Efficacy and Safety of EDP-235 in Nonhospitalized Adults With Mild or Moderate COVID-19: Results From the Phase 2 SPRINT Study

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P0423

BACKGROUND

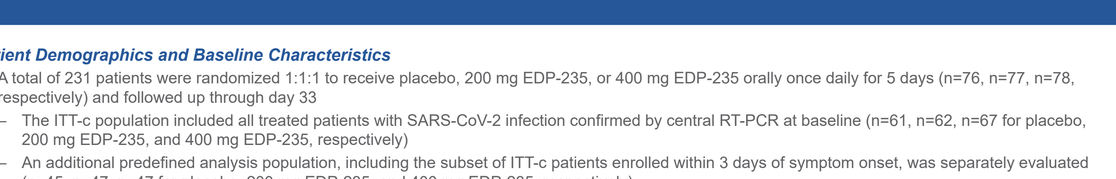
- COVID-19, caused by the highly contagious SARS-CoV-2 virus, continues to be a global health challenge[1-3]
- While vaccination efforts and immunity from prior infections have helped reduce transmission of SARS-CoV-2,[4] COVID-19 continues to cause substantial morbidity and mortality, and emergence of new variants could result in increased viral transmissibility, disease severity, and treatment resistance[3]
- Individuals with COVID-19 need convenient therapies that can prevent progression to severe disease and reduce time to recovery
  - Although mild to moderate COVID-19 can be self-resolving, some patients continue to develop long COVID syndrome[2] or progress to severe disease[4]
  - Therapies such as Paxlovid™ (nirmatrelvir/ritonavir) and Veklury® (remdesivir), are limited in their use; Paxlovid, due to numerous drug-drug interactions, and Veklury, due to its intravenous-only route of administration[3,5-7]
- EDP-235 is a potent ritonavir-free SARS-CoV-2 3C-like (3CL) protease inhibitor now under development as a once-daily oral antiviral therapy for the treatment of COVID-19[8]
  - The target of EDP-235 (3CL protease) is 1 of 2 cysteine proteases necessary for SARS-CoV-2 replication[9] and is highly conserved across coronaviruses (eg, MERS-CoV, SARS-CoV, and SARS-CoV-2) and in variants of SARS-CoV-2 detected thus far[10]
  - In preclinical studies, EDP-235 has demonstrated antiviral activity as early as 12 hours post-infection,[11] a favorable distribution profile with high tissue-to-plasma ratios in the lungs and intracellular uptake in lung epithelium[12]
  - Results from the recent Phase 1 trial (NCT05246878) demonstrated favorable safety, tolerability, and pharmacokinetic outcomes in healthy adult volunteers taking single doses up to 800 mg and multiple doses up to 400 mg (7 days). Once-daily EDP-235 at doses of 200 mg or 400 mg demonstrated plasma drug levels 7 to 13 times higher than the drug concentration that inhibits 90% of the virus (EC_{90}), without ritonavir boosting[13,14]
- Here, we present results from the Phase 2 SPRINT study (NCT05616728), which evaluated the safety and efficacy of EDP-235 in standard-risk adults with mild or moderate COVID-19[15]

METHODS

Study Design

- SPRINT was a Phase 2, randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of EDP-235 in nonhospitalized, standard-risk adults with mild or moderate COVID-19
- After an initial eligibility screening, patients were randomized 1:1:1 to receive once-daily oral doses of placebo, 200 mg EDP-235, or 400 mg EDP-235 over a 5-day, double-blind treatment period, followed by a 28-day safety and efficacy follow-up period (**Figure 1**)
  - Randomization was stratified by age (≤50 years or 51-64 years) and duration of COVID-19 symptoms (≤3 days or between >3 days and ≤5 days)

Figure 1. SPRINT Study Design



[a]Patients were stratified by age (≤50 years or 51-64 years) and duration of COVID-19 symptoms (≤3 days or between >3 days and ≤5 days) before randomization.
QD, once daily.

Key Eligibility Criteria

- Study participants were nonhospitalized adults (aged 18-64 years) with a SARS-CoV-2 infection confirmed by a positive test (either polymerase chain reaction [PCR] or antigen testing) ≤24 hours before randomization who also met the following criteria:
  - COVID-19 symptom onset within 5 days of randomization, and
  - At least 2 COVID-19 symptoms, with 1 being at least moderate in severity
- Participants were excluded from the study if they had a prior infection with SARS-CoV-2 or received any vaccine dose within 90 days of enrollment or if they were at increased risk for developing severe disease

Study Endpoints

- The primary endpoint was safety, measured by the frequency of adverse events (AEs) from day 1 to day 33
- Key secondary endpoints included change from baseline in a US Food and Drug Administration–defined 14-item total symptom score (TSS) and in 6 selected symptoms (TSS-6, post hoc analysis) using a COVID-19 symptom diary, and change from baseline in SARS-CoV-2 RNA viral load analyzed using quantitative reverse transcriptase PCR (RT-PCR)
  - Symptoms included those from respiratory (eg, cough, shortness of breath, sore throat, stuffy or runny nose), systemic (eg, chills or shivering, feeling hot or feverish, headache, low energy or tiredness, muscle or body aches), digestive (eg, nausea, vomiting, diarrhea), and other domains (eg, loss of sense of smell or taste)

Statistics

- Safety parameters were analyzed using descriptive statistics for the safety population, defined as participants who had received at least 1 dose of study drug
- Efficacy analyses were performed on the intent-to-treat confirmed (ITT-c) population, which included all participants in the safety population with confirmatory evidence of SARS-CoV-2 using RT-PCR at baseline, and at least 1 post-baseline efficacy assessment
  - An analysis of covariance (ANCOVA) model with stratification factors (age [≤50 years or 51-64 years] and duration of COVID-19 symptoms [≤3 days or between >3 days and ≤5 days]) and baseline score as the covariate were used for treatment comparisons
  - Time to improvement of targeted COVID-19 symptoms through day 33 was summarized graphically using Kaplan-Meier plots and analyzed by the Cox proportional hazards model

RESULTS

Patient Demographics and Baseline Characteristics

- A total of 231 patients were randomized 1:1:1 to receive placebo, 200 mg EDP-235, or 400 mg EDP-235 orally once daily for 5 days (n=76, n=77, n=78, respectively) and followed up through day 33
  - The ITT-c population included all treated patients with SARS-CoV-2 infection confirmed by central RT-PCR at baseline (n=61, n=62, n=67 for placebo, 200 mg EDP-235, and 400 mg EDP-235, respectively)
  - An additional predefined analysis population, including the subset of ITT-c patients enrolled within 3 days of symptom onset, was separately evaluated (n=45, n=47, n=47 for placebo, 200 mg EDP-235, and 400 mg EDP-235, respectively)
- Baseline characteristics were well balanced between study arms (**Table 1**)
- Nearly all participants were SARS-CoV-2 seropositive at baseline (~96%), and the proportion of vaccinated participants in the study arms ranged from 66% to 77%

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Placebo (n=76)	200 mg EDP-235 (n=77)	400 mg EDP-235 (n=78)
Median age in years (range)	45.5 (19-62)	43.0 (19-64)	46.0 (19-64)
18-50 years, n (%)	51 (67.1)	50 (64.9)	51 (65.4)
Sex: female, n (%)	42 (53.3)	50 (64.9)	47 (60.3)
Race: White, n (%)	70 (92.1)	73 (94.8)	75 (96.2)
Ethnicity: Hispanic/Latino, n (%)	71 (93.4)	74 (96.1)	73 (93.6)
Median BMI, kg/m^2 (range)	24.8 (18.8-32.9)	24.9 (17.0-33.9)	24.9 (20.4-38.5)
Smoking history: never, n (%)	74 (97.4)	76 (98.7)	75 (96.2)
COVID-19 vaccination status: vaccinated, n (%)	50 (65.8)	56 (72.7)	60 (76.9)
Serostatus: seropositive, n (%)	73 (96.1)	74 (96.1)	75 (96.2)
Mean baseline viral load: log10 copies/mL	5.1	5.0	5.1

BMI, body mass index.

Safety Outcomes

- EDP-235 was generally well tolerated across all doses, with a low incidence of treatment-emergent AEs (TEAEs) in groups receiving EDP-235 (**Table 2**)
- Most TEAEs were mild in severity; none were serious or caused study discontinuation

Table 2. Safety Summary

Event	Placebo (n=76)	200 mg EDP-235 (n=77)	400 mg EDP-235 (n=78)
Any TEAE – No. of events	3	1	6
Any TEAE, n (%)	2 (2.6)	1 (1.3)	5 (6.4)
Mild (grade 1)	1 (1.3)	1 (1.3)	4 (5.1)
Moderate (grade 2)	1 (1.3)	0	0
Severe (grade 3)	0	0	1 (1.3)
Preferred term			
Hepatotoxicity	0	1 (1.3)	1 (1.3)
Periorbital edema	0	0	1 (1.3)
Face edema	0	0	1 (1.3)
Gastroenteritis	0	0	1 (1.3)
Fall	0	0	1 (1.3)
Hyperglycemia	1 (1.3)	0	0
Hypertriglyceridemia	1 (1.3)	0	0
Arthralgia	0	0	1 (1.3)
Dysgeusia	1 (1.3)	0	0

n, number of patients; TEAE, treatment-emergent adverse event.

Laboratory values were generally unremarkable

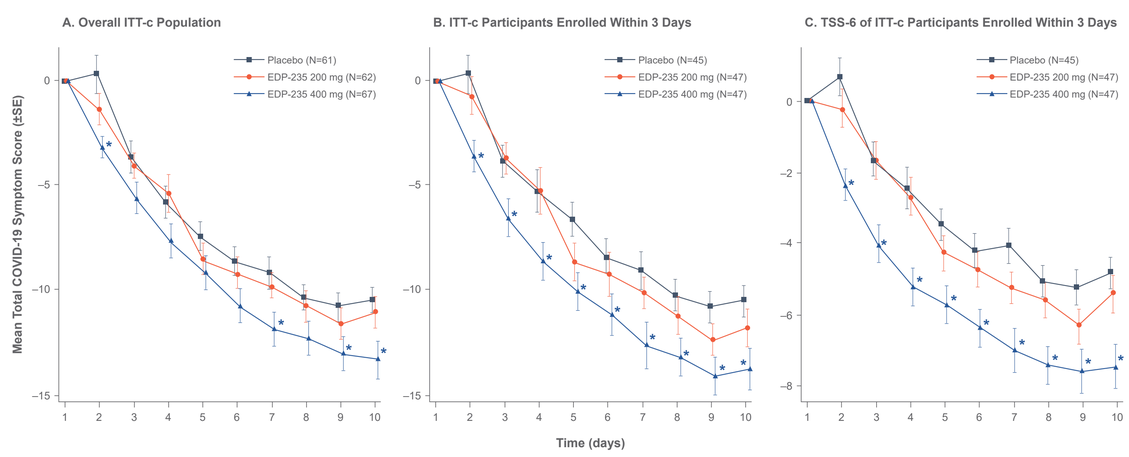
- Transient, dose-dependent elevations in total cholesterol and triglycerides were seen with EDP-235 treatment, trending toward baseline after completion of treatment
- Two events of hepatotoxicity were reported at one site. One patient receiving EDP-235 400 mg who had concomitant use of alcohol and acetaminophen experienced asymptomatic, transient elevation of alanine transaminase (ALT, grade 4), aspartate aminotransferase (AST, grade 3), and gamma-glutamyl transferase (GGT) with normal bilirubin and alkaline phosphatase. Another patient receiving EDP-235 200 mg experienced asymptomatic, transient elevation of ALT (grade 1), AST (grade 1), and GGT with normal bilirubin and alkaline phosphatase

RESULTS (cont.)

Change From Baseline in COVID-19 Symptoms

- There was a dose-dependent improvement in TSS compared with placebo in the ITT-c population. Patients treated with EDP-235 400 mg had statistically significant improvements over placebo on days 2, 7, 9, and 10 (all P<0.05), with a trend for lower TSS observed at all other time points (**Figure 2A**)
- Among participants enrolled within 3 days of symptom onset, the EDP-235 400 mg arm achieved greater mean change in TSS compared with the placebo arm at all time points (P<0.05, all time points; **Figure 2B**)
- A symptom score for a selected group of 6 symptoms (TSS-6) was separately assessed among participants enrolled within 3 days. In this post hoc analysis, the magnitude of the mean change in TSS-6 was greater with EDP-235 400 mg treatment compared with placebo at all time points (P<0.05, all time points; **Figure 2C**)
- Differences among the mean change in TSS in the EDP-235 200 mg and placebo arms were not significant

Figure 2. Change From Baseline in COVID-19 Symptom Scores

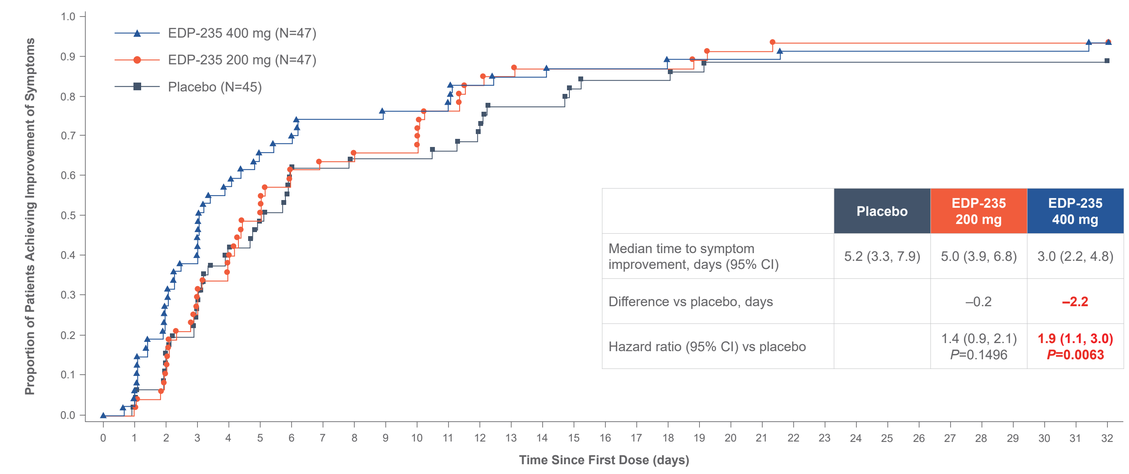


*P<0.05. P value was tested using ANCOVA model, with a 2-sided alpha of 0.05, stratified by age and duration of COVID-19 symptoms at screening. Six selected COVID-19 symptoms included 3 respiratory symptoms (shortness of breath, sore throat, stuffy or runny nose) and 3 systemic symptoms (chills or shivering, feeling hot or feverish, headache).
ANCOVA, analysis of covariance; ITT-c, intent-to-treat population included all treated participants with their SARS-CoV-2 status confirmed by central RT-PCR viral load at baseline ≥ lower limit of quantification; RT-PCR, reverse transcriptase polymerase chain reaction; TSS-6, total symptom score in 6 selected symptoms.

Time to Improvement in COVID-19 Symptoms

- There was no difference in time to improvement in the 14-item TSS among study arms in the overall ITT-c population (data not shown)
- For participants enrolled within 3 days, there was a significantly shorter median time to symptom improvement in TSS-6 in the EDP-235 400 mg arm compared with placebo (3.0 and 5.2 days, respectively; hazard ratio, 1.9; 95% CI, 1.2-3.0; P=0.0063) (**Figure 3**)

Figure 3. Time to Symptom Improvement in TSS-6 in Participants Enrolled Within 3 Days



	Placebo	EDP-235 200 mg	EDP-235 400 mg
Median time to symptom improvement, days (95% CI)	5.2 (3.3, 7.9)	5.0 (3.9, 6.8)	3.0 (2.2, 4.8)
Difference vs placebo, days		–0.2	**–2.2**
Hazard ratio (95% CI) vs placebo		1.4 (0.9, 2.1) P=0.1496	**1.9 (1.1, 3.0) P=0.0063**

P value was tested using an ANCOVA model, with a 2-sided alpha of 0.05, stratified by age and duration of COVID-19 symptoms at screening. Six selected COVID-19 symptoms included 3 respiratory symptoms (shortness of breath, sore throat, stuffy or runny nose) and 3 systemic symptoms (chills or shivering, feeling hot or feverish, and headache).
ANCOVA, analysis of covariance; TSS-6, total symptom score in 6 selected symptoms.

Virologic Effects of EDP-235

- A rapid decline in nasal viral RNA was observed in all treatment arms, indicating rapid clearance of SARS-CoV-2 virus from the nose in this highly immune population
- In the overall study population, mean viral load did not differ among treatment arms; however, statistically significant reductions in viral load were observed in multiple subgroups
  - In participants with a mean baseline viral load >5 log, a viral RNA decline of 0.4 log was observed at day 3 in both EDP-235 treatment arms vs placebo and at day 5 in EDP-235 400 mg vs placebo
  - In participants who were seronegative for antibodies to the nucleocapsid antigen at baseline, a viral RNA decline of 0.8 log was observed in the EDP-235 400 mg (n=30) group vs the placebo group (n=20) at day 5

CONCLUSIONS

- EDP-235 treatment in standard-risk adults with mild or moderate COVID-19 yielded a favorable safety profile and improvements in clinical symptoms
- EDP-235 was generally well tolerated, as reflected by a low frequency of TEAEs that were mostly mild in severity, and there were no serious TEAEs or TEAE-related discontinuations
- The 400 mg dose of EDP-235 achieved statistically significant improvement in TSS at multiple time points in the overall study population
  - In participants enrolled within 3 days of symptom onset, along with significant TSS improvement at all time points, a median 2-day shorter duration of 6 selected COVID-19 symptoms was observed
- The rapid decline of viral load across all study groups was consistent with an enrolled population that had prior immunity
- The results of the Phase 2 SPRINT study support further development of EDP-235 for the treatment of COVID-19
- As the therapeutic target is conserved across variants, EDP-235 may prove an effective tool to combat future variants of SAR-CoV-2 and potentially other coronaviruses[11]

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ACKNOWLEDGMENTS AND DISCLOSURES

Medical writing assistance was provided by Shvetha Srinath, MSc, of InCight, a division of Cadent, powered by Syneos Health, and supported by Enanta Pharmaceuticals, Inc. Presented at the 34th Annual Meeting of the European Congress of Clinical Microbiology and Infectious Diseases, April 27-30, 2024, Barcelona, Spain.

All authors are employees of Enanta Pharmaceuticals, Inc.

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