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ADISINSIGHT REPORT

Amubarvimab/Romlusevimab: First Approval

Sheridan M. Hoy[1]

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Abstract

Amubarvimab 安巴韦单抗注射液/romlusevimab 罗米司韦单抗注射液 is a combination of two neutralizing recombinant human IgG1 monoclonal antibodies (amubarvimab and romlusevimab) against the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). Jointly developed by Brii Biosciences, Tsinghua University and the Third People's Hospital of Shenzhen, it has been approved (in December 2021) by the National Medical Products Administration of China for the treatment of mild COVID-19 in patients aged ≥ 18 years, and those aged 12–17 years with a bodyweight of ≥ 40 kg (conditional approval) who are at high risk of progressing to severe disease, including hospitalization or death. An Emergency Use Authorization application for amubarvimab/romlusevimab is currently under review in the USA. This article summarizes the milestones in the development of amubarvimab/romlusevimab leading to this first approval for the treatment of COVID-19.

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Amubarvimab 安巴韦单抗注射液/Romlusevimab 罗米司韦单抗注射液: Key Points

Combination of two neutralizing monoclonal antibodies against SARS-CoV-2 for coadministration; being jointly developed by Brii Biosciences, Tsinghua University and the Third People's Hospital of Shenzhen for the treatment of COVID-19

Received its first approval on 8 December 2021 in China

Approved for use in patients aged ≥ 18 years, and conditionally approved for use in patients aged 12–17 years with a bodyweight of ≥ 40 kg with mild COVID-19 who are at high risk of progressing to severe disease, including hospitalization or death

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

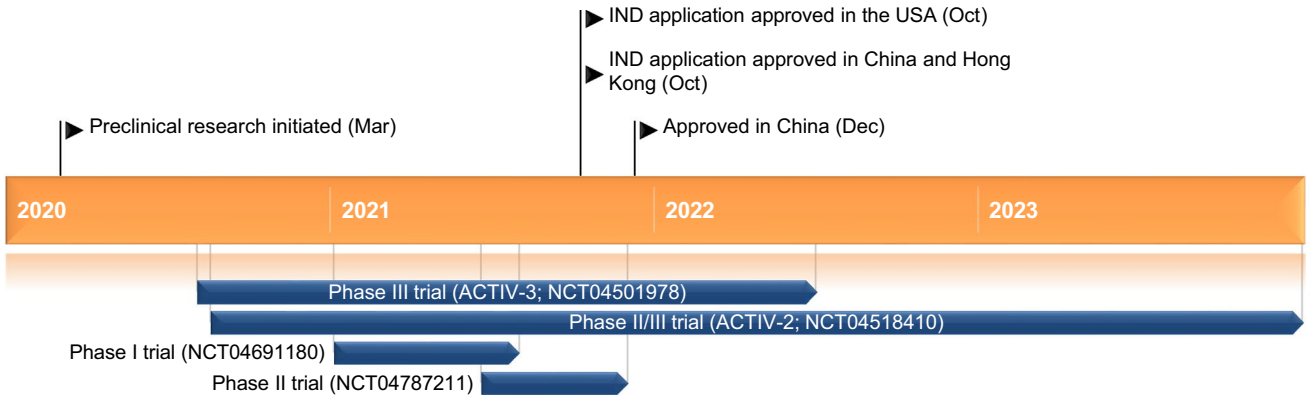
✉ Sheridan M. Hoy
dru@adis.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in late 2019, with the subsequent outbreak spreading rapidly across the world and reaching pandemic status in March 2020 [1, 2]. It targets host cells (e.g. nasal and bronchial epithelial cells, and pneumocytes) through the binding of a structural spike protein to angiotensin-converting enzyme 2 (the primary receptor of SARS-CoV-2) on the cell surface, gaining entry via endocytosis [3, 4]. While different stages of the SARS-CoV-2 lifecycle could be potential therapeutic targets, entry into the host cell is one of the most attractive (as it initiates infection and permits access to cellular receptors and viral entry proteins from the extracellular space), with antibody therapeutics holding immense promise for the treatment of coronavirus disease 2019 (COVID-19) [1, 4, 5].

Amubarvimab 安巴韦单抗注射液/romlusevimab 罗米司韦单抗注射液 is a combination of two neutralizing recombinant human IgG1 monoclonal antibodies (amubarvimab and romlusevimab; derived from a convalesced COVID-19 patient) against the SARS-CoV-2 spike protein that is being jointly developed by Brii Biosciences, Tsinghua University and the Third People's Hospital of Shenzhen [6–9]. In December 2021, it was approved by the National Medical Products Administration of China for the treatment of mild COVID-19 in adults, and patients aged 12–17 years with a bodyweight of ≥ 40 kg (conditional approval) who are at high risk of progressing to severe disease, including hospitalization or death [6, 7, 10–12]. The recommended dose is amubarvimab 1000 mg



Key milestones in the development of amubarvimab/romlusevimab for the treatment of COVID-19. *IND* Investigational New Drug

plus romlusevimab 1000 mg administered as separate sequential intravenous infusions [11, 12]. Romlusevimab should be administered immediately after amubarvimab; if romlusevimab is administered first, amubarvimab can be administered immediately thereafter. Local prescribing information should be consulted for information regarding preparation, storage, administration, patient monitoring during the infusions, warning and precautions, and use in special populations [11, 12].

An Emergency Use Authorization application for amubarvimab/romlusevimab is currently under review in the USA [13]. Clinical development is also underway in various other countries for the treatment of COVID-19.

1.1 Company Agreements

In March 2020, Brii Biosciences, Tsinghua University and the Third People's Hospital of Shenzhen entered into a licensing agreement to discover, develop, manufacture and commercialize fully human neutralizing monoclonal antibodies to address the COVID-19 pandemic [14].

2 Scientific Summary

2.1 Pharmacodynamics

Amubarvimab and romlusevimab bind to distinct epitopes of the SARS-CoV-2 spike protein [5]. Amubarvimab completely blocks viral entry and neutralizes live SARS-CoV-2 infection in cell culture assays; romlusevimab has an additive effect when combined with amubarvimab [5].

In vitro pseudovirus data suggest that the neutralization activity of amubarvimab/romlusevimab is retained against major SARS-CoV-2 variants of concern, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.429 (Epsilon), B.1.617.2 (Delta), AY.4.2, C.37 (Lambda), B.1.621 (Mu), B.1.1.529-BA.1 (Omicron), and B.1.1.529-BA.1.1 and B.1.1.529-BA.2 (Omicron subvariants) [6, 13, 15, 16]. Although there was a substantial drop in the activity of amubarvimab against the Omicron variants, the activity of romlusevimab was largely unaffected against BA.1 and moderately reduced against BA.2, but severely decreased against BA.1.1 [16].

In a mouse model of SARS-CoV-2 infection, a single intraperitoneal injection of amubarvimab/romlusevimab (10/10 mg/kg) protected animals from Omicron infection [16].

2.2 Pharmacokinetics

The pharmacokinetics of amubarvimab/romlusevimab were consistent with those for amubarvimab and romlusevimab as monotherapies, suggesting no interactions between the two monoclonal antibodies [17].

In two first-in-human phase I trials in healthy adults, the pharmacokinetics of amubarvimab (NCT04479631; $n = 12$) and romlusevimab (NCT04479644; $n = 12$) [each administered as a single intravenous infusion of 750, 1500 or 3000 mg] were as expected for monoclonal antibodies; the mean serum pharmacokinetic parameters of each were approximately dose-proportional [8]. Based on human pharmacokinetic data, the exposures of amubarvimab and romlusevimab (each administered as 1000 mg doses via intravenous infusion) are expected to remain above the level required for neutralizing activity against Omicron BA.2 [18]. Specifically, total serum amubarvimab and romlusevimab concentrations will remain 60-fold higher than the level needed for > 90% neutralization [18]. In NCT04479631 and NCT04479644, mean systemic serum clearance values were 72.2–84.7 mL/day for amubarvimab and 63.9–59.4 mL/day for romlusevimab; mean terminal half-life (t½) values were 44.6–48.6 days and 72.2–83.0 days, with the shorter terminal t½ of amubarvimab correlating with its slightly higher systemic clearance [8].

Features and properties of amubarvimab/romlusevimab

Alternative names	Amubarvimab: BRII-196; romlusevimab: BRII-198
Class	Antivirals; monoclonal antibodies
Mechanism of action	Virus internalization inhibitors
Route of administration	Intravenous
Pharmacodynamics	Amubarvimab and romlusevimab bind to distinct epitopes of the SARS-CoV-2 spike protein; neutralization activity of the antibodies in combination appears to be retained against a number of SARS-CoV-2 variants of concern
Pharmacokinetics (amubarvimab and romlusevimab)	Median time to maximum serum concentration of 4.6–6.6 h and 4.7–6.8 h, respectively, with mean systemic serum clearance values of 72.2–84.7 and 63.9–59.4 mL/day, respectively Mean terminal half-life of 44.6–48.6 and 72.2–83.0 days, respectively
Most frequent treatment-emergent adverse events	Diarrhoea, nausea, vomiting, fatigue, fever, chills, COVID-19 pneumonia, bronchitis, infusion-related reactions, increased BP, myalgia, headache, insomnia, oropharyngeal pain, cough, difficulty breathing, runny nose and high BP
ATC codes	
WHO ATC code	J05 (antivirals for systemic use)
EphMRA ATC code	J5 (antivirals for systemic use)

SARS-CoV-2 severe acute respiratory syndrome coronavirus

Clinical drug interaction studies have not been conducted with amubarvimab and romlusevimab [11, 12]. Amubarvimab and romlusevimab are not thought to be excreted via the kidneys nor metabolized by CYP3A4; thus, there is a low potential for interactions with medications that are CYP substrate inducers or inhibitors [11, 12].

2.3 Therapeutic Trials

Amubarvimab/romlusevimab significantly reduced the risk of hospitalization or death from any cause in non-hospitalized adults with symptomatic COVID-19 who were at high risk of clinical progression in the phase III part of an ongoing, adaptive, randomized, double-blind, placebo-controlled, multinational phase II/III trial (ACTIV-2; NCT04518410) [11, 12, 19]. In the amubarvimab/romlusevimab arm of ACTIV-2, 9 of 418 amubarvimab/romlusevimab recipients and 46 of 419 placebo recipients were hospitalized and 0 and 9 patients died in the 28 days following treatment, a statistically significant reduction in the primary endpoint of hospitalization or death from any cause of 81% [hazard ratio 0.187 (95% CI 0.091–0.382); $p = 0.0001$]. Moreover, the benefit seen in this endpoint in the general population favoured amubarvimab/romlusevimab over placebo across all the subgroups assessed apart from the COVID-19 vaccination and current smoking subgroups [11, 12].

The amubarvimab/romlusevimab arm of ACTIV-2 enrolled outpatients aged ≥ 18 years who had tested positive for SARS-CoV-2 infection ≤ 10 days prior to study entry and who were considered to be at high risk of progression to severe COVID-19 [i.e. aged ≥ 60 years, or the presence of comorbidities (e.g. active cancer, body mass index ≥ 30 kg/m^2, cardiovascular disease, chronic kidney disease, chronic lung disease, cirrhosis, diabetes, hypertension, immunosuppression)] [11, 12]. The most common risk factors or comorbidities were hypertension (38% of 837 patients; modified intent-to-treat population), currently smoking (32%) and body mass index ≥ 30 kg/m^2 (27%). Patients who had severe COVID-19 or who were severely immunocompromised and required supplemental oxygen or hospitalization were excluded. Amubarvimab and romlusevimab were administered consecutively (no less than 25 min apart) as single 1000 mg doses via intravenous infusion [11, 12].

Amubarvimab/romlusevimab failed to meet prespecified efficacy criteria in hospitalized adults with symptomatic COVID-19 and will not progress into the phase III part of the adaptive, randomized, double-blind, multinational phase III ACTIV-3 study (NCT04501978) [20, 21]. Based on interim futility analyses of data from the amubarvimab/romlusevimab arm of the phase II part of ACTIV-3, at day 5, patients who received amubarvimab/romlusevimab ($n = 176$) did not have significantly higher odds of more favourable outcomes than those who received placebo ($n = 178$) on either the seven-category pulmonary ordinal scale [adjusted odds ratio (OR) 0.98 (95% CI 0.67–1.43)] or the pulmonary plus extrapulmonary complications scale [adjusted OR 1.00 (95% CI 0.68–1.46)] [21]. By day 90, sustained clinical recovery (primary outcome) was seen in 88% of patients in the amubarvimab/romlusevimab group and 85% of those in the placebo group [adjusted rate ratio 1.08 (95% CI 0.88–1.32)] [21].

Key clinical trials of amubarvimab/romlusevimab in COVID-19

Drug(s)	Phase	Status	Location(s)	Identifier	Sponsor
Amubarvimab/romlusevimab, remdesivir, AZD7442, LY3819253, MP0420, PF-07304814, VIR-7831, placebo	III	Active, not recruiting	Multinational	NCT04501978 (ACTIV-3; TICO)	University of Minnesota
Amubarvimab/romlusevimab, bamlanivimab, camostat, casirivimab + imdevimab, AZD7442, BMS-986414 + BMS-986413, SAB-185, SNG001, placebo	II/III	Active, not recruiting	Multinational	NCT04518410 (ACTIV-2)	National Institute of Allergy and Infectious Diseases
Amubarvimab/romlusevimab, placebo	II	Completed	China	NCT04787211	Brii Biosciences Limited
Amubarvimab/romlusevimab, placebo	I	Completed	China	NCT04691180	Brii Biosciences Limited

The amubarvimab/romlusevimab arm of ACTIV-3 enrolled hospitalized patients aged ≥ 18 years who had tested positive for SARS-CoV-2 infection for up to 12 days prior to study entry [21]. Patients received amubarvimab and romlusevimab as single 1000 mg doses via intravenous infusion (over 60 min). The primary outcome was defined as the time to sustained clinical recovery (i.e. discharge from the hospital to home and remaining at home for 14 consecutive days, up to day 90 following randomization) [21].

2.4 Adverse Events

Amubarvimab/romlusevimab was generally well tolerated in phase I–III clinical studies [22–24]. No new safety concerns were identified in ACTIV-2 [6, 22].

In the amubarvimab/romlusevimab arm (28-day follow-up data) of ACTIV-2, treatment-emergent adverse events (TEAEs) occurred in 27.0% of 418 amubarvimab/romlusevimab recipients and 33.2% of 419 placebo recipients [11, 12]. Frequently reported TEAEs included diarrhoea, nausea, vomiting, fatigue, fever, chills, COVID-19 pneumonia, bronchitis, infusion-related reactions, increased BP, myalgia, headache, insomnia, oropharyngeal pain, cough, difficulty breathing, runny nose and high BP. Treatment-related adverse events (TRAEs) were reported in 4.1% and 3.8% of patients in the amubarvimab/romlusevimab and placebo groups. Adverse events of special interest (AESIs) occurred in five amubarvimab/romlusevimab recipients and four placebo recipients; all of the AESIs were grade 1 or 2 infusion-related reactions. One amubarvimab/romlusevimab recipient developed a grade 2 AESI during the administration of amubarvimab: the infusion rate was subsequently reduced for the remainder of the infusion. Serious adverse events were reported in 9 and 46 patients in the amubarvimab/romlusevimab and placebo groups; no serious TRAEs occurred. Nine patients (all from the placebo group) died during the 28-day follow-up period [11, 12].

There was no evidence of significant anti-drug antibody (ADA) development in two first-in-human phase I studies (NCT04479631 and NCT04479644) [8]. Four subjects receiving amubarvimab and one receiving romlusevimab had positive ADA samples in the screening assay, but all tested negative in the follow-up confirmatory assay [8].

2.5 Ongoing Clinical Trials

Ongoing clinical studies include the phase II/III ACTIV-2 study (NCT04518410), which is evaluating the efficacy and safety of multiple investigational agents, including amubarvimab/romlusevimab, for the outpatient treatment of adults with COVID-19.

3 Current Status

Amubarvimab/romlusevimab received its first approval on 8 December 2021 in China for the treatment of adults, and patients aged 12–17 years with a bodyweight of ≥ 40 kg (conditional approval) with mild COVID-19 who are at high risk of progressing to severe disease, including hospitalization or death [6, 7, 10–12].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01759-3.

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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