# EDP-235, an Oral, Once Daily, Ritonavir-Free, 3CL Protease Inhibitor for the Treatment of COVID-19: Results from Phase 1 Study in Healthy Subjects

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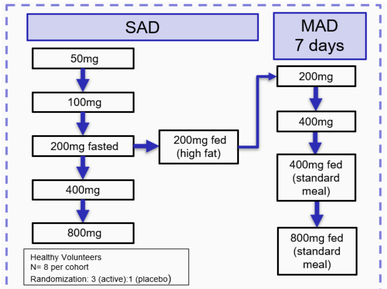
## BACKGROUND

- Despite vaccination efforts, COVID-19 persists as a significant global health challenge, with ongoing emergence of new SARS-CoV-2 variants.
- EDP-235 is a novel, potent, oral inhibitor of the SARS-CoV-2 3CL protease designed for the treatment of COVID-19.
  - In vitro studies indicate potent antiviral activity against SARS-CoV-2 variants, including Omicron
  - EDP-235 is projected to have 4x higher drug levels in lung tissue compared to plasma (T. Zang et al).

## METHODS

- EDP 235-001 is a phase 1, randomized, double-blind, placebo (PBO)-controlled study conducted to assess the safety and PK profile of EDP-235 during single ascending dose (SAD), multiple ascending dose (MAD), and food effect (FE) cohorts in healthy subjects (HS).
- The key objectives were:
  - Primary:
    - To evaluate the safety and tolerability of a single dose and multiple doses of EDP-235 administered to healthy participants
  - Secondary:
    - To evaluate the PK of single and multiple doses of EDP-235 in plasma and urine in healthy participants
    - To evaluate the effect of food intake on PK of EDP-235 administered as a single dose in healthy participants

**Figure 1. Study Design**




- In the SAD phase, 8 subjects per cohort were randomized 3:1 to receive a single oral dose of EDP-235 or placebo fasted (50, 100, 400, 800 mg) or fed (high fat meal) (200 mg).
- In the MAD phase, 8 subjects per cohort were randomized 3:1 to receive multiple, once-daily, oral doses of either EDP-235 or placebo for 7 days fasted (200, 400 mg) or fed with standard meal (400, 800 mg).

- Safety and tolerability assessments:
  - Adverse events, clinical laboratories, physical examination, vital signs, and electrocardiographic evaluations
- Pharmacokinetic (PK) assessments:
  - In the SAD phase, intensive plasma PK samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, 72, and 96 hr
  - In the MAD phase, intensive plasma PK samples were collected as follows:
    - Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15 hr
    - Predose on Days: 2 (24 hr), 3, 4, 5, and 6
    - Day 7: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24 (D8), 30, 36, 48 (D9), 60, 72 (D10), and 96 (D11) hr postdose
  - Urine samples were collected in the SAD phase
  - Concentrations of EDP-235 were measured using a validated method
  - PK parameters were determined using non compartmental methods in Phoenix WinNonlin (Pharsight Corporation version 6.3)

## DISCLOSURES

- K. Mills, C. Marotta, X. Luo, A. Ahmad, and G. De La Rosa are employees of Enanta Pharmaceuticals, Inc. and may be stockholders.
- K. Melchiors is an employee of ICON plc, which was contracted by Enanta Pharmaceuticals, Inc. to conduct the study

## RESULTS

### Subject Disposition and Demographics

- A total of subjects 72 were randomized; n= 40 in SAD, n=32 in MAD
  - Three subjects discontinued dosing during the study, n=1 in MAD 400 mg, n=2 in MAD 800 mg
- The majority of subjects in the SAD phase were White or Black/African American, with a mean (range) age of 40 (19-65) and BMI of 25 (19.0-30.0)
- Demographics for the MAD phase are summarized in **Table 1**

**Table 1**. Demographics of Subjects in MAD Phase

| | 200 mg QD (fasted, n=6) | 400 mg QD (fasted, n=6) | 400 mg QD (fed, n=6) | 800 mg QD (fed, n=6) | Placebo (fasted, n=4) | Placebo (fed, n=4) | Overall (n=32) |
|---|---|---|---|---|---|---|---|
| Male, n (%) | 3 (50.0) | 5 (83.3) | 3 (50.0) | 2 (33.3) | 4 (100.0) | 4 (100.00) | 21 (65.6) |
| Race, n (%) | | | | | | | |
| White | 6 (100.0) | 1 (16.7) | 1 (16.7) | 5 (83.3) | 3 (75.0) | 3 (75.0) | 19 (59.4) |
| Black or African American | 0 | 5 (83.3) | 4 (66.7) | 1 (16.7) | 1 (25.0) | 1 (25.0) | 12 (37.5) |
| Asian | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian/Other Pacific Islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Multiple | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (3.1) |
| Other | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ethnicity, n (%) | | | | | | | |
| Hispanic or Latino | 2 (33.3) | 0 | 2 (33.3) | 1 (16.7) | 1 (25.0) | 0 | 6 (18.8) |
| Age (y)[a] | 46.2 (19, 65) | 29.2 (20, 56) | 37.0 (20, 57) | 53.5 (36, 63) | 44.5 (32, 61) | 47.3 (26, 62) | 42.6 (19, 65) |
| BMI (kg/m$^2$)[a] | 24.8 (21.8, 29.2) | 27.5 (24.7, 29.3) | 25.7 (22.5, 30.0) | 25.2 (21.2, 29.2) | 24.2 (21.8, 26.7) | 26.5 (21.6, 29.1) | 25.7 (21.2, 30.0) |

[a]presented as mean (min, max)
BMI: body mass index; QD: once daily

### Pharmacokinetics

#### Pharmacokinetics: SAD Phase

- In the SAD phase (**Table 2, Figure 2, Figure 3**), EDP-235 exposure increased with ascending single doses in an approximately dose-proportional manner, up to the highest tested dose of 800 mg
- Plasma PK from the 200 mg fed cohort (high fat meal) indicates a 4-fold food effect
- Geometric mean $t_{1/2}$ was 13-18 hr across dose range, supporting once daily dosing

**Table 2**. EDP-235 Plasma PK Parameters Following Oral Administration of Single Doses of EDP-235 (values presented as geometric mean (%GCV) except $T_{max}$ is reported as median (min-max)

| PK Parameters | 50 mg fasted (n=6) | 100 mg fasted (n=6) | 200 mg fasted (n=6) | 200 mg fed (n=6) | 400 mg fasted (n=6) | 800 mg fasted (n=6) |
|---|---|---|---|---|---|---|
| $AUC_{0\text{-}inf}$ (hr*ng/mL) | 3080 (75.7) | 4670 (99.7) | 10100 (50.8) | 40500 (31.8) | 16700 (62.5) | 38300 (45.3) |
| $C_{max}$ (ng/mL) | 189 (79.3) | 249 (87.7) | 434 (50.9) | 1990 (20.6) | 767 (40.0) | 1020 (49.1) |
| $C_{24}$ (ng/mL) | 51.6 (68.5) | 74.2 (88.9) | 181 (66.6) | 738 (24.6) | 255 (73.1) | 683 (23.6) |
| $T_{max}$ (hr) | 3.5 (2.0-10.0) | 4.0 (2.0-5.0) | 4.0 (2.0-5.0) | 5.0 (4.0-6.0) | 4.0 (2.0-5.0) | 2.5 (2.0-24.0) |
| $T_{1/2}$ (hr) | 14.0 (29.9) | 17.8 (27.6) | 13.2 (49.9) | 15.5 (54.3) | 15.3 (16.6) | 17.8 (33.6) |
| CL/F (L/hr) | 16.2 (75.7) | 21.4 (99.7) | 19.7 (50.8) | 4.9 (31.8) | 23.9 (62.5) | 20.9 (45.3) |
| Vd/F (L) | 327 (58.7) | 550 (77.5) | 376 (66.3) | 111 (41.4) | 529 (61.6) | 537 (32.1) |

**Figure 2**. EDP-235 Mean Plasma PK Concentrations vs Time Following Oral Administration of Single Doses of EDP-235 (Linear Scale)

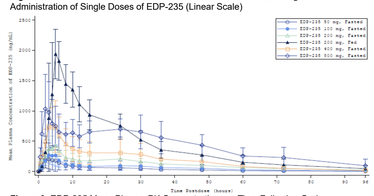



**Figure 3**. EDP-235 Mean Plasma PK Concentrations vs Time Following Oral Administration of Single Doses of EDP-235 (Logarithmic Scale)

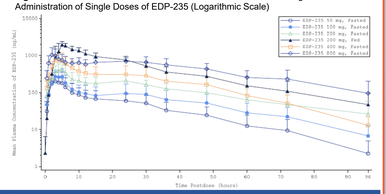



**Figure 4**. EDP-235 Mean Plasma PK Concentrations vs Time on Day 7 Following Oral Administration of Multiple Doses of EDP-235 (Linear Scale)

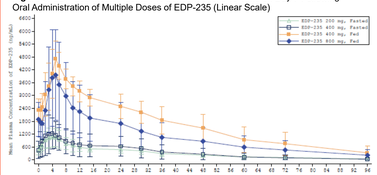
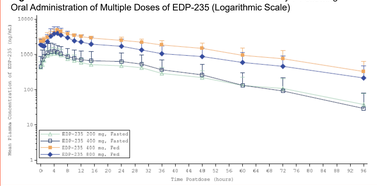



**Figure 5**. EDP-235 Mean Plasma PK Concentrations vs Time on Day 7 Following Oral Administration of Multiple Doses of EDP-235 (Logarithmic Scale)




#### Pharmacokinetics: MAD Phase

- In the MAD phase (**Table 3, Figure 4, Figure 5**), EDP-235 exposure increased with ascending multiple doses in an approximately dose-proportional manner, up to 400 mg
- Accumulation index (AI) ranged from 1.6 to 3.2 for MAD cohorts
- Steady state was reached 48 hours after the 1st dose
  - Geometric mean $t_{1/2}$ ranged from 13 to 22 hr
- There was a 4-fold food effect with a standard meal (400 mg)
- EDP-235 administered once daily for 7 days resulted in steady state $C_{24}$ concentrations up to 13-fold over the protein adjusted $EC_{90}$ determined in Vero E6 cells infected with the B.1.1.529 (Omicron) lineage

**Table 3**. EDP-235 Day 7 Plasma PK Parameters Following Oral Administration of Multiple Doses of EDP-235 (values presented as geometric mean (%GCV) except $T_{max}$ is reported as median (min-max)

| PK Parameters | 200 mg fasted (n=6) | 400 mg fasted (n=6) | 400 mg fed (n=6) | 800 mg fed (n=6) |
|---|---|---|---|---|
| $AUC_{0\text{-}tau}$ (hr*ng/mL) | 15200 (29.6) | 16000 (71.9) | 75700 (14.5) | 68400 (19.3) |
| $C_{max}$ (ng/mL) | 1060 (39.0) | 1180 (54.6) | 4830 (13.2) | 5080 (20.6) |
| $C_{24}$ (ng/mL) | 446 (42.8) | 506 (82.8) | 2450 (23.1) | 2000 (34.1) |
| $T_{max}$ (hr) | 4.0 (2.0-5.0) | 3.0 (2.0-5.0) | 5.0 (3.0-6.0) | 4.5 (3.0-6.0) |
| $T_{1/2}$ (hr) | 16.7 (51.9) | 13.2 (28.1) | 21.5 (47.1) | 19.5 (83.3) |

## RESULTS

### Safety Results

- Overall, EDP-235 was safe and well-tolerated in healthy subjects up to 400 mg once daily for 7 days
- The majority of AEs were mild, with the most frequent being headache and GI related symptoms
- Three MAD dosing discontinuations resulted from one moderate headache in the 400 mg fasted cohort, one severe headache in the 800 mg fed cohort, and one grade 3 ALT/grade 2 AST elevation in the 800 mg fed cohort
- There were no serious TEAEs

**Table 4:** Summary of Treatment-emergent AEs Following Administration of EDP-235 in the MAD Phase

| System Organ Class Preferred Term | 200 mg fasted (n=6) n (%) | 400 mg fasted (n=6) n (%) | 400 mg fed (n=6) n (%) | 800 mg fed (n=6) n (%) | Placebo fasted (n=4) n (%) | Placebo fed (n=4) n (%) | Overall (n=32) n (%) |
|---|---|---|---|---|---|---|---|
| Total Subjects with at Least One TEAE | 2 (33.3) | 1 (16.7) | 2 (33.3) | 4 (66.7) | 1 (25.0) | 1 (25.0) | 11 (34.4) |
| Gastrointestinal disorders | 0 | 0 | 1 (16.7) | 3 (50.0) | 0 | 0 | 4 (12.5) |
| Nausea | 0 | 0 | 0 | 2 (33.3) | 0 | 0 | 2 (6.3) |
| Abdominal pain | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (3.1) |
| Diarrhea | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (3.1) |
| Musculoskeletal and connective tissue disorders | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 | 0 | 2 (6.3) |
| Muscle spasms | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (3.1) |
| Myalgia | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (3.1) |
| Nervous system disorders | 1 (16.7) | 1 (16.7) | 1 (16.7) | 4 (66.7) | 0 | 0 | 7 (21.9) |
| Headache | 0 | 1 (16.7) | 1 (16.7) | 4 (66.7) | 0 | 0 | 6 (18.8) |
| Dizziness | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (3.1) |
| Somnolence | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 1 (3.1) |
| Respiratory, thoracic and mediastinal disorders | 1 (16.7) | 0 | 0 | 0 | 1 (25.0) | 0 | 2 (6.3) |
| Nasal dryness | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 1 (3.1) |
| Oropharyngeal pain | 0 | 0 | 0 | 0 | 1 (25.0) | 0 | 1 (3.1) |
| Skin and subcutaneous tissue disorders | 0 | 0 | 0 | 0 | 0 | 1 (25.0) | 1 (3.1) |
| Dermatitis contact | 0 | 0 | 0 | 0 | 0 | 1 (25.0) | 1 (3.1) |

## CONCLUSIONS

- EDP-235 was generally safe and well tolerated up to 400 mg once daily for 7 days in the fed (standard meal) and fasted state
- EDP-235 was rapidly absorbed, and exposures increased with ascending single and multiple doses
- Exposure was enhanced with food administration regardless of fat content
- EDP-235 exhibited PK supporting once daily dosing
- $C_{24}$ concentrations indicated strong multiples over the $EC_{90}$ (up to 13x for omicron) without the need for ritonavir boosting
- A Phase 2 trial (SPRINT) of EDP-235 in non-hospitalized adults with mild or moderate COVID-19 is currently ongoing, with data expected in 1H2023

## REFERENCES

Zang,T. 2021. *EDP-235, A Potential Oral, Once-Daily Antiviral Treatment and Preventative for COVID-19.* International Society for Influenza and other Respiratory Virus Diseases- World Health Organization Conference, 19-21 October 2021, virtual.

## ACKNOWLEDGEMENTS

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