to support similarity of exposure between adult and paediatric populations.

On the other hand, with the caveat that the sample size was small, the safety profile did not raise any concern. The observed profile for participants treated with casirivimab+imdevimab in the study was consistent with the known safety profile for adult participants in cohort 1 and no new safety signals were identified.

With the emerge of the omicron variant and its subtype a sustained loss of efficacy of casirivimab+imdevimab is observed since it is not active against the variants currently in circulation.

Thus, under the current epidemiologic situation, no efficacy can be expected since Ronapreve has no activity against the current the SARS-CoV-2 variants currently in circulation. This also applies to the other approved monoclonal antibody treatments against COVID-19.

However, treatment options are limited and in case of future circulating variants becoming susceptible to casirivimab+imdevimab, Ronapreve would be a treatment option for paediatric patients who are at high risk of progressing to severe COVID-19.

3.7.2. Balance of benefits and risks

Under the current epidemiologic situation, no efficacy can be expected, however as indicated above the PK characterisation and model-based description is considered adequate to support similarity of exposure between adult and paediatric populations.

3.7.3. Additional considerations on the benefit-risk balance

The MAH was requested to further clarify the PK characterisation and model-based description of PK following the applied (COV-2067) to support similarity of exposure between adult and paediatric populations as formally agreed in the corresponding PIPs.

The comparison between the final pop PK parameters and diagnostics, before and after these updates indicates a slight decrease in IIV and eta shrinkage for some parameters, while for others these values are slightly increased (e.g. IIV CL). The MAH discussed the observed trends in underprediction observed in paediatrics weight cohorts sufficiently. Overall, it could be agreed that the updated model shows an overall acceptable predictive power to support the selected doses to achieve exposure similarity. This conclusion has been supported by simulations of exposure following the dose as administered in the clinical paediatric studies, as well as following the proposed recommended dosing.

It is further agreed that the higher proposed dose levels in children are not considered to be of major concern given the high selectivity of these monoclonal antibodies to an exogeneous target and their established safety/tolerability profiles at doses up to 8 g IV in adults.

3.8. Conclusions

The overall benefit-risk of Ronapreve is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of paediatric patients from 2 to less than 12 years old, weighing at least 10kg, who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 for Ronapreve, based on final results from study COV-2067; this was a seamless, adaptive, Phase 3, randomised, double-blinded, placebo-controlled, multi-centre study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in paediatric and adult outpatients with mild to moderate COVID-19. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. A revised RMP version 4.1 has also been approved.

In addition, the MAH took the opportunity to bring the PI of both strengths in line with the current QRD template version 10.4, Annex of the excipient's guideline.

The variation leads to amendments to the Summary of Product Characteristics, the Annex II, the Labelling and the Package Leaflet as well as to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plans P/0300/2022 and P/0343/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Ronapreve EMEA/H/C/005814/II/0017