Amsterdam, 10 November 2022
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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006



**Ronapreve**

International non-proprietary name or common name: casirivimab / imdevimab

Product No. EMEA/H/C/005814/P46/005

## Note

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

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# 1. Introduction

On 31 March 2022, the MAH submitted final results of Study R10933-10987-COV-2069 involving paediatric patients in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of the post-authorisation measure 005.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that Study R10933-10987-COV-2069 is part of a clinical development program.

## *2.2. Information on the pharmaceutical formulation used in the study*

There is no specific paediatric formulation. Each of the casirivimab and imdevimab formulated drug substances (FDS) consist of purified protein in an aqueous buffered solution, containing L-histidine, pH 6.0, sucrose and polysorbate 80. Casirivmab and imdevimab drug products are supplied as liquid solutions for intravenous (IV) and SC administrations. The DPs are preservative-free and non-pyrogenic.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Submission of final results of Study R10933-10987-COV-2069 involving paediatric patients in accordance with Art.46 of the paediatric regulation and to address the commitment which arose from the original marketing authorization (EMEA-H-C-005814) as reported in the CHMP list of questions dated 16th September 2021. This study was a part of the PIP procedures EMEA-002964-PIP01-21-M01 and EMEA-002965-PIP01-21-M01 (Study 5) - R19033-10987-COV-2069: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2.

The final analysis for Study COV-2069, reported in clinical study report (CSR) Addendum (#2), presents the completed 7-month follow-up period efficacy results and 8-month safety data of a single subcutaneous (SC) administration of casirivimab / imdevimab 1200 mg on the prevention of SARS CoV-2 infections (overall and symptomatic infections) in participants who were uninfected at baseline (Cohort A) and participants who were asymptomatic and SARS-COV-2 positive at baseline (Cohort B). The analyses presented in this addendum are based on the final database lock date of 4 November 2021.

Findings from the COV-2069 study have been previously presented in two separate reports prior to completion of the study:

- The original COV-2069 Primary Analysis CSR (dated 15 Jun 2021) provided the final primary analysis for the primary and key secondary endpoints at Day 29 (end of the efficacy assessment period [EAP]). Findings were presented on two distinct study populations: Cohort A analyses evaluated infection prevention in participants who were uninfected at baseline, and Cohort B focused on early treatment to prevent symptomatic progression in participants with asymptomatic infection at baseline. A total of 3029 participants were randomized and enrolled in Cohort A (N = 2621) and Cohort B (N = 314). Efficacy data for primary and secondary endpoints up to the cutoff date of 11 Mar 2021 were included. The safety population included all participants randomized through 28 January 2021. Additional 554 participants randomized between the study start date through 16 October 2020 were included in the administrative assessment

- Subsequently, a Primary Analysis CSR Addendum (#1) (dated 29 Sep 2021) was submitted to summarize the cumulative key efficacy and safety results for all enrolled participants up to the data cut-off of 1 July 2021, which includes an additional 269 participants enrolled in Cohort A and Cohort B after the data cut-off for the original Primary Analysis CSR. The results for CSR Addendum #1 were considered a sensitivity analysis of the findings presented in the Primary Analysis CSR and corroborated the efficacy and safety conclusions from the primary analysis for the study.

## 2.3.2. Clinical study

**Study R10933-10987-COV-2069: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2**

**Methodology**

Adults and adolescents (age ≥ 12 years) who were household contacts of the first household member known to be infected with SARS-CoV-2 infection (index case), but who were themselves either not infected or asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. In this study, the participant must have been sharing the same residence as the index case and must have had a close exposure to the index case.

Eligible participants were randomized 1:1 to receive a single dose of placebo or casirivimab + imdevimab on Day 1. Randomization was performed on an individual participant basis and was stratified by local diagnostic assay for SARS-CoV-2 and age/weight groups. However, for analysis, cohort allocation was based on results from the central laboratory assessment of SARS-CoV-2 RT-qPCR status at baseline: participants who were negative for SARS-CoV-2 (i.e., uninfected) were allocated to Cohort A, and participants who were positive for SARS-CoV-2 (i.e., with asymptomatic infection) were allocated to Cohort B. Each cohort was further subdivided based on baseline serology results from the central laboratory. To rule-out prior SARS-CoV-2 infection, participants were assessed for the presence of serum anti-SARS-CoV-2 antibodies indicative of prior infection: anti-spike [S1] IgA, anti-spike [S1] IgG, and antinucleocapsid IgG. Participants were considered seronegative if all available serology tests were negative, seropositive if any of the tests were positive, or sero-undetermined if results were missing or inconclusive

No specific paediatric formulation was used in Study COV-2069. Both adult and adolescent participants (i.e., age ≥ 12 years) received a single-dose 1200 mg casirivimab+imdevimab (600 mg per mAb) or single dose matching placebo, administered as 4 SC injections in the abdomen or thigh. For adults and paediatric participants ≥ 10 kg investigators had the option to use an infusion pump for SC administration of study drug containing the combined volume with both mAbs.

For each participant, the study comprised three periods: a 1-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period. During the EAP, nasopharyngeal (NP) swab samples for analysis of SARSCoV-2 RT-qPCR (test) were collected for all participants weekly. The primary efficacy endpoint was assessed by RT-qPCR by the central laboratory up to Day 29 (end of EAP). During the follow-up period, only participants who were RT-qPCR positive and participants who became symptomatic with COVID-19 would continue to have weekly NP swab samples collected. Assessments continued until there were two consecutive negative (≥ 24 hours) RT-qPCR results or until the end of study visit.

**Study Participants**

In this study, 3375 participants were screened. A total of 3298 participants were randomized, of whom 3270 were treated: 2867 in Cohort A; 335 in Cohort B; 1 in Cohort 1A2; and 67 in the SARS-CoV-2 Undetermined group3 (refer to CSR Addendum #2, Study COV-2069, Table 1). A total of 94.2% of participants completed the end of study visit at the time of the study completion.

In Cohort A, adolescents (age ≥ 12 to < 18 years) comprised a total of 74/1683 (4.4%) participants in the efficacy analysis and 98/2867 (3.4%) participants in the safety analysis (Table 1). In addition, a 10-year-old paediatric participant was enrolled into Cohort A1 (placebo group, baseline-seropositive).

**Table 1 Paediatric Patients – Cohort A**

| seronegative mFAS-A population | | | |
|---|---|---|---|
| **Age Group (Years), n (%)** | **Placebo (N=842)** | **REGN10933+ REGN10987 (N=841)** | **Total (N=1683)** |
| ≥12 to <18 | 34 (4.0%) | 40 (4.8%) | 74 (4.4%) |
| **SAF-A population** | | | |
| **Age Group (Years), n (%)** | **Placebo (N=1428)** | **REGN10933+ REGN10987 (N=1439)** | **Total (N=2867)** |
| ≥12 to <18 | 47 (3.3%) | 51 (3.5%) | 98 (3.4%) |

Source: Table 4 and Table 5 Addendum #2 CSR
mFAS=Modified full analysis set; SAF=Safety analysis set

In Cohort B, adolescents (age ≥ 12 to < 18 years) comprised a total of 28/225 (12.4%) participants in the efficacy analysis and 43/335 (12.8%) participants in the safety analysis (Table 2).

**Table 2 Paediatric Patients – Cohort B**

| seronegative mFAS-B population | | | |
|---|---|---|---|
| **Age Group (Years), n (%)** | **Placebo (N=116)** | **REGN10933+ REGN10987 (N=109)** | **Total (N=225)** |
| ≥12 to <18 | 12 (10.3%) | 16 (14.7%) | 28 (12.4%) |
| **SAF-B population** | | | |
| **Age Group (Years), n (%)** | **Placebo (N=170)** | **REGN10933+ REGN10987 (N=165)** | **Total (N=335)** |
| ≥12 to <18 | 20 (11.8%) | 23 (13.9%) | 43 (12.8%) |

Source: Table 7 and Table 8 Addendum #2 CSR
mFAS=Modified full analysis set; SAF=Safety analysis set

**Results**

**Overview of safety**

**Safety in Adolescent Participants Who Were Uninfected at Baseline (Cohort A)**

Adverse Events in Paediatric Participants (SAF-A and SAF-A1) Cohort A included paediatric participants (≥12 years and <18 years of age; termed adolescents). In addition, a 10-year-old paediatric participant was enrolled into Cohort A1 (placebo group, baseline-seropositive) and did not experience any TEAEs during the study.

In cohort A, the proportion of paediatric participants with TEAEs of Asymptomatic COVID-19 andCOVID-19 were significantly higher in the placebo group than the casirivimab+imdevimab group (Table below). Conversely, the proportion of pediatric participants with TEAEs of Injection site reaction (ISR) was higher in the casirivimab + imdevimab group compared to placebo although comparable to adult participants. Overall, the types of TEAEs experienced by adolescent participants were similar to those observed in the adult population.

TEAEs experienced by >1 paediatric participant were:

- Placebo group: Asymptomatic COVID-19, COVID-19, Nasal congestion, and Headache
- Casirivimab+imdevimab group: ISR, Asymptomatic COVID19, Cough, Oropharyngeal pain, and Ligament sprain

**Table 3** **Summary of TEAEs (PT ≥1 Pediatric Participant) by Age Group, SOC and PT During the Overall Study Period (SAF-A)**

| | Age ≥12 to <18 years | | Age ≥18 years | |
|---|---|---|---|---|
| **Primary System Organ Class Preferred Term** | **Placebo (N=47)** | **R10933+R10987 (N=51)** | **Placebo (N=1381)** | **R10933+R10987 (N=1388)** |
| Subjects with at least one TEAE | 18 (38.3%) | 16 (31.4%) | 494 (35.8%) | 389 (28.0%) |
| Infections and infestations | 13 (27.7%) | 8 (15.7%) | 309 (22.4%) | 185 (13.3%) |
| Asymptomatic COVID-19 | 9 (19.1%) | 3 (5.9%) | 110 (8.0%) | 68 (4.9%) |
| COVID-19 | 4 (8.5%) | 0 | 145 (10.5%) | 29 (2.1%) |
| Urinary tract infection | 1 (2.1%) | 0 | 25 (1.8%) | 22 (1.6%) |
| Upper respiratory tract infection | 1 (2.1%) | 0 | 15 (1.1%) | 14 (1.0%) |

| | Age ≥12 to <18 years | | Age ≥18 years | |
|---|---|---|---|---|
| **Primary System Organ Class**<br>**Preferred Term** | **Placebo (N=47)** | **R10933+R10987 (N=51)** | **Placebo (N=1381)** | **R10933+R10987 (N=1388)** |
| Viral infection | 0 | 1 (2.0%) | 3 (0.2%) | 6 (0.4%) |
| Cellulitis | 0 | 1 (2.0%) | 1 (<0.1%) | 1 (<0.1%) |
| Gastroenteritis | 1 (2.1%) | 1 (2.0%) | 3 (0.2%) | 1 (<0.1%) |
| Pharyngitis | 1 (2.1%) | 1 (2.0%) | 3 (0.2%) | 1 (<0.1%) |
| Pharyngitis streptococcal | 0 | 1 (2.0%) | 0 | 0 |
| General disorders and administration site conditions | 1 (2.1%) | 7 (13.7%) | 83 (6.0%) | 97 (7.0%) |
| Injection site reaction | 1 (2.1%) | 5 (9.8%) | 25 (1.8%) | 55 (4.0%) |
| Fatigue | 0 | 1 (2.0%) | 27 (2.0%) | 17 (1.2%) |
| Pain | 0 | 1 (2.0%) | 13 (0.9%) | 12 (0.9%) |
| Pyrexia | 0 | 1 (2.0%) | 11 (0.8%) | 11 (0.8%) |
| Chest pain | 0 | 1 (2.0%) | 3 (0.2%) | 2 (0.1%) |
| Respiratory, thoracic and mediastinal disorders | 4 (8.5%) | 3 (5.9%) | 64 (4.6%) | 86 (6.2%) |
| Cough | 0 | 2 (3.9%) | 21 (1.5%) | 38 (2.7%) |
| Nasal congestion | 2 (4.3%) | 1 (2.0%) | 19 (1.4%) | 27 (1.9%) |
| Oropharyngeal pain | 1 (2.1%) | 2 (3.9%) | 25 (1.8%) | 27 (1.9%) |
| Dyspnoea | 0 | 1 (2.0%) | 4 (0.3%) | 8 (0.6%) |
| Epistaxis | 1 (2.1%) | 0 | 0 | 4 (0.3%) |
| Nervous system disorders | 3 (6.4%) | 1 (2.0%) | 75 (5.4%) | 52 (3.7%) |
| Headache | 2 (4.3%) | 1 (2.0%) | 60 (4.3%) | 38 (2.7%) |
| Dizziness | 1 (2.1%) | 0 | 5 (0.4%) | 7 (0.5%) |
| Presyncope | 1 (2.1%) | 0 | 1 (<0.1%) | 1 (<0.1%) |
| Gastrointestinal disorders | 0 | 1 (2.0%) | 43 (3.1%) | 33 (2.4%) |
| Nausea | 0 | 1 (2.0%) | 14 (1.0%) | 10 (0.7%) |
| Diarrhoea | 0 | 1 (2.0%) | 12 (0.9%) | 10 (0.7%) |
| Injury, poisoning and procedural complications | 3 (6.4%) | 2 (3.9%) | 40 (2.9%) | 32 (2.3%) |
| Ankle fracture | 1 (2.1%) | 0 | 0 | 2 (0.1%) |
| Ligament injury | 1 (2.1%) | 0 | 0 | 1 (<0.1%) |
| Animal bite | 1 (2.1%) | 0 | 0 | 1 (<0.1%) |
| Ligament sprain | 0 | 2 (3.9%) | 2 (0.1%) | 0 |
| Musculoskeletal and connective tissue disorders | 0 | 4 (7.8%) | 37 (2.7%) | 25 (1.8%) |
| Back pain | 0 | 1 (2.0%) | 8 (0.6%) | 5 (0.4%) |
| Arthralgia | 0 | 1 (2.0%) | 8 (0.6%) | 2 (0.1%) |
| Costochondritis | 0 | 1 (2.0%) | 0 | 1 (<0.1%) |
| Scoliosis | 0 | 1 (2.0%) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 1 (2.1%) | 0 | 16 (1.2%) | 20 (1.4%) |
| Eczema | 1 (2.1%) | 0 | 0 | 1 (<0.1%) |
| Metabolism and nutrition disorders | 1 (2.1%) | 0 | 8 (0.6%) | 16 (1.2%) |
| Hypertriglyceridaemia | 1 (2.1%) | 0 | 2 (0.1%) | 1 (<0.1%) |
| Psychiatric disorders | 1 (2.1%) | 0 | 18 (1.3%) | 10 (0.7%) |

| | Age ≥12 to <18 years | | Age ≥18 years | |
|---|---|---|---|---|
| Primary System Organ Class<br>Preferred Term | Placebo<br>(N=47) | R10933+R10987<br>(N=51) | Placebo<br>(N=1381) | R10933+R10987<br>(N=1388) |
| Attention deficit hyperactivity disorder | 1 (2.1%) | 0 | 0 | 2 (0.1%) |
| Hepatobiliary disorders | 1 (2.1%) | 0 | 2 (0.1%) | 2 (0.1%) |
| Hyperbilirubinaemia | 1 (2.1%) | 0 | 0 | 0 |
| Ear and labyrinth disorders | 1 (2.1%) | 0 | 4 (0.3%) | 1 (<0.1%) |
| Vertigo | 1 (2.1%) | 0 | 1 (<0.1%) | 1 (<0.1%) |

Note: Data from all treated participants are included.
MedDRA (Version 24.0) coding dictionary applied.
A subject who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A subject who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
Source: PTT 14.7.1.2.3c

Similar to adults, the majority of TEAEs in the cohort A paediatric population were mild or moderate in severity (i.e., grade 1 or grade 2) (Table below).

One adolescent participant reported a Grade 3 TEAE of bone fracture in the placebo group. No other adolescent participant reported Grade 3 or Grade 4 TEAEs during the overall study period.

**Table 4** **Summary of TEAE Severity by Age Group During the Overall Study Period (SAF-A)**

| | Age ≥12 to <18 years | | Age ≥18 years | |
|---|---|---|---|---|
| | Placebo<br>(N=47) | R10933+R10987<br>(N=51) | Placebo<br>(N=1381) | R10933+R10987<br>(N=1388) |
| Number of subjects with at least one TEAE | | | | |
| Total | 18 (38.3%) | 16 (31.4%) | 494 (35.8%) | 389 (28.0%) |
| Grade 1 | 13 (27.7%) | 10 (19.6%) | 371 (26.9%) | 274 (19.7%) |
| Grade 2 | 4 (8.5%) | 6 (11.8%) | 94 (6.8%) | 89 (6.4%) |
| Grade 3 | 1 (2.1%) | 0 | 25 (1.8%) | 21 (1.5%) |
| Grade 4 | 0 | 0 | 2 (0.1%) | 2 (0.1%) |
| Grade 5 | 0 | 0 | 2 (0.1%) | 3 (0.2%) |

Note: Data from all treated participants are included.
A subject who reported 2 or more TEAEs with different severity was counted in the most severe category.
Source: PTT 14.7.1.3.3c

**Safety in Adolescent Participants with Asymptomatic Infection at Baseline (Cohort B)**

Paediatric participants in cohort B included adolescent participants only (age ≥12 to <18 years). No participant<12 years of age enrolled in cohort B.

COVID-19 was the only TEAE reported by >1 paediatric participant during the study. Regardless of age group in cohort B, the incidence of COVID-19 was higher in the placebo group than the casirivimab+imdevimab group.

**Table 5** Summary of TEAEs (PT ≥1 Pediatric Participant) by SOC, PT, and Age Group During the Overall Study Period (SAF-B)

| Primary System Organ Class<br>Preferred Term | Age ≥12 to <18 years<br>Placebo<br>(N=20) | <br>R10933+<br>R10987<br>(N=23) | Age ≥18 years<br>Placebo<br>(N=150) | <br>R10933+<br>R10987<br>(N=142) |
|---|---|---|---|---|
| Subjects with at least one TEAE | 11 (55.0%) | 3 (13.0%) | 77 (51.3%) | 57 (40.1%) |

| Primary System Organ Class<br>Preferred Term | Age ≥12 to <18 years<br>Placebo<br>(N=20) | <br>R10933+<br>R10987<br>(N=23) | Age ≥18 years<br>Placebo<br>(N=150) | <br>R10933+<br>R10987<br>(N=142) |
|---|---|---|---|---|
| Infections and infestations | 10 (50.0%) | 3 (13.0%) | 62 (41.3%) | 44 (31.0%) |
| COVID-19 | 10 (50.0%) | 3 (13.0%) | 48 (32.0%) | 32 (22.5%) |
| Urinary tract infection | 1 (5.0%) | 0 | 5 (3.3%) | 1 (0.7%) |
| General disorders and administration site conditions | 1 (5.0%) | 0 | 5 (3.3%) | 10 (7.0%) |
| Pyrexia | 1 (5.0%) | 0 | 0 | 1 (0.7%) |
| Gastrointestinal disorders | 0 | 1 (4.3%) | 2 (1.3%) | 3 (2.1%) |
| Vomiting | 0 | 1 (4.3%) | 0 | 0 |
| Injury, poisoning and procedural complications | 0 | 2 (8.7%) | 3 (2.0%) | 3 (2.1%) |
| Joint injury | 0 | 1 (4.3%) | 0 | 0 |
| Vaccination complication | 0 | 1 (4.3%) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 1 (5.0%) | 0 | 5 (3.3%) | 2 (1.4%) |
| Acne | 1 (5.0%) | 0 | 0 | 0 |

Note: Data from all treated participants are included.
MedDRA (Version 24.0) coding dictionary applied.
A subject who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A subject who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
Source: PTT 14.7.1.2.10c

No adolescent participant in cohort B reported grade ≥3 TEAEs during the overall study period

**Table 6** Summary of TEAE Severity by Age Group During the Overall Study Period (SAF-B)

| | Age ≥12 to <18 years<br>Placebo<br>(N=20) | <br>R10933+R10987<br>(N=23) | Age ≥18 years<br>Placebo<br>(N=150) | <br>R10933+R10987<br>(N=142) |
|---|---|---|---|---|
| Number of subjects with at least one TEAE | | | | |
| Total | 11 (55.0%) | 3 (13.0%) | 77 (51.3%) | 57 (40.1%) |
| Grade 1 | 11 (55.0%) | 2 (8.7%) | 50 (33.3%) | 49 (34.5%) |
| Grade 2 | 0 | 1 (4.3%) | 21 (14.0%) | 6 (4.2%) |
| Grade 3 | 0 | 0 | 6 (4.0%) | 2 (1.4%) |
| Grade 4 | 0 | 0 | 0 | 0 |
| Grade 5 | 0 | 0 | 0 | 0 |

Note: Data from all treated participants are included.
A subject who reported 2 or more TEAEs with different severity was counted in the most severe category.
Source: PTT 14.7.1.3.7c

Overall, the types and severity of TEAEs experienced by adolescent participants were similar to those experienced by adults in the study.

**Overview Efficacy**

Supportive exploratory analyses conducted in the paediatric participant population in cohort A was performed.

Treatment with casirivimab+imdevimab resulted in a relative risk reduction for symptomatic SARS-CoV-2 infections (COVID-19) similar to that in baseline-seronegative participants (81.2% compared to placebo) in paediatric (≥12 to <18 years old) participants (100% compared to placebo).

Treatment with casirivimab+imdevimab resulted in a relative risk reduction for all SARS-CoV-2 infections (asymptomatic and symptomatic) similar to that in baseline-seronegative participants (68.2% compared to placebo) for paediatric (≥12 years to <18 years old) participants 74.5% compared to placebo).

**Efficacy Analyses in Participants Regardless of Baseline Serostatus**

Treatment with casirivimab+imdevimab resulted in a relative risk reduction for symptomatic SARS-CoV-2 infections (COVID-19) in participants regardless of baseline serostatus (79.7% compared to placebo) (Table below) similar to that in baseline-seronegative participants (81.2% compared to placebo);

**Table 7** **Proportion of Subjects who have Symptomatic RT-qPCR Confirmed SARS-CoV-2 Infection (Broad Term) by Central Lab or Local Lab during the Study: Raw Data Descriptive (Randomized Subjects in Cohort A Regardless of Baseline Serostatus)**

| | Placebo (N=1143) n/N1 (%) | R10933+R10987 (N=1174) n/N1 (%) |
|---|---|---|
| Proportion of subjects meeting the criteria | 120/1143 (10.5%) | 25/1174 (2.1%) |
| Risk reduction vs Placebo | | 79.7% |
| ≥12 years to <18 years | 4/47 (8.5%) | 0/52 |
| Risk reduction vs Placebo | | 100.0% |
| ≥18 years | 116/1096 (10.6%) | 25/1122 (2.2%) |
| Risk reduction vs Placebo | | 78.9% |

Note: For efficacy analysis, 554 subjects in cohort A who were in the administrative assessment are excluded.
mFAS-A: modified full analysis set for cohort A.
Source: PTT 14.6.2.3.1.33

Treatment with casirivimab+imdevimab resulted in a relative risk reduction for all SARS-CoV-2 infections (asymptomatic and symptomatic) for participants regardless of baseline serostatus (64.4% compared to placebo) (Table below) similar to that in baseline-seronegative participants (68.2% compared to placebo).

**Table 8** **Proportion of Subjects who have RT-qPCR Confirmed SARS-CoV-2 Infection (Regardless of Symptoms) by Central Lab or Local Lab during the Study: Raw Data Descriptive (Randomized Subjects in Cohort A)**

| | Placebo (N=1143) n/N1 (%) | R10933+R10987 (N=1174) n/N1 (%) |
|---|---|---|
| Proportion of subjects meeting the criteria | 197/1143 (17.2%) | 72/1174 (6.1%) |
| Risk reduction vs Placebo | | 64.4% |
| ≥12 years to <18 years | 12/47 (25.5%) | 3/52 (5.8%) |
| Risk reduction vs Placebo | | 77.4% |
| ≥18 years | 185/1096 (16.9%) | 69/1122 (6.1%) |
| Risk reduction vs Placebo | | 63.6% |

Note: For efficacy analysis, 554 subjects in cohort A who were in the administrative assessment are excluded.
mFAS-A: modified full analysis set for cohort A.
Source: PTT 14.6.2.3.1.22



**Assessor's comment**

Very few adolescents are included in Cohort B. The efficacy data are not provided by age i.e. ≥ 12 < 18 years and ≥ 18 years. For completeness, please provide these data.

No results in seropositive patients were provided. Please provide efficacy results separately for seronegative and seropositive subjects.

**Clinical Pharmacology**

Key clinical pharmacokinetics results for adolescent participants are listed below:

As of the final database lock (DBL) for this PK analysis, a total of 3270 subjects (3125 adults, 144 adolescents, and 1 paediatric participant [< 12 years]) were allocated to 1 of 4 cohorts based on age (subjects ≥ 12 years in Cohort A and B; and subjects < 12 years in Cohort A1) and SARS-CoV-2 infection status at baseline (negative subjects in Cohort A and A1; positive subjects in Cohort B and B1), as measured by central laboratory SARS-CoV-2 RT -qPCR.

All subjects ≥ 12 years were randomized to receive a single 1200 mg SC dose of casirivimab +imdevimab or placebo in a 1:1 ratio per cohort. Of the 3270 participants who were in the safety analysis set, 295 participants were included in the PK analysis set (PKAS).

**Table 9** **Accounting of Subjects by Analysis Set, Subset, Age Group and Treatment Group in Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [SAF])**

| | Placebo | | | | Casirivimab+Imdevimab 1200 mg SC | | | |
|---|---|---|---|---|---|---|---|---|
| Analysis Set | Sentinel Subset N (%) | Safety Subset N (%) | Other N (%) | Overall N(%) | Sentinel Subset N (%) | Safety Subset N (%) | Other N (%) | Overall N(%) |
| SAF | 15(100%) | 192(100%) | 1436(100%) | 1643(100%) | 16(100%) | 177(100%) | 1434(100%) | 1627(100%) |
| Pediatrics | 1(6.7%) | 0 | 69(4.8%) | 70(4.3%) | 0 | 0 | 75(5.2%) | 75(4.6%) |
| >= 12 yr | 0 | 0 | 69(4.8%) | 69(4.2%) | 0 | 0 | 75(5.2%) | 75(4.6%) |
| < 12 yr | 1(6.7%) | 0 | 0 | 1(<0.1%) | 0 | 0 | 0 | 0 |
| Adults | 14(93.3%) | 192(100%) | 1367(95.2%) | 1573(95.7%) | 16(100%) | 177(100%) | 1359(94.8%) | 1552(95.4%) |
| Pregnant women | 0 | 1(0.5%) | 5(0.3%) | 6(0.4%) | 0 | 0 | 8(0.6%) | 8(0.5%) |
| PKAS | NA | NA | NA | NA | 16(100%) | 170(96.0%) | 109(7.6%) | 295(18.1%) |
| Pediatrics | NA | NA | NA | NA | 0 | 0 | 72(5.0%) | 72(4.4%) |
| >= 12 yr | NA | NA | NA | NA | 0 | 0 | 72(5.0%) | 72(4.4%) |
| < 12 yr | NA | NA | NA | NA | 0 | 0 | 0 | 0 |
| Adults | NA | NA | NA | NA | 16(100%) | 170(96.0%) | 37(2.6%) | 223(13.7%) |
| Pregnant women | NA | NA | NA | NA | 0 | 0 | 0 | 0 |
| ADA-Casirivimab | 13(86.7%) | 188(97.9%) | 1405(97.8%) | 1606(97.7%) | 16(100%) | 172(97.2%) | 1407(98.1%) | 1595(98.0%) |
| Pediatrics | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| >= 12 yr | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| < 12 yr | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adults | 13(86.7%) | 188(97.9%) | 1337(93.1%) | 1538(93.6%) | 16(100%) | 172(97.2%) | 1335(93.1%) | 1523(93.6%) |
| Pregnant women | 0 | 1(0.5%) | 5(0.3%) | 6(0.4%) | 0 | 0 | 8(0.6%) | 8(0.5%) |
| ADA-Imdevimab | 13(86.7%) | 188(97.9%) | 1405(97.8%) | 1606(97.7%) | 16(100%) | 172(97.2%) | 1407(98.1%) | 1595(98.0%) |
| Pediatrics | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| >= 12 yr | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| < 12 yr | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adults | 13(86.7%) | 188(97.9%) | 1337(93.1%) | 1538(93.6%) | 16(100%) | 172(97.2%) | 1335(93.1%) | 1523(93.6%) |
| Pregnant women | 0 | 1(0.5%) | 5(0.3%) | 6(0.4%) | 0 | 0 | 8(0.6%) | 8(0.5%) |
| NAb-Casirivimab | 13(86.7%) | 188(97.9%) | 1405(97.8%) | 1606(97.7%) | 16(100%) | 172(97.2%) | 1405(98.0%) | 1593(97.9%) |
| Pediatrics | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| >= 12 yr | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| < 12 yr | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adults | 13(86.7%) | 188(97.9%) | 1337(93.1%) | 1538(93.6%) | 16(100%) | 172(97.2%) | 1333(93.0%) | 1521(93.5%) |
| Pregnant women | 0 | 1(0.5%) | 5(0.3%) | 6(0.4%) | 0 | 0 | 8(0.6%) | 8(0.5%) |
| NAb-Imdevimab | 13(86.7%) | 188(97.9%) | 1405(97.8%) | 1606(97.7%) | 16(100%) | 172(97.2%) | 1405(98.0%) | 1593(97.9%) |
| Pediatrics | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| >= 12 yr | 0 | 0 | 68(4.7%) | 68(4.1%) | 0 | 0 | 72(5.0%) | 72(4.4%) |
| < 12 yr | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adults | 13(86.7%) | 188(97.9%) | 1337(93.1%) | 1538(93.6%) | 16(100%) | 172(97.2%) | 1333(93.0%) | 1521(93.5%) |
| Pregnant women | 0 | 1(0.5%) | 5(0.3%) | 6(0.4%) | 0 | 0 | 8(0.6%) | 8(0.5%) |

| Analysis Set | Placebo | | | | Casirivimab+Imdevimab 1200 mg SC | | | |
|---|---|---|---|---|---|---|---|---|
| | Sentinel Subset N (%) | Safety Subset N (%) | Other N (%) | Overall N(%) | Sentinel Subset N (%) | Safety Subset N (%) | Other N (%) | Overall N(%) |
| CRAS | NA | NA | NA | NA | 16(100%) | 167(94.4%) | 108(7.5%) | 291(17.9%) |
| Pediatrics | NA | NA | NA | NA | 0 | 0 | 71(5.0%) | 71(4.4%) |
| >= 12 yr | NA | NA | NA | NA | 0 | 0 | 71(5.0%) | 71(4.4%) |
| < 12 yr | NA | NA | NA | NA | 0 | 0 | 0 | 0 |
| Adults | NA | NA | NA | NA | 16(100%) | 167(94.4%) | 37(2.6%) | 220(13.5%) |
| Pregnant women | NA | NA | NA | NA | 0 | 0 | 0 | 0 |

N = Number of subjects; ADA = Anti-drug antibody; CRAS = Concentration-response analysis set; NA = Not applicable; NAb = Neutralizing antibody; PKAS = Pharmacokinetic analysis set; SAF = Safety analysis set; Other = All other subjects (Subset 3)
Note: PK samples from placebo patients are not analyzed. Percentages are based on the total in the safety analysis set. See Section 2.3 for definitions of analysis populations.

There were three defined subsets for participants ≥ 12 years: sentinel (subset 1) with dense pharmacokinetics (PK) sampling; safety (subset 2) with sparse PK sampling, and all other subjects (subset 3) for which no samples for PK were collected. Paediatric participants < 12 years were to be randomized to receive a single dose of casirivimab+imdevimab (SC [408, 792, or 1200 mg] or intramuscular [48, 96, or 144 mg]; weigh-tiered dose) or placebo in a 1:1 ratio per cohort. There were initially two defined subsets for participants < 12 years: paediatric sentinel (subset 4) with sparse PK sampling schedule, and all other paediatric participants (subset 5) with sparse PK sampling schedule. However, only 1 paediatric participant < 12 years was enrolled in the sentinel subset, in Cohort A1, and received placebo SC.

**Table 10**

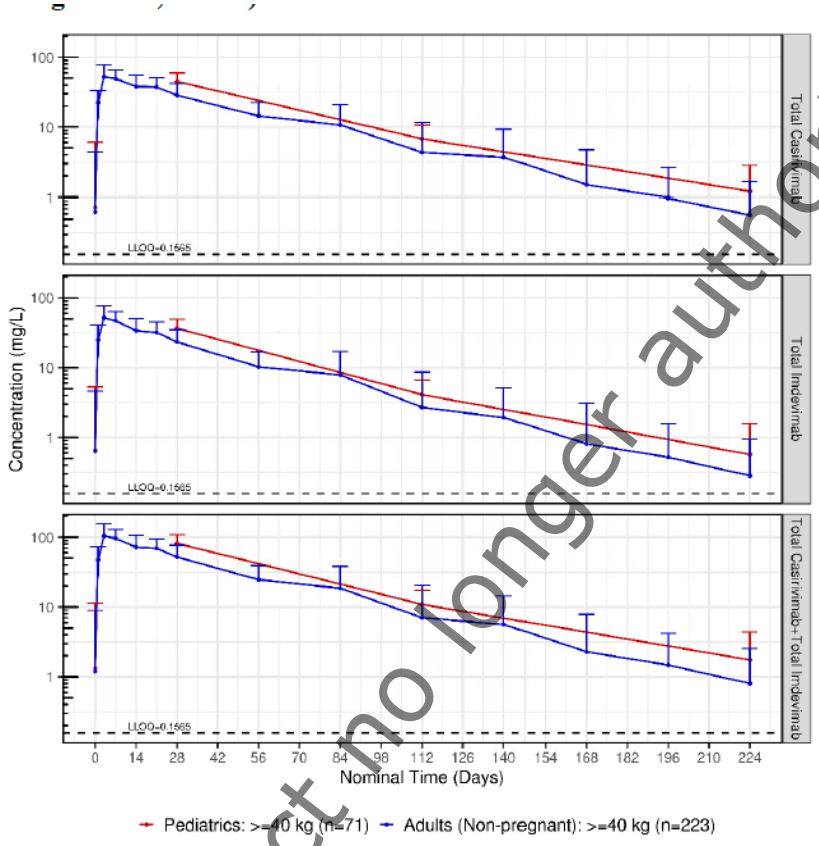
**Summary of Concentrations of Total Casirivimab, Imdevimab and Casirivimab+Imdevimab in Serum by Time in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [PKAS])**

| Nominal Sampling Time (Days) | Casirivimab 600 mg SC (N=72) | | Imdevimab 600 mg SC (N=72) | | Casirivimab+Imdevimab 1200 mg SC (N=72) | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| Weight >=20kg to < 40 kg | | | | | | |
| 0 | 1 | 0 (---) | 1 | 0 (---) | 1 | 0 (---) |
| 28 | 1 | 97.8 (---) | 1 | 73.8 (---) | 1 | 172 (---) |
| 112 | 1 | 8.53 (---) | 1 | 4.44 (---) | 1 | 13.0 (---) |
| 224 | 1 | 1.07 (---) | 1 | 0.328 (---) | 1 | 1.40 (---) |
| Weight >= 40 kg | | | | | | |
| 0 | 65 | 0.660 (5.32) | 65 | 0.582 (4.69) | 65 | 1.24 (10.0) |
| 21 | 1 | 39.3 (---) | 1 | 31.7 (---) | 1 | 71.0 (---) |
| 28 | 63 | 45.0 (14.8) | 63 | 36.7 (13.3) | 63 | 81.7 (27.8) |
| 112 | 66 | 6.78 (3.85) | 66 | 4.11 (2.58) | 66 | 10.9 (6.37) |
| 140 | 1 | 0.490 (---) | 1 | 0 (---) | 1 | 0.490 (---) |
| 224 | 64 | 1.19 (1.66) | 64 | 0.541 (1.02) | 64 | 1.73 (2.66) |

N = Number of subjects; n = Number of subjects at each timepoint; SD = Standard deviation; PKAS = Pharmacokinetic analysis set
Note: BLQs were set to 0. Combined concentrations (total casirivimab+total imdevimab) were calculated only when both the analytes are not missing.

The concentration over time profiles for total casirivimab and total imdevimab following SC administration were similar to each other and were characterized by an initial absorption phase (adults) followed by a mono-exponential elimination phase.

**Figure 1** **Mean (+SD) Concentrations of Casirivimab, Imdevimab, and Casirivimab+Imdevimab in Serum by Nominal Time and Body Weight Category in Pediatric and Adult Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, Log-Scaled, PKAS)**




LLOQ, lower limit of quantitation; n = Number of subjects; PKAS, pharmacokinetic analysis set;
Note: One pediatric patient weighing ≥20 kg and <40 kg was not included.
Approximately 68% of the pediatric subjects who received casirivimab+imdevimab were seronegative at baseline.
Source: Clinical Pharmacology Report 02V1 (Appendix 16.1.15 Figure 1)

**Assessor's comment**

Concentrations in serum in paediatric participants (≥12 and <18) with body weights ≥40 kg were slightly higher than those observed in adults. The argument that this may be contributed to differences in body weight distribution is agreed. External validation of paediatric PK data by use of pop PK modelling is requested.

**Table 11** **Descriptive Statistics of Baseline Body Weight and Age by Body Weight Tier Category in Pediatric and Adult Subjects Who Received 1.2 g of Casirivimab+Imdevimab SC with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [PKAS])**

| | Pediatrics (12-17 yrs) (N=72) | | | | | Adults (>=18 yrs) (N=223) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Weight/Age Body Weight Category | n | Mean (SD) | Median | Min : Max | Q1 : Q3 | n | Mean (SD) | Median | Min : Max | Q1 : Q3 |
| Baseline Body Weight (kg) | | | | | | | | | | |
| >=20 kg to <40 kg | 1 | 32.7 (---) | 32.7 | 32.7 : 32.7 | 32.7 : 32.7 | 0 | | | | |
| >=40 kg | 71 | 69.3 (19.3) | 65.3 | 40.4 : 130 | 55.3 : 76.8 | 223 | 83.6 (20.8) | 81.5 | 43.0 : 171 | 69.1 : 95.3 |
| Baseline Age (year) | | | | | | | | | | |
| >=20 kg to <40 kg | 1 | 12.0 (---) | 12.0 | 12.0 : 12.0 | 12.0 : 12.0 | 0 | | | | |
| >=40 kg | 71 | 15.1 (1.70) | 15.0 | 12.0 : 17.0 | 14.0 : 17.0 | 223 | 42.6 (16.9) | 43.0 | 18.0 : 87.0 | 27.0 : 56.0 |

N = Number of subjects; n = Number of subjects in each category; Min = Minimum; Max = Maximum; Q1 = First quartile; Q3 = Third quartile; SD = Standard deviation; PKAS = Pharmacokinetic analysis set

Due to the sparse nature of sample collection, non-compartmental analysis was not conducted in the paediatric population.

As shown in Figure 6, in the paediatric participants ≥12 years and <18 years (weighing ≥ 40 kg), mono-exponential elimination phase was similar to that observed for adults.
The first post-dose serum sample in paediatric participants was available at Day28, hence no data are available for assessment of the absorption phase in these participants.
Casirivimab and imdevimab concentrations in serum in paediatric participants (≥12 and <18) with body weights ≥40 kg were slightly higher than those observed in adults likely due to differences in body weight distribution.
Casirivimab and imdevimab were detectable in serum over 224 days of sample collection following a single 1200 mg SC dose of casirivimab+imdevimab.

*Immunogenicity*

In paediatric participants, the ADA incidence and titer and the NAb incidence observed were similar to that observed in overall study population.

**Table 12**

**Summary of Casirivimab ADA Status and ADA Category by Treatment Group in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [AAS])**

| ADA Status | Placebo n (%) | Casirivimab+Imdevimab 1200 mg SC n (%) | Overall n (%) |
|---|---|---|---|
| ADA Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| Negative | 67 (98.5%) | 55 (76.4%) | 122 (87.1%) |
| Pre-existing Immunoreactivity | 1 (1.5%) | 1 (1.4%) | 2 (1.4%) |
| Treatment Boosted Response | 0 | 0 | 0 |
| Treatment Emergent Response | 0 | 16 (22.2%) | 16 (11.4%) |

n = Number of subjects; ADA = Anti-drug antibody; AAS = ADA analysis set

**Table 13** **Summary of Imdevimab ADA Status and ADA Category by Treatment Group in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [AAS])**

| ADA Status | Placebo n (%) | Casirivimab+Imdevimab 1200 mg SC n (%) | Overall n (%) |
|---|---|---|---|
| ADA Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| Negative | 66 (97.1%) | 61 (84.7%) | 127 (90.7%) |
| Pre-existing Immunoreactivity | 0 | 1 (1.4%) | 1 (0.7%) |
| Treatment Boosted Response | 0 | 0 | 0 |
| Treatment Emergent Response | 2 (2.9%) | 10 (13.9%) | 12 (8.6%) |

n = Number of subjects; ADA = Anti-drug antibody; AAS = ADA analysis set

**Table 14** **Summary of Casirivimab Treatment-Boosted and Treatment-Emergent ADA Category and Maximum Titer Category in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [AAS])**

| Maximum Titer Category | Placebo n (%) | Casirivimab+Imdevimab 1200 mg SC n (%) | Overall n (%) |
|---|---|---|---|
| ADA Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| TE | | | |
| Persistent | 0 | 0 | 0 |
| Transient | 0 | 0 | 0 |
| Indeterminant | 0 | 16 (22.2%) | 16 (11.4%) |
| TE & TB | | | |
| Low (<1,000) | 0 | 10 (13.9%) | 10 (7.1%) |
| Moderate (1,000 to 10,000) | 0 | 4 (5.6%) | 4 (2.9%) |
| High (>10,000) | 0 | 2 (2.8%) | 2 (1.4%) |

n = Number of subjects; ADA = Anti-drug antibody; AAS = ADA analysis set; TB = Treatment-boosted; TE = Treatment-emergent

**Table 15** **Summary of Imdevimab Treatment-Boosted and Treatment-Emergent ADA Category and Maximum Titer Category in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [AAS])**

| Maximum Titer Category | Placebo n (%) | Casirivimab+Imdevimab 1200 mg SC n (%) | Overall n (%) |
|---|---|---|---|
| ADA Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| TE | | | |
| Persistent | 0 | 1 (1.4%) | 1 (0.7%) |
| Transient | 0 | 0 | 0 |
| Indeterminant | 2 (2.9%) | 9 (12.5%) | 11 (7.9%) |
| TE & TB | | | |
| Low (<1,000) | 2 (2.9%) | 9 (12.5%) | 11 (7.9%) |
| Moderate (1,000 to 10,000) | 0 | 1 (1.4%) | 1 (0.7%) |
| High (>10,000) | 0 | 0 | 0 |

n = Number of subjects; ADA = Anti-drug antibody; AAS = ADA analysis set; TB = Treatment-boosted; TE = Treatment-emergent

**Table 16** **Summary of Casirivimab ADA Status and NAb Status in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [AAS])**

| ADA Status; NAb Status | Placebo n (%) | Casirivimab+Imdevimab 1200 mg SC n (%) | Overall n (%) |
|---|---|---|---|
| ADA Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| NAb Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| ADA- | 67 (98.5%) | 55 (76.4%) | 122 (87.1%) |
| Pre+; NAb- | 1 (1.5%) | 1 (1.4%) | 2 (1.4%) |
| Pre+; NAb+ | 0 | 0 | 0 |
| TE & TB+; NAb- | 0 | 10 (13.9%) | 10 (7.1%) |
| TE & TB+; NAb+ | 0 | 6 (8.3%) | 6 (4.3%) |

n = Number of subjects; ADA = Anti-drug antibody; AAS = ADA analysis set; ADA- = ADA negative; NAb = Neutralizing antibody; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay; Pre+ = Pre-existing immunoreactivity; TB = Treatment-boosted; TE = Treatment-emergent

**Table 17** **Summary of Imdevimab ADA Status and NAb Status in Pediatric Subjects with Household Contact Exposure to Individuals with SARS-CoV-2 Infection (Study R10933-10987-COV-2069, [AAS])**

| ADA Status; NAb Status | Placebo n (%) | Casirivimab+Imdevimab 1200 mg SC n (%) | Overall n (%) |
|---|---|---|---|
| ADA Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| NAb Analysis Set | 68 (100%) | 72 (100%) | 140 (100%) |
| ADA- | 66 (97.1%) | 61 (84.7%) | 127 (90.7%) |
| Pre+; NAb- | 0 | 0 | 0 |
| Pre+; NAb+ | 0 | 1 (1.4%) | 1 (0.7%) |
| TE & TB+; NAb- | 1 (1.5%) | 3 (4.2%) | 4 (2.9%) |
| TE & TB+; NAb+ | 1 (1.5%) | 7 (9.7%) | 8 (5.7%) |

n = Number of subjects; ADA = Anti-drug antibody; AAS = ADA analysis set; ADA- = ADA negative; NAb = Neutralizing antibody; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay; Pre+ = Pre-existing immunoreactivity; TB = Treatment-boosted; TE = Treatment-emergent

## 2.3.3. Discussion on clinical aspects

Starting from protocol amendment 3, adolescent subjects ≥12 to <18 years of age (weight ≥40 kg) were eligible to be enrolled and randomized into the overall study, therefore all paediatric participants who enrolled were adolescents.

Starting from protocol amendment 4, paediatric participants aged <12 years were eligible to be enrolled and randomized into the overall study. A single paediatric participant (aged 10 years) enrolled into cohort A1 and was randomized to the placebo group but was not included in the efficacy analysis because they were seropositive at baseline; however, the participant was included in the safety analysis.

No specific paediatric formulation was used in Study COV-2069. Both adult and adolescent participants (i.e., age > 12 years) received a single-dose SC of 1200 mg casirivimab+imdevimab (600 mg per mAb) or single dose-matching placebo.

In Cohort A, the safety analysis population included 99 paediatric participants, 98 adolescents (age > 12 to < 18 years) and one child participant (age 10 years). Overall, the types and severity of TEAEs experienced by adolescent participants were similar to those experienced by adults in the study. The single child participant (age 10 years) did not experience any TEAEs during the study

In Cohort B, the safety analysis included 43 adolescents (age > 12 to < 18 years). Overall, the types and severity of TEAEs experienced by adolescent participants were similar to those experienced by adults in the study.

Treatment with casirivimab + imdevimab resulted in a relative risk reduction for symptomatic SARS-CoV-2 infections (COVID-19) similar to that in baseline seronegative participants (100% compared to placebo in paediatric participants)

Treatment with casirivimab + imdevimab resulted in a relative risk reduction for all SARS-CoV-2 infections (asymptomatic and symptomatic) similar to that in baseline-seronegative participants (74.5% compared to placebo in paediatric participants)

The interpretation of results in paediatric participants is limited due to small sample sizes and small number of events.

Casirivimab and imdevimab were detectable in serum over 224 days of sample collection following a single 1200 mg SC dose of casirivimab+imdevimab.

Due to the sparse PK sample collection, non-compartmental analysis was not conducted in the paediatric population. However, data indicate that in the paediatric participants ≥12 years and <18 years (weighing ≥ 40 kg), mono-exponential elimination phase is similar to that observed for adults. No data are available for assessment of the absorption phase in these participants.

Concentrations in serum in paediatric participants (≥12 and <18) with body weights ≥40 kg were slightly higher than those observed in adults. The argument that this may be contributed to differences in body weight distribution is agreed. External validation of paediatric PK data by use of population PK modelling is requested.

It is agreed that in paediatric participants, the ADA incidence and titer and the NAb incidence observed were similar to that observed in overall study population.

# 3. CHMP overall conclusion and recommendation

Casirivimab+imdevimab was well tolerated in adolescent (age ≥12 to <18 years). The safety profile in adolescents was comparable to the safety profile in adults. The types of TEAEs experienced by adolescent participants were similar to those observed in the adult population.

The treatment effect observed in supportive exploratory analyses conducted in the adolescent participants in Cohort A was consistent with the treatment effect observed in the adult participants in this cohort for the 8-month study period.

Based on the PK results provided no changes for the SmPC section 5.2 is warranted.

☒ **Fulfilled:**

No regulatory action required.

# 4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Very few adolescents are included in Cohort B. The efficacy data are not provided by age i.e. > 12 < 18 years and > 18 years. For completeness, please provide these data.

2. No results in seropositive patients were provided. Please provide efficacy results separately for seronegative and seropositive subjects

3. External validation of paediatric PK data by use of pop PK modelling should be provided.

## MAH responses to Request for supplementary information

**QUESTION 1**

1. Very few adolescents are included in Cohort B. The efficacy data are not provided by age i.e. ≥ 12 < 18 years and ≥ 18 years. For completeness, please provide these data.

**MAH response**

In the overall cohort B population (asymptomatic SARS-CoV-2 RT-PCR positive at baseline) including adults and adolescents, and regardless of serostatus at baseline (including seronegative, seropositive, and indeterminate), a single 1200 mg SC dose of casirivimab+imdevimab (REGN10933+REGN10987) prevented the progression to symptomatic COVID-19 in recently infected asymptomatic participants during the entire 8 month study period, with a relative risk reduction of 37.8% as compared to placebo.

These results are similar to the Cohort B efficacy results in adults and adolescents, regardless of serostatus at baseline, previously reported in Table 34 of CSR addendum 1 demonstrating a 38.5% relative risk reduction during the primary efficacy analysis period (29 days).

In adolescent participants (age 12 to <18 years), casirivimab + imdevimab as compared to placebo, prevented the progression to symptomatic COVID- 19 during the entire 8-month study period with a relative risk reduction of 73.9% (Table 1). In participants who were age ≥18 years, casirivimab+imdevimab, as compared to placebo, prevented the progression to symptomatic COVID-19 with a relative risk reduction of 29.8% during the entire 8-month study period.

***Table 1 Proportion of Cohort B Participants (Recently Infected Asymptomatic) Who Develop SARS CoV-2 Signs and Symptoms (Broad-Term) during the Study***

| | Placebo (N=171) | REGN10933+ REGN10987 (N=165) |
|---|---|---|
| Proportion of Cohort B participants | 60/171 (35.1%) | 36/165 (21.8%) |
| Risk reduction vs Placebo | | 37.8% |
| >=12 years to <18 years | 10/20 (50.0%) | 3/23 (13.0%) |
| Risk reduction vs Placebo | | 73.9% |
| >=18 years | 50/151 (33.1%) | 33/142 (23.2%) |
| Risk reduction vs Placebo | | 29.8% |

Source: Post hoc Table 14.6.2.7.95.4

REGN10933: casirivimab; REGN10987: imdevimab

Although a greater relative risk reduction is observed in the adolescent population (73.9%) as compared to the adult population (29.8%), interpretation of this post-hoc analysis is limited due to the small number of symptomatic infections in the adolescent population and the small sample size of the adolescent population

**Assessor's comment**

The requested data are provided. We agree with the MAH that although a greater relative risk reduction is observed in the adolescent population (73.9%) as compared to the adult population (29.8%), interpretation of this post-hoc analysis is limited due to the small number of symptomatic infections in the adolescent population and the small sample size of the adolescent population

Issue solved

**QUESTION 2**

2. No results in seropositive patients were provided. Please provide efficacy results separately for seronegative and seropositive subjects

**MAH response**

**Cohort A (prevention of symptomatic infection):**

In Table 2, we provide efficacy results for the prevention of symptomatic infection by casirivimab+imdevimab as compared to placebo, separately for seronegative and seropositive subjects by age group, during the entire 8-month study period.

***Table 2 Proportion of Participants Who have Symptomatic RT-qPCR Confirmed SARS-CoV-2 Infection (Broad Term) by Central Lab or Local Lab during the Study by Baseline Serostatus in Cohort A***

| Baseline Serostatus | Age: 12 to < 18 years | | | Age: ≥18 years | | |
|---|---|---|---|---|---|---|
| | Placebo | REGN10933+ REGN10987 | RR vs Placebo | Placebo | REGN10933+ REGN10987 | RR vs Placebo |
| Seronegative | 4/34 (11.8%) | 0/40 | 100.0% | 108/808 (13.4%) | 21/801 (2.6%) | 80.4% |
| Seropositive | 0/12 | 0/10 | | 6/239 (2.5%) | 4/266 (1.5%) | 40.1% |
| Other* | 0/1 | 0/2 | | 2/49 (4.1%) | 0/55 | 100.0% |

RR: Risk reduction

REGN10933: casirivimab; REGN10987: imdevimab
*Other includes neither seronegative nor seropositive participants.
Source: Post hoc 14.6.2.3.89.2, Post hoc Table 14.6.2.3.89.3

Although greater relative risk reduction is observed in the seronegative adolescent population (100%) compared to the seronegative adult population (80.4%) (Table 17 in CSR addendum 2) and compared to the combined seronegative adult and adolescent population (81.2%) (Table 16 in CSR addendum 2), interpretation of this post-hoc analysis is limited due to the small number of symptomatic infections in the adolescent population and the small sample size of the adolescent population.

In seropositive adolescents aged 12 to < 18 years, there were no symptomatic SARS-CoV-2 infections in either casirivimab+imdevimab or placebo groups. The interpretation of the relative risk reduction with casirivimab+imdevimab in the seropositive adult population (40.1%) limited due to low symptomatic infection events in both the casirivimab+imdevimab and placebo groups, consistent with pre-existing natural immunity (seropositivity) conferring protection against infection.

**Cohort A (prevention of any infection, including symptomatic and asymptomatic):**

In Table 3, we provide efficacy results for the development of any infection (including symptomatic and asymptomatic) during the entire 8-month study period, separately for seronegative and seropositive subjects by age group.

***Table 3 Proportion of Participants Who Have RT-qPCR Confirmed SARS-CoV-2 Infection (Regardless of Symptoms) by Central Lab or Local Lab during the Study by Baseline Serostatus in Cohort A***

| Baseline Serostatus | Age: 12 to < 18 years | | | Age: ≥18 years | | |
|---|---|---|---|---|---|---|
| | Placebo | REGN10933+ REGN10987 | RR vs Placebo | Placebo | REGN10933+ REGN10987 | RR vs Placebo |
| Seronegative | 10/34 (29.4%) | 3/40 (7.5%) | 74.5% | 163/808 (20.2%) | 52/801 (6.5%) | 67.8% |
| Seropositive | 1/12 (8.3%) | 0/10 | 100.0% | 19/239 (7.9%) | 14/266 (5.3%) | 33.8% |
| Other* | 1/1 (100.0%) | 0/2 | 100.0% | 3/49 (6.1%) | 3/55 (5.5%) | 10.9% |

RR: Risk reduction

REGN10933: casirivimab, REGN10987: imdevimab
*Other includes neither seronegative nor seropositive participants.
Source: Post hoc Table 14.6.2.3.90.2, Post hoc Table 14.6.2.3.90.3

Although a greater relative risk reduction is observed in the seronegative and seropositive adolescent populations (74.5% and 100% respectively) compared to the seronegative and seropositive adult

populations, interpretation of this post-hoc analysis is limited due to the small number of infections in the adolescent population and the small sample size of the adolescent population. The interpretation of the relative risk reduction with casirivimab+imdevimab in the seropositive adult population (33.8%) is limited due to low infection events in both the casirivimab+imdevimab and placebo groups, consistent with pre-existing natural immunity (seropositivity) conferring protection against infection.

**Cohort B:**

In Table 4, we provide efficacy results for cohort B participants (asymptomatic SARSCoV- 2 RT-PCR positive at baseline) who develop symptomatic infection, separately for seronegative and seropositive subjects by age group, during the entire 8-month study period.

***Table 4 Proportion of Cohort B Participants (Recently Infected Asymptomatic) Who Develop SARS CoV-2 Signs and Symptoms (Broad-Term) during the Study by Baseline Serostatus and Age group***

| Baseline Serostatus | Age: 12 to < 18 years | | | Age: ≥18 years | | |
|---|---|---|---|---|---|---|
| | Placebo | REGN10933+ REGN10987 | RR vs Placebo | Placebo | REGN10933+ REGN10987 | RR vs Placebo |
| Seronegative | 6/12 (50.0%) | 3/16 (18.8%) | 62.5% | 44/102 (43.1%) | 30/92 (32.6%) | 24.4% |
| Seropositive | 3/7 (42.9%) | 0/4 | 100.0% | 3/36 (8.3%) | 3/45 (6.7%) | 20.0% |
| Other* | 1/1 (100%) | 0/3 | 100% | 3/13 (23.1%) | 0/5 | 100% |

RR: Risk reduction

REGN10933: casirivimab, REGN10987: imdevimab
*Other includes neither seronegative nor seropositive participants.
Source: Post hoc Table 14.6.2.7.95.1, 14.6.2.7.95.2, 14.6.2.7.95.3

Similar to the overall Cohort B efficacy results in seronegative adults and adolescents, previously reported in Table 29 of CSR addendum 1, demonstrating a 31.1% relative risk reduction during the 29-day primary efficacy analysis period, new analyses demonstrate a relative risk reduction of 30.3% during the entire 8-month study period. In the new analyses where efficacy results are reported separately by age group, there is a greater relative risk reduction observed in the seronegative adolescent population (62.5%) compared to the seronegative adult population (24.4%).

Interpretation of this post-hoc analysis by age group is limited by the small sample size of the subgroups. The interpretation of the relative risk reduction with casirivimab+imdevimab in the seropositive adolescent (100%) and adult population (20%) is limited to low infection events in both groups, consistent with their known pre-existing natural immunity (seropositivity) conferring protection against infection.

**Assessor's comment**

The requested information is provided.

We agree with the MAH that interpretation of this post-hoc analysis by age group is limited by the small sample size of the subgroups.

Issue solved

**QUESTION 3**

3. External validation of paediatric PK data by use of pop PK modelling should be provided.

**MAH Response**

The external validation of population PK modelling is presented below. The results demonstrate that the population PK models, which incorporated allometric scaling and age impact to account for the effect of body weight and age on PK parameters in pediatric subjects, were able to predict

concentrations of casirivimab and imdevimab in serum in pediatric subjects for the pediatric dose equivalents to the adult 1200 mg SC dose well, indicating the model-based predictions based on adult data are consistent with the observed pediatric data.

Method

Two population pharmacokinetic (PopPK) models with the same model structure were developed for casirivimab and imdevimab based on an analysis dataset comprised of 3687 casirivimab and 3716 imdevimab adult subjects from three clinical studies (R10933-10987-COV-2067, R10933-10987-COV-2069, and R10933-10987-COV-20145). The developed PopPK models for casirivimab and imdevimab were 2-compartment models with linear elimination and first-order absorption following subcutaneous (SC) dosing (R10933-PK-21053-SR-01V1). The PopPK models for casirivimab and imdevimab were used to perform simulations in virtual adult and pediatric populations receiving weight-tiered single dose of casirivimab+imdevimab given subcutaneously as outlined below. PopPK model parameters were fixed to the estimates from the final PK models of casirivimab and imdevimab (R10933-PK-21053-SR-01V1) with inter-subject variability incorporated via simulated interindividual random effects. Given the uncertainty in the estimation of the weight related exponents scaling the structural parameters in the analyses of the adult data, allometric scaling based on theoretical weight related exponents and age impact were applied to account for the effect of body size and age on PK parameters in pediatric populations (Basu et al., 2020).Simulated concentration-time profiles (median and 90% prediction interval) of casirivimab and imdevimab overlaid with observed data from Study R10933-10987-COV- 2069 are presented.

• Dosing setup:

- 1200 mg SC single dose casirivimab+imdevimab for ≥40 kg group

- 792 mg SC single dose casirivimab+imdevimab for ≥20 to <40 kg group

**RESULTS**

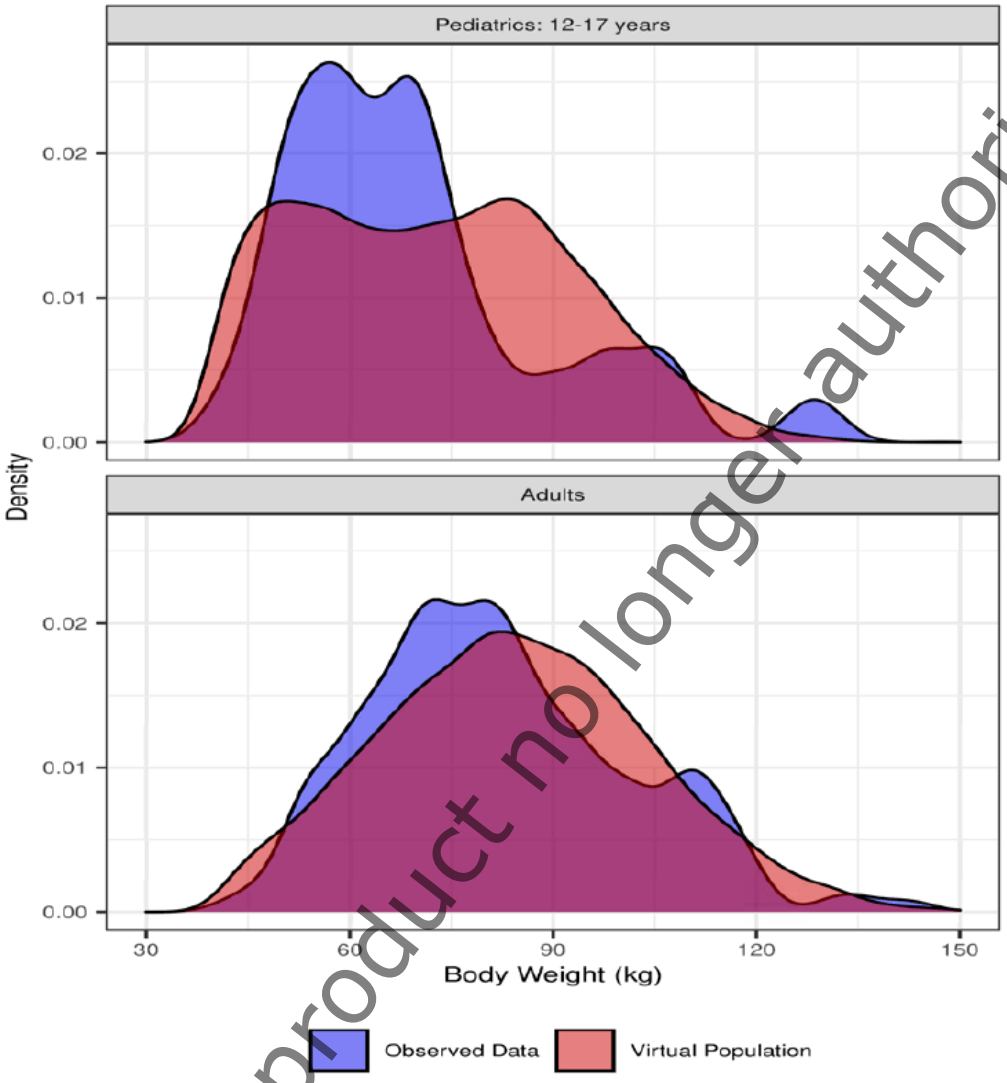
1. ACCOUNTING OF SUBJECTS

**Table 5 Accounting of Subject by Age and Weight in the PK Analysis set ( PKAS) of Study R10933-10987-COV-2069**

| Population | Weight Group | N | Median Weight (kg) | Mean (SD) Weight (kg) | Min, Max |
|---|---|---|---|---|---|
| Adults | >=40 kg | 223 | 79.80 | 82.6 (20) | 43, 170.8 |
| Pediatrics: 12 - 17 years | >=20 kg to <40 kg | 1 | 32.70 | 32.7 (0) | 32.7, 32.7 |
| Pediatrics: 12 - 17 years | >=40 kg | 71 | 65.95 | 69.62 (20) | 40.4, 130.2 |

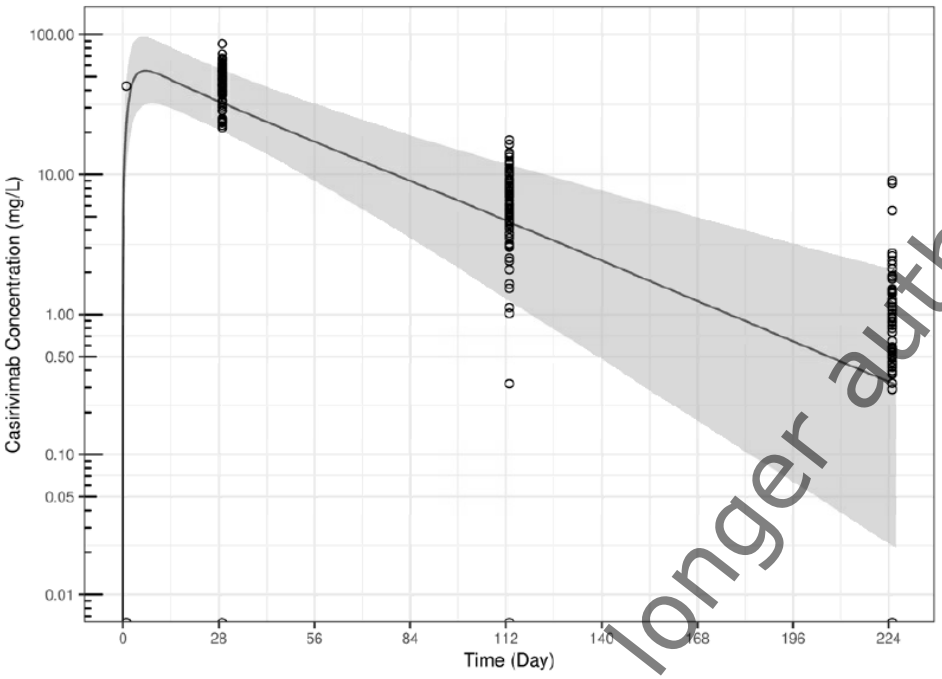
2. DISTRIBUTION OF BODY WEIGHT

***Figure 1: Density Plot of Body Weight for Virtual Population used in Simulation and Observed Dataset from Study R10933-10987-COV-2069***



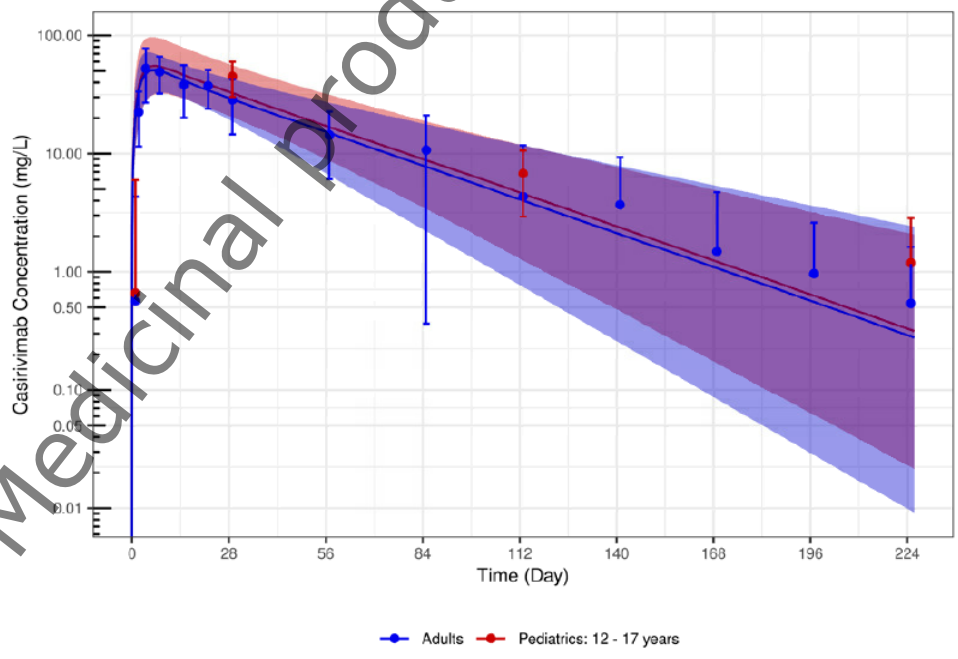
3. SIMULATED CONCENTRATION-TIME PROFILES FOR CASIRIVIMAB

***Figure 2: Simulated Concentration-time Profiles of Casirivimab Following 1200 mg SC Single Dose, Overlaid with Observed Individual Pediatric Data (12 – 17 years, ≥40 kg Group) in Study R10933-10987-COV-2069***



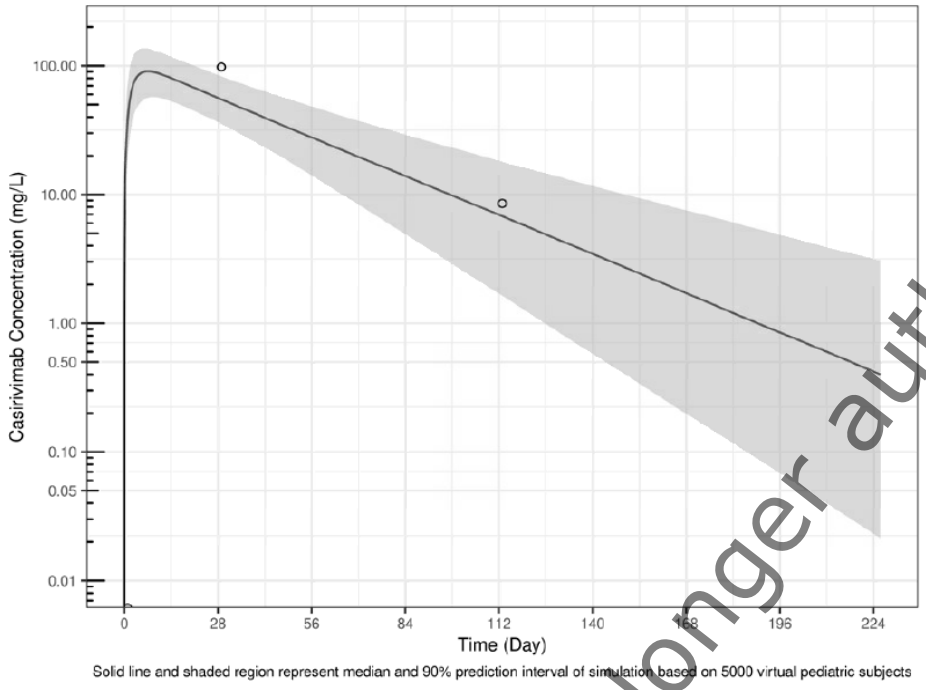

Solid line and shaded region represent median and 90% prediction interval of simulation based on 5000 virtual pediatric subjects

***Figure 3: Simulated Concentration-time Profiles of Casirivimab Following 1200 mg SC Single Dose, Overlaid with Observed Mean (±SD) Data (≥40 kg) in Study R10933-10987-COV-2069, by Age Groups***



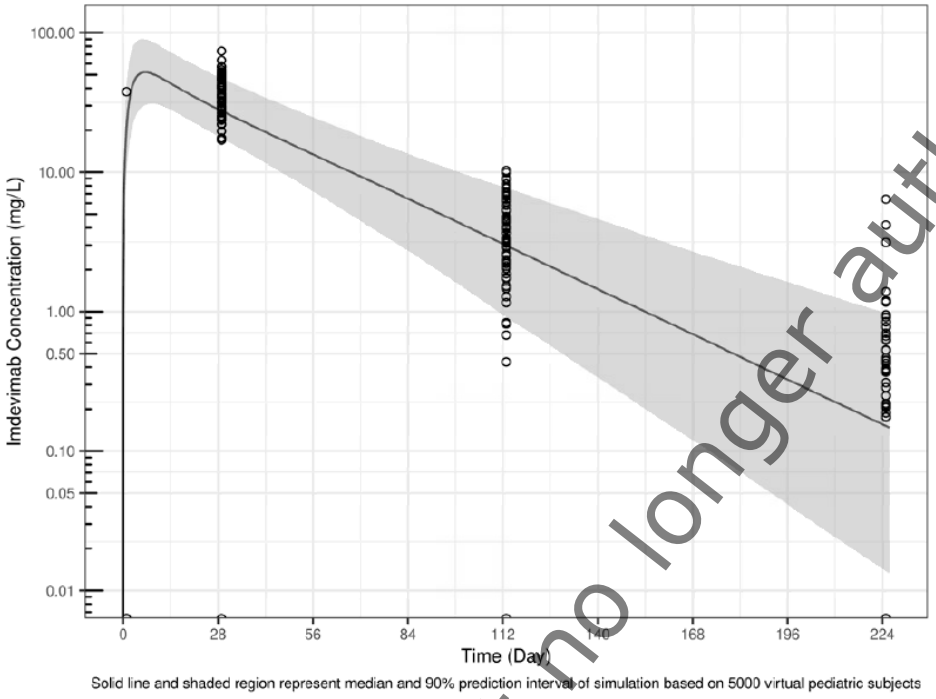

Solid line and shaded region represent median and 90% prediction interval of simulation based on 5000 virtual subjects in each age group; symbols and errorbars represent mean and SD of observed data

***Figure 4: Simulated Concentration-time Profiles of Casirivimab Following 792 mg SC Single Dose, Overlaid with Observed Individual Pediatric Data (12 – 17 years, ≥20 to <40 kg Group) in Study R10933-10987-COV-2069***



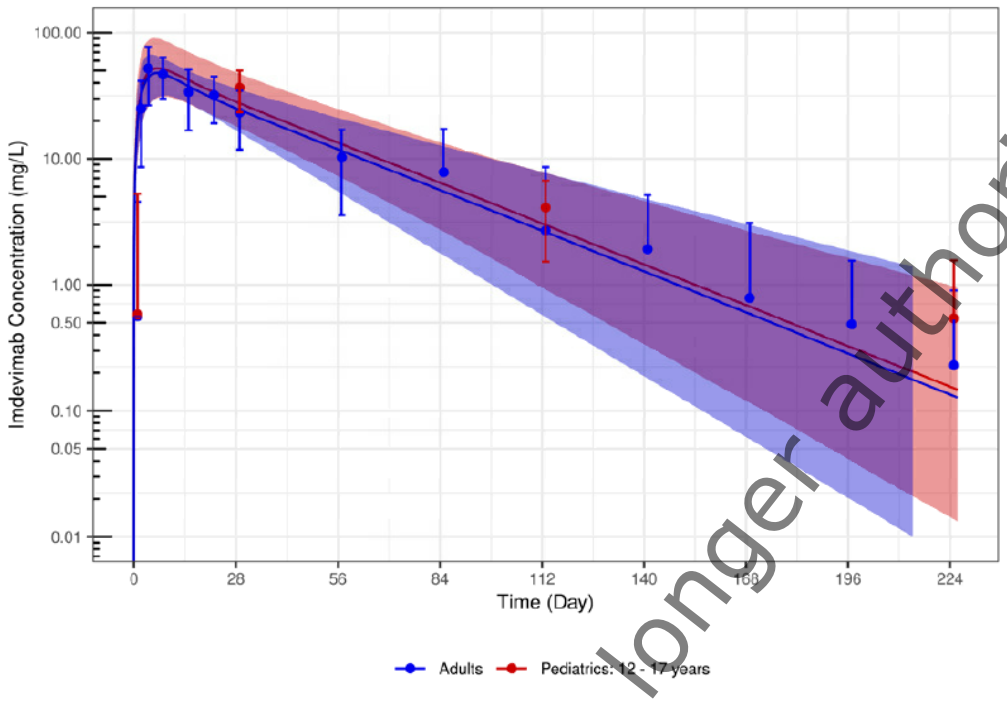
4. SIMULATED CONCENTRATION-TIME PROFILES FOR IMDEVIMAB

***Figure 5: Simulated Concentration-time Profiles of Imdevimab Following 1200 mg SC Single Dose, Overlaid with Observed Individual Pediatric Data (12 – 17 years, ≥40 kg Group) in Study R10933-10987-COV-2069***



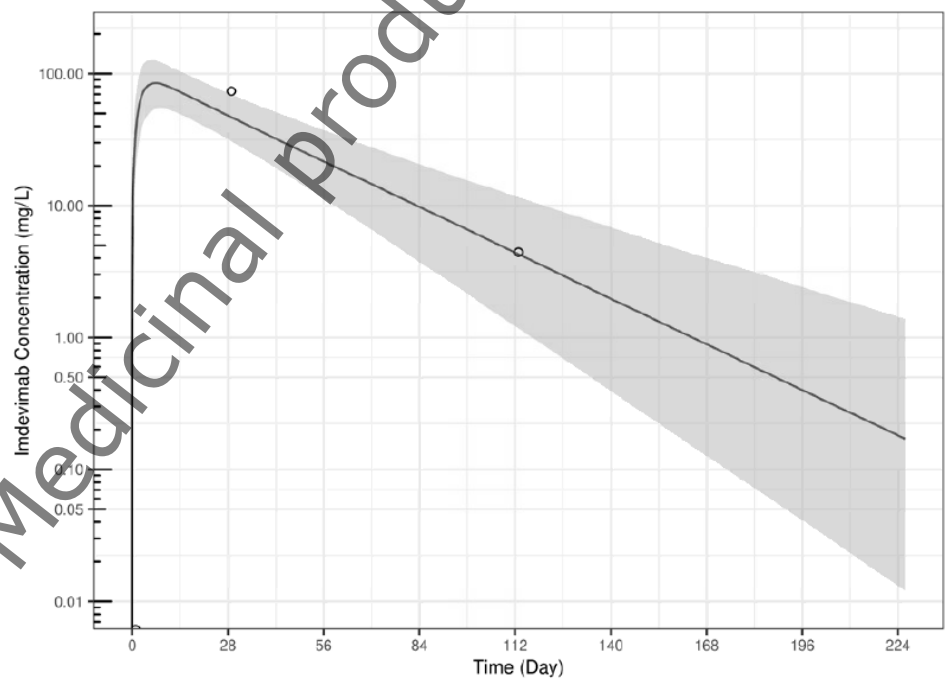

Solid line and shaded region represent median and 90% prediction interval of simulation based on 5000 virtual pediatric subjects

***Figure 6: Simulated Concentration-time Profiles of Imdevimab Following 1200 mg SC Single Dose, Overlaid with Observed Mean (±SD) Data (≥40 kg) in Study R10933-10987-COV-2069, by Age Groups***




Solid line and shaded region represent median and 90% prediction interval of simulation based on 5000 virtual subjects in each age group; symbols and errorbars represent mean and SD of observed data

***Figure 7: Simulated Concentration-time Profiles of Imdevimab Following 792 mg SC Single Dose, Overlaid with Observed Individual Pediatric Data (12 – 17 years, ≥20 to <40 kg Group) in Study R10933-10987-COV-2069***




Solid line and shaded region represent median and 90% prediction interval of simulation based on 5000 virtual pediatric subjects

**MAH's CONCLUSION**

Overlay plots of population PK simulated concentrations of casirivimab and imdevimab in serum [median (90% Prediction Interval)] versus observed concentrations for each pediatric body weight tier showed good agreement between predicted and observed concentrations through day 112, with the population PK model slightly underestimating concentrations at day 224.

These results from the validation demonstrate that the population PK models, which incorporated allometric scaling and age impact to account for the effect of body weight and age on PK parameters in pediatric subjects, were able to predict concentrations of casirivimab and imdevimab in serum in pediatric subjects for the pediatric dose equivalents to the adult 1200mg SC dose well, indicating the model-based predictions based on adult data are consistent with the observed pediatric data.

**Assessor's comment**

From a methodological point of view, the MAH's approach is not supported and is contradictory to the EMA Q&A (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers).

Maturation effect in terms of additional age-related effects in addition to the weight effect is not expected to affect the PK of mabs in subjects at the age of 12 and above but only at very young age and thus at weight below 20 kg. Thus, the MAH's approach to include age-related effects in addition to weight-related effects for simulating the exposure for adolescents above 20 kg of weight is not supported. Of note, there is data of only one adolescent subjects at weight below 40 kg.
The MAH was reasoning that age impact was applied to account for the effect of body size and age on PK parameters in paediatric populations, given the uncertainty in the estimation of the weight related exponents scaling the structural parameters in the analyses of the adult data. Instead, the MAH may have tried to estimate the weight effect based on a comprehensive weight range, to investigate the impact of fixed versus estimated allometric exponents. No definite model selection to justify the chosen maturation function has been provided, in addition. External validation based on the adult pop PK model is thus considered missing, even for the weight category above 40 kg (adolescents).

Simulated concentration-time profiles (median and 90% prediction interval) of casirivimab and imdevimab overlaid with observed data from Study R10933-10987-COV- 2069 are presented, with is supported.

Nevertheless, paediatric PK data (observations) and presented simulations indicate the predominant weight effect and the observed paediatric PK data indicate consistency. Nevertheless, the issue of accounting for weight and age-related effects may become relevant in case of a potential extension of indication for other paediatric age groups.

**Issue not further pursued.**