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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

EVUSHELD

International non-proprietary name: tixagevimab, cilgavimab

Pharmaceutical form: solution for injection

Dosage strength(s): 100 mg/ml, 100 mg/ml

Route(s) of administration: intramuscular use

Marketing authorisation holder: AstraZeneca AG

Marketing authorisation no.: 68704

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 27.04.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested extension of the therapeutic indication

EVUSHELD is indicated for the treatment of COVID-19 in adults and paediatric individuals (12 years of age and older weighing at least 40 kg) (see "Dosage/Administration" and "Pharmacokinetics").

2.2.2 Approved extension of the therapeutic indication

Treatment
EVUSHELD is indicated for the treatment of mild-to-moderate COVID-19 in adults and adolescents (from 12 years of age with minimum body weight of 40 kg) who do not require supplemental oxygen or hospitalisation due to COVID-19 and who are at risk of progressing to severe COVID-19 (see "Dosage/Administration" and "Pharmacokinetics").

Decisions regarding the use of EVUSHELD for pre-exposure prophylaxis or treatment should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences, as well as available information about susceptibility to EVUSHELD (see "Properties/Effects" and "Warnings").

The use of EVUSHELD should be based on official recommendations.

These indications have been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is strictly dependent on the timely fulfilment of conditions. Once the conditions have been fulfilled, the time-limited authorisation can be changed to a standard authorisation.

2.2.3 Requested dosage

Summary of the requested standard dosage for the extension of the therapeutic indication:

Posology
The recommended dosage is 600 mg of tixagevimab + cilgavimab administered as 2 separate consecutive intramuscular injections of 3 ml each:
• 300 mg of tixagevimab
• 300 mg of cilgavimab

For the treatment of mild to moderate COVID-19, tixagevimab + cilgavimab should be given as soon as possible after a positive virus test for a SARS-CoV-2 infection and within 7 days after onset of symptoms.

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Paediatric population
The safety and efficacy of tixagevimab + cilgavimab have not been shown in children younger than 18 years of age. No data are available.
It is expected that the recommended dosages in persons of 12 years of age and older weighing at least 40 kg show comparable serum exposures of tixagevimab and cilgavimab as observed in adults, as adults with a similar body weight were included in the TACKLE clinical study (see "*Properties/Effects - Pharmacodynamics*" and "*Pharmacokinetics*").

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 September 2022
Formal control completed	9 September 2022
Preliminary decision	16 November 2022
Response to preliminary decision	12 December 2022
2nd Preliminary decision	31 January 2023
2nd Response to preliminary decision	1 March 2023
Final decision	27. April 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical context

Coronavirus Disease 2019 (COVID-19) is a pandemic disease that started in Wuhan, China, in December 2019. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The COVID-19 clinical spectrum ranges from asymptomatic infection to severe disease. The majority of patients will present non-severe (flu-like syndrome) or mild symptoms (mild pneumonia). However, up to 20% of patients will present severe (important lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan dysfunction) that might ultimately lead to death. Patients with risk factors (e.g. old age, obesity, chronic lung, kidney or heart disease, active cancer, or immunosuppression, diabetes) are especially at higher risk of severe course and death.

Vaccines based on various technologies have been developed for the prevention of COVID-19 and are widely used in Switzerland.

For the management of COVID-19, several drugs have been approved throughout the course of the pandemic. Evusheld was approved on 09.09.2022 in Switzerland for the pre-exposure prophylaxis of COVID-19. It consists of a combination of 2 recombinant human IgG1κ monoclonal antibodies (tixagevimab and cilgavimab). They simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of the SARS-CoV-2, hindering its interaction with the human ACE2 receptor, resulting in a blockade of virus entry. Of note, the half-lives of these monoclonal antibodies have been extended (to 90 days) by introducing YTE and TM substitutions in the Fc part. This indication extension application concerns the use of Evusheld for the treatment of proven COVID-19 in non-hospitalised adults.

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4 Nonclinical aspects

No new nonclinical documentation was submitted to support the new indication for EVUSHELD (treatment of COVID-19) and a new dose for this indication (600 mg). This is accepted, as the efficacy and safety studies for the proposed indication were submitted as part of the documentation with the initial submission. No safety issues were identified in toxicity studies. According to the results of in vitro assays with pseudoviruses, submitted as an answer to stipulations, EVUSHELD does not retain neutralising activity against variants BF.7, BA.2.75.2, BQ.1, and BQ.1.1 (IC50 fold change >10,000), and the activity against BJ.1 is reduced up to 400-fold. EVUSHELD retained neutralising activity against BA.2.12.1, BA.3, and BA.4/BA.5 variants in pseudovirus assays (slightly increased IC50 fold change). EVUSHELD also retained neutralising activity against the BA.5 variant in an assay using authentic virus (2.8- to 16.4-fold change from wild type). However, according to published data (Wang Q. et al., 2023, Cell 186, 279–286), EVUSHELD has no neutralisation activity against the currently circulating variants XBB, XBB.1, and XB.1.5. The clinical relevance of in vitro data is not known.

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5 Clinical and clinical pharmacology aspects

5.1 Clinical pharmacology

Pharmacokinetics

The application included PK data from a Phase 1 study and from the Phase 3 TACKLE study. The PK data from TACKLE were consistent with the data in other studies (PROVENT and STORM CHASER) for the prophylaxis indication.

Pharmacodynamics

The dose justification was in part based on a viral dynamic model which was used for simulations of the effects of Evusheld on viral load dynamics for virus variant BA.1 for different dose levels. The model has been qualified with external data for the placebo situation, but the effect of Evusheld on viral load has not been qualified with observed data. Therefore, the simulations based on this model are associated with uncertainty.
Simulations were conducted to compare the anti-viral effect of different EVUSHELD doses against either the original SARS-CoV-2 strain or the Omicron BA.1 variant.
The simulations indicated that the timing of treatment was more important than the potency or dose, and that when dosing occurred after the peak viral load, as was the case in TACKLE, the effects of Evusheld are comparable against the original SARS-CoV-2 strain or Omicron subvariant BA.1.
Whether and to what extent the simulated effects of Evusheld on the viral load dynamics are expected to translate into a clinically relevant benefit remains uncertain.

Relationship between plasma concentration and effect

The exposure-efficacy relationship of Evusheld in TACKLE was investigated using serum Evusheld AUC and the probability of progression from mild to moderate COVID-19 to severe COVID-19 or death from any cause that occurred within 5 days or within 28 days after a 600 mg i.m. dose. Kaplan-Maier curves by exposure quartiles did not indicate any trends for an exposure-efficacy relationship, and statistical testing also did not result in a significant effect.

This result could be due to the limited dose range studied in Phase 3 and/or to high neutralising concentrations achieved in all participants. Furthermore, the result that no exposure-response relationship was detected during the first 5 days indicated that lack of efficacy during this period was not driven by exposure but more likely due to the timing of treatment relative to onset of infection.

5.2 Dose finding and dose recommendation

No specific dose-finding study was performed. The treatment dose rationale for 600 mg (300 mg of tixagevimab plus 300 mg of cilgavimab), which represents a doubling in comparison to the prophylaxis studies, is based on *in vitro* potency data (neutralising activity), PK data, as well as a viral-dynamic model whose concepts were also used in the pre-exposure studies.

Even though there are limitations to this approach, the selected 600 mg dose for current SARS-CoV-2 variants with reduced susceptibility that were not present during the pivotal phase 3 TACKLE study. Efficacious drug levels will likely be reached within 24 h, which is probably sufficient from a clinical point of view. However, Evusheld administration at an early timepoint following symptom onset is of paramount importance.

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5.3 Efficacy

This indication extension of Evusheld for the treatment of proven COVID-19 in non-hospitalised adults was supported by a single Phase 3 pivotal study (**TACKLE**).

The TACKLE study was a randomised, double blind, placebo-controlled, multicentre study performed in 95 sites (in Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, UK, Ukraine, USA). The current evaluation is based on an interim report from 31.05.2022 that reports 2 data cut-offs. The primary analysis at the first data cut-off (DCO, 21 August 2021) was conducted 30 days after 52 primary endpoint events were observed, followed by a key secondary data cut-off (14 January 2022) for the Day 169 follow-up.

Included participants were unvaccinated outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 test (PCR or antigenic) from a sample collected ≤ 3 days and presenting with ≤ 7 days of COVID-19 symptoms. Patients needed to present a WHO Clinical Progression Scale (CPS) score > 1 and < 4 and a $SatO_2$ ≥ 92% on room air (except for those regularly receiving supplemental oxygen for an underlying lung condition). Participants were randomised 1:1 to receive either intramuscular Evusheld at a dose of 600 mg (300 mg of tixagevimab and 300 mg of cilgavimab) or placebo. The dose of Evusheld was twice the dose used for the pre-exposure prophylaxis (PROVENT study). At least 60% of participants should have met the protocol definition of being at high-risk of progression to severe COVID-19 (e.g. ≥ 65 years old, BMI > 30 kg/m^2, end-organ disease, immunosuppression). Randomisation was stratified by (i) time from symptom onset (≤ 5 days versus > 5 days) and (ii) high-risk versus low risk of progression to severe COVID-19, which is appropriate.

The **primary endpoint** was a composite of either severe COVID-19 or death from any cause through Day 29 (severe COVID-19 was characterised by a minimum of either pneumonia - fever, cough, tachypnoea, or dyspnoea, AND lung infiltrates - or hypoxaemia - SpO2 < 90% on room air and/or severe respiratory distress, and a WHO Clinical Progression Scale score of 5 or higher). The **key secondary endpoint** was a composite of either death from any cause or hospitalisation for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169). **Other secondary or exploratory** endpoints typically analysed symptom duration, rate of respiratory failure, or the evolution of viral load.

Because of the changing nature of the pandemic, several amendments were implemented during the study, but they are not considered to alter its results. Overall, the study design, as well as its objectives and endpoints, are appropriate.

A total of 910 participants were randomised (Evusheld 456, Placebo 454), 903 of whom received treatment (Evusheld 452, Placebo 451). Baseline demographics and characteristics were balanced between groups. The majority of participants were young, with a median age of 46 years, and 87.2% of participants were < 65 years old. This might limit study extrapolability to the elderly population. 89.8% of participants were classified as having high-risk comorbidities for progression to severe COVID-19 or death. These were essentially obesity (43%), hypertension (28.6%), diabetes (12.1%), chronic lung disease (12%), and cardiovascular disease (8.9%). Immunocompromised patients were few (5.1%). Since the study began before the availability of dedicated vaccines, 84.1% of subjects were seronegative for SARS-CoV-2.

Regarding disease presentation, this was also balanced between groups, with a median time from symptom onset of 5 days, with 59% ≤ 5 days and 41% > 5 days. 87.9% had a WHO clinical progression scale score of 2 (ambulatory; symptomatic, and independent) and 12.1% a WHO CPS of 3 (ambulatory; symptomatic, and assistance needed).

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During the study, there was a significant number of important protocol deviations, with 45.7% of participants with at least 1 important protocol deviation (balanced between groups). Important protocol deviations were mainly related to eDiary non-compliance, and in line with the conclusion from the EMA, were not considered to have a major impact since the more objective endpoints of clinical outcomes (as in the primary endpoint) are considered to be unaltered.

At the primary DCO the study met its primary endpoint, since 4.4% (18/407) of subjects in the Evusheld group vs 8.9% (37/415) in the Placebo group either developed severe COVID-19 or died through Day 29. The relative risk reduction is of 50.49% (95% CI: 14.56, 71.31). Results for the primary endpoint were consistent at the time of the secondary DCO analysis (4.4% vs 8.8%, RRR 50.38%). Of note, at the secondary DCO there were 7 deaths in the Evusheld group, whereas there were 6 in the Placebo group (all infection-related). Therefore, the effect of Evusheld on the primary endpoint was driven by the incidence of severe COVID-19 and not the prevention of death. In the FAS that better represents the real-world situation and is in line with the intention-to-treat principle, 5.4% (24/446) of subjects in the Evusheld arm vs 9.2% (41/444) in the Placebo arm either developed severe COVID-19 or died through Day 29, with an RRR of 41.59% (95% CI: 5.01, 64.08).

Relevant supportive estimands of the primary endpoint at the primary DCO indicated that, in the early intervention analysis set (EIAS, patients dosed ≤ 5 days from symptoms – in contrast to ≤ 7 days for the mFAS), 3.6% (9/253) of subjects in the Evusheld arm vs 8.9% (27/251) in the Placebo arm either developed severe COVID-19 or died through Day 29. There was indeed a clear trend between the time of administration after symptom onset and the magnitude of treatment benefit. Sensitivity analyses indicate that, after 5 days of symptom evolution, there was no benefit of Evusheld treatment in the high-risk group, with 7.6% (11/145) and 6.5% (10/153) of subjects meeting the primary endpoint in the Evusheld and Placebo groups, respectively.

In the seronegative analysis set (SNAS), 4.0% (14/347) of subjects in the Evusheld arm vs 10.4% (36/345) in the Placebo arm either developed severe COVID-19 or died through Day 29, with an RRR of 61.26% (95% CI: 29.67, 78.66). No benefit could be shown in seropositive subjects, with 4 participants in the Evusheld arm experiencing an event of either severe COVID-19 (n=3) or death from any cause (n=1, sudden cardiac death), in comparison to 1 participant in the Placebo arm (RRR -436.15, CI: -5515.20, 48.81; 114 subjects). Subgroup analyses are limited by low numbers but, with an actual Swiss population approaching 100% seropositivity (either through natural infection or vaccination), the current clinical benefit of Evusheld might be lower than that determined during the study period. The EMA raised this issue at the time of its LoQ. According to the document, the applicant stated that, in the ACTIV-3 study (performed in adults hospitalised for COVID-19 with symptoms for up to 12 days), hazard ratios for Day 90 mortality reduction (a secondary endpoint) in the Evusheld group versus placebo were similar in the seronegative (0.70, 0.44-1.2) and seropositive subgroups (0.76, 0.46-1.27). The applicant also provided real-world evidence data from an observational, retrospective prophylaxis study, but these are not considered supportive. The number of seropositive subjects in TACKLE is low indeed (n=114), and it is difficult to draw conclusions. Determination of the serostatus is nonetheless considered not very relevant. Currently, nearly 100% of the Swiss population is seropositive (whether through vaccination or previous infection), although there is variation in the level of antibodies and their neutralising activity against the diverse SARS-CoV-2 variants. Furthermore, the contribution of cell-mediated immunity towards SARS-CoV-2 virus infection is currently not fully understood or routinely assessed in patients. Overall, while it can be hypothesised that the benefit of Evusheld in seropositive patients might be lower, there is currently no sufficient data to estimate a different benefit/risk ratio between the seronegative and seropositive populations.

Further subgroup analyses of the primary endpoint in the mFAS at the primary DCO indicate that the benefit of Evusheld was essentially driven by results from participants included in the Latin America region (RRR 74.52%, CI: 32.76, 90.34; 367 subjects) whereas no benefit could be shown in Europe (RRR -3.49%, CI: -128.99, 53.23; 348 subjects) or the USA (RRR 30.30%, CI: -359.70, 89.43; 98

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subjects). Event rates in the Placebo group were twice as high in Latin America as in Europe or the USA (approx. 12% vs 6%). Also, event rates in the Evusheld group were twice as high in Europe in comparison with Latin America/USA (approx. 6% vs 3%). The EMA raised this issue at the time of its LoQ. According to the document, the applicant stated (i) there is no mechanistic rationale why efficacy would be different across regions, (ii) the proportion of participants > 65 years was higher in Europe vs other regions (19.3% Europe, 6.6% Latin America, 7.7% USA), and WHO clinical progression scores were also higher in Europe (20.6% had a score of 3 vs 3.9% in Latin America, 5.8% USA), and these differences, albeit balanced across arms, may have contributed to the incidence of more severe disease in participants in the Europe subgroup, (iii) high-risk comorbidities, timing of treatment, median time to onset of symptoms was similar across regions and, although some differences in baseline patient characteristics were observed across regions, these factors were balanced across the arms and therefore cannot provide an explanation for the result observed, (iv) mortality/infection rates differ between regions and the increased prevalence of the Delta variant in Latin America is linked to a higher placebo event rate. The EMA was of the opinion that "*as results were balanced between treatment arms within the region subgroups, results cannot explain differences in risk reduction seen between region subgroups. However, prognostic differences might have contributed to differences in placebo performance seen between region subgroups. In particular, the higher number of elderly subjects in the European population with a trend towards poor efficacy might have contributed".* The EMA acknowledged that "*there is no mechanistic rationale for region effects on efficacy"* and that "*TACKLE was not designed to detect regional differences"* and that *"it can further be agreed that various dynamic factors may impede interpretation of sub-group data by region"*. The EMA underscored that "*the potential impact of certain potentially resistant viral variants on worse outcome after Evusheld treatment in the European population was not discussed by the applicant"*. The EMA concluded that "*the dynamic changes in the ongoing pandemic situation add uncertainty to transferability of study results obtained in Latin America (and determining the treatment effect) on the European population […] the study was not designed to estimate efficacy in regional subgroups with high certainty and thus, chance findings are possible […]. The risk of viral resistance will be adequately addressed post approval by pharmacovigilance activities for lack of efficacy".* In consequence, the EMA decided not to pursue the issue further. Swissmedic acknowledges that subgroup analyses are limited by low numbers of subjects and low numbers of events. Studies indicated a higher risk of hospitalisation for the Delta and the B.1.1.519 variants that were more prevalent in Latin America at the time of TACKLE, and this might explain the higher rate of patients in the Placebo group hospitalised in Latin America. However, enrolled subjects in Europe were older and sicker than in Latin America, and efficacy in the European population would have been expected. Overall, it is considered plausible that variations in the virus, the human host, and the countries' healthcare systems might explain some of the regional differences seen in the TACKLE study. However, there is no fully satisfactory explanation regarding the lack of effect of Evusheld in both the European and US populations.

For the key secondary endpoint, in the mFAS, in comparison to placebo, Evusheld led to a 49.11% (95% CI: 14.47, 69.72) reduction in the composite endpoint of either death or hospitalisation for COVID-19 complications or sequelae through Day 169 at the secondary DCO. The event rates were 5.0% in the Evusheld arm (20/399) and 9.8% in the Placebo arm (40/407). There were therefore few additional cases with severe COVID-19 or death after Day 29, since there were already 18 subjects in the Evusheld group vs 37 in the Placebo group who met the primary endpoint at Day 29. Data were missing for 14 cases in each group. As for the primary endpoint, subgroup analysis of the key secondary endpoint by baseline serology showed no benefit and, in fact, a higher event rate in the Evusheld arm in comparison to placebo in the seropositive population (7.84%, 4/51 vs 1.64%, 1/61), but the small number of seropositive subjects precludes a meaningful interpretation.

Other secondary endpoints at the primary DCO indicated that, in comparison with placebo, Evusheld reduced the incidence of respiratory failure at Day 29 (3 events vs 11, RRR 71.86%, 95% CI: 0.25, 92.06), with similar results at the key secondary DCO. An exploratory endpoint indicated that, at the

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Key Secondary DCO, once a participant required hospitalisation fewer were admitted to the ICU in the Evusheld group (0.7%, n=3) in comparison to placebo (2.6%, n=11).

Regarding assessments of COVID-19 symptom severity through Day 29, for the majority of symptoms there was no difference between Evusheld and Placebo groups and, for a few symptoms (cough and muscle aches), the reduction was minimal. A post-hoc analysis of time to COVID-19 symptom resolution through Day 29 showed an essentially nonsignificant median time to symptom resolution in the Evusheld arm of 11 (95% CI: 10, 13) days, compared to 13 (95% CI: 11, 15) days in the Placebo arm, with a Cox regression of time symptom resolution through Day 29 resulting in a hazard ratio of 1.17 (95% CI: 0.97, 1.42). Analysis of return to usual health at the primary DCO indicated a similar probability of returning to normal health by Day 29 in the Evusheld and Placebo groups, but this assessment might have been confused by erroneous reporting (anchoring bias on study visit days). Nevertheless, symptom outcomes are considered less relevant than severe COVID-19 evolution or death.

From a virological point of view, sequencing data were available for 745 of 904 participants (380/452 AZD7442 and 365/452 placebo) at the baseline visit. The majority (n=262) of patients were infected with the Alpha variant of SARS-CoV-2, followed by the Delta strain. During the study, the variant of concern Omicron (B.1.1.529 and descendent lineages) was not yet in worldwide circulation. There are not enough data to assess whether Evusheld clinical activity is reduced for certain variant types. Virological studies indicated that, at the Primary DCO, treatment with Evusheld resulted in greater reductions in $\log_{10}$ SARS-CoV-2 RNA mean change from baseline at Day 6, but the difference was small: least squares mean difference of -0.39 $\log_{10}$ (95% CI: -0.56 to -0.22).

5.4 Safety

5.4.1 Overall safety database

In total, in the TACKLE study, of 903 participants who received the investigational medicinal product (IMP), 452 received Evusheld and 451 received placebo. At the Key Secondary DCO, median duration for safety follow-up was 170 days (the study itself is ongoing, with a total follow-up of 457 days).

5.4.2 Adverse events

In the phase 3 pre-exposure prophylaxis studies (PROVENT and STORM CHASER, 300 mg Evusheld dosing) the most frequent TEAEs were headache, fatigue, and cough with no significant differences between groups. Furthermore, in PROVENT there was a small difference between Evusheld and Placebo for cardiac (0.7% vs 0.3%) and thromboembolic (0.8% vs 0.6%) events.

In TACKLE, at the time of the Key Secondary DCO, 174 (38.5%) participants on Evusheld and 196 (43.5%) participants on placebo experienced at least 1 AE. By System Organ Class (SOC) and Preferred Term (PT), the most frequently reported AE was COVID-19 pneumonia, with a lower occurrence in the Evusheld group (5.8%) compared to placebo (10.9%). All other AEs occurred in ≤ 2% of the participants. Between the Evusheld and Placebo groups, SAEs (8.8%, 40/452 vs 13.5%, 61/451), AEs with outcome of death (1.5% vs 1.3%), Grade 3 or 4 AEs (6.9% vs 10.6%), and AESI (3.3% vs 3.3%) were either lower or similar in the Evusheld group compared to Placebo. For Grade 3 or 4 AEs, the most common PT was either COVID-19 pneumonia or COVID-19 (total in Evusheld 5.1%, 23/452, total in Placebo groups 8.2%, 37/451), and all other SAEs were essentially single events within all PTs. AEs with fatal outcome were balanced between groups. As assessed by the investigator, IMP-related AEs were 5.1% vs 4.7% in the Evusheld and Placebo groups, respectively, and the most frequent AE was injection site pain, with similar rates for Evusheld (1.8%) and placebo (2.4%). IMP-related adverse events of special interest (anaphylaxis and other serious hypersensitivity

reactions) were low, with 15 events (3.3%) in both groups, and the vast majority were injection site reactions, none of them serious. There were no treatment-related SAEs, Grade 3 or 4 AEs, or deaths. Study discontinuations due to adverse events were minimal at the Key Secondary DCO, with 5 (1.1%) in the Evusheld group and 7 (1.6%) in the Placebo group, and the majority of discontinuations were due to participant death related to COVID-19.

Overall, deaths at the secondary DCO were balanced, at 1.5% (7/452) in the Evusheld group and 1.3% (6/451) in the Placebo group. In the Evusheld group, 2 deaths were related to cardiac events (see below), 2 to cancers, and 3 to COVID-19. In the Placebo group, 5 were related to COVID-19 and 1 was a septic shock. No deaths were considered related to the IMP by the investigator, and this is indeed acceptable.

At both the Primary DCO and the Key Secondary DCO, there were no notable differences in vital signs, ECGs, clinical laboratory evaluations, physical findings, or other observations related to safety.

Regarding anti-drug antibodies up to 168 days post-dose (DCO date of 14 January 2022), at baseline 4.3% (15/346) of Evusheld ADA-evaluable participants were positive. The percentage subsequently increased, reaching 22.4% (35/156) by Day 169. Median ADA titre to Evusheld did not increase over the same time period, which suggests that maturation of Evusheld ADA did not occur over time, and the majority of positive subjects had low titres close to the limit of detection. Of note, at the secondary DCO, all 4 participants in the Evusheld group who had reported cardiac or thromboembolic SAEs were ADA-negative. Furthermore, there was no evidence that the presence of ADA resulted in in loss of Evusheld efficacy.

In the TACKLE study in the Evusheld group there were 2/452 (0.4%) Grade 3 or 4 AEs and 2 deaths related to cardiac disorders. There was no imbalance compared to the placebo group and none of the events were considered drug-related. A detailed overview of all cardiac events and all thromboembolic events (AEs and SAEs) was requested and assessed by the EMA. The conclusion that regarding cardiac events there is no imbalance between treatment groups is endorsed. In line with findings from previous studies PROVENT and STORMCHASER, thromboembolic events were slighty more often observed under Evusheld treatment compared to placebo. However, available non-clinical and clinical data does not allow a clear conclusion on an association between Evusheld and thromboembolic events.

From a virological point of view, treatment-emergent substitutions at an allele fraction ≥ 25% (n=137) were observed in 59/380 participants in the Evusheld group. None of these were observed in more than 5 participants. The individual impact of 33/137 treatment-emergent substitutions on sensitivity to Evusheld was tested in vitro using pseudovirus neutralisation assays, and in all cases the change in susceptibility was < 5-fold.

Overall, Evusheld was well tolerated. The incidence of AEs (including grade 3/4) and SAEs were lower in the Evusheld than the Placebo group. In the TACKLE study, there was a slight imbalance of cardiac/thromboembolic events between the Evusheld and Placebo arms, but the number of events was small and they occurred in patients with confounding factors. However, the elderly population was underrepresented in this study, since nearly 90% of participants were ≤ 65 years old and only 3.6% were ≥ 75 years old. In fact, the mean age in TACKLE was 46 years old, vs 57 years old in PROVENT. In consequence, the safety profile in the elderly population cannot be fully assessed.

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5.5 Final clinical and clinical pharmacology benefit risk assessment

In patients with risk factors, monoclonal antibodies targeting the SARS-CoV-2 spike protein RBD are a useful addition to the available therapeutic arsenal to prevent severe COVID-19 outcomes.

The pharmacokinetics of tixagevimab and cilgavimab and Evusheld (combination of both mAbs) in the newly requested treatment indication are comparable to the PK observed in the prophylaxis indication.

The results of 1 ongoing randomised, double-blind, placebo-controlled phase 3 study (TACKLE) to investigate the safety and efficacy of a single 600 mg intramuscular dose of Evusheld to prevent severe COVID-19 outcomes or death in symptomatic SARS-CoV-2 patients were presented to support a treatment indication for Evusheld. The TACKLE study randomised 910 participants, 903 of whom received treatment (Evusheld 452, Placebo 451). Participants were young, with a mean age of 46 years, and presented within 7 days of symptom onset. Nearly 90% were classified as high-risk, essentially because of obesity and hypertension. At the primary DCO, the study met its primary endpoint of reducing the risk of developing severe COVID-19 or death from any cause in non-hospitalised adults with less than 7 days of symptom evolution, since 4.4% (18/407) of subjects in the Evusheld arm vs 8.9% (37/415) in the Placebo arm either developed severe COVID-19 or died through Day 29. The benefit of Evusheld was driven by the incidence of severe COVID-19 since there was no difference in death events.

Supportive estimands indicated that the benefit was greater when Evusheld was administered early after symptom onset (≤ 3 days: RRR 88.01%) whereas no benefit could be shown after 5 days of symptom evolution.

The key secondary endpoint at the secondary DCO showed consistent findings as, compared to placebo, Evusheld led to a 49.11% relative risk reduction in the composite endpoint of either death or hospitalisation for COVID-19 complications or sequelae through Day 169. Sensitivity analyses supported the results. Other secondary endpoints at the primary DCO indicated that, compared with placebo, Evusheld reduced the incidence of respiratory failure at Day 29 (3 events vs 11, RRR 71.86%, 95% CI: 0.25, 92.06), with similar results at the key secondary DCO. An exploratory endpoint indicated that, at the Key Secondary DCO, once a participant required hospitalisation, fewer were admitted to the ICU in the Evusheld group (0.7%, n=3) compared to placebo (2.6%, n=11).

The dose justification is partly based on a viral dynamic model that was used for simulations of Evusheld effects on viral load dynamics for virus variant BA.1 or other dose levels. This model has been qualified with external data for the placebo situation, but the Evusheld effects on viral load have not been qualified with external data. If, and to what extent, the simulated effects of Evusheld on the viral load dynamics are expected to translate into a clinically relevant benefit remains uncertain.

The TACKLE clinical trial was designed and started early in the SARS-CoV-2 pandemic, before vaccines were available. In consequence, the vast majority of patients included in the study were seronegative, thus the efficacy of Evusheld in a population that has previously been infected and/or vaccinated is unknown. It is difficult to ascertain the efficacy of Evusheld in certain subgroups because of a small number of subjects and/or events. In particular, and this seems to be in line with the viral model, administration of Evusheld after 5 days of symptoms is not substantiated by data. The differential activity of Evusheld within regions is not fully understood.

Importantly, the continuous evolution of the SARS-CoV-2 virus implies that the activity of Evusheld on emerging variants needs to be actively monitored. Simulations for other variants of concern (BA.2, BA.4, and BA.5) have been submitted and suggest retention of efficacy under most scenarios. However, whereas BA.5 was the widely prevalent Omicron subvariant in Switzerland from summer

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until the end of November 2022, it has rapidly been replaced by the BQ.1 subvariant since December 2022, followed by the XBB lineages, which represent the majority of sequenced samples (see Hodcroft, 2021, https://covariants.org/per-country?region=Switzerland. Furthermore, whereas *in vitro* assays indicated a reduced, but measurable, EC_{50} for BA.4 and BA.5, based on recent data Evusheld does not show any *in vitro* activity against the BQ.1 and XBB subvariants. Altogether, the current situation indicates that Evusheld might be inactive against currently circulating Omicron subvariants. However, it cannot be excluded that future SARS-CoV-2 variants might exhibit restored susceptibility to Evusheld.

The information for professionals includes guidance on the proper use of Evusheld so that the healthcare provider can assess whether Evusheld administration is appropriate within a specific epidemiological situation. In parallel, the applicant added a warning on breakthrough infections in the information for professionals.

In the TACKLE study, there was a slight imbalance of cardiac/thromboembolic events between the Evusheld and Placebo arms, but the number of events was small and they occurred in patients with confounding factors. In the PROVENT prophylaxis study, there was an imbalance for participants in the EVUSHELD arm compared to those in the Placebo arm, as regards serious cardiovascular (0.7% vs 0.3%) and thromboembolic events (0.8% vs 0.6%), which is reflected in the information for professionals.

The applicant provided post-marketing surveillance data form various sources. While obviously confounded by many factors, some post-marketing data indicate that cardiac and thromboembolic events are reported more often with Evusheld than with other monoclonal antibodies or placebo. In consequence, so that the healthcare provider can provide useful information to the patients, the applicant has updated the cardiac and thromboembolic SAEs paragraph of the “Warnings and Precautions” section with exact data from the PROVENT and TACKLE studies.

Safety data in elderly and immunosuppressed patients are very limited. Finally, current safety follow-up is restricted to 170 days, the overall follow-up is planned for 457 days and will be provided with the final study report that is planned for June 2023.

There remains a risk that, since the monoclonal antibody components interact with the spike protein used as an immunogen in all current vaccines, Evusheld administration might interfere with the efficacy of subsequent vaccinations.

Overall, in the TACKLE study, Evusheld showed a statistically significant effect for the clinically relevant primary endpoint of either severe COVID-19 or death from any cause through Day 29, as well as for some secondary endpoints. Uncertainties remain on the generalisability of study results for some subgroups (elderly, seropositive patients, European citizens). Adverse events were lower in the Evusheld group in comparison with the Placebo group, and the imbalance in cardiac/thromboembolic events observed in PROVENT was not as important in the TACKLE study.

Within the context of the TACKLE study, the benefit/risk for Evusheld in the treatment of mild to moderate COVID-19 in individuals at risk of developing severe COVID-19 is considered positive. However, in the current epidemiological environment characterised by XBB lineages for which in vitro data indicate a complete loss of activity of Evusheld, in conjunction with a potential safety concern, the benefit/risk must be weighed taking into account these 2 parameters. In consequence, an *ex officio* temporary authorisation for the treatment indication has been proposed and accepted by the applicant.

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6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for EVUSHELD was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

EVUSHELD has been authorised temporarily, see the “Indications/Uses” section.

EVUSHELD

Composition

Active substances

Tixagevimab, cilgavimab (produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology)

Excipients

Vial of tixagevimab: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 (E433), water for injections q.s. for 1.5 ml solution.
Vial of cilgavimab: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 (E433), water for injections q.s. for 1.5 ml solution.

Pharmaceutical form and active substance quantity per unit

Solution for injection.
For intramuscular (i.m.) use.
Each carton of EVUSHELD contains two vials:

- 150 mg tixagevimab in 1.5 ml (100 mg/ml)
- 150 mg cilgavimab in 1.5 ml (100 mg/ml)

Indications/Uses

Pre-exposure prophylaxis
EVUSHELD (tixagevimab and cilgavimab) is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents (aged 12 years and older and with body weight at least 40 kg):

- who are not able to mount an adequate immune response to SARS-CoV-2 vaccination and
- who are not currently infected with SARS-CoV-2 and who have not had recent contact with an individual infected with SARS-CoV-2.

See *“Dosage/Administration*” and *“Pharmacokinetics*”.
EVUSHELD is not authorised for post-exposure prophylaxis of COVID-19.
EVUSHELD not intended as a substitute for vaccination against COVID-19.

Treatment
EVUSHELD is indicated for the treatment of mild-to-moderate COVID-19 in adults and adolescents (from 12 years of age with minimum body weight of 40 kg) who do not require supplemental oxygen or hospitalisation due to COVID-19 and who are at risk of progressing to severe COVID-19 (see "*Dosage/Administration" and "Pharmacokinetics").*

Decisions regarding the use of EVUSHELD for pre-exposure prophylaxis or treatment should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences, as well as available information about susceptibility to EVUSHELD (see *"Properties/Effects" and "Warnings"*).

The use of EVUSHELD should be based on official recommendations.

These indications have been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is strictly dependent on the timely fulfilment of conditions. Once the conditions have been fulfilled, the time-limited authorisation can be changed to a standard authorisation.

Dosage/Administration

Treatment must be initiated and monitored under the supervision of a qualified physician. Treatment should take place under conditions where management of an allergic reaction is possible (see "Warnings and precautions").

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

Pre-exposure prophylaxis
The recommended dosage is 300 mg of EVUSHELD, administered as two separate, sequential intramuscular injections, each of 1.5 ml:

- 150 mg tixagevimab
- 150 mg cilgavimab

There are no data available on repeat dosing.

Treatment
The recommended dosage is 600 mg of EVUSHELD, administered as two separate, sequential injections, each of 3.0 ml:

- 300 mg tixagevimab
- 300 mg cilgavimab

For the treatment of mild-to-moderate COVID-19, EVUSHELD should be used as soon as possible after a positive viral test for SARS-CoV-2 (see *Properties/Effects*).

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is required for patients with hepatic impairment (see "*Pharmacokinetics – Kinetics in specific patient groups*").

Patients with renal disorders

No dose adjustment is required for patients with impaired renal function (see "Pharmacokinetics – Kinetics in specific patient groups").

Elderly patients

No dose adjustment is required for patients aged 65 years or older (see "*Pharmacokinetics- Kinetics in specific patient groups*").

Children and adolescents

The safety and efficacy of EVUSHELD in children <18 years of age have not yet been established. No data are available.

The recommended dosing regimens are expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals aged 12 years or older who weigh at least 40 kg as observed in adults, since adults with similar body weight have been included in the PROVENT, STORM CHASER and TACKLE clinical trials (see *Properties/Effects - Pharmacodynamics* and *Pharmacokinetics*).

Mode of administration

EVUSHELD is intended for intramuscular (i.m.) use only.

Tixagevimab and cilgavimab should be given as separate sequential intramuscular injections at different injection sites, preferably one injection in each gluteal muscle.

Each carton of EVUSHELD contains two vials:

- tixagevimab solution for injection (vial with dark grey cap);
- cilgavimab solution for injection (vial with white cap).

Each vial contains an overfill to guarantee the withdrawal of 150 mg (1.5 ml).

Table 1 Dosage of tixagevimab and cilgavimab

Indication	EVUSHELD dose (tixagevimab and cilgavimab)	Antibody dose	Number of vials required	Volume to withdraw from vial
Pre-exposure prophylaxis of COVID-19	300 mg	Tixagevimab 150 mg	1 vial	1.5 ml
		Cilgavimab 150 mg	1 vial	1.5 ml
Treatment of mild-to-moderate COVID-19	600 mg (2 cartons)	Tixagevimab 300 mg	2 vials	3.0 ml
		Cilgavimab 300 mg	2 vials	3.0 ml

Contraindications

Hypersensitivity to the active substances or to any of the other ingredients listed under Excipients.

Warnings and precautions

Hypersensitivity including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed rarely with other monoclonal IgG1 antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate treatment with appropriate medicinal products and/or supportive therapy.

Clinically significant coagulation disorders

As with any other intramuscular injection, EVUSHELD should be given with caution to patients with thrombocytopenia or any other coagulation disorder.

Cardiovascular and/or thromboembolic events

In the PROVENT study, a higher proportion of participants in the EVUSHELD arm reported myocardial infarction and heart failure, including one fatal serious adverse event, compared to those in the placebo arm (Table 2). All subjects who experienced events had cardiac risk factors and/or history of cardiovascular diseases, and there was no clear temporal pattern.

In the PROVENT study, a higher proportion of participants in the EVUSHELD arm reported serious thromboembolic adverse events compared to those in the placebo arm (Table 3).

In the TACKLE study (N=903, data cut-off: 21 August 2021), four participants reported serious cardiac adverse events. Acute myocardial infarction was reported in two participants who received EVUSHELD (one of whom also experienced heart failure resulting in death), and sudden cardiac

death was reported in one participant who received EVUSHELD. Arrhythmia was reported in one participant who received placebo. All subjects who experienced serious cardiac adverse events had cardiac risk factors at baseline and/or history of cardiovascular diseases.

In the TACKLE study, four participants in the EVUSHELD group reported serious thromboembolic adverse events, including two cases of acute myocardial infarction, one case of pulmonary embolism, and one case of peripheral artery thrombosis. In the placebo group, two participants reported serious adverse events of portal vein thrombosis and thrombosis of the superior sagittal sinus.

A causal relationship between EVUSHELD and these events has not been established.

The risks and benefits should be considered prior to initiating treatment with EVUSHELD in patients at high risk for cardiovascular or thromboembolic events. Patients should be advised of signs or symptoms suggestive of a cardiovascular or thromboembolic event and instructed to seek immediate medical attention if such symptoms occur.

Table 2 Exposure-adjusted incidence rate (EAIR) of serious cardiac adverse events in the PROVENT study, regardless of causality, using the median 6.5-month data cut-off date*

System organ class Preferred term	**EVUSHELD 300 mg i.m.** **N=3461** **Events (EAIR† (person-years))**	**Placebo** **N=1736** **Events (EAIR† (person-years))**
Cardiac disorders‡	23 (1.2)	5 (0.5)
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Acute left ventricular failure	0	1 (0.1)
Paroxysmal atrioventricular block	1 (0.1)	0
Cardiac failure congestive	4 (0.2)	0
Atrial fibrillation	1 (0.1)	2 (0.2)
Angina pectoris	1 (0.1)	0
Arrhythmia	1 (0.1)	0
Arteriosclerosis coronary artery	1 (0.1)	0
Cardiac failure	1 (0.1)	0
Cardiac failure acute	1 (0.1)	0
Cardio-respiratory arrest	1 (0.1)	0
Cardiomegaly	1 (0.1)	0
Cardiomyopathy	1 (0.1)	0
Coronary artery disease	1 (0.1)	0

* Data cut-off: 29 August 2021

† EAIR is calculated by the number of participants with the events divided by the duration of exposure (in years) x 100. Exposure time is calculated from the first dose date to the end of study date, or data cut-off if the participant is ongoing at the time of the data cut-off. Exposure time is converted to patient years by dividing the number of days by 365.25.

‡ One EVUSHELD recipient had two cardiac SAEs

Table 3 Exposure Adjusted Incidence Rate (EAIR) of thromboembolic events in the PROVENT study, regardless of causality, using the median 6.5-month data cut-off date*

System organ class Preferred term	**EVUSHELD 300 mg i.m.** **N=3461** **Events (EAIR† (person-years))**	**Placebo** **N=1736** **Events (EAIR† (person-years))**
Thromboembolic serious adverse events	**17 (0.9)**	**4 (0.4)**
Cardiac disorders		
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Gastrointestinal disorders		
Mesenteric artery thrombosis	1 (0.1)	0
Nervous system disorders		
Cerebral infarction	1 (0.1)	0
Transient ischaemic attack	2 (0.1)	0
Lacunar infarction	0	1 (0.1)
Cerebrovascular accident	2 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	2 (0.1)	0

* Data cut-off: 29 August 2021
† EAIR is calculated by the number of participants with the events divided by the duration of exposure (in years) x 100. Exposure time is calculated from the first dose date to the end of study date, or data cut-off if the participant is ongoing at the time of the data cut-off. Exposure time is converted to patient years by dividing the number of days by 365.25.

Antiviral resistance

Based on in vitro data, some SARS-CoV-2 variants are not neutralised by monoclonal antibodies, which may impair clinical efficacy (see “Properties/Effects”). The clinical trials with EVUSHELD were conducted when Alpha, Beta, Gamma and Delta variants were predominant. Clinical data regarding the efficacy of EVUSHELD against the current virus variants are not currently available.

Interactions

No interaction studies have been performed.

Pharmacokinetic interactions

Tixagevimab and cilgavimab are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with other medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.
Based on pharmacokinetic (PK) modelling, SARS-CoV-2 vaccination following EVUSHELD administration had no clinically relevant impact on the clearance of EVUSHELD.

COVID-19 vaccines

Tixagevimab and cilgavimab bind to epitopes on the spike protein that is used as the immunogen in all COVID-19 vaccines. An interaction with COVID-19 vaccines has not been investigated and cannot therefore be ruled out. With regard to the timing of the vaccination following treatment with monoclonal antibodies against SARS-CoV-2, the current vaccination guidelines apply.

Pregnancy, lactation

Pregnancy

There are only limited data from the use of tixagevimab and cilgavimab in pregnant women.

Preclinical reproductive toxicity studies have not been performed with tixagevimab and cilgavimab (see “Preclinical data”).
Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta. It is not known whether the potential transfer of tixagevimab and cilgavimab represents a benefit or a risk to the developing foetus. EVUSHELD should only be used during pregnancy if the potential benefit justifies the potential risk for the mother and the foetus, taking into consideration all associated health factors. If a woman becomes pregnant during the use of this medicinal product, she must be informed that it is not known whether there is a potential risk for the foetus.

Lactation

It is not known whether tixagevimab and cilgavimab are excreted in human milk. Exposure of the breastfed infant cannot be ruled out.
The developmental and health advantages of breastfeeding should be considered against the clinical need of the mother for EVUSHELD and all potential adverse effects of EVUSHELD on the breastfed infant or the underlying disease of the mother.

Fertility

There are no data on the effects of tixagevimab and cilgavimab on human fertility. Effects on male and female fertility were not investigated in the animal studies.

Effects on ability to drive and use machines

EVUSHELD has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

A total of 4,762 subjects have been treated with 300 mg or 600 mg EVUSHELD via i.m. injection in placebo-controlled Phase III studies. Overall, the safety profile in patients who received 300 mg EVUSHELD was generally similar to that in patients who received 600 mg EVUSHELD.
In the Phase III prophylaxis studies (PROVENT and STORM CHASER), a total of 4,210 adult participants received 300 mg EVUSHELD as an i.m. injection. The most commonly reported adverse reactions were injection site reactions (1.3%) and hypersensitivity (1.0%).
In the Phase III treatment study (TACKLE), a total of 452 non-hospitalised adult patients with mild to moderate COVID-19 received 600 mg EVUSHELD as an i.m. injection. The most commonly reported adverse reaction was injection site reaction (2.4%).

List of adverse reactions

The adverse reactions are arranged according to MedDRA system organ classes (SOC) and frequency using the following convention:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)
Within each system organ class, the preferred terms are listed in order of decreasing frequency and then by decreasing seriousness in Table 4.

Table 4 Undesirable effects

System organ class	Adverse reaction	Frequency †
Immune system disorders	Hypersensitivity*	Common (1.0%)§
General disorders and administration site conditions	Injection-related reaction°	Uncommon (0.2%)§
Injury, poisoning and procedural complications	Injection site reaction*	Common (1.3%)§

† Frequencies are based on exposure to 300 mg EVUSHELD in the pooled data from the prophylaxis studies.
* Including the terms: Hypersensitivity (including Rash and Urticaria); Injection site reaction (including Injection site pain, Injection site erythema, Injection site pruritus, Injection site reaction and Injection site induration).
§ Frequency categories observed in a clinical trial with 600 mg EVUSHELD: Hypersensitivity: uncommon; Injection-related reaction: none reported; Injection site reaction: common.
° Description of the events reported under the preferred term Injection-related reaction include headache, chills and redness, discomfort or soreness near where the injection was given.

Paediatric population

No data are available for children and adolescents <18 years old (see *Dosage/Administration* and *Pharmacokinetics*).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for overdose with EVUSHELD. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient.
In clinical trials, intramuscular doses of up to 600 mg (300 mg each of tixagevimab and cilgavimab) and intravenous (i.v.) doses of up to 3,000 mg (1,500 mg each of tixagevimab and cilgavimab) have been administered without dose-limiting toxicity.

Properties/Effects

ATC code

J06BD03

Mechanism of action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies, with amino acid substitutions to extend antibody half-life and to reduce antibody effector function and the potential risk of antibody-dependent enhancement of disease. Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Tixagevimab, cilgavimab and their combination bind to the spike protein with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, which blocks the interaction of the wild-type variant of the virus with the human ACE2 receptor, resulting in a blockade of virus entry and effectively neutralising the SARS-CoV-2 virus. Tixagevimab, cilgavimab and their combination blocked RBD binding to the human ACE2 receptor with IC_{50} values of 0.32 nM (48 ng/ml), 0.53 nM (80 ng/ml) and 0.43 nM (65 ng/ml), respectively.

Antiviral activity

In a SARS-CoV-2 virus neutralisation assay on Vero E6 cells, tixagevimab, cilgavimab and their combination neutralised SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/ml), 211.5 pM (32 ng/ml) and 65.9 pM (10 ng/m), respectively. These *in-vitro* values correlate with clinically effective *in-vivo* serum concentrations of 2.2 µg/ml of EVUSHELD.

In cell-based assays, tixagevimab and cilgavimab showed no antibody-dependent cellular cytotoxicity (ADCC), no antibody-dependent cellular phagocytosis (ADCP), no complement-dependent cytotoxicity and no antibody-dependent NK cell activation (ADNKA).

Antibody-dependent enhancement (ADE)

In vitro studies showed no antibody-dependent enhancement (ADE).

The potential for ADE was also assessed in a non-human primate model of SARS-Cov-2 with the use of EVUSHELD. Intravascular use prior to virus inoculation resulted in a dose-dependent improvement in all measured parameters (total viral RNA in the lungs or nasal mucosa, infectious virus concentrations in the lungs based on $TCID_{50}$ measurements, and lung damage and pathology based on histological measurements). No evidence of disease enhancement was observed at any of the doses evaluated, including sub-neutralising doses of just 0.04 mg/kg.

Antiviral resistance

SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein were serially passaged in cell cultures in the presence of cilgavimab or tixagevimab individually, or tixagevimab and cilgavimab in combination. Escape variants were identified following passage with cilgavimab, but not with tixagevimab or tixagevimab and cilgavimab in combination. Variants with reduced susceptibility to cilgavimab alone included the spike protein amino acid substitutions R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold) and K444R (>200-fold). All variants retained sensitivity to tixagevimab alone and tixagevimab and cilgavimab in combination.

Pseudovirus and authentic SARS-CoV-2 neutralisation data for SARS-CoV-2 variant substitutions with tixagevimab and cilgavimab in combination are summarised in the following table (Table 5).

The data regarding the neutralisation activity of EVUSHELD against pseudovirus and/or live virus SARS-CoV-2 variant strains are summarised in Table 5. Data collection is ongoing to better understand how small reductions in activity seen in authentic SARS-CoV-2 or pseudotyped VLP assays may correlate with clinical outcomes.

Table 5 Pseudovirus and authentic SARS-CoV-2 neutralisation data for SARS-CoV-2 variant substitutions with tixagevimab and cilgavimab in combination

Lineage with spike protein substitutions		**Reduction in susceptibility [a]**		**IC_{50} (ng/ml)**	
Pango nomenclature (origin)	**WHO name**	**Pseudovirus[b]**	**Authentic SARS-CoV-2[c]**	**Pseudovirus[b]**	**Authentic SARS-CoV-2[c]**
B.1.1.7 (UK)	Alpha	No change[d]	No change[d]	1.1-9.0	4-39.5
B.1.351 (South Africa)	Beta	No change[d]	No change[d]	5.6-11.4	6.5-256
P.1 (Brazil)	Gamma	No change[d]	No change[d]	1.8-2.7	3.2-8
B.1.617.2 (India)	Delta	No change[d]	No change[d]	1.9-2.2	3-7.5
AY.1/AY.2 (India)	Delta [+K417N]	No change[d]	ND[d]	1.9	ND
B.1.1.529 (South Africa)	Omicron BA.1	132–183-fold	12–30-fold	51-277	147–278
BA.1.1 (multiple countries)	Omicron BA.1.1	424-fold	176-fold	466	1147
BA.2 (multiple countries)	Omicron BA.2	No change[d]	No change[d]	9.8	35
BA.2.12.1 (United States)	Omicron BA.2.12.1	No change	ND	10.7	ND
BA.2.75 (India)	Omicron BA.2.75	2.4–15-fold	ND	1.2-14	ND
BA.2.75.2 (India)	Omicron BA.2.75.2	>5000-fold [f]	ND	>10000 [f]	ND
BA.3 (multiple countries)	Omicron BA.3	16-fold	ND	34.5	ND
BA.4 (multiple countries)	Omicron BA.4	33–65-fold	ND	65-69.4	ND
BA.4.6 (United States)	Omicron BA.4.6	>1000-fold[f]	ND	>1000	ND
BA.5 (multiple countries)	Omicron BA.5	33–65-fold	2.8–16-fold	65-69.4	56.6-229
BF.7 (United States/ Belgium)	Omicron BF.7	>5000-fold [f]	ND	>10,000[f]	ND
BJ.1 (multiple countries)	Omicron BJ.1	228 to 424-fold	ND	228-848	ND
BQ.1 (Nigeria)	Omicron BQ.1	>2000-fold[f]	ND	>10,000[f]	ND

Lineage with spike protein substitutions		Reduction in susceptibility [a]		IC_{50} (ng/ml)	
Pango nomenclature (origin)	WHO name	Pseudo-virus[b]	Authentic SARS-CoV-2[c]	Pseudo-virus[b]	Authentic SARS-CoV-2[c]
BQ.1.1 (multiple countries)	Omicron BQ.1.1	>2000-fold [f]	ND	>10,000 [f]	ND
BN.1 (multiple countries)	Omicron BN.1	68-fold	ND	61-68	ND
XBB (multiple countries)	Omicron XBB	>1400-fold[f]	ND	>1000[f]	ND
XBB.1.5	Omicron XBB.1.5	> 5,000[f]	ND	>10,000[f]	ND
B.1.525 (multiple countries)	Eta	No change[d]	ND	5-9.5	ND
B.1.526 (United States)	Iota	No change[d]	No change[d]	1.9-5.2	1.0-7.0
B.1.617.1 (India)	Kappa	No change[d]	No change[d]	2.5-5.1	2.0-5.0
C.37 (Peru)	Lambda	No change[d]	ND	1.1	ND
B.1.621 (Columbia)	Mu	No change[d]	ND	17.3	ND
B.1.427 / B.1.429 (United States)	Epsilon	No change[d]	No change[d]	1.0-4.54	5.0-14.0
R.1 (multiple countries)	-	No change[d]	ND	4.6	ND
B.1.1.519 (multiple countries)	-	No change[d]	ND	2.3	ND
C.36.3 (multiple countries)	-	No change[d]	ND	3.9	ND
B.1.214.2 (multiple countries)	-	No change[d]	ND	1.6	ND
B.1.619.1 (multiple countries)	-	No change[d]	ND	7.6	ND
P.2 (Brazil)	Zeta	No change[d]	ND	10.4	ND
B.1.616 (France)	-	No change[d]	ND	1.1-1.2	ND
A.23.1 (UK)	-	No change[d]	ND	0.5	ND
A.27 (multiple countries)	-	No change[d]	ND	1.8	ND

Lineage with spike protein substitutions		Reduction in susceptibility [a]		IC_{50} (ng/ml)	
Pango nomenclature (origin)	WHO name	Pseudovirus[b]	Authentic SARS-CoV-2[c]	Pseudovirus[b]	Authentic SARS-CoV-2[c]
AV.1 (multiple countries)	-	No change[d]	ND	13.0	ND

[a] Range of reduced *in-vitro* potency across multiple sets of co-occurring substitutions and/or testing labs using appropriate assays; mean change in half-maximal inhibitory concentration (IC_{50}) of monoclonal antibody required for a 50% reduction in infection compared to wild type reference strain.
[b] Pseudoviruses expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions except L452Q were tested, including Alpha (+L455F, E484K, F490S, Q493R, and/or S494P), and Delta (+K417N) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.
[c] Authentic SARS-CoV-2 expressing the entire variant spike protein was tested, including Alpha (+E484K or S494P) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.
[d] No change: <10-fold reduction in susceptibility.
[e] Omicron spike mutations: A67V, H69-, V70-, T95I, G142D, V143-,Y144-, Y145-, N211-,L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.
[f] It is unlikely that tixagevimab and cilgavimab together are effective against this variant.
ND, not determined; RBD, receptor binding domain.

It is possible that resistance-associated variants to tixagevimab and cilgavimab in combination could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. Tixagevimab and cilgavimab in combination retained activity against pseudoviruses harbouring individual SARS-CoV-2 spike substitutions (E484D/K/Q, F490S, Q493R, S494P, K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, F486V, and Q493K) identified in neutralisation escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

It is not known how pseudovirus or authentic SARS-CoV-2 neutralisation susceptibility data correlate with clinical outcome.

Clinical data about antiviral resistance

In the PROVENT study, sequencing data collected at illness visits was available for 21 participants with COVID-19 infection (6 who received tixagevimab and cilgavimab, and 15 who received placebo). At an allele fraction ≥25%, 14 participants were infected with variants of concern or variants of interest, including 8 participants with Alpha (B.1.1.7) (8 placebo), 1 participant with Beta (B.1.351) (1 person who received tixagevimab and cilgavimab), 3 participants with Delta (B.1.617.2) (3 placebo), and 2 participants with Epsilon (B.1.429) (2 people who received tixagevimab and cilgavimab). Seven further participants were infected with B.1.375 (1 person who received tixagevimab and cilgavimab) or the A_1 lineages harbouring a constellation of spike protein substitutions, including D614G and P681H or Q677P (3 people who received tixagevimab and cilgavimab, and 3 people who received

placebo). Additional spike protein RBD substitutions detected at an allele fraction of 3% included V503F in the tixagevimab and cilgavimab group. Data collection and analysis is not yet complete.

In TACKLE, baseline visit sequencing data was available for 834 out of 903 participants (413/452 who received EVUSHELD and 421/451 who received placebo). At an allele fraction ≥25%, the proportion of participants infected with variants of concern or variants of interest was balanced between the treatment groups, including participants with ALPHA (139 who received EVUSHELD and 119 placebo), BETA (0 who received EVUSHELD and 1 placebo), GAMMA (37 who received EVUSHELD and 46 placebo), Delta (33 who received tixagevimab+cilgavimab and 33 placebo), LAMBDA (11 who received EVUSHELD and 9 placebo), and MU (0 who received EVUSHELD and 2 placebo). Baseline and follow-up SARS-CoV-2 spike sequences were available for 18 participants treated with EVUSHELD. At an allele fraction ≥25% (N=18) or 3-25% (N=17), treatment-induced substitutions were observed in 4/18 and 6/18 participants, respectively. Of a total of 35 treatment-induced substitutions, 15 were tested *in vitro* in pseudovirus microneutralisation assays of appropriate quality, and in all cases the change in susceptibility was <3-fold.

Pharmacodynamics

In the PROVENT study, following a single intramuscular dose of 300 mg EVUSHELD, neutralising antibody GMT at 7, 28, 57 and 91 days post-dose were similar to those observed in the Phase I study in healthy subjects and were 16-, 22-, 17- and 12-fold higher, respectively, than the GMT measured in convalescent plasma from COVID-19 patients (GMT= 30.8).

In the TACKLE study, the geometric mean titre (GMT) of neutralising antibodies following a single intramuscular dose of 600 mg EVUSHELD at 6, 15, 29, 85 and 169 days post-dose was 16-, 14-, 22-, 18- and 5-fold higher, respectively, than the values measured with placebo.

Immunogenicity

In the PROVENT study, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected up to Day 183 following a single intramuscular dose of 300 mg EVUSHELD in 3.2% (101/3,152), 3.7% (113/3,068) and 4.9% (156/3,158) participants, respectively, who were evaluable for anti-drug antibodies (ADA).
In the TACKLE study, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected up to Day 169 following a single intramuscular dose of 600 mg EVUSHELD in 5.2% (14/271), 10.7% (33/307) and 10.7% (37/346) participants, respectively, who were evaluable for ADA.

No evidence of an association between ADA and an impact on PK or safety has been observed.

Clinical efficacy

Pre-exposure prophylaxis of COVID-19

PROVENT

PROVENT is an ongoing Phase III, randomised (2:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age. All participants were individuals considered to be at increased risk for inadequate response to active immunisation (due to age ≥60 years, co-morbidity, pre-existing chronic illness, immunocompromised, or intolerant of vaccination) or at increased risk of SARS-CoV-2 infection (due to their location or circumstances at time of study enrolment). Participants received either a single dose (administered as two intramuscular injections) corresponding to 300 mg EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab, administered separately) or placebo. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening.
The baseline demographic data were well balanced across the EVUSHELD and placebo arms. The median age was 57 years (43% of participants were aged 60 years or older), 46% of participants were female, 73% were White, 3.3% were Asian, 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 participants, 78% had co-morbidities or characteristics associated with an increased risk for severe COVID-19, including immunosuppressive disease (<1%), treatment with immunosuppressive medications (3%), diabetes (14%), severe obesity (42%), heart disease (8%), chronic obstructive pulmonary disease (5%), chronic kidney disease (5%), and chronic liver disease (5%).

The primary analysis included 5,172 participants who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3,441 received EVUSHELD and 1,731 received placebo. EVUSHELD significantly (p-value <0.001) reduced the risk of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo (Table 6). The median follow-up time post-administration was 83 days.

Table 6 Incidence of COVID-19 (complete pre-exposure analysis set)

	N	**Number of events[a], n (%)**	**Relative risk reduction, % (95% CI)**
EVUSHELD 300 mg[b]	3,441	8 (0.2%)	77% (46-90)
Placebo	1,731	17 (1.0%)	

CI = Confidence Interval, N = number of participants in analysis.

[a] Primary endpoint, a participant was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred after administration and prior to Day 183.

[b] 300 mg i.m. (150 mg tixagevimab and 150 mg cilgavimab).

Efficacy was consistent across pre-defined sub-groups, including age, sex, ethnicity and baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19.

There was a statistically significant reduction in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause in participants who had received EVUSHELD (12/3,441) compared to placebo (19/1,731); relative risk reduction 69% (95% CI: 36, 85), p-value = 0.002.

Efficacy was assessed in participants who had no serological evidence of previous SARS-CoV-2 infection (SARS-CoV-2 nucleocapsid antibody negative) at baseline. EVUSHELD significantly reduced the risk of SARS-CoV-2 infection (symptomatic or asymptomatic, SARS-CoV-2 nucleocapsid antibodies positive at any time after baseline) compared to placebo; SARS-CoV-2 nucleocapsid antibodies were observed in 0.7% (21/3,123) of participants who received EVUSHELD, and in 1.3% (21/1,564) of participants who received placebo (relative risk reduction 51%, 95% CI: 11, 73; p-value = 0.020).
Among participants who received EVUSHELD, there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterised by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnoea, and lung infiltrates] or hypoxaemia [SpO2 <90% in room air and/or severe respiratory distress] and a WHO Clinical Progression Scale score of 5 or higher) compared to one event (0.1%) among participants who received placebo.
An additional data cut-off was conducted to provide post-hoc updated safety and efficacy analyses; the median follow-up was 6.5 months for participants in both the EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI 66-91), with 11/3,441 [0.3%] events in the EVUSHELD arm and 31/1,731 [1.8%] events in the placebo arm. Among participants who received EVUSHELD, there were no severe/critical COVID-19 events compared to five events among participants who received placebo.
The Kaplan Meier curves for the time to occurrence of first SARS-CoV-2 RT-PCR-positive symptomatic illness after administration of EVUSHELD or placebo showed a continuous separation from Day 5 across the entire observation period of 180 days. The hazard ratio is in favour of the EVUSHELD arm with a value of 0.17 (95% CI: 0.08, 0.33) and a p-value of less than 0.001.

Treatment of mild to moderate COVID-19

TACKLE is an ongoing Phase III, randomised (1:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the treatment of adult patients with mild to moderate COVID-19. The study enrolled individuals who had not received COVID-19 vaccination, who were not hospitalised for COVID-19 treatment, and who had at least one COVID-19 symptom that was at least mild in severity. Treatment was initiated within 3 days of obtaining the sample for a positive SARS-CoV-2 viral infection and at the latest 7 days after onset of COVID-19 symptoms. In addition to standard of care treatment, patients received a single dose (administered as two i.m. injections) of either 600 mg EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab, given separately; N = 413) or placebo (N = 421). Participants were stratified by time from symptom onset (≤5 days versus >5 days) and risk of progression to severe COVID-19 (high risk versus low risk).

Demographics and disease characteristics were comparable in the treatment and placebo groups. At baseline, the median age was 46 years (with 13% of subjects aged 65 years or older), 50% of the subjects were female, 62% were White, 5.6% were Asian, 4.0% were Black/African American, and 52% were Hispanic/Latino.
The majority of participants (84%) were seronegative at baseline, and 90% were considered at higher risk of progressing to severe COVID-19, defined as either individuals aged 65 years or older at randomisation, or individuals aged <65 years and having at least one medical condition or other factor that placed them at higher risk of progression to severe COVID-19. High risk comorbidities included: obesity (BMI ≥30) (43%), smoking (current or former) (40%), hypertension (28%), chronic lung disease or moderate to severe asthma (12%), diabetes (12%), cardiovascular disease (including history of stroke) (9%), immunocompromised state (from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines) (5%), cancer (4%), chronic kidney disease (2%), or chronic liver disease (2%).

At baseline, 88% of patients had WHO clinical progression scale of 2 and 12% had WHO clinical progression scale of 3 COVID-19, the median duration of symptoms prior to treatment was 5 days.
The primary efficacy endpoint was a combination of either severe COVID-19 or death from any cause up to Day 29 in patients who received treatment within 7 days from symptom onset and were not hospitalised at baseline. Severe COVID-19 was defined as either pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates observed on chest X-ray or lung computed tomography scan) or hypoxaemia (SpO_2 <90% in room air and/or severe respiratory distress) and a WHO clinical progression scale score of 5 or higher. Primary endpoint events occurred in 4.4% (18/407) of patients treated with EVUSHELD, compared to 8.9% (37/415) of patients who received placebo, and this represented a statistically significant (p=0.010) 50% (95% CI: 15, 71) reduction in severe COVID-19 or death from any cause compared to placebo (Table 6).

The relative risk reduction based on time of administration after symptom onset is shown in Figure 1. Patients treated at the start of their disease course appeared to experience the greatest benefit from treatment. In participants who were seronegative at baseline, EVUSHELD significantly reduced the risk of severe COVID-19 or death from any cause by 61% (95% CI: 30, 79; p-value = 0.001) compared to placebo, with 14/347 (4%) and 36/345 (10%) events, respectively. Given the small sample size, no conclusion can be drawn regarding the efficacy in seropositive patients.

Table 7 Incidence of severe COVID-19 or death from any cause up to Day 29

Population	Treatment	N	Number of events, n (%)	Relative risk reduction, % (95% CI)	p-value [a]
Non-hospitalised patients treated ≤7 days	EVUSHELD[b]	407	18 (4.4%)		

Population	Treatment	N	Number of events, n (%)	Relative risk reduction, % (95% CI)	p-value [a]
from symptom onset (mFAS)	Placebo	415	37 (8.9%)	50% (15, 71)	p = 0.010
All randomised participants, including hospitalised and non-hospitalised patients (FAS)	EVUSHELD[b]	446	24 (5.4%)	42% (5, 64)	p = 0.028
	Placebo	444	44 (9.2%)		

CI = Confidence Interval, N = Number of participants included in analysis, mFAS = Modified full analysis set, FAS = Full analysis set.

a. Results from a CMH test stratified by time from symptom onset (≤5 vs. >5 days) and risk of progression to severe COVID-19 (high vs. low).

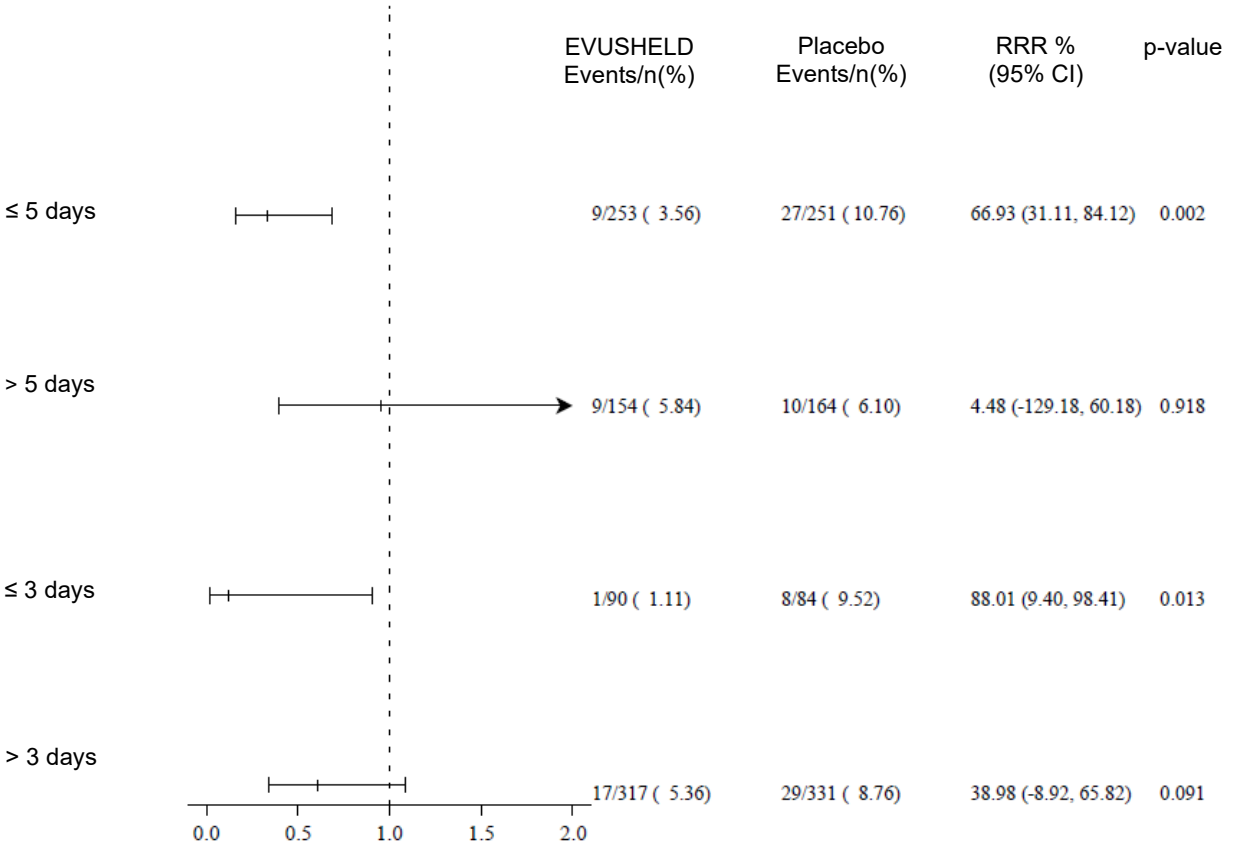
b. 300 mg tixagevimab and 300 mg cilgavimab

Missing response data were not imputed.

The results of the primary composite endpoint were driven by the incidence of severe COVID-19. Up to Day 29, 7 deaths had been reported, 3 in the EVUSHELD arm and 4 in the placebo arm. Of the 7 deaths, 2 were not COVID-19 related. Both of these were in the EVUSHELD arm and contributed to the primary composite endpoint.

Respiratory failure (defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or oxygen via high-flow nasal tube) occurred in 3 (0.7%) of participants treated with EVUSHELD and 11 (2.7%) of participants treated with placebo (relative risk reduction 72%, 95% CI: 0.25, 92).

Figure 1 Forest plot: Relative risk reduction (RRR) by time of administration following symptom onset



Pharmacokinetics

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional between 150 mg and 3,000 mg tixagevimab or cilgavimab following a single intravenous administration, and between 300 mg and 600 mg following a single intramuscular administration.

Absorption

After a single intramuscular dose of 600 mg (300 mg of each antibody) in COVID-19 participants in TACKLE, the mean (% coefficient of variation) maximum concentration (C_{max}) was 21.9 (61.7%) and 20.3 (63.6%) µg/ml for tixagevimab and cilgavimab, respectively, which was reached at a median time (T_{max}) of 15 days. The estimated absolute bioavailability in healthy subjects after a single intramuscular dose of 300 mg (150 mg of each antibody) was 68.5% for tixagevimab and 65.8% for cilgavimab.

Based on pharmacokinetic/pharmacodynamic models, it is estimated that 90% of patients achieve a protective serum concentration within 24 hours.

Distribution

Based on PK modelling, the central volume of distribution was 2.72 litres for tixagevimab and 2.48 litres for cilgavimab. The peripheral volume of distribution was 2.64 litres for tixagevimab and 2.57 litres for cilgavimab.

Metabolism

Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination

The clearance (CL) was 0.041 L/day for tixagevimab and 0.041 L/day for cilgavimab, with interindividual variability of 21% and 29%, respectively. The estimated population median terminal elimination half-life was 89 days for tixagevimab and 84 days for cilgavimab.

In PROVENT, following a single intramuscular dose of 300 mg EVUSHELD, the geometric mean serum concentration was 23.4 µg/ml (geoSD: 1.9) on Day 29 and 12.2 µg/ml (geoSD: 1.4) on Day 183.

In TACKLE, following a single intramuscular dose of 600 mg EVUSHELD, the geometric mean serum concentration was 37.2 µg/ml (geoSD: 2.1) on Day 29. There was no clinically relevant difference in the clearance of tixagevimab or cilgavimab between participants with COVID-19 enrolled in TACKLE and those enrolled in the prophylaxis studies.

Kinetics in specific patient groups

Renal impairment

No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of tixagevimab and cilgavimab.
Tixagevimab and cilgavimab are not eliminated intact in the urine, thus renal impairment is not expected to significantly affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.
Based on a population PK analysis, there is no difference in the clearance of tixagevimab and cilgavimab in patients with mild (N= 978) or moderate (N= 174) renal impairment compared to patients with normal renal function. In the population PK model, there were insufficient participants with severe renal impairment (N= 21) to draw conclusions.

Hepatic impairment

No specific studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is expected to be low.
Tixagevimab and cilgavimab are expected to be catabolised by multiple tissues through proteolytic degradation into amino acids and recycling into other proteins. Therefore hepatic impairment is not expected to affect the exposure of tixagevimab and cilgavimab.

Elderly patients

Of the 2,560 participants in the pooled PK analysis, 21% (N= 534) were 65 years of age or older, and 4.2% (N= 107) were 75 years of age or older. There is no clinically relevant difference in the PK of tixagevimab and cilgavimab in elderly patients (>65 years) compared to younger patients.

Children and adolescents

The PK of tixagevimab and cilgavimab in individuals <18 years old has not been evaluated.
Using population PK models and simulations, the recommended dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in adolescents aged 12 years or older who weigh at least 40 kg as observed in adults, since adults with similar body weight have been included in the PROVENT clinical trial.

Patients with high body weight
Based on a population PK analysis, a decrease in EVUSHELD serum concentrations was observed with increasing body weight. The average serum concentration in an adult weighing >95 kg following a dose of 150 mg tixagevimab and 150 mg cilgavimab is expected to be 37% lower than in an adult weighing 65 kg.

Other special populations

Based on a population PK analysis, sex, age, ethnicity, cardiovascular disease, diabetes and immunocompromise had no clinically relevant effect on the PK of tixagevimab and cilgavimab.

Preclinical data

Based on studies of tissue binding and a single-dose toxicity study on cynomolgus monkeys, including the evaluation of safety pharmacology and local tolerability, preclinical data reveal no special hazard for humans.
No binding has been found in tissue cross-reactivity studies with human adult and foetal tissue.
Carcinogenesis, mutagenesis, and reproductive toxicology studies have not been conducted.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Shelf life after opening

The solutions for injection do not contain any preservative and for this reason the prepared syringes should be administered immediately. If immediate administration is not possible and the prepared syringes of tixagevimab and cilgavimab need to be stored, the total time from puncture of the vials to administration should not be longer than 4 hours, either:

- in a refrigerator at 2–8°C
- or at room temperature up to 25ºC

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze. Do not shake.
Keep the vials in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

Inspect the vials visually for particulate matter and discolouration. Both tixagevimab and cilgavimab are clear to opalescent, colourless to slightly yellow solutions with a pH of 6.0. Discard the vials if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vials.
The solutions for injection do not contain any preservative. Any unused solution should be discarded.

Authorisation number

68704 (Swissmedic)

Packs

Each carton contains two vials:
Tixagevimab
1.5 ml of solution for injection in a clear glass single-dose vial closed by a chlorobutyl elastomeric stopper sealed with a dark-grey aluminium flip-off top. [A]
Cilgavimab
1.5 ml of solution for injection in a clear glass single-dose vial closed by a chlorobutyl elastomeric stopper sealed with a white aluminium flip-off top. [A]

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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