The SARS-CoV-2 Mpro Inhibitor Ibuzatrelvir is a Substrate but not an Inducer nor Inhibitor of CYP3A

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Introduction

- Ibuzatrelvir- a potent and selective inhibitor of the SARS-CoV-2 main protease (Mpro) currently under development as an oral treatment for COVID-19.
- In-vitro evaluation results showed:
  - Metabolism of ibuzatrelvir was predominantly mediated by CYP3A4
  - No inhibition of CYP3A
  - Low potential to induce CYP3A
- The effect of ibuzatrelvir on the pharmacokinetics (PK) of midazolam (a sensitive 3A probe substrate) and the effect of itraconazole (a strong 3A inhibitor) on the PK of ibuzatrelvir were evaluated to assess potential for 3A-mediated DDI of ibuzatrelvir.

Methods

- Two clinical phase 1 studies were conducted.
- Study 1: 2-treatment, 2-sequence, 2-period, cross-over study to evaluate the effect of steady-state ibuzatrelvir on the PK of midazolam in healthy adult participants (NCT05580003).
- Study 2: Open label, 2-period, fixed-sequence study to estimate the effect of the strong CYP3A inhibitor, itraconazole at steady state on the PK of ibuzatrelvir in healthy adult participants (NCT05822440).
- In both studies, midazolam and ibuzatrelvir PK parameters were estimated using non-compartmental analysis. The estimates of the adjusted geometric mean ratios (Test/Reference) and corresponding 90% confidence intervals (CI) were obtained using a mixed effects model.
- Safety and tolerability were monitored throughout both studies.
- Both studies were conducted at Pfizer Clinical Research Unit (PCRU) at New Haven, CT.

- ***Ibuzatrelvir had no meaningful effect on midazolam PK, demonstrating lack of induction or inhibition of CYP3A***
- ***Ibuzatrelvir exposure increased ~2-fold when administered with itraconazole, a strong CYP3A inhibitor***

Figure 1: Plasma PK Profile of Midazolam Alone or in Presence of Ibuzatrelvir

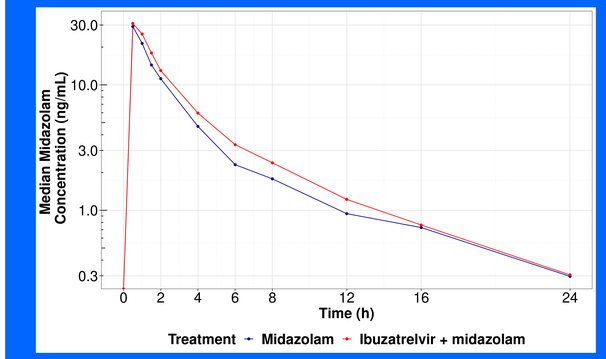

Figure 2: Plasma PK Profile of Ibuzatrelvir Alone or in Presence of Itraconazole

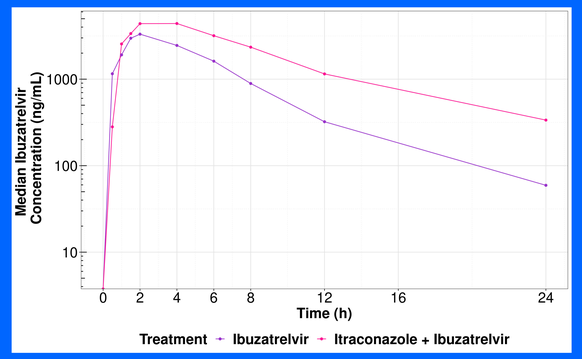

Table 1: Statistical Summary of Effect of Steady-state Ibuzatrelvir on PK of Midazolam

Parameter	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means	90% CI of Ratio
	Ibuzatrelvir 600 mg BID+ Midazolam 5 mg (Test)	Midazolam 5 mg (Reference)		
AUC_{inf}	93.85	79.75	117.69	(104.80, 132.17)
AUC_{last}	91.79	77.39	118.61	(105.35, 133.53)
C_{max}	34.29	30.15	113.75	(98.86, 130.89)

Values have been back-transformed from the log scale.
The model is a mixed effect model with sequence, period and treatment as fixed effects and participant within-sequence as a random effect.
Abbreviations: CI = confidence interval; PK = pharmacokinetic;
Units of AUC_{inf} and AUC_{last} are ng•h/mL and the unit for C_{max} is ng/mL.

Table 2: Statistical Summary of Effect of Steady-state Itraconazole on PK of Ibuzatrelvir

Parameter	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means	90% CI of Ratio
	Itraconazole 200 mg QD+ Ibuzatrelvir 300 mg SD (Test)	Ibuzatrelvir 300 mg SD (Reference)		
AUC_{inf}	46230	21720	212.83	(183.76, 246.50)
AUC_{last}	44910	21570	208.21	(176.76, 245.25)
C_{max}	5011	4030	124.35	(100.22,154.29)

Values have been back-transformed from the log scale.
The model is a mixed effect model with treatment as fixed effects and participant as a random effect.
Abbreviations: CI = confidence interval; PK = pharmacokinetic;
Units of AUC_{inf} and AUC_{last} are ng•h/mL and unit for C_{max} is ng/mL

Figure 3: Study 1 Design

A = Midazolam 5 mg SD with 2-day washout
B = Ibuzatrelvir 600 mg BID for 10 days + Midazolam 5 mg SD on day 10 with 7-day washout

	Period 1	Period 2
Sequence 1	A	B
Sequence 2	B	A

Figure 4: Study 2 Design

A = Ibuzatrelvir 300 mg SD
B = Itraconazole 200 mg solution QD (Period 2, Days 1-7) + Ibuzatrelvir 300 mg SD (Period 2, Day 4)

Period 1	Period 2
A	B

Results

- Participants:
  - Study 1: Participants assigned to treatment: 14, Male (71.4%), Mean (Range) Age: 45.1 (27-58) years.
  - Study 2: Participants assigned to treatment: 12, Male (66.7%), Mean (Range) Age: 38.7 (25-50) years.
- All treatments were generally well-tolerated, with all adverse events reported mild or moderate in severity.
- Midazolam plasma exposure was similar when co-administered with multiple doses of ibuzatrelvir or administered alone.
- The Test/Reference ratios of the adjusted geometric means for ibuzatrelvir AUC_{inf} and C_{max}, following ibuzatrelvir administration with itraconazole (Test) and administration alone (Reference), were 212.83% and 124.35%, respectively (Figure 2, Table 2). Ibuzatrelvir mean $t_{½}$ was almost doubled when ibuzatrelvir was co-administered with itraconazole (10.92 hours) compared to that when ibuzatrelvir was administered alone (5.502 hours).