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ORIGINAL ARTICLE

Phase 1 study of safety, pharmacokinetics, and antiviral activity of SARS-CoV-2 neutralizing monoclonal antibody ABBV-47D11 in patients with COVID-19

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Abstract

ABBV-47D11 is a neutralizing monoclonal antibody that targets a mutationally conserved hydrophobic pocket distal to the ACE2 binding site of SARS-CoV-2. This first-in-human safety, pharmacokinetics, and antiviral pharmacodynamic assessment in patients with COVID-19 provide an initial evaluation of this antibody that may allow further development. This multicenter, randomized, double-blind, and placebo-controlled single ascending dose study of ABBV-47D11 (180, 600, or 2400 mg) as an intravenous infusion, was in hospitalized and non-hospitalized (confined) adults with mild to moderate COVID-19. Primary outcomes were grade 3 or higher study drug-related adverse events and infusion-related reactions. Secondary outcomes were pharmacokinetic parameters and concentration-time profiles to Day 29, immunogenicity (anti-drug antibodies), and antiviral activity (change in RT-PCR viral load) from baseline to Days 15 and 29. ABBV-47D11 single doses up to 2400 mg were safe and tolerated and no safety signals were identified. The pharmacokinetics of ABBV-47D11 were linear and showed dose-proportional increases in serum concentrations with ascending doses. The exploratory anti-SARS-CoV-2 activity revealed a reduction of viral load at and above the 600 mg dose of ABBV-47D11 regardless of patient demographics and baseline characteristics, however; because of the high inter-individual variability and small sample size a statistical significance was not reached. There is

Abbreviations: ACE2, angiotensin-converting enzyme 2; ADA, anti-drug antibody; AE, adverse event; AUC, area under the serum concentration time curve; Cis, confidence intervals; C_{max}, maximum serum concentration; COVID-19, coronavirus-19; ECG, electrocardiogram; ECL, electrochemiluminescence; FIH, first-in-human; IC50, 50% inhibitory concentration; IgG1, immunoglobulin G1; IL, interleukin; IV, intravenous; LLOQ, lower limit of quantitation; mAb, monoclonal antibody; MT, mid-turbinate; NIH DAIDS, National Institutes of Health Division of Acquired Immunodeficiency Syndrome; PaO_2/FiO_2, ratio of arterial pressure of oxygen to fraction of inspired oxygen; PK/PD, pharmacokinetics/pharmacodynamics; RT-PCR, reverse transcriptase-polymerase chain reaction; S, spike protein; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO2, oxygen saturation; $t_{1/2}$, terminal phase elimination half-life; TEAEs, treatment-emergent adverse events.

Stanley Wang and Negar N. Alami: AbbVie employee at the time the research was conducted.

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potential for anti-SARS-CoV-2 activity with ABBV-47D11 doses of 600 mg or higher, which could be evaluated in future clinical trials designed and powered to assess viral load reductions and clinical benefit.

KEYWORDS
ABBV-47D11, COVID-19, first-in-human study, monoclonal antibodies, SARS-CoV-2

1 | INTRODUCTION

So far over 5 million deaths from COVID-19 and approximately 269 million cases have been reported globally since the beginning of the pandemic in early 2020.[1] Neutralizing antibodies have demonstrated benefit in the treatment of viral infection, with monoclonal antibodies (mAb) of great interest in treating and preventing COVID-19 due to SARS-CoV-2.[2–9] Antibody combinations of casirivimab plus imdevimab (REGEN-COV), bamlanivimab plus etesevimab, bebtelovimab, and sotrovimab have been given emergency use authorization by the US Food and Drug Administration for treating mild to moderate COVID-19 in adults and children not admitted to the hospital.[7,10–14] Bebtelovimab is currently the only mAb that is recommended for treatment of the Omicron variant of concern based on retaining in vitro activity against the Omicron subvariants.[14,15] Thus, because of reduced in vitro activity by the other mAbs against Omicron subvariants there are fewer treatments that can be used for treating the most dominant variants of concern. Recently, progress has been made in the development and authorization of COVID-19 oral anti-virals.[16,17] Although significant progress has been made in the treatment of COVID-19, the emergence of viral variants of concern has made clear the need for additional therapeutic agents, and to treat a wider range of disease severity.

ABBV-47D11 is a fully human immunoglobulin G1 (IgG1) mAb with an unmodified Fc domain which targets a site on the spike (S) protein on the surface of SARS-CoV-2. The SARS-CoV-2 S protein consists of two primary domains, S1 (consisting of N-terminal domain $S1_A$ and receptor binding domain $S1_B$) is involved in binding to the angiotensin-converting enzyme 2 (ACE2) receptor while S2 is involved in membrane fusion with the target cell. ABBV-47D11 targets a conserved epitope in the SARS-CoV-2 S1B domain distal to the ACE2 binding site and results in the neutralization of SARS-CoV-2 in vitro and in vivo.[18–20] ABBV-47D11 has been shown to potently inhibit SARS-CoV-2 infection of VeroE6 cells with 50% inhibitory concentration (IC_{50}) = 0.57 μg/ml.[19]

The primary objective of this study was to evaluate the safety and tolerability of single ascending doses of ABBV-47D11 in patients with COVID-19 and secondary objectives included evaluation of the pharmacokinetics, immunogenicity, and antiviral effect.

2 | MATERIALS AND METHODS

The study was conducted in accordance with the ethical principles from the Declaration of Helsinki and was overseen by the Institutional Review Board. Patients were enrolled at 10 sites (8 sites in the United States [US] and 2 in Israel).

2.1 | Study design

This was a Phase 1, multicenter, randomized, double-blind, and placebo-controlled single ascending dose study of ABBV-47D11 in adults with mild to moderate COVID-19. The patient population included both hospitalized and non-hospitalized adults who were willing to be confined in an inpatient setting. Non-hospitalized participants were confined for the first 48 h post-dose for safety monitoring and were discharged from confinement (if medically appropriate) after completing study procedures on Day 3 or for any additional period up to Day 8.

In 24 patients, three dose levels (180, 600, 2400 mg) for intravenous (IV) administration were evaluated: 6 participants were randomized to receive ABBV-47D11 and 2 participants were randomized to receive a placebo at each dose level. Patients received a single dose of the study drug on Day 1 and were evaluated for primary and secondary outcome measures through Day 29 and then followed to Day 106. Dose selection is described in the electronic Appendix S1 section.

2.2 | Patients

Patients were required to meet the following criteria to be included in the study (full list in electronic Appendix S1).

2.2.1 | Inclusion criteria

Provide informed consent; be at least 18 years of age (inclusive) for hospitalized participants, and non-hospitalized confined participants of at least 18 to <65 years of age, or to <55 of age if there was a history of cardiovascular disease, hypertension, chronic obstructive pulmonary disease/other chronic respiratory disease; must weigh at least 45 kg (hospitalized) and have a body mass index between ≥18 to <35 kg/m^2 for non-hospitalized confined participants; have a confirmed SARS-CoV-2 infection based on initial nucleic acid or antigen testing from respiratory swab, saliva, or other bodily fluid within 7 days prior to randomization; must have ≥1 symptom associated with COVID-19 with an onset of ≤8 days

prior to randomization; must be hospitalized or planned for hospital admission due to COVID-19 at the time of randomization or not currently hospitalized but willing to be confined for at least 48 h post-dose for participation; and willing to use contraception (females negative serum pregnancy test at screening and urine test on Day 1 prior to randomization).

2.2.2 | Exclusion criteria

Subject with oxygen saturation (SpO_2) <88% on room air at rest for 5 min or ratio of arterial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ≤ 200 mmHg at randomization; requiring high-flow nasal cannula oxygen therapy/non-invasive or invasive mechanical ventilation/extracorporeal membrane oxygenation; history of clinically significant medical conditions that would interfere with participation in the study; non-hospitalized confined subjects with a history of chronic kidney disease, diabetes mellitus, immunosuppressive disease, currently receiving immunosuppressive treatment; non-hospitalized confined subjects with a history of cardiovascular disease, hypertension, or chronic obstructive pulmonary disease/other chronic respiratory diseases if ≥55 years of age.

2.3 | Randomization and intervention

All patients were assigned a unique identification number at the screening visit and enrollment a randomization number that encoded the treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. The site pharmacist received a copy of the site participant randomization notification and maintained the randomization codes and individual drug accountability logs in a restricted and secure location separate from the overall site drug accountability logs. The unblinded pharmacist prepared the individual participant doses for the study staff to administer. All study-site personnel was blinded to the treatment throughout the study, except for the study drug preparation designee and pharmacist; all study-site personnel and patients were blinded to SARS-CoV-2 RNA results through Day 22.

2.4 | Primary and secondary outcomes

The primary endpoints were safety and tolerability measured as study drug-related Grade ≥ 3 adverse events (AEs) and Grade ≥ 3 infusion-related reactions according to the National Institutes of Health Division of Acquired Immunodeficiency Syndrome (NIH DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1).[21] Secondary endpoints were pharmacokinetics, immunogenicity (anti-drug antibody [ADA] formation), and antiviral activity (effects on SARS-CoV-2 viral load). The values for the pharmacokinetic parameters of ABBV-47D11 including the maximum observed serum concentration (C_{max}), the time to C_{max}, and the area under the serum concentration-time curve (AUC) from Day 1 (0 h) to Day 29 (672 h) (AUC_{0-672h}) were determined using non-compartmental methods. Additional pharmacokinetic parameters including terminal phase elimination half-life ($t_{1/2}$) and AUC from time 0 to infinite time (AUC_{inf}) were estimated based on sample availability. The immunogenicity of ABBV-47D11 was assessed by a tiered approach for detecting ADAs. Secondary pharmacodynamic endpoints included evaluation of the following in mid-turbinate (MT) swab, nasopharyngeal swab, or saliva samples: AUC for change from baseline (Day 1) in SARS-CoV-2 viral RNA by reverse transcription polymerase chain reaction (RT-PCR) from Day 1 to Day 15 and from Day 1 to Day 29; time to negative SARS-CoV-2 by RT-PCR through Days 15 and 29; and negative SARS-CoV-2 by RT-PCR at Days 2, 3, 4, 5, 8, and 15.

2.5 | Sample analysis

ABBV-47D11 concentrations were measured using a fully validated analytical method (bridging electrochemiluminescence [ECL] immunoassay). The lower limit of quantification (LLOQ) was 1000 ng/ml. All ADA samples were analyzed using a validated titer-based ECL immunoassay.

2.6 | Viral load

Viral load evaluation was conducted by the central lab. Briefly, the SARS-CoV2 RNA RT- PCR quantitative test was based on CDC's 2019-nCoV EUA assay, which included three sets of primers and probes, one being used for the quantification of SARS-CoV-2 (N1), one for qualitative detection (N2), and one used as control (RP). RNA isolated and purified either from plasma or upper and lower respiratory specimens were reverse transcribed to cDNA and subsequently amplified in the Applied Biosystems QuantStudio 12 K Flex Real-Time PCR system. The absolute quantification was based on the SARS-CoV2 N1 amplicon and performed using the standard curve method. The standard curve was constructed using a dilution series of known titer SARS-CoV2 synthetic RNA and tested in triplicate with each assay. The viral titer in each patient sample was determined by plotting PCR quantification cycle values of each triplicate patient sample against the log10 titer of the synthetic RNA. For MT and nasopharyngeal swabs, the linear range of detection was 2228–2230, 902 954 copies/ml and for saliva, the linear range of detection was 1390–100 693 167 copies/ml. Results below LLOQ were reported as <LLOQ, and if the Ct threshold exceeded 40 cycles value was reported as "not detected".

2.7 | In vitro SARS-CoV-2 neutralization activity against circulating variants

The SARS-CoV-2 S gene nucleotide sequence from isolate Wuhan-Hu-1 (GenBank accession number MN908947), with the D614G

amino acid substitution, was codon-optimized and synthesized and cloned in pUCIDT-Kan vector (Integrated DNA Technologies). The N-terminal 13 signal peptide residues were replaced with the CD5 signal peptide sequence. Nineteen C-terminal amino acids were removed to enhance the incorporation of the spike protein into lentivirus-derived pseudovirus particles. Amino acid substitutions were introduced using site-directed mutagenesis kits (Agilent or New England Biolabs) using standard protocols. Amino acid substitutions included in variants were as follows: SARS2 ZA-B.1.351.2: L18F, D80A, D215G, 242–244 del, K417N, E484K, N501Y, D614G, and A701V; SARS2 Brazil P.1: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F; SARS2 Brazil P.2: E484K, D614G, and V1176F; SARS2 US-CA-B.1.427: W152C, L452R, and D614G; SARS2 US-NY-B.1.525: Q52R, A67V, H69del, V70del, Y144del, E484K, D614G, Q677H, and F888L; SARS2 US-NY-B.1.526: T95I, D253G, E484K, D614G, and A701V; SARS2 India-B.1.617.1: G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H; SARS2 India-B.1.617.2: T19R, del156, del157, R158G, L452R, T478K, D614G, P681R, D950N.

SARS2-S pseudovirus was generated by co-transfection of 293 T cells with a SARS2 spike expression construct and the pNL4-3. Luc.R-E- lentiviral backbone plasmid containing the firefly luciferase reporter gene. Neutralization activity was assessed by calculating the percent inhibition of the luciferase signal in the presence of an antibody (spanning concentration 30.0–0.00011 μg/ml) relative to pseudovirus alone. Data were analyzed using the nonlinear regression curve fitting to the 4-parameter logistic equation in GraphPad Prism 9 software. (GraphPad).

2.8 | Sample size

A typical sample size of 6–8 participants per dose level and the pooled placebo for first-in-human (FIH) Phase 1 studies were used to evaluate initial safety and pharmacokinetics. No formal power calculations for sample size considerations have been performed for this study where analyses were descriptive and exploratory.

2.9 | Statistical analyses

The Safety Analysis Set that included all participants who received any amount of study drug was used in safety analyses, which included AEs, laboratory, vital signs, and electrocardiogram data. Safety data were summarized by ABBV-47D11 dose, hospitalization status, and overall. Patients were classified by the dose level actually received. AEs were coded using the Medical Dictionary for Regulatory Activities. Specific AEs were counted once for each participant for calculating percentages unless stated otherwise. In addition, if the same AE occurred multiple times for a participant, the highest severity and level of relationship to the investigational product was reported. Laboratory values were assigned a grade according to the National Institutes of Health Division of Acquired Immunodeficiency Syndrome (NIH DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1).[21]

Categorical variables were summarized with the number and percentage of participants; percentages were calculated based on the number of non-missing observations. Continuous variables were summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

Time to negative SARS-CoV-2 was estimated by the treatment group using the Kaplan–Meier method with median event onset time calculated along with the 95% confidence intervals (CIs), and the survival curves between each ABBV-47D11 dose level group, as well as the combined ABBV-47D11 group, to the placebo group, were compared using the log-rank tests. The number and percentage of participants with negative SARS-CoV-2 by RT-PCR at Days 2, 3, 4, 5, 8, and 15 were summarized by treatment group and for the combined ABBV-47D11 group, along with the 95% CI using the Wilson score method.

3 | RESULTS

3.1 | Patients

The first patient visit was on December 10, 2020, and the last patient visit was on August 24, 2021. There were 25 patients randomized (one patient was randomized to placebo but withdrew consent before dosing) and a total of 24 patients received a single dose of ABBV-47D11 or matching placebo in an ascending fashion, where a total of 6 patients were treated with placebo and 18 patients were treated with ABBV-47D11 (5:7:6 patients for 180/600/2400 mg; Figure S1). One patient in the placebo group and one patient in the ABBV-47D11 group prematurely discontinued the study prior to Day 29, and all other patients in the study completed the scheduled Day 29 visit. The 600 mg and 2400 mg dose groups had more non-hospitalized (confined) patients who had milder clinical status compared to hospitalized patients only in the 180 mg dose group. One patient was randomized to the ABBV-47D11 180 mg group but received the 600 mg dose instead. Key demographics and baseline characteristics are summarized in Table 1, where the demographic and disease characteristics were generally balanced among groups. As observed in other studies comparing patients with mild versus severe disease,[22,23] hospitalized patients had lower total lymphocyte, CD4+ T cell, CD8+ T cell counts, and higher neutrophil counts, C-reactive protein, D-dimer, ferritin, interferon-gamma, interleukin (IL)-6, IL-8, and IL-10 levels as compared to non-hospitalized patients (Table S1).

3.2 | Safety and tolerability

The incidences of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of Grade ≥ 3 in the active dose groups were similar

TABLE 1 Demographic and baseline characteristics based on treatment received

Baseline variable	Placebo (*N* = 6)	180 mg IV (*N* = 5)	600 mg IV (*N* = 7)	2400 mg IV (*N* = 6)	Hospitalized (*N* = 10)	Non-Hospitalized (*N* = 14)	Overall (*N* = 24)
Female, *n* (%)	4 (66.7)	4 (80.0)	1 (14.3)	4 (66.7)	6 (60.0)	7 (50.0)	13 (54.2)
Race, *n* (%)							
White	4 (66.7)	3 (60.0)	5 (71.4)	6 (100.0)	6 (60.0)	12 (85.7)	18 (75.0)
Black/African American	2 (33.3)	2 (20.0)	1 (14.3)	0	3 (30.0)	2 (14.3)	5 (20.8)
Asian	0	0	1 (14.3)	0	1 (10.0)	0	1 (4.2)
Ethnicity, Hispanic or Latino, *n* (%)	3 (50.0)	0	3 (42.9)	6 (100)	0	12 (85.7)	12 (50.0)
Age (years), median (min, max)	51.5 (32, 69)	47.5 (30, 62)	46.5 (27, 70)	47.5 (31, 55)	47.5 (30, 70)	50.0 (27, 57)	50.0 (27, 70)
≥55 years, *n* (%)	2 (33.4)	1 (20.0)	3 (42.9)	1 (16.7)	4 (40.0)	3 (21.4)	7 (29.1)
BMI (kg/m^2), mean (SD)	35.8 (7.93)	41.3 (11.06)	28.9 (3.81)	34.3 (3.60)	38.7 (9.26)	31.6 (5.25)	34.6 (7.85)
BMI ≥35, *n* (%)	3 (50.0)	3 (60.0)	0	3 (50.0)	5 (50.0)	4 (28.6)	9 (37.5)
Clinical status ordinal scale, *n* (%)							
1-not hospitalized	3 (50.0)	0	5 (71.4)	6 (100.0)	0	14 (100.0)	14 (58.3)
3- hospitalized, not requiring suppl. O_2	0	2 (40.0)	1 (14.3)	0	3 (30.0)	0	3 (12.5)
4- hospitalized, requiring suppl. O_2	3 (50.0)	3 (60.0)	1 (14.3)	0	7 (70.0)	0	7 (29.2)
Tobacco use, current or former, *n* (%)	3 (50.0)	0	5 (71.4)	3 (50.0)	3 (30.0)	8 (57.2)	11 (45.8)
Supplemental oxygen use[a], *n* (%)	3 (50.0)	3 (60.0)	1 (14.3)	0	7 (70)	0	7 (29.2)
Oxygen flow rate (L/min), mean (min, max)	2.7 (1, 4)	2.7 (2, 3)	2.0 (2, 2)	—	2.6 (1, 4)	—	2.6 (1, 4)
SARS-CoV-2 viral RNA (log10 copies/ml), mean (min, max)							
Mid-turbinate	3.3 (0, 7)	4.7 (3, 8)	5.5 (3, 8)	3.0 (0, 5)	4.9 (3, 8)	3.7 (0, 8)	4.1 (0, 8)
Nasopharyngeal	3.9 (0, 6)	4.6 (0, 8)	6.0 (5, 8)	1.4 (0, 4)	5.0 (0, 8)	3.7 (0, 8)	4.2 (0, 8)
Saliva	5.8 (4, 8)	7.7 (7, 9)	5.3 (4, 7)	3.4 (0, 6)	6.8 (4, 9)	4.4 (0, 7)	5.4 (0, 9)
COVID-19 symptom onset duration prior to baseline (days), mean (SD)	4.5 (1.76)	5.2 (1.92)	3.3 (1.11)	5.7 (1.21)	5.2 (1.48)	4.1 (1.75)	4.6 (1.69)
≤4.5 days, *n* (%)[b]	3 (50.0)	2 (40.0)	6 (85.7)	1 (16.7)	4 (40.0)	8 (57.1)	12 (50.0)

[a]Interface of nasal prongs for all patients on supplemental oxygen at baseline.

[b]Half of the subjects had COVID-19 symptom onset duration ≤4.5 days prior to baseline.

to the placebo group. No SAEs or AEs of Grade ≥ 3 were considered related to the study drug (Table 2). The incidence rates of Grade 3 and 4 (NIH DAIDS) laboratory values were low, and similar between placebo and ABBV-47D11 groups. No clinically significant abnormal ECG assessments were observed. None of the mean changes in vital signs were clinically significant. The incidence of TEAEs in hospitalized patients was numerically higher than in non-hospitalized patients. Two hospitalized patients, one in the 600 mg group and one in the placebo group, died; neither was considered related to the study drug. There were no AEs leading to discontinuation of treatment, no Grade ≥ 3 infusion-related reactions, and no AEs of special interest (Grade ≥ 2 infusion-related reactions assessed as being related to ABBV-47D11 by the investigator). The TEAEs by the patient are listed in Table S2.

3.3 | Pharmacokinetics

The pharmacokinetics data following IV administration of 180, 600, and 2400 mg of ABBV-47D11 are summarized in Table 3 and Figure 1. The mean *C*max for 180, 600, and 2400 mg cohorts following the first single dose was 24.1, 105, and 591 μg/ml, respectively. The ABBV-47D11 serum exposures following dosing represented as dose-normalized C_{max} and AUC_{0-672} are approximately dosed proportional. The $t_{1/2}$ for ABBV-47D11 ranged from 20 to 21 days, which is consistent with the previously published half-life range for other IgG1 mAbs.[24] Overall, inter-patient variability in pharmacokinetic parameters was low (% coefficient of variance between 30% and 46%). Serum exposures were comparable to the model-predicted exposures and provided serum concentrations above the in vitro SARS-CoV-2 neutralization IC90 for at least 22 days for the lowest dose and more than 29 days from the 600 mg and 2400 mg (Figure 1). With the assumption of 15% biodistribution of ABBV-47D11 into the lung tissue, the evaluated doses in this study are projected to achieve dose-dependent efficacious exposures at the site of action.

Three of 24 patients were ADA positive (1/6 patient in the placebo group on Day 1 [pre-dose], 1/5 patient in the 180 mg group on Day 15, and 1/5 patient in the 180 mg group at Day 85), however, ADA titers for all three patients were low (<18.7 titer units, the limit of detection <10 titer units), with no apparent impact on the pharmacokinetics of ABBV-47D11.

3.4 | Antiviral activity

Viral load data at baseline were available for 21 patients with MT samples, 14 patients with nasopharyngeal samples, and 17 patients with saliva samples. Among those patients, some baseline viral loads were at or below the LLOQ. Data analysis focused on MT swab results. Only one patient in the 2400 mg dose group had detectable viral load limiting analysis in this dose group. MT swabs SARS-CoV-2 viral load kinetics in the placebo group were characteristic of those described in literature[25] and appeared to change from baseline by a mean −2.5 $\log_{10}$ copies/ml by Day 8. ABBV-47D11 180, 600, and 2400 mg single IV infusions caused a −2.6, −4.1, −2.9 $\log_{10}$ copies/ml change from baseline at Day 8, respectively (Figure 2), with a similar trend of positive treatment effect in a subgroup of patients with onset of symptoms ≤4.5 days. Change from baseline for SARS-CoV-2 viral RNA as measured by AUC through Day 15 was highest in the 600 mg group (mean −50.5 $\log_{10}$ copies/ml*day) relative to placebo (mean −24.7 $\log_{10}$ copies/ml*day) (Figure S2), however, this effect was indeterminate due to high between-patient variability and small sample size per group. Time to negative SARS-CoV-2 analysis revealed a trend of faster time (i.e., a smaller area under the Kaplan–Meier curve) to negative MT SARS-CoV-2 through Day 29 in the ABBV-47D11 2400 mg group (4.5 ±0.43 days) compared to placebo (7.2 ±2.52 days), however, this difference was not statistically significant (*p*-value = .290) nor conclusive given the high between-patient variability in viral load measurements. Baseline patient characteristics and demographics or stratification by serological status did not appear to have an impact on the anti-viral response of ABBV-47D11 across treatment arms (Figure S3). Exploratory exposure-response and pharmacokinetic/pharmacodynamic (PK/PD) analyses were conducted to evaluate the relationship between exposure

TABLE 2 Overview of treatment-emergent adverse events (TEAEs)

TEAE overview	Placebo (*N* = 6)	180 mg IV (*N* = 5)	600 mg IV (*N* = 7)	2400 mg IV (*N* = 6)	Hospitalized (*N* = 10)	Non-hospitalized (*N* = 14)	Overall (*N* = 24)
AE, *n* (%)	4 (66.7)	5 (100.0)	3 (42.9)	3 (50.0)	10 (100.0)	5 (35.7)	15 (62.5)
Related to study drug[a]	2 (33.3)	0	0	1 (16.7)	2 (20.0)	1 (7.1)	3 (12.5)
Serious AE[b]	1 (16.7)	2 (40.0)	1 (14.3)	0	4 (40.0)	0	4 (16.7)
Related to study drug	0	0	0	0	0	0	0
AE of grade 3 or higher	1 (16.7)	2 (40.0)	1 (14.3)	0	4 (40.0)	0	4 (16.7)
Related to study drug	0	0	0	0	0	0	0
Deaths	1 (16.7)	0	1 (14.3)	0	2 (20.0)	0	2 (8.3)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

[a]Two patients (both placebo) had pyrexia (Grade 1) on day 2 and pyrexia (Grade 2) on day 1, respectively. Another subject in the 2400 mg group experienced pain in the extremity (Grade 1) on day 5.

[b]SAEs reported include cardiac arrest, COVID-19 pneumonia, septic shock, acute respiratory failure, pulmonary embolism, and deep vein thrombosis.

TABLE 3 Summary statistics for ABBV-47D11 pharmacokinetic parameters by dose group

Pharmacokinetic parameter (unit)	180 mg IV ($N = 5$)	600 mg IV ($N = 5$)[c]	2400 mg IV ($N = 6$)
C_{max} (μg/ml)	24.1 (28.0, 44)	105 (111, 38)	591 (658, 39)
T_{max} (h)[a]	2.5 [0.8–2.6]	2.5 [0.3–2.5]	1.6 [0.8–2.5]
AUC_{0-672h} (day × μg/ml)	227 (266, 45)	1172 (1218, 32)	5413 (5905, 37)
AUC_{inf} (day × μg/ml)	349 (418, 46)	1862 (1924, 30)[c]	8624 (9384, 39)
CL (L/d)	0.5 (0.7, 111)	0.3 (0.3, 26)	0.3 (0.3, 59)
V_d (L)	16.0 (19, 78)	10.4 (11.2, 39)	8.2 (9.0, 55.2)
$t_{1/2}$ (day)[b]	21.0 (5.91)	19.9 (4.63)	20.1 (3.07)

Note: Data presented as geometric mean (mean, %CV) unless otherwise indicated.

Abbreviations: AUC_{0-672h}, area under the concentration-time curve from time 0 to time 672 h; AUC_{inf}, area under the concentration-time curve from time 0 to time infinite time; CL, clearance; C_{max}, maximum plasma concentration; IV, intravenous; $t_{1/2}$, terminal elimination phase half-life; T_{max}, time to maximum plasma concentration; V_d, volume of distribution.

[a]Median [minimum–maximum].

[b]Harmonic mean (pseudo SD).

[c]Two patients were excluded due to missing data (one subject missing 0–2 h time points and another missing 0–72 h time points).

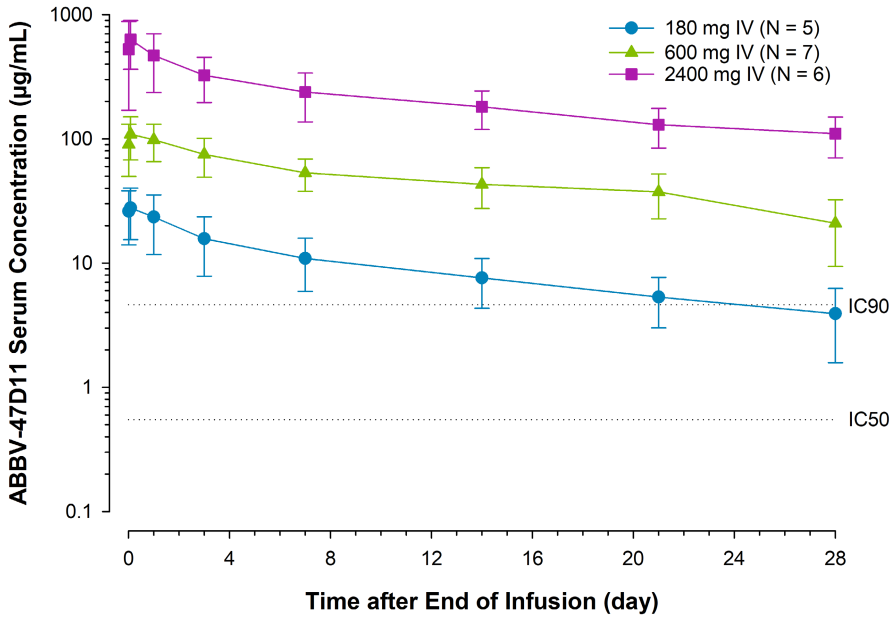
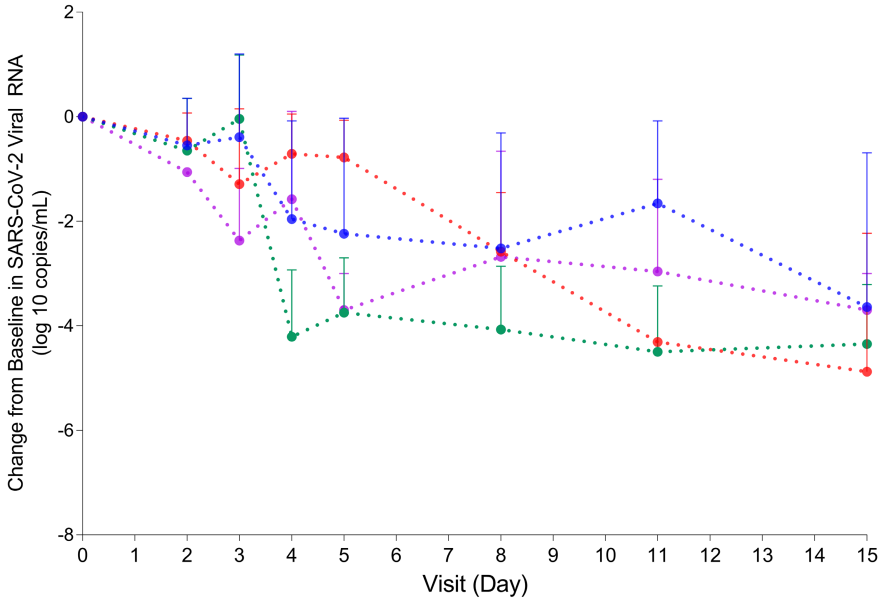


FIGURE 1 ABBV-47D11 concentration-time profiles following single ascending doses in patients with COVID-19. Data presented as mean ± SD; In vitro SARS-CoV-2 neutralization IC_{50} and IC_{90} values are shown as dotted lines for reference.

(i.e., ABBV-47D11 serum concentrations) and virological response. However, with the limited virological data available there was not a clear exposure-response or PK/PD relationship.

3.5 | Activity of ABBV-47D11 against circulating strains of SARS-CoV-2

The baseline sequence of S protein was available for 2/6 patients in the placebo group, 4/5 patients in the 180 mg group, and 3/7 patients in the 600 mg dose group. Based on phylogenetic analysis of the baseline S sequences, 1 of 2 placebo patients with available sequence data was infected with strain B.1.526 (Iota); 3/5 patients in the 180 mg group and 3/7 patients in 600 mg dose group were infected with B.1.1.7 strain (alpha). ABBV-47D11 retained potency against these variants in vitro.[26] Baseline polymorphisms in ABBV-47D11 epitope associated with reduced binding of ABBV-47D11 to SARS-CoV-2 receptor binding domain[20] were not detected in any of the patients with available sequence data. The neutralization activity of ABBV-47D11 has been evaluated against some of the currently circulating strains as described under electronic Appendix S1. ABBV-47D11 neutralized pseudotyped SARS-CoV-2 wild-type (D614G) with an IC_{50} value of 68 ng/ml. The activity against B.1.617.2 (delta) strain was similar with an IC_{50} value of 77 ng/ml; ABBV-47D11 also retained activity against B.1.351.2, P.1, P.2, B.1.427, B.1.525, B.1.526, B.1.617.1 strains with IC_{50} values ranging between 52 and 113 ng/ml.



	Baseline	D2	D3	D4	D5	D8	D11	D15
Placebo	6	5	5	5	5	5	5	4
180 mg	4	4	4	4	3	4	1	3
600 mg	6	5	3	5	5	6	4	6
2400 mg	5	1	2	3	4	4	5	4

FIGURE 2 Change from baseline in SARS-CoV-2 viral RNA based on mid-turbinate swab. On Day 15, the number of patients in each group was as follows: Placebo ($n = 4$), 180 mg ($n = 3$), 600 mg ($n = 6$), and 2400 mg ($n = 4$).

4 | DISCUSSION

The COVID-19 pandemic remains a global challenge. The main objectives of this study were to evaluate the safety, tolerability, and pharmacokinetics of ABBV-47D11 in patients with COVID-19. The study was fully enrolled according to the study protocol, with 24 patients randomized to placebo or treatment. During the study, a protocol amendment to allow enrollment of non-hospitalized patients with mild disease, and were willing to be confined, was implemented due to study enrollment challenges posed by the frequent use of convalescent plasma, authorization of the vaccines, and availability of other mAb therapeutics to treat patients with severe disease status. This amendment enabled the completion of the study enrollment as planned, however, more than half (58%) of randomized patients were non-hospitalized. Although the heterogeneity of the enrolled patients may have resulted in higher inter-patient variability in viral load data, the primary objectives of this study to evaluate the FIH safety and tolerability of ABBV-47D11 were achieved.

Single doses of ABBV-47D11 up to 2400 mg administered as IV infusion were safe and well-tolerated, and no safety signals were identified. Across all the tested doses of ABBV-47D11 compared to the placebo there were no SAEs or AEs of Grade 3 or higher and no infusion-related AEs. The pharmacokinetics of ABBV-47D11 were linear, with low clearance, volume of distribution, $t_{1/2}$ between 20 and 21 days, and the serum exposures following drug administration appeared to be dose proportional. Immunogenicity assessed by incidence of ADA formation was low with no apparent impact on pharmacokinetics or safety. ABBV-47D11 serum exposures were comparable to the generic IgG1 mAb population pharmacokinetic model predicted exposures and showed serum concentrations above the in vitro SARS-CoV-2 neutralization IC_{90} of ABBV-47D11. Based on the observed serum pharmacokinetics, the 600 and 2400 mg doses are expected to achieve lung exposures above the IC_{80}-IC_{90} for at least 29 days. This is based on the assumption of approximately 15% biodistribution of ABBV-47D11 into lung tissue, an assumption consistent with literature reports of IgG1 mAb tissue distribution.[27] These results are important in the context of the in vitro neutralization data showing similar susceptibility of the SARS-CoV-2 delta variant (B.1.617.2) and wildtype to ABBV-47D11. However, due to the large inter-patient variability in viral load data and limited evaluable measurements in this study, the assessment of viral load results was indeterminate, especially for the ABBV-47D11 2400 mg dose group. It is noteworthy that ABBV-47D11 retains in vitro neutralizing potency against the B.1.617.2 delta variant and other circulating strains compared to the "wild-type" D614G strain. ABBV-47D11 is an ideal candidate for antibody combinations targeting non-overlapping epitopes to increase potency and the barrier to resistance.

Conclusions regarding the anti-viral activity of ABBV-47D11 from this study were limited by the small number of patients, but this was an expected limitation because it was a Phase 1 FIH study to evaluate safety and PK. During the time the study was conducted, vaccines for SARS-CoV-2 became available, which introduced additional heterogeneity into the study population besides the variability introduced between hospitalized and non-hospitalized patients. An additional limitation was the timing of the study with regard to the dominant variant of concern, after the study concluded different SARS-CoV-2 variants (i.e., Omicron) became more prominent. However, at the time the study was conducted the antiviral activity

of ABBV-47D11 was tested against the most prominent variants during that time frame.

Results from this FIH Phase 1 study demonstrate favorable safety, tolerability, and pharmacokinetics of ABBV-47D11 at the evaluated doses. Exploratory analyses show potential for anti-SARS-CoV-2 activity at doses of 600 mg or higher. The 600 mg IV dose of ABBV-47D11 appeared to have the greatest effect on MT swab SARS-CoV-2 viral load AUC change from baseline through Day 15 compared to placebo (−50.5 log10 copies/ml versus −24.7 log10 copies/ml). However, as the current study was not designed or statistically powered to detect an anti-viral effect, this anti-viral potential should be evaluated in controlled studies designed to assess virologic and clinical endpoints. Given the ongoing emergence of variants of concern with variable susceptibility to mAb therapy, further evaluation of ABBV-47D11 alone or in combination with other COVID-19 therapeutics in clinical studies designed to assess viral load reductions and clinical benefit may be warranted.

AUTHOR CONTRIBUTIONS

Mohamad Shebley: wrote the Manuscript, designed the research, and analyzed the data. Stanley Wang: performed and designed the research and analyzed the data. Izna Ali: wrote the manuscript, designed the research, and analyzed the data. Preethi Krishnan: wrote the manuscript, designed and performed the research, and analyzed the data. Rakesh Tripathi; Joseph M. Reardon; John Cafardi; Galia Rahav; Yoseph Caraco; Jihad Slim; Fadi Al Akhrass: performed the research. Mengjia Yu: wrote the manuscript, performed the research, and analyzed the data. Yiran Hu: wrote the manuscript, designed and performed the research, and analyzed the data. Rosa De Abreu Ferreira: performed the research and analyzed the data. Negar N. Alami: wrote the manuscript, performed the research, and analyzed the data.

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DISCLOSURE

Mohamad Shebley, Izna Ali, Preethi Krishnan, Rakesh Tripathi, Mengjia Yu, Yiran Hu, and Rosa De Abreu Ferreira are employees of AbbVie and may hold AbbVie stock. Stanley Wang (Aligos Therapeutics) and Negar N. Alami (Pfizer) are former employees of AbbVie and may hold AbbVie stock. Joseph Reardon consults for AbbVie. John Cafardi has received grant funding and advisory board compensation from Gilead Sciences and grant funding from AbbVie, Merck, CTI BioPharma, and Ansun BioPharma. Galia Rahav has no disclosures. Yoseph Caraco served as principal investigator at the Hadassah-Hebrew University Medical Center. Jihad Slim is on the speaker bureau of Gilead, AbbVie, Merck, ViiV, and Jansen. Fadi Al Akhrass is on the speaker bureau and advisory board for AbbVie and Gilead.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following the review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

ETHICS STATEMENT

This study was approved by all institutions and Advarra (master), University of Illinois at Chicago, Helsinki Committee Hadassah Medical Center-Hebrew University, University of Miami, METC Utrecht, Helsinki Committee Sheeba Medical Center, and Saint Michael's Medical Center ethics committees and performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study.

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REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2021. https://covid19.who.int/. Accessed 14 December, 2021.

2. Prabakaran P, Zhu Z, Xiao X, et al. Potent human monoclonal antibodies against SARS CoV, Nipah and Hendra viruses. *Expert Opin Biol Ther*. 2009;9(3):355-368.
3. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *Jama*. 2021;325(7):632-644.
4. Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science*. 2020;369(6506):1014-1018.
5. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2021;384(3):229-237.
6. Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. *Viruses*. 2021;13(4):628.
7. Mahase E. Covid-19: FDA authorises neutralising antibody bamlanivimab for non-admitted patients. *BMJ*. 2020;371:m4362.
8. Jones BE, Brown-Augsburger PL, Corbett KS, et al. The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates. *Sci Transl Med*. 2021;13(593):1906.
9. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol*. 2020;20(6):339-341.
10. Coronavirus (COVID-19). *Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19* [press release]. Food and Drug Administation; 2020. Accessed November 21, 2020.
11. Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021.
12. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody Sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950.
13. GlaxoSmithKline. *GSK Sotrovimab Factsheet for HCP 11032021*. *In*. GlaxoSmithKline LLC; 2021.
14. Administration. FaD. Fact sheet for healthcare providers: emergency use authorization for bebtelovimab. 2022.
15. National Institutes of Health. COVID-19 treatment guidelines: anti-SARS-CoV-2 monoclonal antibodies. Drug Info. 2022. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/. Accessed 8 June, 2022.
16. Pfizer. *Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (Nirmatrelvir Tablets; Ritonavir Tablets)*. Pfizer; 2021.
17. Merck & Co. Inc. *Fact Sheet for Healthcare Providers: Emergency Use Authorization for Molnupiravir (Molnupiravir Capsules)*. Merck & Co., Inc.; 2021.
18. Haagmans BL, Noack D, Okba NMA, et al. SARS-CoV-2 neutralizing human antibodies protect against lower respiratory tract disease in a hamster model. *J Infect Dis*. 2021;223(12):2020-2028.
19. Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun*. 2020;11(1):2251.
20. Fedry J, Hurdiss DL, Wang C, et al. Structural insights into the cross-neutralization of SARS-CoV and SARS-CoV-2 by the human monoclonal antibody 47D11. *Sci Adv*. 2021;7(23):5632.
21. US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, AIDS. Do. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. 2017.
22. Zhang X, Tan Y, Ling Y, et al. Viral and host factors related to the clinical outcome of COVID-19. *Nature*. 2020;583(7816):437-440.
23. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. 2020;55:102763.
24. Chen P, Datta G, Li YG, et al. First in human study of bamlanivimab in a randomized trial of hospitalized patients with COVID-19. *Clin Pharmacol Ther*. 2021;110:1467-1477.
25. Savela ES, Winnett A, Romano AE, et al. SARS-CoV-2 is detectable using sensitive RNA saliva testing days before viral load reaches detection range of low-sensitivity nasal swab tests. *J Clin Microbio*. 2022;60(2):21.
26. Chen RE, Winkler ES, Case JB, et al. In vivo monoclonal antibody efficacy against SARS-CoV-2 variant strains. *Nature*. 2021;596(7870):103-108.
27. Shah DK, Betts AM. Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. *MAbs*. 2013;5(2):297-305.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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