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Virologic Response and Safety of Ibuzatrelvir, A Novel SARS-CoV-2 Antiviral, in Adults With COVID-19

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Background. Despite effective vaccines and treatments for COVID-19, clinical burden persists. An unmet need exists for additional effective agents with safety profiles allowing use across a broad population. Ibuzatrelvir is an orally bioavailable SARS-CoV-2 M^{pro} inhibitor with demonstrated in vitro antiviral activity and low potential for safety concerns, including drug–drug interactions.

Methods. This phase 2b, double-blind, randomized clinical trial enrolled US adults aged 18 to <65 years with symptomatic COVID-19 and no risk factors for severe disease. Participants were randomized 1:1:2:2 to receive 100, 300, or 600 mg ibuzatrelvir or placebo orally twice daily for 5 days. Nasopharyngeal specimens were collected on days 1 (baseline), 3, 5, 10, 14, and 21; adverse events (AEs) were recorded through day 33. The primary end point was change in SARS-CoV-2 RNA level (viral load [VL]) from baseline to day 5 among participants with baseline VL ≥4 $\log_{10}$ copies/mL.

Results. Of 240 enrollees, 237 received ≥1 dose; 199 were included in the primary analysis. Placebo-adjusted least squares mean (80% confidence interval) change from baseline in VL ($\log_{10}$ copies/mL) at day 5 was significant across all doses: 100 mg, −0.7 (−1.1 to −0.3) $\log_{10}$ copies/mL, $P = .02$; 300 mg, −0.8 (−1.3 to −0.3), $P = .01$; and 600 mg, −1.2 (−1.5 to −0.8), $P < .0001$. AEs occurred in similar percentages of participants across groups. No deaths from any cause or treatment-related serious AEs occurred through day 33, and no participants reported dysgeusia.

Conclusions. All 3 ibuzatrelvir doses were associated with robust antiviral activity and an acceptable safety profile, supporting continued clinical development.

Clinical Trials Registration. NCT05799495.

Keywords. COVID-19; SARS-CoV-2; antiviral; clinical trial; ibuzatrelvir.

Vaccination, naturally acquired immunity, antiviral therapies such as nirmatrelvir/ritonavir (NMV/r; Paxlovid; Pfizer Inc, New York, NY), and improved understanding of coronavirus disease 2019 (COVID-19) management have led to better outcomes for patients with COVID-19 compared with early during the pandemic [1–8]. However, new variants evade immune response [5, 9], allowing COVID-19 to continue causing high mortality and straining global healthcare systems [10, 11]. This burden persists partly because antiviral therapies for patients at high risk for severe COVID-19 are underused; one reason for this is potential risk of drug–drug interactions with NMV/r [12–14]. New, efficacious antiviral therapies with safety profiles appropriate for a broader population are needed.

Ibuzatrelvir (PF-07817883) is a second-generation, orally bioavailable, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) M^{pro} inhibitor that has demonstrated potent, pan-human coronavirus antiviral activity [15]. Ibuzatrelvir achieves expected therapeutic systemic concentrations (>90% of the population achieving free minimum observed plasma concentration [C_{min}] ≥90% maximal effective concentration [EC_{90}]) without the need for a co-administered agent (eg, ritonavir) to increase drug exposures [15–17]. Because ritonavir is a potent cytochrome P450 (CYP) 3A inhibitor [13, 14], administration of ibuzatrelvir alone (without ritonavir), as well as low potential of ibuzatrelvir to affect the pharmacokinetics (PK) of other drugs, may simplify clinical management [15, 16, 18]. Our aim in this study was to evaluate virologic response and

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safety of different ibuzatrelvir doses among nonhospitalized adults with confirmed, symptomatic COVID-19.

METHODS

Study Design and Participants

This phase 2b, randomized, double-blind, parallel-group, dose-ranging study was conducted across 31 sites in the United States. Eligible individuals were aged 18 to <65 years with no predefined underlying conditions associated with increased risk for severe COVID-19, SARS-CoV-2 infection confirmed by rapid antigen testing (RAT) of a nasopharyngeal (NP) specimen collected within 48 hours before randomization, onset of COVID-19 signs or symptoms within 5 days before randomization, and ≥1 specified COVID-19 sign or symptom on the day of randomization. Key exclusion criteria were current or expected hospitalization, oxygen saturation <92%, receipt of COVID-19 vaccine within 14 days of randomization, or receipt of any other antiviral treatment or monoclonal antibody therapy for COVID-19 within 30 days or 5 half-lives.

Participants were randomized 1:1:2:2 to a 100-mg, 300-mg, or 600-mg dose of ibuzatrelvir or matching placebo orally every 12 hours for 5 days, with or without food. Study duration was 5 weeks, which included the screening period and a 4-week follow-up after the final ibuzatrelvir or placebo dose. The protocol and statistical analysis plan are provided in Supplementary Material 1, and full eligibility criteria and study blinding details are further described in Supplementary Material 2.

All participants provided written informed consent. The study was conducted in accordance with ethical principles derived from international guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonization Good Clinical Practice guidelines, and local laws and regulations. The protocol and other relevant documents were approved by an institutional review board/ethics committee before study initiation.

Study Procedures

Randomization was performed within 48 hours of screening and RAT. The schedule of study procedures is detailed in the text and Supplementary Figure 1 in Supplementary Material 2. NP samples were collected on days 1 (baseline predose), 3, 5, 10, 14, and 21. Additional NP samples were collected following study drug completion if a participant made an unscheduled site visit because of symptom recurrence or worsening during the study period. NP swab collection, transport, and handling, as well as SARS-CoV-2 viral RNA level (viral load [VL]) measurements, were conducted as previously described and are briefly outlined in Supplementary Material 2 [19]. Plasma samples for PK analysis were collected on days 1, 3, and 5. Participants were required to complete a daily electronic diary from days 1 to 29 to record the severity or absence of 11 targeted COVID-19 signs and symptoms (stuffy or runny nose, sore throat, cough, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, and headache; see Supplementary Material 2 for severity scales). Participant compliance was monitored during all in-person visits and during optional phone calls on days 2 and 4; any deviations from planned interventions, as determined through direct questioning as well as counting the number of returned doses at each site visit, were documented.

Objectives and End Points

Efficacy

The primary objective was to evaluate the effect of different doses of ibuzatrelvir treatment on VL in NP samples, and the primary end point was change in VL from baseline to day 5 among participants with baseline VL ≥4 $\log_{10}$ copies/mL (the modified full analysis set [MFAS]). The value of 4 $\log_{10}$ copies/mL was chosen because it corresponds to a positive RAT [20]. The primary end point analysis was prespecified from the MFAS population to ensure positive SARS-CoV-2 infection status based on commercial RAT sensitivity. The secondary end point was change in VL from baseline to days 3, 10, and 14 in the MFAS.

Exploratory efficacy end points included the proportion of participants with VL less than the lower limit of quantification (LLOQ; defined as 2.0 $\log_{10}$ copies/mL) [21] at days 3, 5, 10, 14, and 21 and the proportions of participants with VL rebound, sustained resolution and alleviation of all targeted signs and symptoms, and symptom rebound (evaluated among participants who had ≥2 consecutive symptom-free days) by day 29 (see Supplementary Material 2). VL rebound among day 5 virologic responders was defined as follows: if day 5 VL was less than the LLOQ at day 5, rebound occurred if VL was >LLOQ at day 10, 14, or 21 or if VL was ≥LLOQ at day 5 and an increase of ≥0.5 $\log_{10}$ copies/mL was observed on day 10, 14, or 21. Day 5 virologic responders were defined as participants who had a day 5 VL <LLOQ or a day 5 VL change from baseline of ≥1 $\log_{10}$ copies/mL. Symptom rebound was defined as having 2 consecutive days without symptoms that were followed by either hospitalization from any cause or ≥2 consecutive diary entries on 2 separate days after day 5 indicating the presence of ≥1 targeted symptom of any severity (regardless of missing entries in between).

Pharmacokinetics Assessment

Ibuzatrelvir plasma PK collection and data analysis are described in Supplementary Material 2.

Safety

Incidence of adverse events (AEs), serious AEs (SAEs), and AEs and SAEs that led to study discontinuation were evaluated through day 33.

SARS-CoV-2 Viral Whole-Genome Sequencing

To monitor substitutions that arose during treatment, whole-genome sequencing was performed for NP specimens that met the viral RNA limit of detection for sequencing of ≥3.0 $\log_{10}$ copies/mL. Any substitution absent at baseline but present after baseline was monitored (see Supplementary Material 2).

Data Analysis

Analysis Sets

Most virologic assessments, including the primary analysis, were conducted in the MFAS, which included randomized participants who received ≥1 dose of study treatment and had baseline VL ≥4 $\log_{10}$ copies/mL. VL rebound and all symptom analyses were conducted in the full analysis set (FAS), which included randomized participants who had received ≥1 dose of study treatment regardless of baseline VL. Within the FAS, VL was calculated among all participants who had available data from day 5 and day 10, 14, or 21. Percentages of participants with symptom rebound were evaluated within the subset of FAS participants who had any available symptom data entered through day 29, regardless of missing entries in between. Safety was evaluated within the safety analysis set, which included all randomized participants who had received ≥1 dose of study treatment. PK was evaluated in the PK analysis set, which included all FAS participants who received ibuzatrelvir and had ≥1 plasma concentration value reported. Additional details are included in Supplementary Material 2.

Statistical Analyses

An enrollment target of 228 was anticipated to yield 180 participants who would complete day 5 and qualify for the primary analysis, a target based on a predicted standard deviation of 1.81 from a comparable COVID-19 study and a 1-sided alpha of 10%. The study was not designed to identify differences between groups regarding secondary or exploratory end points, including symptom end points.

Differences in mean change from baseline VL at days 3, 5, 10, and 14 were calculated using a longitudinal mixed model for repeated measures (MMRM). The MMRM was fitted to the change from baseline in VL through day 5. A 1-sided alpha of 0.1 was used for each statistical comparison of ibuzatrelvir dose to placebo. No adjustments were made for multiplicity.

The MMRM was repeated with VL at days 3 and 5 in the FAS as a sensitivity analysis to assess the difference in treatment effect between the enriched primary analysis population (MFAS) and a real-world patient population (FAS).

RESULTS

Participants

A total of 240 participants were enrolled between 24 May 2023 and 8 September 2023 (ibuzatrelvir 100 mg, n = 40; ibuzatrelvir 300 mg, n = 40; ibuzatrelvir 600 mg, n = 80; placebo, n = 80; Figure 1). Among all enrolled participants, 237 received ≥1 dose of the study drug (100 mg, n = 40; 300 mg, n = 39;

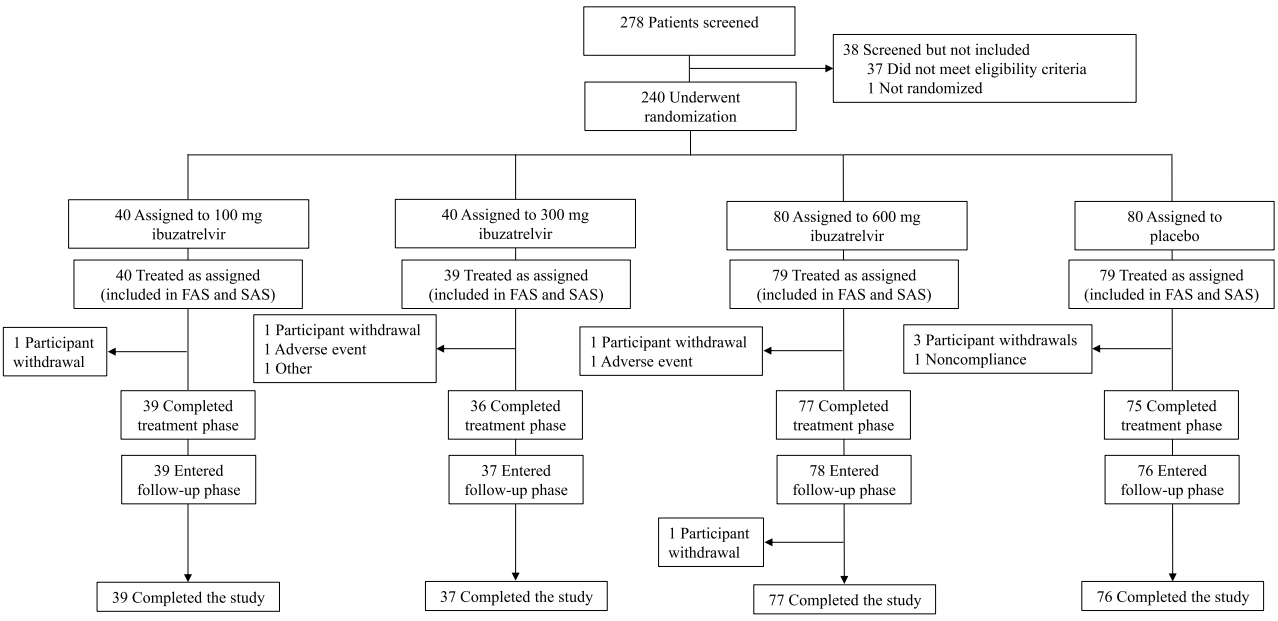

Figure 1. Participant disposition during treatment and follow-up phases. Three participants (n = 1 each in the 300-mg ibuzatrelvir, 600-mg ibuzatrelvir, and placebo groups) did not complete treatment but were still included in the follow-up phase. Abbreviations: FAS, full analysis set; SAS, safety analysis set.

600 mg, n = 79; placebo, n = 79); 3 participants were randomized but did not receive the study drug. Of the 237 participants in the FAS, baseline VL level was ≥4 $\log_{10}$ copies/mL in 199 participants (82.9%) who, therefore, comprised the MFAS (100 mg, n = 36; 300 mg, n = 28; 600 mg, n = 71; placebo, n = 64).

Demographic and clinical characteristics were generally similar across groups in the MFAS (Table 1). Median (range) age of MFAS participants was 43 years (19–64), 60.3% were women, and 85.9% were White (81.4% Hispanic). The majority of participants had received a full primary series of COVID-19 vaccine (69.8%) and either reported a prior SARS-CoV-2 infection (44.7%) or had presence of anti-N (79.4%) or anti-S (99.5%) antibodies. Most participants reported symptom onset within 3 days before study entry (88.4%); the reported symptoms at baseline ranged from mild (6.5%) to moderate (60.8%) and severe (29.6%), with a higher percentage of severe symptoms reported in the 600-mg group compared with other groups. All baseline SARS-CoV-2 variants belonged to the Omicron lineage.

Virologic Assessments

Change From Baseline in Viral Load at Day 5

The least squares (LS) mean change from baseline in VL at day 5 in the MFAS was lowest among participants treated with placebo and increasingly greater among each ibuzatrelvir dosing group (Table 2, Figure 2). Placebo-adjusted LS mean change from baseline in VL at day 5 was statistically significant across all doses. VL decreases were dose-dependent according to maximum effect (E_{max}) model analyses, consistent with the primary MMRM results (Supplementary Material 2). Similar results were also generated by the MMRM sensitivity analyses of the FAS (Supplementary Table 1, Supplementary Figure 2 of Supplementary Material 2).

Change From Baseline in Viral Load at Days 3, 10, and 14

In the MFAS, the placebo-adjusted LS mean (80% confidence interval [CI]) change from baseline in VL at day 3 was statistically significant across all dose arms (Table 2, Figure 2). Most samples had VL <LLOQ at days 10 and 14; therefore, differences

Table 1. Demographics and Baseline Clinical Characteristics in the Modified Full Analysis Set

Characteristic	Placebo (n = 64)	Ibuzatrelvir (n = 135)		
		100 mg (n = 36)	300 mg (n = 28)	600 mg (n = 71)
Age, median (range), y	41.5 (19–64)	47.5 (22–61)	41.0 (24–61)	43.0 (19–64)
Sex, n (%)				
Female	36 (56.3)	20 (55.6)	21 (75.0)	43 (60.6)
Male	28 (43.8)	16 (44.4)	7 (25.0)	28 (39.4)
Race or ethnicity, n (%)				
White	55 (85.9)	35 (97.2)	25 (89.3)	56 (78.9)
Black	5 (7.8)	0	1 (3.6)	9 (12.7)
Asian	2 (3.1)	1 (2.8)	2 (7.1)	5 (7.0)
Hispanic or Latino	50 (78.1)	31 (86.1)	23 (82.1)	58 (81.7)
Body mass index, median (range), kg/m^2	27.3 (19.4–29.9)	27.9 (19.0–29.8)	27.8 (18.2–29.8)	27.8 (18.5–29.9)
SARS-CoV-2 vaccination status,[a] n (%)				
Complete	38 (59.4)	24 (66.7)	23 (82.1)	54 (76.1)
SARS-CoV-2 serology status, n (%)				
Anti-SARS-CoV-2 anti-N antibody				
Negative	12 (18.8)	10 (27.8)	2 (7.1)	17 (23.9)
Positive	52 (81.3)	26 (72.2)	26 (92.9)	54 (76.1)
SARS-CoV-2 serology status, n (%)				
Anti-SARS-CoV-2 anti-S antibody				
Positive	64 (100)	36 (100)	28 (100)	70 (98.6)
Participant reported a prior coronavirus disease 2019 diagnosis, n (%)				
No	35 (54.7)	15 (41.7)	16 (57.1)	44 (62.0)
Yes	29 (45.3)	21 (58.3)	12 (42.9)	27 (38.0)
SARS-CoV-2 viral load, median (range), $\log_{10}$ copies/mL	6.2 (4.1–9.6)	6.3 (4.3–9.1)	5.9 (4.1–8.4)	6.3 (4.1–9.1)
Severity of the worst targeted sign or symptom, n (%)				
Mild	3 (4.7)	3 (8.3)	0 (0.0)	7 (9.9)
Moderate	44 (68.8)	23 (63.9)	21 (75.0)	33 (46.5)
Severe	16 (25.0)	9 (25.0)	6 (21.4)	28 (39.4)
Time since first symptom, median (range), d	2.0 (0–4)	2.0 (0–5)	2.0 (0–5)	2.0 (0–4)

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]A status of Complete indicates that the participant received the full coronavirus disease 2019 vaccine primary series.

Table 2. Least Squares Mean Change From Baseline and Difference From Placebo in Nasopharyngeal Viral Load: Modified Full Analysis Set

Treatment Group	n[a]	LS Mean (80% CI) Change From Baseline	LS Mean Difference From Placebo (80% CI) in Change From Baseline	*P* Value
Day 3				
Placebo	63	−1.3 (−1.6 to −1.0)		
Ibuzatrelvir 100 mg	35	−2.0 (−2.4 to −1.7)	−0.7 (−1.2 to −0.3)	.0114
Ibuzatrelvir 300 mg	27	−2.5 (−3.0 to −2.1)	−1.2 (−1.7 to −0.8)	.0003
Ibuzatrelvir 600 mg	70	−2.5 (−2.8 to −2.2)	−1.2 (−1.5 to −0.8)	<.0001
Day 5[b]				
Placebo	60	−3.2 (−3.5 to −2.9)		
Ibuzatrelvir 100 mg	34	−3.9 (−4.2 to −3.5)	−0.7 (−1.1 to −0.3)	.0181
Ibuzatrelvir 300 mg	24	−4.0 (−4.5 to −3.6)	−0.8 (−1.3 to −0.3)	.0127
Ibuzatrelvir 600 mg	66	−4.4 (−4.7 to −4.1)	−1.2 (−1.5 to −0.8)	<.0001

Abbreviations: CI, confidence interval; LS, least squares.

[a]Number of participants with non-missing data at each time point.

[b]The primary study end point was evaluated at day 5.

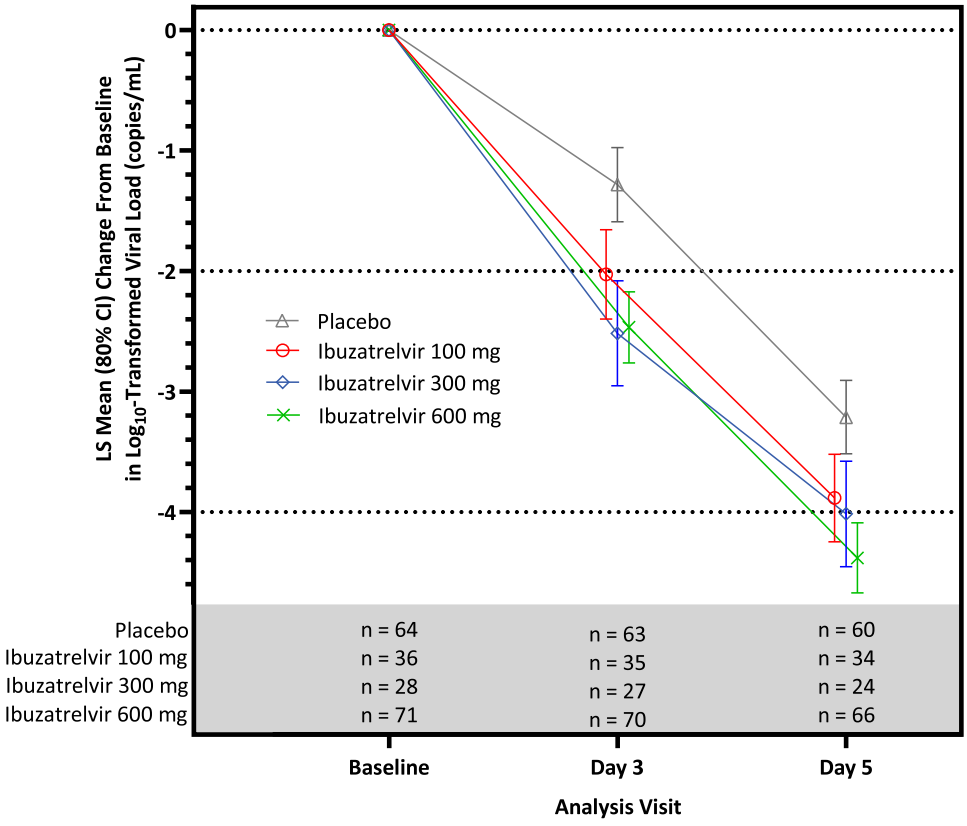

Figure 2. LS mean change from baseline in nasopharyngeal viral load over time (modified full analysis set). Abbreviations: CI, confidence interval; LS, least squares.

between dose arms and placebo were not significant at these time points. Similar results were generated by the sensitivity analysis of the FAS (Supplementary Table 1, Supplementary Figure 2 of Supplementary Material 2). Proportions of participants with VL <LLOQ over time are described in Supplementary Figure 3 of Supplementary Material 2.

Pharmacokinetics

Model-estimated median free ($f_{u,human} = 0.469$) C_{min} of ibuzatrelvir at steady state was approximately 2.5-, 7.5-, and 13.8-fold greater than in vitro EC_{90} in differentiated normal human bronchial epithelial cells on day 3 in the 100-, 300-, and 600-mg ibuzatrelvir groups, respectively, with approximately

79%, 96%, and 99% of participants achieving $C_{min} > EC_{90}$ (Supplementary Table 2 of Supplementary Material 2).

Symptom Assessments

Although this study was underpowered to identify differences in symptom end points between groups, descriptive analyses were performed. The rate of compliance with symptom diary responses was 86.0%. By day 29, high percentages of participants (80% CI) achieved complete resolution of all signs and symptoms for 4 continuous days across dose groups: placebo, 73.4% (66.9%–79.9%); 100 mg ibuzatrelvir, 76.9% (67.4%–84.9%); 300 mg ibuzatrelvir, 76.9% (67.4%–84.9%); and 600 mg ibuzatrelvir, 72.2% (65.4%–78.8%). In a post hoc assessment, the percentages of participants who achieved symptom resolution under a 1-day definition (all symptoms absent for ≥1 day through day 29) were 81.0% (74.7%–86.0%), 89.7% (81.2%–95.5%), 92.3% (84.9%–96.0%), and 92.4% (87.7%–95.8%) for placebo and 100-, 300-, and 600-mg ibuzatrelvir groups, respectively. Median times to sustained sign and symptom resolution are provided in Supplementary Material 2; no significant differences were observed between groups. By day 29, percentages of participants who achieved sustained alleviation of all targeted signs and symptoms for 4 continuous days were similar across treatment groups: 75.9% (69.4%–81.9%), 89.7% (81.2%–95.5%), 84.6% (75.5%–91.7%), and 73.4% (66.9%–79.9%).

Viral Load Rebound and Mutation Assessment

Eight participants had VL rebound, and 21 had symptom rebound. Among virologic responders, VL rebound was observed among 1 of 69 participants in the placebo group (1.4%) and among 3 of 37 (8.1%), 2 of 30 (6.7%), and 2 of 73 (2.7%) participants in the 100-mg, 300-mg, and 600-mg ibuzatrelvir groups, respectively. Symptom rebound was observed among 5 of 62 (8.1%) participants in the placebo group and among 4 of 35 (11.4%), 3 of 33 (9.1%), and 9 of 68 (13.2%) in the 100-, 300-, and 600-mg ibuzatrelvir groups, respectively. Two participants (n = 1 each from the 100-mg and 300-mg ibuzatrelvir groups) had both VL and symptom rebound.

One participant had both VL rebound and emergent substitution in the M^{pro} region; however, that participant was in the placebo group. No one had both symptom rebound and emergent substitution. Further details are provided in Supplementary Material 2.

Safety

AEs were reported in 9 participants (11.4%) in the placebo group, 2 participants (5.0%) in the 100-mg ibuzatrelvir group, 5 participants (12.8%) in the 300-mg group, and 11 participants (13.9%) in the 600-mg group (Table 3). Most AEs (98.0%) were mild or moderate in severity. One SAE was reported by 1 participant who received 300 mg ibuzatrelvir: a 57-year-old man

Table 3. Summary of Adverse Events, Serious Adverse Events, and Subsequent Discontinuations Through Day 33: Safety Analysis Set

		Ibuzatrelvir (n = 158)		
AE Category	Placebo (n = 79)	100 mg (n = 40)	300 mg (n = 39)	600 mg (n = 79)
AEs during treatment or follow-up				
Number of AEs	12	3	9	25
Participants with AE, n (%)				
Any	9 (11.4)	2 (5.0)	5 (12.8)	11 (13.9)
SAE	0 (0.0)	0 (0.0)	1 (2.6)[a]	0 (0.0)
Grade 3 or 4	0 (0.0)	0 (0.0)	1 (2.6)[a]	0 (0.0)
Death from any cause	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to discontinuation of ibuzatrelvir or placebo; trial participation continued	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)[b]
AE leading to study withdrawal	0 (0.0)	0 (0.0)	1 (2.6)[c]	0 (0.0)
AEs considered related to ibuzatrelvir or placebo				
Number of AEs	5	1	2	3
Participants with AE, n (%)				
Any	4 (5.1)	1 (2.5)	2 (5.1)	2 (2.5)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3 or 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to discontinuation of ibuzatrelvir or placebo; trial participation continued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to study withdrawal	0 (0.0)	0 (0.0)	1 (2.6)[c]	0 (0.0)
Treatment-related AEs reported by ≥2 participants				
Alanine aminotransferase increased	3 (3.8)	0 (0.0)	1 (2.6)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.3)
Diarrhea	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.3)

Abbreviations: AE, adverse event, SAE, serious adverse event.

[a]Exacerbation of a preexisting condition (first-degree atrioventricular conduction block caused by uncontrolled hypertension).

[b]Exacerbation of baseline elevated alanine aminotransferase and aspartate aminotransferase levels.

[c]Withdrew from the study following a grade 1 instance of vomiting.

with preexisting first-degree atrioventricular block and hypertension was hospitalized on day 10 for evaluation of supraventricular extrasystoles noted on electrocardiogram. The patient later recovered, and the investigator determined that the incident was not treatment-related. No other hospitalizations were reported, no deaths or treatment-related SAEs occurred, and no participants reported dysgeusia. AEs considered to be treatment-related occurred more frequently among participants who received placebo (5.1%) than among participants who received ibuzatrelvir (3.2%).

DISCUSSION

This study met its primary end point in demonstrating that all 3 evaluated doses of ibuzatrelvir were associated with a significantly greater decrease from baseline in VL compared with placebo after 5 days, and this difference was apparent 3 days after treatment initiation. Treatment at all doses was generally safe and well tolerated; no participant reported dysgeusia, which has been reported among approximately 5% of patients who used NMV/r [13]. AEs and treatment-related AEs were reported at similar rates across ibuzatrelvir and placebo groups.

Although our study was not designed to be compared with standard of care, the impact of ibuzatrelvir on VL after 3 or 5 days appeared comparable with results from phase 2/3 clinical studies of other SARS-CoV-2 antivirals, including NMV/r [19], simnotrelvir/ritonavir [22], and ensitrelvir [23], and was superior to results from phase 2 clinical studies of pomotrelvir [24] and EDP-235 [25], both of which had no significant effect on VL compared with placebo. Compared with currently available antivirals, viral dynamics observed with ibuzatrelvir treatment also appeared superior to those following remdesivir or molnupiravir treatment [26, 27].

Ibuzatrelvir had good coverage over in vitro EC_{90}. Values were comparable with those observed with NMV/r and consistent with values from studies that showed that NMV/r and ibuzatrelvir have similar effects on VL [19]. Dosing was conducted without regard to food based on results from phase 1 (to be published separately).

This phase 2 dose-ranging study was not powered to assess symptom end points. Furthermore, differences in baseline symptom severity among dosing groups (eg, more severe symptoms at baseline in the 600-mg ibuzatrelvir group) and intersubject symptom variability due to small sample size confounded exploratory symptom end point analysis. No meaningful differences were reported in percentages of participants who achieved ≥4 consecutive symptom-free days across groups. However, when symptom resolution was defined as 1 day without symptoms, a greater percentage of participants achieved resolution with 600-mg ibuzatrelvir compared with placebo. A larger study is needed to assess how VL decline from ibuzatrelvir relates to symptom resolution; however, it is widely established that VL in COVID-19 patients is associated with meaningful clinical outcomes (including hospitalization, death, and supplemental oxygen requirements) [28–30].

We also evaluated VL and symptom rebound. As previously reported, rebound can occur with or without antiviral treatment (reflecting natural COVID-19 disease progression and/or technical variability in virology assessment) [31, 32], and neither rebound nor antiviral treatment has been associated with progression to severe illness [31–33]. Here, VL and symptom rebound were rare across ibuzatrelvir and placebo groups, similar to other antivirals [32], and only 1 participant each in the 100- and 300-mg ibuzatrelvir groups experienced both VL and symptom rebound. Neither VL nor symptom rebound in ibuzatrelvir-treated participants was associated with emergent substitutions.

This study had strengths and limitations. We recruited a representative sample of US adults aged 18 to <65 years, irrespective of vaccination and without risk factors for severe disease, who were infected with COVID-19 during the Omicron era. Almost all participants had SARS-CoV-2 antibodies, indicating prior COVID-19 exposure or vaccination similar to the real-world population [34]. Thus, it is notable that we observed robust VL reductions despite this high previous exposure. Only participants with baseline VL ≥4 $\log_{10}$ copies/mL were included in the primary analysis; VL was assessed for up to 21 days, and symptoms were assessed for up to 29 days. This study design enabled optimal evaluation of ibuzatrelvir's effect on viral dynamics to facilitate dose selection, but these stipulations may have limited generalizability of results. As mentioned, the study was not powered to assess between-group differences in symptom end points.

Based on results here, as well as results of a dose-selection study to be reported separately, a 600-mg ibuzatrelvir dose was selected for evaluation during phase 3.

CONCLUSIONS

All evaluated doses of ibuzatrelvir were safe and well tolerated, with no reports of dysgeusia, and showed robust antiviral activity comparable with approved agents and superior to other antivirals in clinical development [19, 22–25]. Ibuzatrelvir is, therefore, a new single antiviral agent with low potential for drug–drug interactions that may be appropriate for a broad population. Larger clinical studies are required to assess the effect of ibuzatrelvir on clinically meaningful end points.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. A. S., R. S. P. S., J. H. K., N. S., S. S. T., M. L. B., A. Bergman, A. Banerjee, C. A., and N. N. A. contributed to study concept

and design. M. M. and N. S. contributed to study recruitment and enrollment. M. M., J. H. K., and N. S. contributed to data collection. M. M., A. S., R. S. P. S., L. F. C., J. H. K., J. P., M. L. B., A. Bergman, A. Banerjee, C. A., and N. N. A. contributed to data analysis. All authors reviewed and critically revised the manuscript for important intellectual content and approved the final draft.

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Data sharing statement. On request and subject to review, Pfizer Inc will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer Inc may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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