PBI-0451: An Orally Administered 3CL Protease Inhibitor of SARS-CoV-2 for COVID-19

Review of Data Presented at 29th Conference on Retroviruses and Opportunistic Infections (CROI)

February 14, 2022

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Introduction and Key Takeaways

- PBI-0451 is a potent, orally bioavailable investigational 3CL protease (3CLpro)[1] inhibitor being developed as a potential stand-alone antiviral for SARS-CoV-2, the virus responsible for COVID-19
- In *in vitro* studies PBI-0451 exhibited selectivity and was not mutagenic or phototoxic
- In *in vivo* toxicology studies PBI-0451 was determined not to exhibit adverse findings at the highest doses tested
- PBI-0451 is being evaluated in an ongoing phase 1 study, and has shown (to date):
  - Favorable tolerability with all Treatment Emergent Adverse Events (TEAEs) assessed as mild in severity
  - Good oral bioavailability and dose-linear single- and multiple-dose pharmacokinetics upon administration with food over a >20-fold dose range
  - A lack of a clinically significant drug-drug interactions due to P-gp/CYP450 3A inhibition (ritonavir)
- PBI-0451 700 mg (2 × 350 mg tablets) administered twice-daily as a stand-alone agent achieved and maintained PK exposures that company believes have potential to provide potent antiviral activity against SARS-CoV-2
- Additional dose escalations and PK evaluations in this ongoing phase 1 study will inform on phase 2/3 dose selection

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1. 3CLpro is also called the viral main protease (M^{pro}) and plays a major role in coronaviral replication

Background

- Coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection has resulted in an unprecedented global health emergency and is now the 3rd leading cause of death in the U.S.[1]
- There is a need for safe, highly effective, and simple-to-use orally administered agents that can be deployed globally as a simple outpatient therapy for SARS-CoV-2 infection, particularly for those at greatest risk (e.g., patients who take multiple medications for comorbid conditions)
- The coronavirus (CoV) 3-chymotrypsin like protease (3CLpro, also called the viral Main Protease, or M^{pro}) is an essential viral enzyme necessary for early steps of coronaviral replication[2]
- 3CLpro is highly conserved across known coronaviruses, including emerging SARS-CoV-2 variants of concern (VOCs) such as Delta and Omicron[3]
- 3CLpro is a clinically validated target and treatment of SARS-CoV-2 infection with a protease inhibitor has been demonstrated to reduce the risk of hospitalization and death from COVID-19[3]

1. https://www.statista.com/statistics/1254560/leading-causes-of-death-in-the-us-average-number-daily/
2. Jin Z, et al. Nature. 2020;582(7811):289-293.
3. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

In Vitro Virology Studies

- PBI-0451 was observed to have broad activity against a range of human pathogenic coronavirus proteases (229E, HKU1, NL63, OC43, SARS-CoV-1, MERS), as well as SARS-CoV-2 variants of concern (including the Omicron P132H)
  - *In vitro* activity (K_i) against SARS-CoV-2 $3CL^{pro}$ enzyme = 2.7 nM
- Antiviral activity was also assessed in multiple cell-based SARS-CoV-2 assays, including in inducible pluripotent stem cell-derived alveolar type II (iPS-AT2) lung cells, A549-ACE2 lung cells and the Vero E6 cell line

Virus	Cell line	Antiviral assay	EC_{50} [nM, mean (SD)]	EC_{90} [nM, mean (SD)]	CC_{50} [nM]
SARS-CoV-2 WA1[1] (MOI 0.004)	iPS-AT2	SARS-CoV-2 (PFU/mL)	32 (25), n=4	106 (90)	>2,000
SARS-CoV-2 WA1[1] (MOI 0.004)	iPS-AT2	SARS-CoV-2 (RNA copy/mL)	37 (19), n=4	67 (35)	>2,000
SARS-CoV-2_NLuc[1] (MOI 0.025)	A549-ACE2	SARS CoV-2 (nanoluciferase)	23 (16), n=6	114 (85)	>10,000
SARS-CoV-2, Wuhan[2] (MOI 0.001)	Vero E6 cell line (+efflux inhibitor)	Cytopathic effect (GFP assay)	48, n=2	--	>30,000
SARS-CoV-2[3] (Delta, MOI 0.002)	Vero E6 cell line (+efflux inhibitor)	Cytopathic effect (neutral red assay)	--	78, n=1	37,000
SARS-CoV-2[3] (Delta, MOI 0.002)	Vero E6 cell line (+efflux inhibitor)	Viral yield reduction	--	<32, n=1	37,000

CC_{50}, half-maximal cytotoxic concentration; EC_{50}, half-maximal effective concentration; EC_{90}, 90% effective concentration; MOI, multiplicity of infection (PFU/cell); PFU, plaque-forming unit.
1. Vanderbilt University Medical Center; Stevens LJ, et al. ASV 2021; Nidovirus Symposium 2021. 2. Rega Institute for Medical Research. 3. Utah State University.

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Non-Clinical Toxicology Studies

- Potential for off-target toxicity was assessed with respect to activity against human receptors and proteases
  - High selectivity (no effect observed at ≥10 µM or >600-fold) against 44 human receptors
  - Greater than 160-fold selectivity over human proteases tested, including Cathepsin-S, -K, and -L
- In Good Laboratory Practice (GLP) *in vitro* and *in vivo* toxicology studies PBI-0451 demonstrated
  - Lack of mutagenic potential observed in Ames or *in vitro* and *in vivo* micronucleus tests
  - Lack of phototoxicity observed in 3T3 cells
- Fourteen-day GLP general toxicology studies were conducted in CD1 mouse and beagle dogs
  - High-dose groups in the mouse (240 mg/kg) and dog (30 mg/kg) were deemed to be the no adverse effect level (NOAEL)
  - No adverse findings were observed clinically, on gross necropsy, or in chemistry and hematology
  - No adverse findings were observed on the central nervous, respiratory, or cardiovascular systems
  - No clinically relevant adverse histopathology changes were observed
    - Mouse: finding of increased liver weight at 240 mg/kg evidenced reversibility
    - Dog: all observed changes considered spontaneous in nature

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Ongoing First-in-Human Phase 1 Study[1]: Design

- Placebo-controlled, blinded, randomized (8:2, active PBI-0451 : placebo), dose-escalation phase 1 study in healthy adult participants[1]
- Single-ascending dose (SAD) and multiple (10-day) -ascending dose (MAD) cohorts to date
  - 100 & 300 mg fasted SAD (suspension)[2]
  - 100, 300, 1050, 2100 mg with food SAD (suspension)[2]
  - 150 mg once-daily (QD), 225 mg twice-daily (BID) (suspension), 700 mg BID (2 x 350 mg tablet)[2]
- Preliminary food effect assessment: administration with a representative meal (500 Kcal, 12% fat)
- Potential for drug-drug interaction (DDI) due to P-glycoprotein (P-gp) and CYP450 3A (CYP3A) inhibitors was explored upon single and multiple doses with ritonavir 100 mg (PBI-0451 20 & 50 mg QD)
- Safety is being assessed throughout the study, including physical examinations, laboratory testing, and electrocardiograms
- TEAEs were assessed by the Investigator as to relatedness to the blinded study drug and severity
- PBI-0451 measured in plasma with LC-MS/MS; non-compartmental (NCA) PK determined using Phoenix WinNonlin v8.3

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1. NCT05011812
2. Blinded study drug administered orally with 240 mL of water

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Ongoing First-in-Human Phase 1 Study: Results

To date, PBI-0451 has been generally well tolerated over a >20-fold single- and >14-fold multiple-total daily dose range

- Results for SAD, MAD & ritonavir DDI cohorts, data through 01/31/22
- There have been no treatment or study interruptions or discontinuations reported
- No serious adverse events or deaths have been reported
- Investigator-reported TEAEs (See next slide for details)
  - All TEAEs were assessed as mild in severity, and resolved without intervention
  - The majority of TEAEs were considered not or unlikely related to blinded study drug
  - Possibly or probably related TEAEs reported in >2 participants: gastrointestinal-related (abdominal bloating, decreased appetite, diarrhea, dyspepsia, flatulence, nausea) and headache

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Interim Assessment of Blinded TEAE: All Mild in Severity To Date[1]

Blinded† TEAEs (N=10, 8 active : 2 placebo per cohort)

Cohort	Total	Not related	Unlikely related	Possibly related	Probably related	Definitely related
Single-dose cohorts (through day 6 post-dose and day 15 post-study follow-up)						
100 mg fasted	4 (10)	2 (4)	2 (6)	0	0	0
100 mg fed	6 (8)	6 (7)	1 (1)	0	0	0
300 mg fasted	4 (4)	2 (2)	1 (1)	1 (1)	0	0
300 mg fed	5 (8)	3 (5)	1 (1)	2 (2)	0	0
1050 mg fed	7 (17)	5 (13)	1 (1)	2 (3)	0	0
2100 mg fed	8 (16)	6 (10)	3 (4)	1 (2)	0	0
20 mg + ritonavir	4 (6)	3 (4)	0	2 (2)	0	0
Multiple-dose cohorts (through day 11 post-dose and day 26 post-study follow-up)						
50 mg + ritonavir	9 (32)	6 (15)	3 (3)	7 (14)	0	0
150 mg QD	5 (9)	4 (6)	2 (3)	0	0	0
225 mg BID	10 (32)	7 (12)	4 (4)	7 (16)	0	0
700 mg BID (tablets)	10 (30)	7 (11)	5 (9)	7 (8)	2 (2)	0

Data reported: number of participants experiencing TEAEs (total number of reported TEAEs). QD, once-daily; BID, twice daily.

† Combined PBI-0451 & Placebo groups (N=10/cohort) as study is ongoing and remains blinded

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1. Data through 01/31/22

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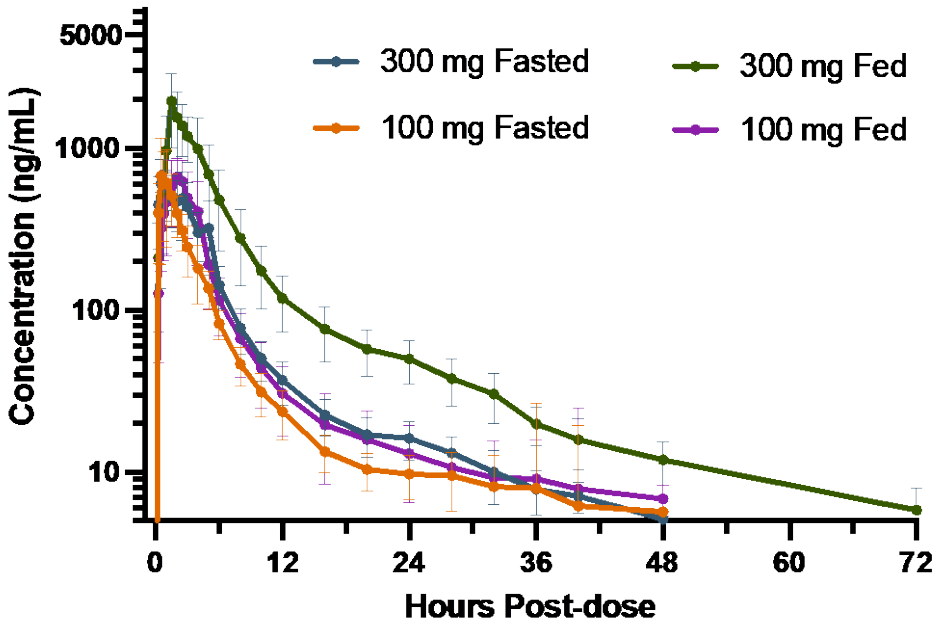
Ongoing First-in-Human Phase 1 Study: Positive Food Effect Observed

PBI-0451 single ascending doses administered in the fasted state or with food (N=8/cohort, suspension)

PBI-0451 concentration-time profile



Mean +/- 95% CI

PBI-0451 single ascending dose pharmacokinetics

NCA PK estimates	Fasted administration		Administration with food	
	100 mg (N=8)	300 mg (N=8)	100 mg (N=8)	300 mg (N=8)
AUC_{inf} (µg*hr/mL), mean (CV%)	2.40 (31)	3.30 (25)	3.11 (41)	9.04 (33)
C_{max} (µg/mL), mean (CV%)	0.771 (71)	0.728 (22)	0.821 (31)	2.29 (38)
T_{max} (hr), median (IQR)	0.75 (0.5, 1.5)	2.0 (0.94, 2.5)	2.00 (2.0, 2.5)	1.5 (1.5, 2.3)
Terminal $t_{1/2}$ (hr), median (IQR)	13.6 (10.6, 15.2)	11.1 (10.0, 12.3)	11.2 (8.3, 13.3)	12.3 (10.6, 15.7)

AUC_{inf}, area under the curve from time zero to infinity; CV%, coefficient of variation; IQR, interquartile range; T_{max}, time of maximum plasma concentration; $t_{1/2}$, estimated terminal elimination half-life.

- PBI-0451 PK showed improved oral bioavailability with food vs. fasted administration
  - 34% higher at 100 mg when administered with food versus fasted administration
  - 247% higher at 300 mg when administered with food versus fasted administration

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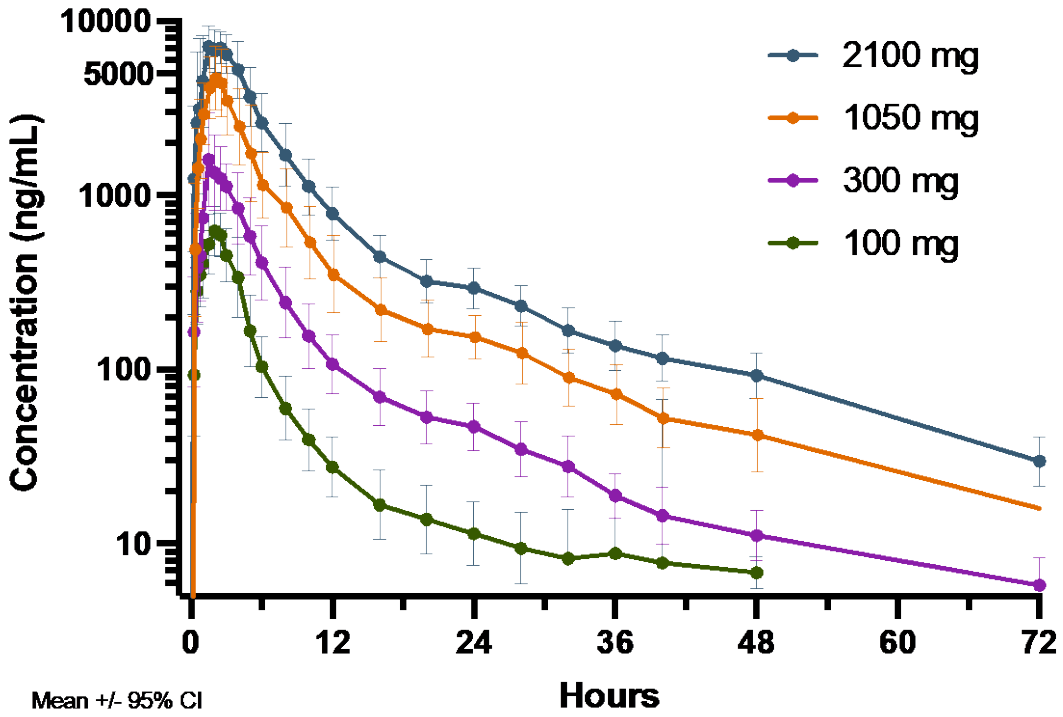
Ongoing First-in-Human Phase 1 Study: Good Oral Bioavailability and Dose-Proportional Exposure

PBI-0451 single ascending doses administered with food (N=8/cohort, suspension)

PBI-0451 concentration-time profile



PBI-0451 single ascending dose pharmacokinetics

NCA PK estimates	Administration with food			
	100 mg (N=8)	300 mg (N=8)	1050 mg (N=8)	2100 mg (N=8)
AUC_{inf} (µg*hr/mL), mean (CV%)	3.11 (41)	9.04 (33)	30.5 (54)	52.6 (28)
C_{max} (µg/mL), mean (CV%)	0.821 (31)	2.29 (38)	5.98 (53)	8.22 (23)
T_{max} (hr), median (IQR)	2.00 (2.0, 2.5)	1.5 (1.5, 2.3)	2.0 (1.9, 2.1)	2.0 (1.5, 3.25)
Terminal $t_{1/2}$ (hr), median (IQR)	11.2 (8.3, 13.3)	12.3 (10.6, 15.7)	13.9 (12.7, 15.9)	16.3 (15.9, 17.8)

AUC_{inf}, area under the curve from time zero to infinity; CV%, coefficient of variation; IQR, interquartile range; T_{max}, time of maximum plasma concentration; $t_{1/2}$, estimated terminal elimination half-life.

- Exhibited good oral bioavailability and was observed to have dose-proportional increases in exposure over a >20-fold dose range when administered with food
- Concentration-time profile provides evidence for a two-compartment PK profile

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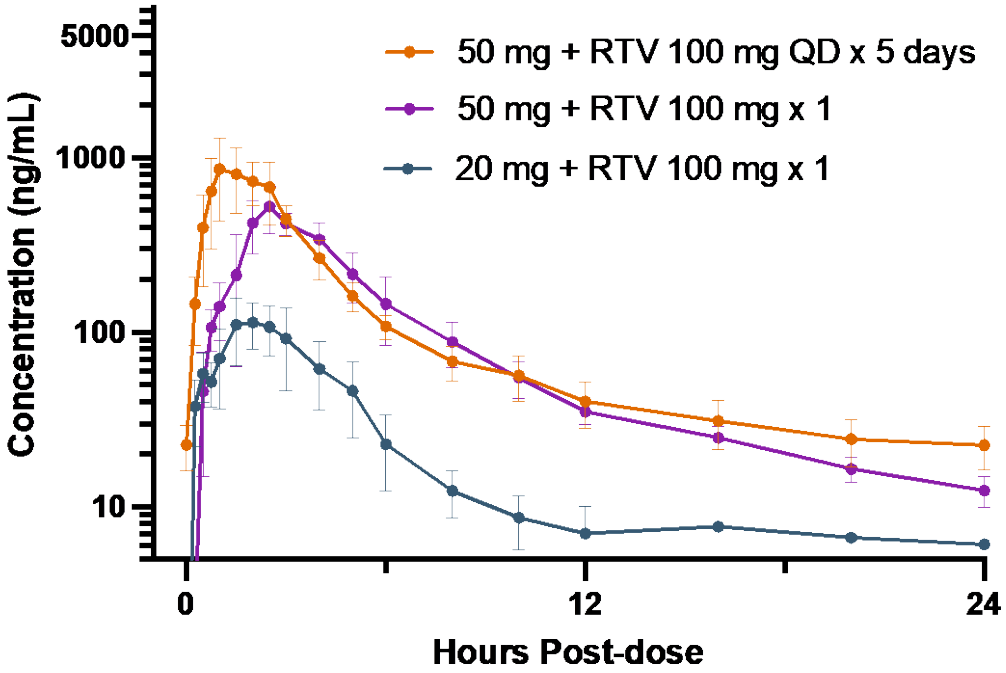
Ongoing First-in-Human Phase 1 Study: Interim Results
No Evidence for a Clinically Significant DDI due to P-gp/CYP3A Inhibitor†

PBI-0451 co-administered with ritonavir 100 mg, with food (N=8/cohort, suspension)

PBI-0451 concentration-time profile



mean +/- 95% CI

PBI-0451 PK upon coadministration w/ritonavir 100 mg

NCA PK estimates	20 mg + ritonavir 100 mg (N=8)	50 mg + ritonavir 100 mg (N=8)	
	Single dose	Day 1 (first dose)	Day 5 (QD dosing)‡
$AUC_{inf/tau}$ (µg*hr/mL), mean (CV%)	0.564 (41)	1.90 (13)	1.66 (36)
C_{max} (µg/mL), mean (CV%)	0.156 (23)	0.589 (24)	0.574 (47)
T_{max} (hr), median (IQR)	2.0 (1.5, 2.5)	2.0 (1.5, 2.0)	2.0 (1.5, 2.5)
$t_{1/2}$ (hr), median (IQR)	4.1 (3.9, 4.2)	3.9 (2.7, 4.2)	4.1 (3.8, 4.7)

AUC_{inf}, area under the curve from time zero to infinity; AUC_{tau}, area under the curve over the dosing interval (tau, 24 hr on Day 5); CV, coefficient of variation; T_{max}, time of maximum plasma concentration; $t_{1/2}$, estimated terminal elimination half-life; QD, once-daily; IQR, interquartile range.
‡ PK results from Day 1 and Day 5 of a 10-day dosing regimen.

† Dose-normalized effect of ritonavir on systemic exposure (AUC): ~25%
(estimated for 50 mg + ritonavir Day 1 versus 100 mg fed single dose cohort)

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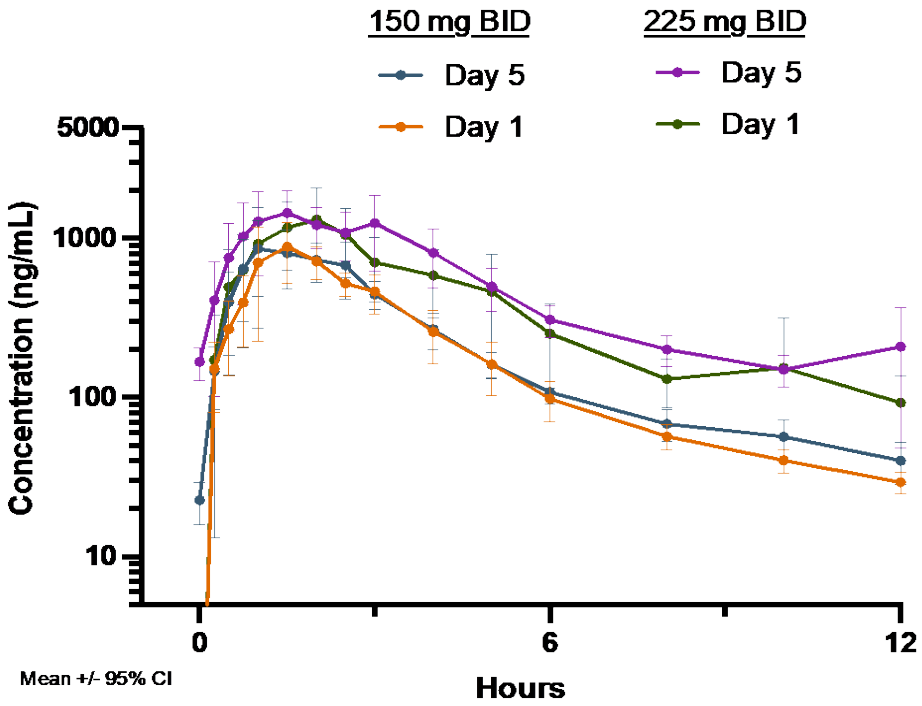
Ongoing First-in-Human Phase 1 Study: Interim Results
Good Oral Bioavailability and Dose-Proportional Exposure

PBI-0451 multiple ascending doses administered with food (N=8/cohort, suspension)

PBI-0451 concentration-time profile



PBI-0451 Multiple Ascending Dose PK†

Mean (CV%) NCA PK estimates	Multiple dose administration with food			
	150 mg QD		225 mg BID	
	Day 1	Day 5	Day 1	Day 5
$AUC_{inf/tau}$ (µg*hr/mL)	3.09 (25)	2.92 (23)	5.46 (29)	6.48 (21)
C_{max} (µg/mL)	1.09 (50)	1.10 (39)	1.87 (39)	1.94 (36)
C_{tau} (µg/mL)	0.014 (26)	0.023 (39)	0.093 (57)	0.209 (92)

AUC_{inf}, area under the curve from time zero to infinity (Day 1); AUC_{tau}, area under the curve over the dosing interval (tau, 12 hr on Day 5); CV, coefficient of variation.
† PK results from Day 1 and Day 5 of a 10-day dosing regimen.

- Dose-proportional increases were observed upon single- to multiple-dose administration as the suspension formulation
- Single- to multiple-dose exposure observed accumulation ratios correspond to an estimated effective $t_{1/2}$ of 4 to 6 hours

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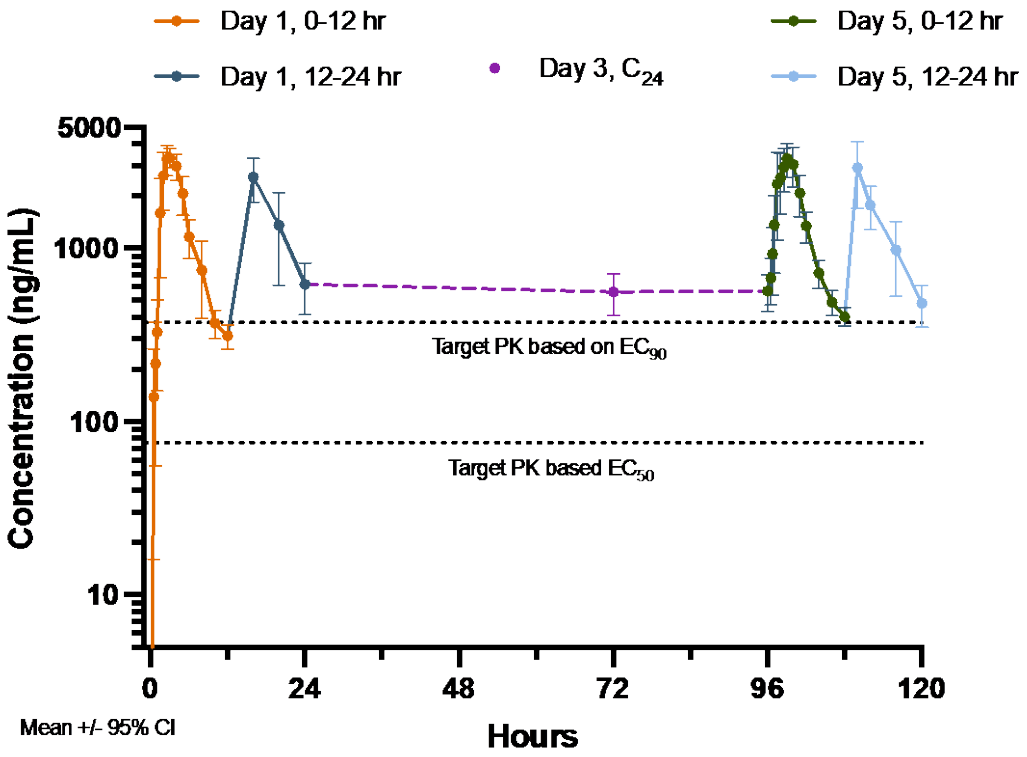
Ongoing First-in-Human Phase 1 Study: Interim Results
Multiple Dose Human Pharmacokinetics 700 mg (2 x 350 mg tablets)

PBI-0451 700 mg (2 x 350 mg tablets) x 5 days administered with food (N=8/cohort, Tablets)

PBI-0451 concentration-time profile



0-24 hour PK sampling on Days 1 & 5; C24, trough sample (C12) for the second dose on Day 3

PBI-0451 single and multiple ascending dose PK†

Mean (CV%) NCA PK parameter	700 mg (2 × 350 mg) Tablets BID	
	Day 1	Day 5
$AUC_{inf/tau}$ (µg*hr/mL)	17.0 (16)	17.4 (18)
C_{max} (µg/mL)	3.65 (14)	3.78 (19)
C_{tau} (µg/mL)	0.312 (19)	0.404 (14)

AUC_{inf}, area under the curve from time zero to infinity (Day 1); AUC_{tau}, area under the curve over the dosing interval (tau, 12 hr on Day 5); CV, coefficient of variation.
† PK results from Day 1 and Day 5 of a 10-day dosing regimen.

Target PK values:

- EC_{50} derived: 23 nM [76.0 ng/mL]
- EC_{90} derived: 114 nM [374 ng/mL]
- Derived by applying a 7.25-fold protein binding-shift[1] to SARS-CoV-2_NLuc assay values (Slide 5, *in vitro* virology)

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1. Comparative equilibrium dialysis method in human serum. Method by Mo H. et al. *J Viral Hepat*. 2011 May;18(5):338-48.

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Interim Conclusions and Next Steps

- PBI-0451 demonstrated potent antiviral activity in both enzymatic and cellular assays and had high selectivity against human receptors and proteases in vitro
- In in vitro studies PBI-0451 exhibited selectivity and was not mutagenic or phototoxic
- In in vivo toxicology studies PBI-0451 was determined not to exhibit adverse findings at the highest doses tested
- Single- and multiple-doses of PBI-0451 in this ongoing phase 1 study shown (to date):
  - Favorable tolerability with all TEAEs assessed as mild in severity
  - Good oral bioavailability and dose-linear single- and multiple-dose PK upon administration with food over a >20-fold dose range
  - A lack of a clinically significant DDI due to P-gp/CYP3A inhibition (ritonavir)
- PBI-0451 700 mg (2 × 350 mg tablets) administered twice-daily as a stand-alone agent achieved and maintained PK exposures that company believes has potential to provide potent antiviral activity against SARS-CoV-2
- Additional dose escalations and PK evaluations in this ongoing phase 1 study continue and will inform on phase 2/3 dose selection

Thank you

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