Virologic Response and Safety After Oral Administration of Ibuzatrelvir, a Novel SARS-CoV-2 M^{pro} Inhibitor, in Non-Hospitalized Adults With Symptomatic COVID-19

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INTRODUCTION

- Although vaccination has had a dramatic impact on outcomes for patients with SARS-COV-2 infection, new variants continue to evade immune response, leading to symptomatic disease and a substantial burden on global healthcare systems.[1-3]
- In January 2024 alone, the World Health Organization recorded 315,748 new cases of COVID-19 across reporting countries in Europe, illustrating the continued burden of the disease.[4]
- For the management of non-hospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression, both the European Society of Clinical Microbiology and Infectious Diseases and the United States National Institutes of Health recommend nirmatrelvir/ritonavir (Paxlovid®) as the preferred therapy.[5,6]
- Like nirmatrelvir, ibuzatrelvir is an orally bioavailable, potent SARS-CoV-2 main protease (M^{pro}) inhibitor that has demonstrated pan-human coronavirus antiviral activity in vitro and in preclinical animal studies.[7-9]
  - Ibuzatrelvir can achieve high systemic concentrations without the need for pharmacokinetic enhancement (eg, ritonavir), and in vivo and in vitro studies suggest that the drug-drug interaction (DDI) potential is likely to be minimal.[7,9]

OBJECTIVE

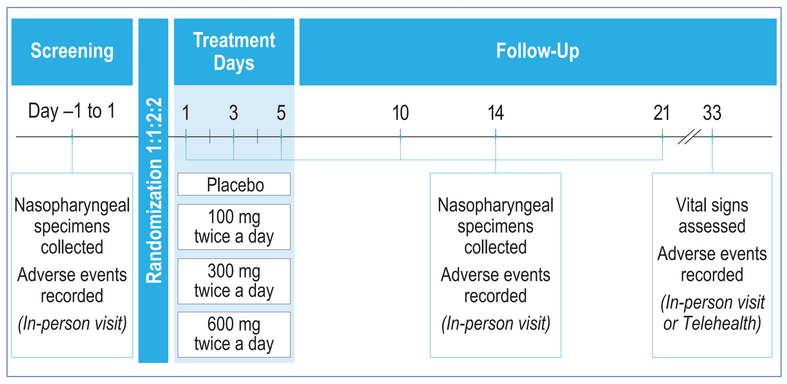
- The goal of this study (NCT05580003) was to evaluate the virologic response and safety of different doses of ibuzatrelvir among non-hospitalized, symptomatic 18- to <65-year-old patients with rapid antigen test (RAT)–confirmed SARS-CoV-2 infection.

METHODS

Study Design and Patients

- This phase 2b, randomized, double-blind, parallel-group, dose-ranging study enrolled participants aged ≥18 to <65 years across the United States who had ≤5 days of symptomatic SARS-CoV-2 infection confirmed by RAT of a nasopharyngeal (NP) specimen collected within 48 hours before randomization.
  - Eligible participants had onset of COVID-19 symptoms within 5 days before randomization and ≥1 specified COVID-19 symptom on the day of randomization.
  - Individuals were excluded from the study if they had any of the following underlying conditions: body mass index ≥30 kg/m^2, current smoker status, chronic lung disease, asthma requiring daily therapy, oxygen saturation <92% on room air, known history of cardiovascular disease, kidney disease requiring dialysis or known renal impairment with an estimated glomerular filtration rate <30 mL/min/1.73m^2, neurodevelopmental disorder, active cancer, history of liver disease, or immunocompromised status.
- Participants were randomized in a 1:1:2:2 ratio **(Figure 1)** to receive a 100-mg, 300-mg, or 600-mg dose of ibuzatrelvir or placebo orally every 12 hours (±4 hours) for 5 days. NP swabs were collected at baseline and Days 3, 5, 10, 14, and 21 for all participants, and SARS-CoV-2 RNA levels (viral load [VL]) were measured by RT-PCR as previously reported.[10]

Figure 1. Study Design, Treatment Assignments, and Follow-Up



Assessments and Statistical Analyses

- The primary endpoint was change from baseline (CFB) in VL at Day 5 across all treatment arms and was evaluated in the modified full analysis set (mFAS), which included participants who received ≥1 dose of the study intervention and who had a baseline VL ≥4 $\log_{10}$ copies/mL.
- Additional secondary virologic endpoints evaluated in the mFAS included CFB in VL at Days 3, 10, and 14 and proportion of patients with VL levels <2 $\log_{10}$ copies/mL (lower limit of quantification [LLOQ]) at Days 3, 5, 10, and 14.
- Differences in VL were analyzed using a mixed model for repeated measures (MMRM) with a 1-sided alpha of 0.1.
- Safety and tolerability through Day 33 were evaluated in the safety analysis set, which included all participants who received ≥1 dose of the study drug; assessments included incidence of treatment-emergent adverse events (AEs); serious AEs (SAEs); and AEs leading to study discontinuation.

RESULTS

Patient Population

- Out of 240 enrolled patients, 199 (82.9%) were qualified for the mFAS.
  - Demographics and clinical characteristics of the 199 participants in the mFAS were similar across treatment groups **(Table 1)**.

Table 1. Demographic and Clinical Characteristics (Modified Full Analysis Set)

Characteristic	Placebo (n=64)	Ibuzatrelvir (n=135)		
		100 mg (n=36)	300 mg (n=28)	600 mg (n=71)
Median age (range), years	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)
Race, n (%)				
White	55 (85.9)	35 (97.2)	25 (89.3)	56 (78.9)
Black	5 (7.8)	0 (0.0)	1 (3.6)	9 (12.7)
Asian	2 (3.1)	1 (2.8)	2 (7.1)	5 (7.0)
Ethnicity, n (%)				
Hispanic or Latino	50 (78.1)	0 (86.1)	23 (82.1)	58 (81.7)
Body mass index, kg/m^2				
Median (range)	27.3 (19.4–29.9)	27.9 (19.0–29.8)	27.8 (18.2–29.8)	27.8 (18.5–29.9)
Duration since first symptom, days				
Median (range)	2.0 (0–4)	2. (0–5)	2.0 (0–5)	2.0 (0–4)
SARS-CoV-2 vaccination status, 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)
SARS-CoV-2 viral load, $\log_{10}$ copies/mL				
Median (range)	6.2 (4.1–9.6)	6.3 (4.3–9.1)	5.9 (4.1–8.4)	6.3 (4.1–9.1)

*A status of Complete indicated that the participant received the full COVID-19 vaccine primary series.

Change From Baseline in Viral Load

- On Day 5, participants receiving ibuzatrelvir at any dose experienced significantly greater reductions in VL from baseline compared with placebo **(Table 2, Figure 2)**.
- Differences in CFB VL between treatment and placebo arms were also significant across all dosing groups on Day 3 **(Table 2, Figure 2)**.

Table 2. LS Mean Change From Baseline and Difference From Placebo in Nasopharyngeal Viral Load (Modified Full Analysis Set)

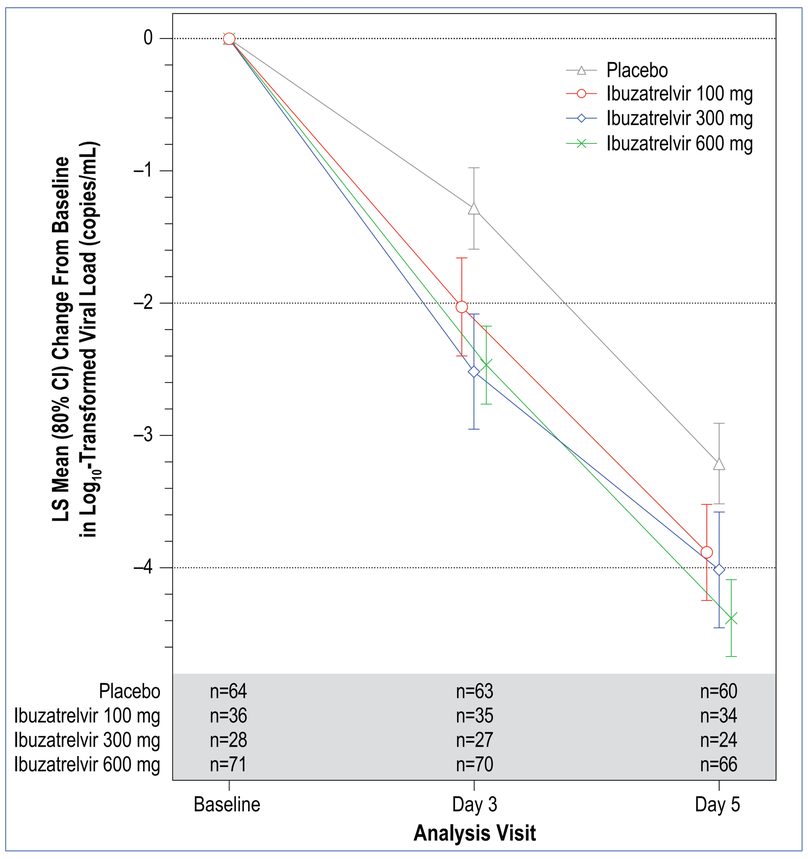
Visit	Treatment Group	n	LS Mean (80% CI) Change From Baseline	LS Mean Difference From Placebo (80% CI) in Change From Baseline	*P* value
Day 3	Placebo	63	-1.3 (-1.6, -1.0)		
	Ibuzatrelvir 100 mg	35	-2.0 (-2.4, -1.7)	-0.7 (-1.2, -0.3)	0.0114
	Ibuzatrelvir 300 mg	27	-2.5 (-3.0, -2.1)	-1.2 (-1.7, -0.8)	0.0003
	Ibuzatrelvir 600 mg	70	-2.5 (-2.8, -2.2)	-1.2 (-1.5, -0.8)	<.0001
Day 5*	Placebo	60	-3.2 (-3.5, -2.9)		
	Ibuzatrelvir 100 mg	34	-3.9 (-4.2, -3.5)	-0.7 (-1.1, -0.3)	0.0181
	Ibuzatrelvir 300 mg	24	-4.0 (-4.5, -3.6)	-0.8 (-1.3, -0.3)	0.0127
	Ibuzatrelvir 600 mg	66	-4.4 (-4.7, -4.1)	-1.2 (-1.5, -0.8)	<0.0001

*Primary endpoint

Percentages of Participants With Viral Load <LLOQ

- A higher percentage of participants receiving ibuzatrelvir had VL <LLOQ compared with placebo on Days 3 and 5; percentages were similarly high across all treatment arms on Days 10 and 14, and therefore no meaningful differences between dosing groups and placebo were observed at these time points (data not shown).

Figure 2. LS Mean Change From Baseline in Nasopharyngeal Viral Load Over Time (Modified Full Analysis Set)



Safety Assessments

- All doses were well tolerated and had a safety profile similar to placebo through Day 33 **(Table 3)**.
- No participants reported dysgeusia.
- There were no treatment-related grade 3/4 AEs, SAEs, or deaths from any cause in this study.

Table 3. Summary of AEs, SAEs, and Subsequent Discontinuations Through Day 33 (Safety Analysis Set)

	Placebo (n=79)	Ibuzatrelvir (n=158)		
		100 mg (n=40)	300mg (n=39)	600 mg (n=79)
AEs during treatment or follow up				
Number of AEs	12	3	9	25
Participants with AEs, n(%)				
Any AE	9 (11.4)	2 (5.0)	5 (12.8)	11 (13.9)
SAE	0	0	1 (2.6)*	0
Grade 3 or 4 AE	0	0	1 (2.6)*	0
Death from any cause	0	0	0	0
AE leading to discontinuation of participation in trial	0	0	1 (2.6)†	0
AE leading to discontinuation of ibuzatrelvir or placebo; trial participation continued	0	0	0	1 (1.3)‡
AEs considered related to ibuzatrelvir or placebo				
Number of AEs	5	1	2	3
Participants with AEs, n(%)				
Any AE	4 (5.1)	1 (2.5)	2 (5.1)	2 (2.5)
SAE	0	0	0	0
Grade 3 or 4 AE	0	0	0	0
AE leading to discontinuation of participation in trial	0	0	1 (2.6)†	0
AE leading to discontinuation of ibuzatrelvir or placebo; trial participation continued	0	0	0	0

AE, adverse event; SAE, serious adverse event
*Exacerbation of a pre-existing condition (first degree atrioventricular conduction block caused by uncontrolled hypertension)
†Participant withdrew from the study due to vomiting (mild; treatment-related)
‡Participant discontinued treatment due to elevation from baseline levels of liver enzymes (mild/moderate severity)

CONCLUSIONS

- **Ibuzatrelvir is an oral SARS-CoV-2 M^{pro} inhibitor without the need for pharmacokinetic enhancement and with low potential for DDIs.[7,9]**
- **In this study, ibuzatrelvir showed robust antiviral activity across all doses, with statistically significant, dose-dependent decreases in VL relative to placebo at Days 3 and 5.**
- **All doses were well tolerated with a safety profile similar to placebo and no reports of dysgeusia (a reported AE during treatment with nirmatrelvir/ritonavir).[8]**

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Disclosures

All authors are employees of Pfizer and may hold stock or stock options.

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