Clinical Therapeutics 48 (2026) 232–239

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Original Research

Phase I Study Evaluating a Monoclonal Fc-Silenced SARS-CoV-2 Antibody in Patients With Moderate-to-Severe COVID-19

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ARTICLE INFO

Key words:
Antibody-dependent enhancement (ADE)
Fc-silenced mAbs
Monoclonal antibodies (mAbs)
SARS-CoV-2
Phase I trial
COVID-19

ABSTRACT

Purpose: The evolution of Severe Acute Respiratory Syndrome Coronavirus 2 challenged the effectiveness of vaccines, while monoclonal antibodies (mAbs) were discontinued due to emergent resistance. This study evaluated the safety and explored the preliminary efficacy of COR-101, a novel mAb with a silenced Fc region designed to minimize antibody-dependent enhancement in hospitalized patients with moderate-to-severe disease.

Methods: Thirty-three participants were enrolled across Germany and Ukraine in a randomized, double-blind, placebo-controlled Phase Ib/II trial. Patients received either a single dose of COR-101, or placebo, as add-on therapy to the standard of care.

Findings: COR-101 was well tolerated, with no treatment-related severe adverse events (AEs), grade ≥3 AEs, or acute infusion reactions. Four unrelated severe AEs were observed, and 2 patients died due to coronavirus disease 2019. COR-101 showed dose-proportional pharmacokinetics, long half-life, and serum concentrations above IC_{50}. Patients were treated in different dose groups, and in exploratory analysis, viral clearance was observed at day 28 in 80%, 55.6%, 16.7%, and 42.9% of patients in the 4.0, 10.0, 25.0 mg/kg, and placebo groups, respectively. The

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https://doi.org/10.1016/j.clinthera.2026.01.004
Accepted 10 January 2026

predominant virus variant changed from alpha to delta and omicron, resulting in reduced in vitro neutralization, potentially explaining the observed reduced efficacy.
Implications: COR-101 demonstrated a favorable safety profile, but exploratory data showed limited efficacy against omicron, highlighting the tolerability of Fc-silenced mAbs and the need for adaptive therapeutic strategies against rapidly evolving viral pathogens (ClinicalTrials.gov identifier: NCT04674566).

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has displayed a propensity for mutation, resulting in 5 variants of concern (VOCs), namely alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529) and numerous subvariants,[1] which limited the efficacy of novel vaccines and targeted therapies.[2,3]

The development of monoclonal antibodies (mAbs) focused on the original Wuhan strain's spike protein, due to its critical role in viral entry into host cells via the ACE2 receptor.[4,5] Early candidates, such as bamlanivimab[6] and casirivimab with imdevimab,[7] received US Food and Drug Administration emergency use authorization (EUA) in late 2020. Subsequently, sotrovimab[8] and tixagevimab with cilgavimab[9] were approved for both treatment and prophylaxis in high-risk populations. Approval was based on reduction of viral load, hospitalization rates, and disease severity, particularly in patients presenting mild-to-moderate symptoms.[7–10] However, as the pandemic progressed, the spike protein gained mutations in its receptor-binding domain (RBD) conferring advantages in transmission, immune escape,[11,12] and resistance to approved mAbs.[2,13]

COR-101 (STE90-C11) is a recombinant human immunoglobulin G1 (IgG1) antibody that neutralizes SARS-CoV-2 by targeting the RBD.[14] It differentiates itself from other mAbs due to its fully silenced Fc-region, introduced to reduce the risk of antibody-dependent enhancement (ADE).[15] This was assumed to provide a key safety advantage, allowing for the first time a targeted treatment of severe cases of coronavirus disease 2019 (COVID-19) in hospitalized patients at high risk of death, for whom other mAbs were not indicated.

Here, we report on the tolerability, pharmacodynamics (PDs), pharmacokinetics (PKs), and preliminary efficacy of COR-101 as assessed during a first-in-human, placebo-controlled, multicenter, single-dose escalating study in patients with moderate to severe disease according to the World Health Organization criteria.

Materials and Methods

COR-101

COR-101 is a SARS-CoV-2 RBD-neutralizing recombinant human IgG1 mAb with a fully silenced Fc part. Specific properties of COR-101 have been previously reported.[14]

Study Design

This study (NCT04674566, EUDRACT 2020-005952-39) was a multicenter, international, randomized, double-blind, placebo-controlled Phase Ib/II trial investigating safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of COR-101 in hospitalized patients with moderate-to-severe COVID-19. The study was divided into a dose-escalating, safety-focused part 1 (Phase Ib), aimed at defining the dose for the dose-expansion, efficacy-focused part 2 (Phase II).

A total of 10 sites across Germany and Ukraine participated in this study, and 8 sites enrolled at least 1 patient (Supplementary Methods).

During part 1, patients were randomized to receive either COR-101 (as a single intravenous infusion of 4, 10, and 25 mg/kg on day 1, with dose groups initiated sequentially) or placebo in addition to the best available standard of care treatment. They were then followed up for 28 days, with an additional safety visit on day 80. The primary safety endpoint was the incidence of severe adverse events (SAEs), treatment-emergent adverse events (TEAEs), mortality, and adverse events (AEs) requiring medical intervention until day 28. All events were reported according to the European Medicines Agency guideline on expedited reporting (CPMP/ICH/377/95) and were graded according to the Common Terminology Criteria for AE (CTCAE) V5, Nov 2017. The Medical Dictionary for Regulatory Activities version 23.1 was used to code AEs. Secondary endpoints were the evaluation of the preliminary efficacy, PK and PD, including viral clearance. All efficacy endpoints were assessed in an exploratory/descriptive manner due to the small sample size. Further details about study designs and outcomes are available in the Supplementary Methods.

Inclusion and Exclusion Criteria

Adults (aged 18 or above) SARS-CoV-2 positive patients were included in the study, provided that (i) they had been hospitalized due to COVID-19 within 72 hours before randomization and that (ii) symptoms of moderate or severe COVID-19 (Supplemental Table I) could be assessed before the administration of the study drug. Subjects with only mild or already critical presentations, as well as those presenting with history or signs of severe neurologic conditions or severe cardiac, liver, or renal dysfunction, were excluded from the study. Notably, a recent vaccination against SARS-CoV-2 (within 30 days before treatment) or the administration of approved mAbs or convalescent plasma (concomitant to the study drug or within 120 days before treatment) were considered exclusion criteria. Extensive criteria can be found in Supplemental Table II.

Symptoms Scoring System

The symptoms and severity of COVID-19 were described according to both criteria of intensity defined as per protocol (Supplemental Table I) and international scoring systems (Supplemental Tables III and IV), namely the Clinical Status Related to COVID-19 on the National Institute of Allergy and Infectious Diseases 8-Point Ordinal Scale (NIAID-score), and the National Early Warning Score 2 (NEWS2-score)at days 1, 6, 14, 21, 28, and 80 (NIAD only at day 80).

Viral Load and Biomarkers

Viral load was analyzed on nasal swabs collected at days 1, 2, 4, 6, 14, 21, 28, and 80 at PPD Global Central Labs US. Details on isolation and purification of viral RNA are in the Supplementary Methods.

Blood samples were obtained at days 1, 4, 6, 14, 21, and 28 to measure biomarkers (including IL-6, ferritin, C3, and sIL-2R) in a central laboratory.

Evaluation of COR-101 Neutralization Activity Against VOCs

The neutralization efficiency of COR-101 against different virus variants was analyzed in vitro using a pseudovirus assay. In principle, a pseudovirus has been used that expresses the SARS-CoV-2 spike protein of different SARS-CoV-2 variants (delta and omicron) and that contains a gene for luciferase expression. 293T cells overexpressing hACE2 and hTMPRSS2 genes were incubated with the pseudovirus and different amounts of COR-101. Luminescence was measured to check internalization of the pseudovirus particles into the 293T cells. Decrease of the

relative luminescence units was observed due to the blocking of the interaction of the pseudovirus particles and 293T cells by COR-101, and half maximal inhibitory concentration (IC_{50}) was calculated.

Additionally, binding of COR-101 to RBD, including representative mutations for different variants (alpha, delta, and omicron), was determined by direct ELISA. To this aim, the RBD was directly immobilized in the wells of an ELISA plate and, after blocking, different concentrations of COR-101 were added. The interaction of COR-101 and RBD was measured by adding a Horseradish Peroxidase coupled anti-human Fc antibody and staining with 3,3′, 5,5′-tetramethylbenzidine substrate.

Statistical analysis

A standard group size of 5–10 participants was utilized to assess preliminary safety and pharmacokinetics. No official power calculations for part 1 were done, as this was intended to be exploratory and descriptive.

The Safety Analysis Set comprised all participants who were administered any dose of the COR-101 or placebo. Patients were categorized based on the dose received. Specific AEs were counted only once per patient. If a participant experienced the same AE multiple times, the most severe instance was recorded. Categorical variables were presented with the number and percentage of participants, and percentages were calculated based on the count of nonmissing observations. Descriptive statistics were used to summarize continuous variables.

The pharmacokinetic analysis set included all patients who received COR-101 and had at least 1 evaluable PK parameter measurement after baseline. The dataset for the PD analysis comprised 162 viral load measurements from 29 patients who received COR-101/placebo. Three patients from the 25 mg/kg dose group were excluded as they had only 1 viral load measurement or exclusively measurements below the lower limit of quantification. Data from day 80 were excluded as a reinfection was possible.

The Kaplan–Meier method was used to estimate time to reach negative SARS-CoV-2 status by treatment group (median time and 95% CI). Groups were compared using log-rank tests. The number and percentage of participants testing negative were summarized by treatment and the combined COR-101 group, with 95% CIs from the Wilson score method.

Population Pharmacokinetic and PK/PD Analysis

Plasma concentrations of COR-101 were measured by implementing an electrochemiluminescence immunoassay validated over a range of 5 to 400 μg/mL.

A population PK/PD analysis was conducted to assess the effect of COR-101 exposure on SARS-CoV-2 viral load. Model development utilized NONMEM 7.4.3 with the FOCEI[16] method for parameter estimation. Model evaluation was based on objective function value, relative standard errors,[17] and goodness-of-fit plots.[18] R 3.6.1 was used for dataset creation and result visualization. Covariate models were developed using forward inclusion and backward elimination. Further model development and evaluation criteria are detailed in the Supplementary Methods.

Declaration and Ethics

The trial adhered to the European Union Directive 2001/20/EC and the Declaration of Helsinki. It was approved by country-specific authorities, including 10 local ethics committees. Written informed consent was obtained from all patients prior to inclusion.

Results

Study Participants

Between April 2021 and November 2022, the eligibility of 45 subjects was assessed and 33 were enrolled in the study (18 in Germany and 15 in Ukraine). Overall, 28 patients completed the study, 1 (4 mg/kg group) was considered a dropout due to an accidental randomization, while 5 (10mg/kg group) withdrew (Figure 1). Termination reasons included fatal SAE (2 cases), patient choice (2 cases), and lost to follow-up (1 case). Seven patients received placebo, 5 received COR-101 4 mg/kg, 10 received COR-101 10 mg/kg, and 10 received COR-101 25 mg/kg. A list of demographics and baseline features can be found in Table I. Of note, patients receiving COR-101 were older than those enrolled in the placebo group (median age 66 and 57 years, respectively), with controls receiving oxygen supplementation less frequently than patients enrolled in the 4 mg/kg and 10 mg/kg dose groups (57.1% vs 100% and 100%, respectively). On the contrary, only 1 patient (10%) enrolled in the 25 mg/kg study group was under oxygen supplementation at the time of treatment.

All study participants received COR-101 or placebo as add-on therapy to standard of care. Accordingly, 26 patients (81.3%) received systemic corticosteroids and 1 received tocilizumab. Antibiotics and antiviral treatments, that is, one among remdesivir and molnupiravir, were used in 21 and 22 patients (65.6%), respectively, while 1 patient received sotrovimab. Concomitant medications are summarized in Supplemental Table V. Of note, patients in the placebo groups received antivirals (ie, remdesivir or molnupiravir) more often than patients treated with COR-101 (71% vs 52%).

Recruitment in Study Groups and VOC Evolution Over Time

Patients in the 4 mg/kg group were recruited from 21 April to 19 May 2021, during the alpha variant prevalence.[1] The 10 mg/kg group enrolled from 31 August 2021 to 1 February 2022, during the delta variant dominance and transition to omicron. The 25 mg/kg group was recruited from 11 February to 17 August 2022, after omicron prevailed. Placebo patients were recruited throughout the entire study period (Supplemental Figure 1).

Baseline S protein sequences were available for 5 of 7 patients in the placebo, 3 of 5 in the 4 mg/kg, 3 of 10 in the 10 mg/kg, and 5 of 10 in the 25 mg/kg groups. Phylogenetic analysis showed placebo patients were infected with B.1.1.7 (n = 2) and B.1.1 alpha strains, BE.1.1, and BF.6 omicron strains. In the 4 mg/kg group, patients had B.1.1.7 (n = 1) and B.1.1 (n = 2) alpha strains. In the 10 mg/kg group, 2 patients had B.1.617.2 (delta) and 1 had BA.1.1 (omicron). All 5 patients in the 25 mg/kg group were infected with omicron variants (BE.1.1, BA.2, BA.5, and BA.5.2). Limited data prevented correlation analysis between strain and outcomes.

Safety

COR-101 was well tolerated across all dose levels, with no acute infusion reactions, treatment-related SAEs, grade ≥3 AEs, or TEAEs reported. All COR-101/placebo doses were fully administered. TEAEs occurred in 60.0%, 60.0%, 50.0%, and 71.4% of patients in the 4, 10, and 25 mg/kg COR-101 and placebo groups, respectively, with 6 unrelated grade ≥3 TEAEs. An overview of all events is available in Table II and Supplemental Table VI. Two patients in the 10 mg/kg group died due to COVID-19 complications (sepsis and severe acute respiratory syndrome in 1; respiratory failure in the other). Hypertension and respiratory failure were the only non-severe TEAEs reported in ≥2 patients. Four TEAEs (nausea, dizziness, peripheral swelling, pyrexia) were considered treatment related, although the swelling did not meet the criteria for acute infusion-related reactions. Unrelated SAEs were reported in 1 and 3 patients in the 4 and 10 mg/kg groups (Supplemental Table VI). No notable changes from baseline in laboratory markers were noted in any treatment group (data not shown).

COR-101 Neutralization Activity Against VOCs and Viral Clearance

In vitro studies showed that COR-101 maintained effectiveness against the alpha and delta strains; however, it was un-

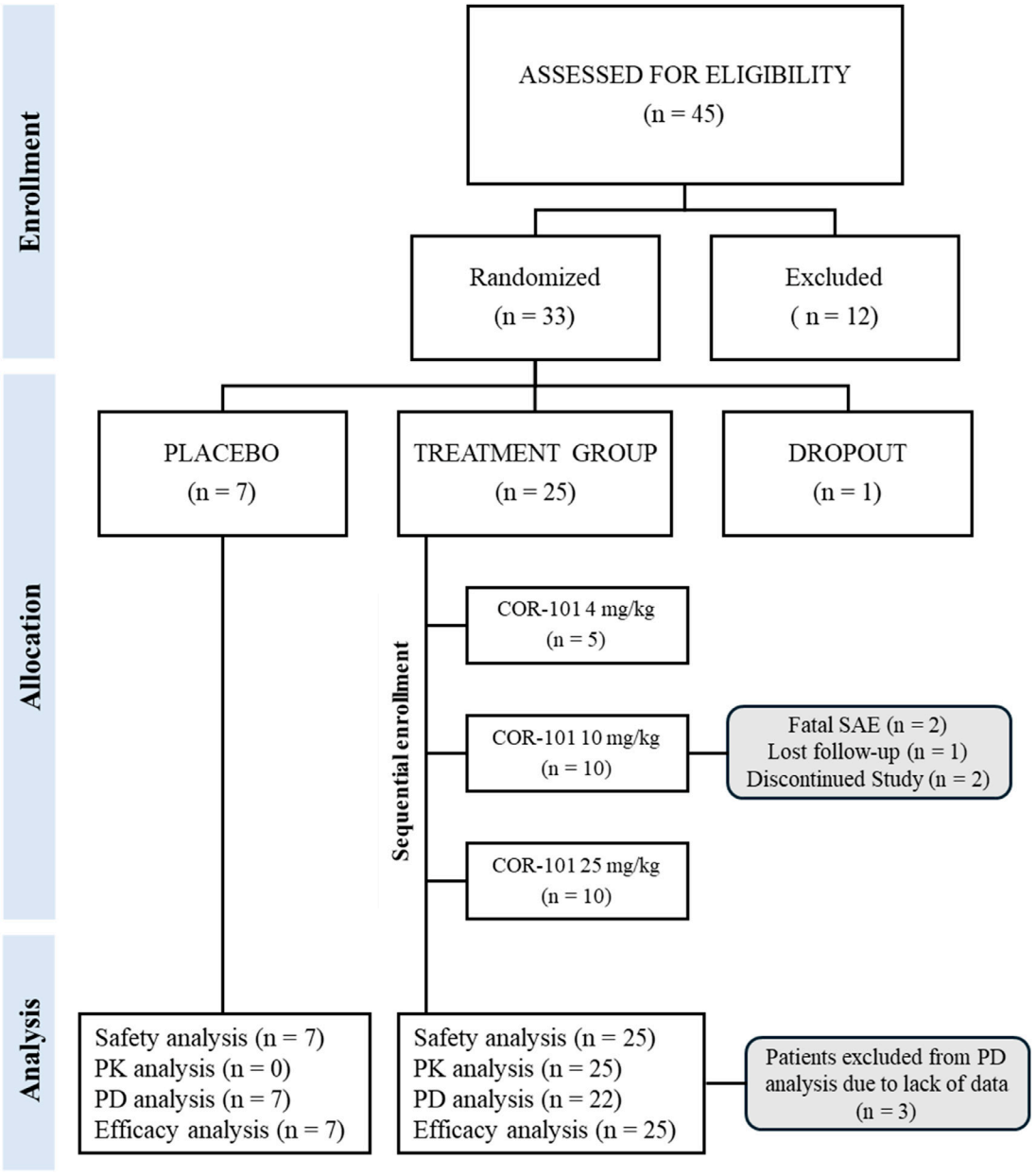

Figure 1. Consolidated Standards of Reporting Trials diagram. Sequential enrollment across the study is shown, with each subsequent dose group initiated after completion of the previous one. Patients were randomized to receive a single intravenous infusion of COR-101 (4, 10, or 25 mg/kg) or placebo, along with the standard of care. n = number of patients in the specified category; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse events.

able to bind and neutralize the omicron strains (Supplemental Table VII).

At day 28, viral clearance was achieved in 80.0%, 55.6%, 16.7%, and 42.9% of patients in the 4, 10, 25 mg/kg, and placebo groups, respectively. Even though more patients were negative at day 28 in the 4 and 10 mg/kg COR-101 groups compared to placebo, no statistical significance was reached (Table III).

Pharmacokinetics *and Population-PK/PD analysis*

Pharmacokinetic data for COR-101 after administration are summarized in Table IV and Fig. 2. Peak concentrations (C_{max}) were 86.38, 228.5, and 531.1μg/ml for the 4, 10, and 25mg/kg groups, respectively. Serum exposure (dose-normalized C_{max} and AUC_{inf}) was approximately dose-proportional. The half-life ($t_{1/2}$) ranged from 201 to 380 hours. Serum concentrations remained above the in vitro SARS-CoV-2 neutralization IC_{50} (0.52 for the delta strain 0.85 nM for the original Wuhan-Hu-1 strain) for at least 10 days (4mg/kg) and >25 days (10 and 25mg/kg). Furthermore, the pharmacokinetics of COR-101 were captured by a 3-compartment model incorporating a saturable clearance mechanism at concentrations exceeding 282 μg/mL. Interindividual variability in clearance (32.7% coefficient of variation (CV)) and volume of distribution (20.1% CV) was substantially reduced when adjusting for C-reacitve protein (CRP), albumin, age, and body height, indicating these covariates significantly influence COR-101 disposition. A schematic representation of the final model, diagnostic plots, and model parameter estimates are provided in the Supplement (Supplemental Figures 2 and 3; Supplemental Table VIII).

To characterize the antiviral effect of COR-101, the PK model was linked to a published viral kinetics model incorporating immune-mediated viral clearance.[19,20] Most parameters were retained from the original framework, except for a diminished T-cell response (69.3% of

Table I
Demographic and baseline characteristics by study treatment.

Baseline Variable	4 mg/kg (n = 5)	10 mg/kg (n = 10)	25 mg/kg (n = 10)	Placebo (n = 7)
Female, n (%)	0	2 (20)	6 (60)	2 (28.6)
White or caucasian, n (%)	5 (100)	10 (100)	10 (100)	7 (100)
Age (y), median (min, max)	57.0 (39, 74)	66.5 (34, 96)	65.0 (53, 85)	57.0 (30, 83)
Age >65 y, n (%)	1 (20.0)	6 (60.0)	5 (50.0)	1 (14.3)
BMI (kg/m^2), mean (SD)	25.8 (2.8)	26.2 (4.2)	25.9 (5.5)	32.2 (4.2)
Tobacco (current or former use), n (%)	2 (40.0)	4 (40.0)	2 (20.0)	2 (28.6)
COVID-19 severity, n (%)				
Moderate	1 (20.0)	0	6 (60.0)	2 (28.6)
Severe	4 (80.0)	10 (100)	4 (40.0)	5 (71.4)
ARDS	0	2 (20.0)	0	0
Supplementary O_2, n (%)	5 (100)	10 (100)	1 (10)	4 (57.1)
SARS-CoV-2 viral RNA (copies/mL; nasopharyngeal swap)				
Mean (SD)	27,861.9 (32224.9)	142,728.8 (335641.3)	670,360.5 (1144899.8)	368,736.7 (566981.0)
Missing, n (%)	1 (20.0)	2 (20.0)	4 (40.0)	0 (0.0)

BMI = body max index; COVID=19 = coronavirus disease 2019; n = number of patients per subanalysis; N = total number of patients in the specified analysis set; O2 = oxygen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table II
Overview of adverse events by study treatment.

Events	4.0 mg/kg (n = 5), n (%)	10.0 mg/kg (n = 10), n (%)	25.0 mg/kg (n = 10), n (%)	Placebo (n = 7), n (%)
Patients with at least one*				
AE	3 (60.0)	6 (60.0)	6 (60.0)	5 (71.4)
TEAE	3 (60.0)	6 (60.0)	5 (50.0)	5 (71.4)
TEAE with CTCAE severity grade 3 or 4†	2 (40.0)	3 (30.0)	1 (10.0)	0
Treatment-related TEAE‡	0	0	3 (30.0)	1 (14.3)
Treatment-related TEAE with CTCAE severity grade 3 or 4†,‡	0	0	0	0
SAE	1 (20.0)	3 (30.0)	0	0
Serious treatment-related AE‡	0	0	0	0
TEAE leading to study drug discontinuation	0	0	0	0
Treatment-related TEAE leading to study drug discontinuation‡	0	0	0	0
TEAE leading to study discontinuation	0	2 (20.0)	0	0
Treatment-related TEAE leading to study discontinuation‡	0	0	0	0
TEAE of special interest (sponsor)	0	0	0	0
TEAE of new onset of chronic disease	0	2 (20.0)	0	0
TEAE leading to death	0	2 (20.0)	0	0
TEAE requiring medical intervention§	3 (60.0)	6 (60.0)	2 (20.0)	3 (42.9)
AE during long-term follow-up period	2 (40.0)	2 (20.0)	2 (20.0)	0
AE during long-term follow-up period with CTCAE severity grade 3 or 4†	1 (20.0)	1 (10.0)	0	0

AE = adverse event; CTCAE = common terminology criteria for adverse events; n = number of patients in the specified analysis set; n = number of patients with at least 1 event in the category; % = percentage based on N; SAE = severe adverse event; TEAE = treatment-emergent adverse event.

* A patient may have findings in more than 1 category.

† Toxicity grades defined according to CTCAE version 5.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening, grade 5 = death.

‡ Treatment-related event defined as any AE for which the relationship to study drug was reported as possibly, probably, definitely related, or missing.

§ AE requiring medical intervention: Any AE for which action taken regarding AE was reported as concomitant medication, concomitant procedure, or other action.

the reference value) observed in this cohort, independent of COR-101 exposure.

COR-101 reduced viral infectivity, with a steep, sigmoidal exposure–response relationship modeled using a Hill function. The estimated EC50 was 169 μg/mL for alpha and delta variants, increasing to 856 μg/mL for omicron, suggesting reduced efficacy against this variant due to lower drug exposure levels following 25 mg/kg dosing (observed C_max: 343–763 μg/mL) (Fig. 2). The time between infection and study inclusion was included in the model as the sum of the known time between hospitalization and study inclusion and an estimated time between infection and hospitalization. Interindividual differences in this estimated time could be explained by differences in baseline viral loads and sex, where higher baseline viral loads and male sex were associated with shorter time intervals. Viral load model estimates and goodness-of-fit assessments are provided in the Supplement (Supplemental Table IX, Supplemental Figure 4).

Exploratory Efficacy Data

Disease progression, defined as death, respiratory failure, or study discontinuation due to disease worsening, occurred in 40.0%, 20.0%, 10.0%, and 0% of the 4, 10, 25 mg/kg, and placebo groups, with no significant differences (Table V). Two deaths (20.0%) occurred in the 10.0 mg/kg group until day 28, with unchanged mortality rates until day 80. Limited events precluded the evaluation of odds ratios.

Using the NIAID-8 ordinary scale, no significant differences in disease severity were observed between active groups and placebo. The 10 mg/kg group had the highest baseline total NEWS2 score (mean [SD]: 5.3 [1.49]), showing a gradual decline from baseline to day 28 (mean [SD]: −3.9 [2.27]) similar to the 4 mg/kg group (mean [SD] change: −3.4 [1.34]) and the 25 mg/kg group (mean [SD] change: −3.5 [0.58]), but smaller compared to placebo (mean [SD] change: −4.8 [0.50]) (Supplemental Table X).

Table III
Viral clearance: logistic regression model

Visit		4.0 mg/kg (n = 5)	10.0 mg/kg (n = 9)	25.0 mg/kg (n = 6)	Placebo (n = 7)
Day 6	Viral clearance, n (%)	0	2 (22.2)	1 (16.7)	2 (28.6)
	Odds ratio (95% CI)*	<0.001 (<0.001–>999)	0.600 (0.053–6.795)	1.500 (0.055–40.632)	
	P value[a]	0.9632	0.6800	0.8096	
	Treatment effect *P* value				0.9467
	Baseline COVID-19 severity effect *P* value				0.9518
Day 14	Viral clearance, n (%)	3 (60.0)	4 (44.4)	3 (50.0)	2 (28.6)
	Odds ratio (95% CI)*	4.566 (0.253–82.477)	1.914 (0.177–20.659)	1.668 (0.117–23.875)	
	P value[a]	0.3037	0.5929	0.7064	
	Treatment effect *P* value				0.7826
	Baseline COVID-19 severity effect *P* value				0.8543
Day 21	Viral clearance, n (%)	1 (20.0)	1 (11.1)	5 (83.3)	2 (28.6)
	Odds ratio (95% CI)*	<0.001 (<0.001–>999)	<0.001 (<0.001–>999)	<0.001 (<0.001–>999)	
	P value*	0.9733	0.9733	0.9362	
	Treatment effect *P* value				0.9999
	Baseline COVID-19 severity effect *P* value				0.9251
Day 28	Viral clearance, n (%)	4 (80.0)	5 (55.6)	1 (16.7)	3 (42.9)
	Odds ratio (95% CI)*	1.765 (0.060–51.666)	>999 (<0.001–>999)	0.581 (0.010–35.334)	
	P value[a]	0.7416	0.9478	0.7956	
	Treatment effect *P* value				0.9469
	Baseline COVID-19 severity effect *P* value				0.5584

N = number of patients in the specified analysis set; n = number of patients in the category; % = percentage based on N.
Viral clearance: SARS-CoV-2 nasopharyngeal/nasal swab result changing from positive to negative.
* Odds ratio, CI, as well as *P* values obtained from a logistic regression model with treatment arm and baseline COVID-19 severity (moderate, severe) as covariates.

Table IV
Summary Statistics for COR-101 pharmacokinetic parameters by COR-101 dose.

Parameter	4.0 mg/kg	10.0 mg/kg	25.0 mg/kg
C_{max} (μg/mL), geometric mean (mean, geometric CV%)	86.38 (89.7, 32.4) (n = 5)	228.5 (233.7, 23) (n = 10)	531.1 (549.1, 28.2) (n = 10)
T_{max} (h), median (min, max)	1 (1, 24) (n = 5)	1.083 (1, 4.17) (n = 10)	1 (1, 5.98) (n = 10)
AUC_{inf} (h × μg/mL), geometric mean (mean, geometric CV%)	13,140 (13,880, 41.7) (n = 4)	30,590 (32,190, 37.2) (n = 9)	12,0600 (130,800, 49.3) (n = 6)
CL(L/h), geometric mean (mean, geometric CV%)	0.025 (0.026, 33.3) (n = 4)	0.025 (0.025, 25.4) (n = 9)	0.014 (0.015, 33.3) (n = 6)
V_z(L), geometric mean (mean, geometric CV%)	6.119 (6.221, 21.7) (n = 4)	5.478 (5.73, 32.4) (n = 9)	6.56 (6.71, 23.5) (n = 6)
$T_{1/2}$ (h) median (min, max)	235.2 (115, 274) (n = 5)	201.7 (83.3, 325) (n = 10)	380.5 (59.4, 7350) (n = 10)

C_{max} = maximum observed concentration; CL = volume of plasma cleared of drug per unit time; N = in the specified analysis set; T_{max} = time to achieve maximum plasma concentration; T1/2 = time required to reduce the plasma concentration to $\frac{1}{2}$ of its initial value; Vz = volume of distribution.

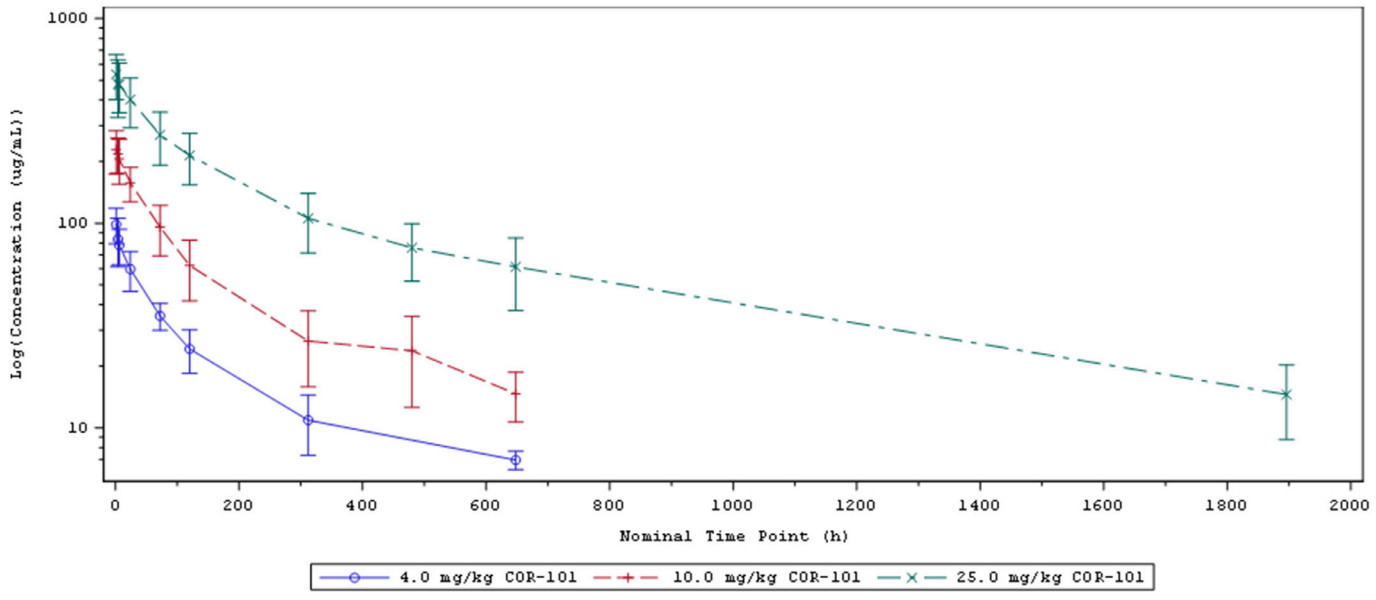

Figure 2. COR-101 concentration time profiles following single ascending doses in patients with coronavirus disease 2019. Concentrations of COR-101 over time are shown as mean and SD of values analyzed in patients receiving 4.0 mg/kg (blue line), 10.0 mg/kg (red line), and 25.0 mg/kg (green line) of COR-101.

Table V
Disease progression at day 6: logistic regression model

Visit		4.0 mg/kg (n = 5)	10.0 mg/kg (n = 10)	25.0 mg/kg (n = 10)	Placebo (n = 7)
Day 6*	Disease progression, n (%)	2 (40.0)	2 (20.0)	1 (10.0)	0
	Odds Ratio (95% CI)†,‡	>999 (<0.001; >999)	>999 (<0.001; >999)	>999 (<0.001; >999)	
	p-value†	0.9554	0.9604	0.9593	
	Treatment effect *P* value				0.7481
	Baseline COVID-19 Severity effect *P* value				0.9517
	Estimated disease progression rate§	–5.80	–7.19	–6.90	–18.22
	Difference in estimated disease progression rate (95% CI)§	12.41 (–422.363; 447.189)	11.03 (–423.747; 445.801)	11.31 (–423.463; 446.092)	

Disease progression: patients who were not alive, had respiratory failure, or discontinued study due to progression of disease.
mITT = modified intent-to-treat analysis set; N = number of patients in the specified analysis set; n = number of patients in the category; % = percentage based on N.

* Day 6: no disease progression was observed after day 6, and therefore results for days 14, 21, and 28 are not displayed.+Odds ratio, CI, as well as *P* values obtained from a logistic regression model with treatment arm and baseline COVID-19 severity (moderate, severe) as covariates.

‡ Odds ratio value of <1: lower odds of disease progression in the active group compared to placebo; odds ratio value >1: higher odds of disease progression in the active group compared to placebo.

§ Estimated disease progression rate, differences, and 95% CI derived based on the logistic regression model noted in a. estimated difference derived as estimated active treatment arm disease progression rate—estimated placebo disease progression rate.

The rate of symptom resolution at days 6, 14, 21, and 28, were numerically higher in the 25 mg/kg group (20%, 90%, 100%, and 90%, respectively) compared to the 4 mg/kg (0%, 20%, 20%, and 20%), 10 mg/kg (0%, 0%, 0%, and 20%), and placebo groups (0%, 42.9%, 57.1%, and 57.1%); however, the difference was not significant (Supplemental Table XI).

Discussion

During the SARS-CoV-2 pandemic, convalescent plasma and neutralizing antibodies were administered to non-severe COVID-19 patients, or as a preventive measure in immunocompromised subjects unable to mount a response to vaccines.[21,22] On the contrary, no major benefits were achieved in severely ill patients, partially due to the limited neutralization activity of mAbs in the presence of high viral loads.[23] We aimed to assess the tolerability and preliminary, exploratory efficacy of a novel mAb COR-101 for severe COVID-19. High doses of COR-101 were assumed to be able to overcome high viral load while remaining well tolerated, due to the particular Fc-silenced design, which was introduced to prevent the ADE effect described during previous coronavirus outbreaks.[24–26]

Although the availability of vaccines (exclusion criteria) and already approved mAbs slowed down recruitment, 33 participants were enrolled from April 2021 to November 2022 and randomized to receive either COR-101 as a single dose of up to 25 mg/kg or placebo, which allowed for an extensive safety assessment. COR-101 was well tolerated and no related SAEs, or AEs of grade ≥3 were reported, with similar frequency and severity of TEAEs between treatment and placebo, supporting its safety. Overall, 13 TEAEs were reported, with 2 fatal SAEs due to COVID-19.

The extraordinary medical need during the SARS-CoV-2 outbreak prompted an expedited development of novel therapeutic products. Therefore, the trial entailed an efficacy-focused part 2, which was not conducted due to the emergence of the resistant omicron virus strain. The small patient number in part 1 lacked statistical power for a conclusive assessment of efficacy, and viral sampling was not always feasible due to patient transfers to intensive care units or discharges during lockdowns. Additionally, administering COR-101 or placebo as an add-on treatment ensured access to the best available therapies for all participants, leading to more uniform outcomes. Notably, a nonsignificant trend toward more frequent use of antiviral therapies in the placebo group was observed. This, together with broadly comparable outcomes, is compatible with a potential effect of the study drug. However, despite older age and more severe baseline conditions in the COR-101 group, which would also point to preliminary efficacy in the higher-risk setting, no significant conclusions regarding its efficacy could be drawn when compared to the placebo group. Furthermore, the heterogeneous time from symptom onset to study enrollment, largely driven by patient- and physician-level decisions, limits the generalizability of these exploratory efficacy findings, as delayed inclusion may be associated with more advanced or aggressive disease at the time of therapy and could attenuate observable treatment effects. Evolution of the coronavirus resulted in the emergence of the omicron strain, which proved resistant to the neutralizing activity of COR-101.[27] This mirrors data for several mAbs granted EUA, which became ineffective as new variants emerged.[2,13] For example, bamlanivimab[10] and etesevimab lost efficacy with the onset of the delta and omicron variants.[13] Similarly, the emergence of omicron led to the discontinuation of casirivimab and imdevimab, effective against delta, and the revocation of sotrovimab's EUA in April 2022[28] due to resistance. The prophylactic use of tixagevimab/cilgavimab was also limited because of reduced effectiveness against omicron subvariants.[29]

Patients treated with 10 mg/kg of COR-101 during predominance of alpha and delta variants achieved plasma concentrations exceeding the estimated EC_{50}, suggesting potential for improved outcomes. However, while there were higher failure rates at day 28 in the initial treatment groups, these results lacked statistical significance, most likely due to high variability in viral loads and the low number of treated individuals. COR-101 exhibited reduced in vitro neutralization for the omicron variant with an EC_{50} of 856 μg/mL, a concentration not attainable even at the highest dosage. This limitation further challenged the efficacy evaluation of COR-101 against omicron and ultimately hindered its further clinical development in part 2 and subsequent trials.

Notably, COR-101 was designed to neutralize the original SARS-CoV-2 strain while minimizing the risk of ADE described during previous coronavirus outbreaks, as it was observed that SARS and MERS virus entry into host cells was facilitated via Fc or complement receptors.[30] Thus, COR-101 represented an alternative and potentially safer mAb, although early concerns about mAbs exacerbating COVID-19 were ultimately not confirmed by subsequent studies.[31] However, ADE remains a risk during viral infections, and it is hard to distinguish from a natural disease worsening after targeted therapy.[32] This highlights the potential value of Fc-silenced neutralizing antibodies in the context of future epidemics, making the good tolerability of COR-101 particularly insightful for the development of similar products.

Overall, the present study represents a proof of concept for the safety and pharmacologic viability of Fc-silenced antibodies, even as a treatment option for severe infections. Furthermore, this trial underlines how

the dynamic of a highly virulent virus requires promptly available and flexible therapeutic tools, able to address evolving medical needs, while avoiding unpredictable ADE-mediated risks.

Declaration of competing interest

A.F., M.H. and S.D. are inventors on a patent application on COR-101. A.F. and A.H. are officers at CORAT Therapeutics GmbH, a company founded by YUMAB GmbH for the clinical and regulatory development of COR-101. S.D. and M.H. are advisors to CORAT Therapeutics GmbH. A.F., S.D., and M.H. are shareholders of YUMAB GmbH. The other authors declare no competing interests.

Acknowledgments

We are grateful to the technical and clinical staff of the participating trial. We would like to thank our colleagues who forwarded patients to trial sites, as well as the patients and their families.

Funding

This project received funding from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF). Further C.H., J.S.W., M.S., H.S. and J.S.H. were funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy—EXC 2180—390900677. MS and SJ were in part supported by the Robert Bosch Stiftung, Stuttgart, Germany. The sponsor of the clinical trial was CORAT Therapeutics GmbH.

Author Contributions

A.H, M.D., H.F., G.J, H.R.S., and J.S.H. were involved in the design of the study and strategy. M.M., C.H., S.J., M.B, C.K., S.G, T. K., A.G., M.C., M.S., H.W., J.S., T. B., J.S.W., H.R.S., and J.S.H. collected data as study investigators. A.F., M.H., and. S.D. provided data on the in vitro neutralization activity of COR-101. C.D. and T.L. conducted statistical modelling of PK and PD data. M.M., J.S.H., M.D., H.F., C.D., and H.R.S drafted the manuscript. All authors supported the creation of the manuscript by reviewing and editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2026.01.004.

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