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# EDP-323, a First-In-Class, Once-Daily, Oral L-Protein Inhibitor for the Treatment of RSV: Results From a Phase 1 Study in Healthy Adults

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## ABSTRACT

Respiratory syncytial virus (RSV) remains a significant health concern, particularly for vulnerable populations. Despite preventive strategies, there remains a need for effective antiviral treatments. EDP-323 is a first-in-class, potent oral selective non-nucleoside inhibitor of the large protein (L polymerase) of RSV under investigation for the treatment of RSV infection. This phase 1, randomized, double-blind, placebo-controlled study evaluated the safety and pharmacokinetics of EDP-323. This study included fasted single ascending dose (SAD; EDP-323 50/100/200/400/600/800 mg doses, 3:1 to placebo), fed multiple ascending dose (MAD; EDP-323200/400/600/800 mg doses, 3:1 to placebo), and food effect (EDP-323200 mg dose, 4:1 to placebo) cohorts in healthy adult participants. Key objectives were to assess the safety, tolerability, and pharmacokinetic (PK) profile of EDP-323 in plasma and urine, and to evaluate the effect of food intake on its pharmacokinetics. Among 82 randomized participants (SAD, $n = 50$; MAD, $n = 32$), EDP-323 was well tolerated up to the highest tested dose (800 mg once daily for 7 days). Adverse events (AEs) were reported in 14.6% of total participants, with the majority being mild and deemed unlikely related to the study drug. Headache was the most frequent AE ($n = 3$). PK analysis showed that EDP-323 was rapidly absorbed ($T_{max} = 3.0–5.0$ h), with exposures increasing with ascending dose. The half-life of EDP-323 ($t_{1/2} = 10.8–16.6$ h) supported once-daily dosing, and no food effect was observed. EDP-323 demonstrated a favorable safety and PK profile, supporting its potential as a once-daily oral treatment for RSV.

## 1 | Introduction

Respiratory syncytial virus (RSV) is a ubiquitous virus that repeatedly infects human populations of all ages worldwide [1, 2]. Although RSV generally promotes annual wintertime epidemics, in more tropical regions, patterns of continuous transmission occur [3, 4]. During these epidemics, RSV circulates widely, infecting 68% of infants at least once within their first year of life, with nearly all children being infected at least once by the time they have passed through 2 RSV seasons [5, 6]. Since RSV induces relatively poor and short-lived natural immune responses, children and adults experience repeated infections throughout their lives [7, 8]. These infections produce disease of varying severity across all ages, with the most severe disease concentrated at the extremes of age and in those with comorbid conditions [1].

In children, RSV causes bronchiolitis and pneumonia and is the leading cause of infant hospitalization [1, 6]. Within North America and Europe, approximately 2% of all children are hospitalized for RSV within their first year of life [9–11]. The hospitalization rate for RSV in this age group is 16 times that

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**Summary**

- What is the current knowledge on the topic?
  - Respiratory syncytial virus (RSV) is a significant health concern in the vulnerable and general population. Despite existing preventive strategies, there is a pressing need for effective antiviral treatments. EDP-323 is a novel potent oral selective non-nucleoside inhibitor targeting the large protein (L polymerase) of RSV, currently under investigation for treating RSV infections.
- What question did this study address?
  - This phase 1, randomized, double-blind, placebo-controlled study aimed to evaluate the safety and pharmacokinetics of EDP-323. Specifically, it assessed the safety, tolerability, and pharmacokinetic (PK) profile of EDP-323 in plasma and urine, and examined the effect of food intake on its pharmacokinetics.
- What does this study add to our knowledge?
  - The study found that EDP-323 was well tolerated up to the highest tested dose of 800 mg once daily for 7 days. Adverse events were reported in 18% of participants who received EDP-323 (15% of total participants), mostly mild and not likely related to the study drug, with headache being the most frequent. PK analysis showed rapid absorption of EDP-323, with dose-proportional increases in exposure. EDP-323 exhibited a half-life suitable for once-daily dosing and showed no significant food effect.
- How might this change clinical pharmacology or translational science?
  - The favorable safety and PK profile of EDP-323 supports its potential as a once-daily oral treatment for RSV. This could significantly impact clinical pharmacology by providing a new effective antiviral option for RSV, potentially helping to bridge the gap in treatment options for patients with RSV, including those outside the hospital setting.

of influenza and results in mortality rates 9 times that of influenza [12, 13]. In children of all ages, RSV is the leading cause of community-acquired pneumonia, with the overwhelming majority of hospitalizations occurring in those who were previously healthy [14, 15]. Worldwide, RSV is the leading viral cause of pediatric respiratory-related mortality [16]. The burden of RSV in the pediatric outpatient setting is even greater. In the United States (US), 2.1 million children aged < 5 years require medical attention annually due to RSV, of which > 73% are treated as outpatients [11]. A similarly high burden is seen in Europe, where RSV-related medically attended visits occur in 14% of children within their first year of life, even when children with comorbidities are excluded [9].

RSV infections continue to occur throughout adulthood, causing a range of disease severity depending on the degree of prior immunity, increased age, and presence and severity of comorbidities, including pneumonia, respiratory failure, and exacerbations of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and asthma [17]. As with children, RSV is the leading cause of community-acquired pneumonia requiring hospitalization in adults [18]. Annually, RSV infections develop in 3%–7% of the healthy elderly population (aged ≥ 65 years) and in 4%–10% of adults with high-risk comorbidities [19]. In adults, health care utilization due to RSV infection is similar to rates due to influenza, with comparable lengths of hospital stay and mortality [19].

Current strategies to prevent RSV in children rely on passive antibody approaches, either through maternal vaccination, providing transplacental antibody transfer, or monoclonal antibodies with limited half-lives [20–23]. These approaches provide protection against severe disease primarily through the child's first winter season [1]. This leaves a majority of the childhood RSV medical encounters unaddressed [11].

Active vaccination of elderly and high-risk adult populations against RSV has been recently approved and will benefit those who elect to receive the vaccine. Studies indicate the vaccine confers significant but incomplete protection, with vaccine efficacy against RSV-related lower respiratory tract infections in the range of 67%–83% [23, 24]. Therefore, the development of RSV antivirals is crucial to address the unmet medical needs that these prevention strategies fail to cover.

The only antiviral approved for the treatment of RSV is aerosolized ribavirin [25]. While it demonstrates that an antiviral can effectively reduce the severity of RSV disease, ribavirin is not considered standard care and is seldom used due to its cumbersome administration, potential mutagenicity, concerns about exposing hospital caregivers and family members to risks, and its limited efficacy [26, 27]. As a result, current therapy for RSV infections primarily involves supportive care [26]. There is a pressing need for a safe, easily administered, and effective antiviral therapy for RSV.

EDP-323 is a first-in-class, potent oral selective non-nucleoside inhibitor of the large protein (L polymerase) of RSV under investigation for the treatment of RSV infection [28]. Viral resistance studies coupled with biochemical and structural analyses suggest that EDP-323 binds the capping domain of the L protein and disrupts the activity of the RSV RNA-dependent RNA polymerase (RdRp), blocking viral transcription and replication [29]. The L protein is highly conserved across all known isolates of RSV-A and RSV-B, making it a viable target irrespective of virus strain [30]. EDP-323 is active against clinical and laboratory strains of both RSV-A and RSV-B subtypes, with picomolar in vitro potency [31]. Additionally, the RSV RdRp is an ideal antiviral target due to its distinct difference from human DNA-dependent RNA polymerase, ensuring high specificity [32]. Preclinical studies also indicated favorable target tissue distribution of EDP-323 into lungs and alveolar macrophages without off-target brain distribution [28].

In mice and other preclinical models, EDP-323 demonstrated excellent bioavailability and favorable preclinical pharmacokinetic (PK) properties [26, 27, 29]. In addition, orally dosed EDP-323 demonstrated antiviral activity in mice, with a dose-dependent reduction in viral RNA, viral lung titers, viral-induced pathology, and lung staining histopathology scores [28, 29, 33]. These

preclinical data support the clinical development of EDP-323 as a first-in-class non-nucleoside polymerase inhibitor antiviral against RSV. Here, we report the outcomes of a first-in-human phase 1 study conducted to characterize the PK profile, safety, and tolerability of EDP-323 in healthy adult participants.

## 2 | Methods

### 2.1 | Ethics

The study was conducted at ICON-EDS, Lenexa, KS, US, in compliance with the principles of the International Council for Harmonization—Good Clinical Practice, Declaration of Helsinki, and all applicable national regulations. Study documents, including protocol and informed consent, were reviewed and approved by an institutional review board (approval no. PRA-9191638 Pro00066269, September 13, 2022). All participants provided informed consent before enrollment.

### 2.2 | Study Design

This was a phase 1, randomized, double-blind, placebo-controlled study (NCT05587478) with a single ascending dose (SAD) phase, including a 2-part food effect (FE) cohort, and a multiple ascending dose (MAD) phase (Figure 1). The primary objective was to evaluate the safety and tolerability of a single dose and multiple doses of EDP-323 in healthy participants. Secondary objectives included evaluation of the pharmacokinetics of single and multiple doses of EDP-323 in plasma and urine, and the effect of food intake on the pharmacokinetics of EDP-323 administered as a single dose.

EDP-323 or matching placebo was administered as oral capsules once daily throughout the study. In the SAD phase, participants were randomized to receive single doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg once daily of EDP-323 or placebo in a 3:1 ratio. Participants received EDP-323 after fasting overnight. The sentinel group consisted of 1 participant each treated with 50 mg of EDP-323 or placebo; thereafter, other participants in the 50 mg group began once-daily dosing. Doses were escalated only after the previous cohort safety data review. The initial dose of 50 mg was deduced from the results of preclinical mouse and monkey 28-day repeat-dose toxicology studies (conducted under good laboratory practice guidelines) in accordance with the FDA guidance for maximum starting dose in clinical trials [27].

To assess the effect of food on PK characteristics of EDP-323, the EDP-323 200 mg cohort was designated the SAD-FE cohort. Participants were randomized to receive EDP-323 (200 mg) or placebo in a 4:1 ratio. SAD-FE participants received the first dose of the study drug in a fasted state (part 1) and, after a 7-day washout period, received the same dose after consuming a standard high-fat meal (part 2) (Table S1).

The first MAD cohort was initiated after reviewing available safety and PK data from the SAD-FE cohort so that the fed/fasted status could be determined. During the MAD phase, participants were randomized to receive EDP-323 or placebo (3:1 active: placebo) once daily for 7 days. EDP-323 was administered at 4 ascending dose levels (200 mg, 400 mg, 600 mg, or 800 mg) with participants in a fed state (following a standard meal).

### 2.3 | Participant Selection

Key eligibility criteria included healthy male and female participants of any racial or ethnic origin aged 18–65 years at screening, with a body mass index (BMI) of 18–30 kg/m$^2$ and a minimum weight of 50 kg at screening. Participants were eligible if they had no clinically relevant abnormality on physical examination, medical history, vital sign assessment, and clinical laboratory testing at screening and admission. The Data S1 in Appendix S1 contains a detailed list of eligibility criteria.

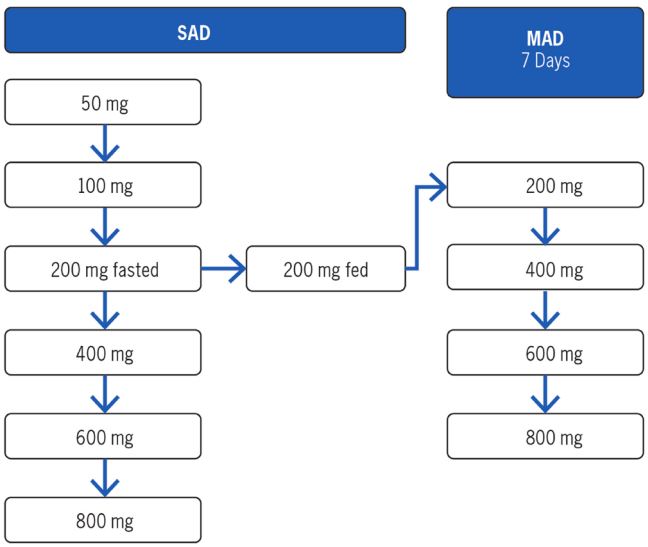



**FIGURE 1** | Study design. Healthy volunteers were randomized 3 (active): 1 (placebo), 4:1 in the FE cohort. All SAD participants were fasted except for those in a 200 mg FE cohort (high-fat meal). All MAD participants were fed a standard meal. FE, food effect; MAD, multiple ascending dose; SAD, single ascending dose.

Exclusion criteria included pregnancy and clinically relevant evidence or history of illness or disease as determined by the investigator. Participants were excluded if infection with HIV, hepatitis B virus, or hepatitis C virus was confirmed at screening. All potential participants underwent polymerase chain reaction testing for COVID-19 on the day before first dosing and were excluded if the results were positive. Participants with a history of routine smoking, illicit drug use, or alcohol abuse were excluded as well.

### 2.4 | Study Assessments

To assess safety and tolerability, participants were monitored for adverse events (AEs) and serious AEs. Additional monitoring included physical examinations, assessment of vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests (chemistry, hematology, and urinalysis).

To assess the pharmacokinetics of EDP-323 during the SAD phase, plasma samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, 72, and 96 h post-dose. Similarly, in the MAD phase, blood sampling occurred over a 24-h period on Day 1 and over a 96-h period starting on Day 7. A single pre-dose sample was collected on Days 2 through 6. In the SAD phase, urine samples were collected pre-dose and at various intervals post-dose (0–6, 6–12, 12–24, 24–48, and 48–96 h post-dose). All samples were collected and stored per a prespecified process, as detailed in Table S2.

EDP-323 and metabolite concentrations were quantified using high-performance liquid chromatography with tandem mass spectrometry (LC–MS/MS) detection (assay range 1.00 ng/mL [lower limit of quantification] to 1000.00 ng/mL [upper limit of quantification]). All methods were fully validated by the ICON Bioanalytical Laboratory (Whitesboro, NY, US) by assessing the precision, accuracy, sensitivity, and specificity of the assay tests for EDP-323 and its metabolites.

### 2.5 | Statistical Analysis

No formal sample size calculations were performed for this study. The number of participants in each cohort was considered sufficient to characterize the safety, tolerability, pharmacokinetics, and food effect on the PK characteristics of EDP-323 in each phase of the study. All statistical analyses and reporting were performed using SAS for Windows (version 9.4 or higher; SAS Institute Inc.). Safety and tolerability data, including AEs and results of physical examinations, assessments of vital signs, ECGs, and clinical laboratory tests, were summarized by cohort using descriptive statistics. Descriptive statistics were used to summarize the plasma concentrations and PK of EDP-323 in each treatment group at each scheduled time point (number of participants, mean, geometric mean, SD, % coefficient of variation [$C_V$], % geometric $C_V$, median, minimum, and maximum). For time to maximum plasma concentration ($T_{max}$), only median, minimum, and maximum were presented. Plasma PK parameters were calculated for EDP-323 and its metabolites (EP-038725 and EP-039082) using noncompartmental and best-fit regression methods with Phoenix WinNonlin (WNL) (version 8.1 or higher; Certara, L.P.). Urine PK parameters were calculated using the cumulative amount of EDP-323 and its metabolites excreted from zero to last quantifiable concentration. In estimating the parameters, all missing values were recorded as missing, and all below-quantification level values were set at zero. The effect of food was assessed using ratio and 90% CIs of the geometric least-squares (LS) mean of each plasma PK parameter for EDP-323. A linear mixed effects model with fixed effects for treatment (fasted or fed state) and a random effect for participant was performed using the natural log-transformed parameters.

## 3 | Results

### 3.1 | Participant Disposition and Baseline Characteristics

This study was conducted between September 29, 2022, and March 29, 2023. A total of 82 participants were randomized (SAD, $n = 50$; MAD, $n = 32$) to receive at least one dose of either EDP-323 or placebo (Figure S1). Of the total participants, 62 received EDP-323 (SAD, $n = 38$; MAD, $n = 24$). One participant discontinued dosing due to an AE of syncope (SAD EDP-323 200 mg fed cohort). SAD and MAD participants had similar baseline characteristics (Table 1); slightly more than half of the total cohort was male, and most participants were White or Black/African American. The mean age was ~38 years and the mean BMI was ~25 kg/m$^2$.

### 3.2 | Safety

Overall, EDP-323 was generally well tolerated in healthy participants up through the highest tested dose of 800 mg once daily for 7 days. Of the 62 participants who received EDP-323 in SAD or MAD, 11 (17.7%) had treatment-emergent adverse events (TEAEs). AEs were generally balanced between EDP-323 and placebo recipients, and there was no apparent dose-related trend for the incidence of AEs with ascending doses of EDP-323. The majority of AEs were mild; headache was the most commonly reported AE ($n = 3$). There were no severe or serious TEAEs.

During the SAD phase, 2 (4.0%) participants had a total of 4 TEAEs, with most AEs considered mild in severity and all deemed unlikely or not related to the study drug by the investigator (Table 2). One participant receiving 200 mg EDP-323 experienced dehydration and syncope while fasting, which was considered moderate in severity and deemed unlikely to be related to the study drug. This AE of syncope led to the discontinuation of the participant from the study.

During the MAD phase, 10 (31.3%) participants had a total of 13 TEAEs, one of whom had received placebo (Table 2). Among the 9 participants receiving EDP-323 who had TEAEs, only 3 of the TEAEs were considered to be possibly related to EDP-323, and all were mild. The most common TEAE was headache ($n = 3$). No discontinuations occurred during the MAD phase.

**TABLE 1** | Participant demographic and baseline characteristics.

| Characteristics | SAD phase | | | | | | | | | | MAD phase | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phases** | **Placebo (fasted, *n* = 12)** | **Placebo (fed, *n* = 2)** | **EDP-323 50 mg (fasted, *n* = 6)** | **EDP-323 100 mg (fasted, *n* = 6)** | **EDP-323 200 mg (fasted, *n* = 8)** | **EDP-323 200 mg (fed, *n* = 7)** | **EDP-323 400 mg (fasted, *n* = 6)** | **EDP-323 600 mg (fasted, *n* = 6)** | **EDP-323 800 mg (fasted, *n* = 6)** | **Overall (*n* = 50)** | **Placebo (fed, *n* = 8)** | **EDP-323 200 mg (fed, *n* = 6)** | **EDP-323 400 mg (fed, *n* = 6)** | **EDP-323 600 mg (fed, *n* = 6)** | **EDP-323 800 mg (fed, *n* = 6)** | **Overall (*n* = 32)** |
| Male, *n* (%) | 6 (50.0) | 2 (100.0) | 5 (83.3) | 3 (50.0) | 6 (75.0) | 6 (85.7) | 4 (66.7) | 3 (50.0) | 2 (33.3) | 29 (58.0) | 4 (50.0) | 3 (50.0) | 4 (66.7) | 2 (33.3) | 5 (83.3) | 18 (56.3) |
| Race, *n* (%) | | | | | | | | | | | | | | | | |
| White | 9 (75.0) | 1 (50.0) | 4 (66.7) | 4 (66.7) | 5 (62.5) | 5 (71.4) | 5 (83.3) | 3 (50.0) | 5 (83.3) | 35 (70.0) | 6 (75.0) | 4 (66.7) | 1 (16.7) | 4 (66.7) | 3 (50.0) | 18 (56.3) |
| Black or African American | 2 (16.7) | 0 | 1 (16.7) | 2 (33.3) | 2 (25.0) | 2 (28.6) | 0 | 2 (33.3) | 0 | 9 (18.0) | 2 (25.0) | 2 (33.3) | 3 (50.0) | 1 (16.7) | 3 (50.0) | 11 (34.4) |
| Asian | 1 (8.3) | 1 (50.0) | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4.0) | 0 | 0 | 2 (33.3) | 0 | 0 | 2 (6.3) |
| Multiple | 0 | 0 | 0 | 0 | 1 (12.5) | 0 | 1 (16.7) | 1 (16.7) | 1 (16.7) | 4 (8.0) | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (3.1) |
| Ethnicity | | | | | | | | | | | | | | | | |
| Hispanic or Latino | 2 (16.7) | 0 | 1 (16.7) | 0 | 1 (12.5) | 1 (14.3) | 0 | 2 (33.3) | 2 (33.3) | 8 (16.0) | 3 (37.5) | 0 | 0 | 3 (50.0) | 1 (16.7) | 7 (21.9) |
| Age in years, mean (min, max) | 43.0 (26, 64) | 32.5 (28, 37) | 31.0 (21, 44) | 38.5 (27, 62) | 44.4 (23, 63) | 47.4 (33, 63) | 35.7 (22, 45) | 35.7 (25, 47) | 31.3 (21, 49) | 38.1 (21, 64) | 36.4 (21, 55) | 48.7 (41, 62) | 39.2 (25, 53) | 36.2 (22, 59) | 33.5 (21, 41) | 38.6 (21, 62) |
| BMI ($kg/m^2$) | 26.2 (18.8, 29.2) | 27.5 (26.9, 28.0) | 25.3 (21.9, 27.8) | 24.2 (19.5, 28.7) | 26.6 (19.6, 29.8) | 26.8 (19.6, 29.8) | 24.3 (21.1, 27.8) | 24.5 (20.9, 28.1) | 23.8 (19.1, 28.7) | 25.2 (18.8, 29.8) | 25.4 (20.4, 29.3) | 23.3 (20.7, 25.5) | 27.0 (23.8, 29.4) | 27.3 (25.7, 28.6) | 24.4 (22.3, 27.7) | 25.5 (20.4, 29.4) |

Abbreviations: BMI, body mass index; MAD, multiple ascending dose; max, maximum; min, minimum; *n*, number of participants; SAD, single ascending dose.

**TABLE 2** | Incidence of TEAEs following administration of EDP-323.

| System organ class preferred term | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **SAD phase** | **Placebo (fasted, *n* = 12)** | **Placebo (fed, *n* = 2)** | **EDP-323 50 mg (fasted, *n* = 6)** | **EDP-323 100 mg (fasted, *n* = 6)** | **EDP-323 200 mg (fasted, *n* = 8)** | **EDP-323 200 mg (fed, *n* = 7)** | **EDP-323 400 mg (fasted, *n* = 6)** | **EDP-323 600 mg (fasted, *n* = 6)** | **EDP-323 800 mg (fasted, *n* = 6)** |
| Total participants with at least one TEAE [number of TEAEs] | 0 | 0 | 0 | 0 | 1 (12.5) [2] | 0 | 0 | 0 | 1 (16.7) [2] |
| Drug-related TEAE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinued for TEAE | 0 | 0 | 0 | 0 | 1 (12.5) | 0 | 0 | 0 | 0 |
| General disorders, administration site conditions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) |
| Infusion site extravasation[a] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7)[b,c] |
| Metabolism and nutrition disorders | 0 | 0 | 0 | 0 | 1 (12.5) | 0 | 0 | 0 | 0 |
| Dehydration | 0 | 0 | 0 | 0 | 1 (12.5)[b,c] | 0 | 0 | 0 | 0 |
| Nervous system disorders | 0 | 0 | 0 | 0 | 1 (12.5) | 0 | 0 | 0 | 0 |
| Syncope | 0 | 0 | 0 | 0 | 1 (12.5)[d,e] | 0 | 0 | 0 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) |
| Rhinitis allergic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7)[b,c] |

| **MAD phase** | **Placebo (fed, *n* = 8)** | **EDP-323 200 mg (fed, *n* = 6)** | **EDP-323 400 mg (fed, *n* = 6)** | **EDP-323 600 mg (fed, *n* = 6)** | **EDP-323 800 mg (fed, *n* = 6)** |
|---|---|---|---|---|---|
| Total participants with at least one TEAE [number of TEAEs] | 1 (12.5) [1] | 3 (50.0) [3] | 2 (33.3) [2] | 4 (66.7) [7] | 0 |
| Drug-related TEAE | 0 | 1 (16.7) | 0 | 2 (33.3) | 0 |
| Eye disorders | 0 | 0 | 0 | 1 (16.7) | 0 |

(Continues)

**TABLE 2** | (Continued)

| MAD phase | Placebo (fed, $n=8$) | EDP-323 200 mg (fed, $n=6$) | EDP-323 400 mg (fed, $n=6$) | EDP-323 600 mg (fed, $n=6$) | EDP-323 800 mg (fed, $n=6$) |
|---|---|---|---|---|---|
| Conjunctivitis allergic | 0 | 0 | 0 | 1 (16.7)[b,c] | 0 |
| Gastrointestinal disorders | 0 | 0 | 1 (16.7) | 2 (33.3) | 0 |
| Dyspepsia | 0 | 0 | 1 (16.7)[b,e] | 1 (16.7)[b,c] | 0 |
| Frequent bowel movements | 0 | 0 | 0 | 1 (16.7)[b,f] | 0 |
| Metabolism and nutrition disorders | 1 (12.5) | 0 | 0 | 0 | 0 |
| Hypoglycemia | 1 (12.5)[b,e] | 0 | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 |
| Back pain | 0 | 0 | 1 (16.7)[c,d] | 0 | 0 |
| Pain in extremity | 0 | 0 | 0 | 1 (16.7)[b,c] | 0 |
| Nervous system disorders | 0 | 3 (50.0) | 0 | 1 (16.7) | 0 |
| Headache | 0 | 2 (33.3)[b,e,f] | 0 | 1 (16.7)[b,f] | 0 |
| Syncope | 0 | 1 (16.7)[c,d] | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | 0 | 0 | 0 | 2 (33.3) | 0 |
| Blister | 0 | 0 | 0 | 1 (16.7)[b,c] | 0 |
| Papule | 0 | 0 | 0 | 1 (16.7)[b,c] | 0 |

*Note:* Based on the safety analysis set, defined as all participants who received at least 1 dose of study drug. The same participants in the FE cohort received the 200 mg single dose of EDP-323/placebo in the fasted and fed condition.
Abbreviations: MAD, multiple ascending dose; *n*, number of patients; SAD, single ascending dose; TEAE, treatment-emergent adverse event.
[a]Reaction at the site of blood sample collection (phlebotomy reaction) coded as infusion site extravasation. The study had no infusions except prephlebotomy flushing of the venous line.
[b]Mild.
[c]Deemed not related to study drug by investigator.
[d]Moderate.
[e]Deemed unlikely related to study drug by investigator.
[f]Deemed possibly related to study drug by investigator.

During the SAD and MAD phases, there were no clinically meaningful trends or changes observed in vital signs, ECG parameters, or clinical laboratory results associated with EDP-323. In both phases, all clinically significant abnormal physical examination findings linked to AEs were considered to be not related to the study drug. A complete listing of all AEs can be found in Table S3.

## 3.3 | Pharmacokinetics

### 3.3.1 | Single Ascending Dose Cohort

Geometric mean EDP-323 plasma exposures (maximum plasma concentration [$C_{max}$], plasma concentration between 0 to last quantifiable time point [$AUC_{0\text{-last}}$], and to infinity [$AUC_{0\text{-inf}}$]) in fasted participants generally increased with escalating doses of 50 mg to 600 mg. The highest mean concentrations up to 24 h were observed with 600 mg. EDP-323 plasma exposures observed at the 800 mg dose were lower than those at the 600 mg dose and comparable with those at the 400 mg dose (Table 3, Figure 2). Median $T_{max}$ ranged from 3 to 4 h and geometric mean terminal half-life [$t_{1/2}$] ranged from 12.4 to 16.6 h and appeared to be independent of dose. Overall, oral clearance ($C_{L/F}$) ranged from 16.4 to 45.6 L/h, and volume of distribution ($V_{d/F}$) ranged from 337 to 860 L. In urinary concentration analysis, EDP-323 urinary excretion appeared to be extremely low, with mean fraction excreted (Fe, %) not exceeding 0.237% at any dose level.

### 3.3.2 | Food Effect Cohort

Overall, plasma exposure (AUC and $C_{max}$) of a single dose of EDP-323 was similar in the 200 mg fasted cohort and 200 mg fed (SAD-FE) cohort. There was a slight delay in $T_{max}$ in the fed state compared with the fasted state (5.0 vs. 3.5 h, respectively). The geometric mean $t_{1/2}$, $C_{L/F}$, and $V_{d/F}$ were similar in the 200 mg fasted and 200 mg fed groups (Table S4, Figure S2).

### 3.3.3 | Multiple Ascending Dose Cohort

In the MAD phase, EDP-323 plasma exposure increased with ascending multiple doses in an approximately dose-proportional manner (Table 4, Figure 3). On Day 1, $C_{max}$ and $AUC_{0\text{-tau}}$ increased with increasing doses up to 800 mg. After 7 days of daily dosing, $C_{max}$ and $AUC_{0\text{-tau}}$ increased with increasing doses up to 600 mg, with exposures at 800 mg similar to those at 600 mg. EDP-323 steady state occurred by Day 3 based on visual estimation (Figure S3). A slight accumulation was observed following multiple doses of EDP-323, with the geometric mean accumulation index ranging from 1.32- to 1.54-fold. Geometric mean $t_{1/2}$ ranged from 10.8 to 15.4 h and was independent of dose. EDP-323 administered once daily for 7 days resulted in steady state plasma concentration 24 h after dose [$C_{24}$] concentrations 11- to 44-fold greater than the protein-adjusted 90% effective concentrations ($EC_{90}$; 0.3 nM) determined using primary human airway epithelial cells (pHAEC) grown in a 3-dimensional cell culture system against both the RSV-A and RSV-B strains [27].

### 3.3.4 | EDP-323 Metabolites

Trends in plasma PK parameters of both metabolites (EP-038725 and EP-039082) in the SAD phase were generally comparable with those of EDP-323 (Table S5). In human plasma, the EP-038725 metabolite to parent ratio ranged from approximately 25%–69% based on AUC, which compares to 25%–45% preclinically. Mean $t_{1/2}$ was slightly longer for EP-038725 than for EDP-323 and exposure was reduced following consumption of a high-fat meal (fed state) compared with the corresponding estimates seen with the fasted state. Concentrations of the second metabolite, EP-039082, were very low across the collection duration; hence, PK parameter estimates were available only for the EDP-323 dose groups ranging from 400 mg to 800 mg. For this metabolite, PK parameters appeared to be similar to those for EDP-323. EP-039082 plasma levels were very low (0.4%–1.6%) both clinically and preclinically. In the

**TABLE 3** | Plasma PK parameters following oral administration of single doses of EDP-323.

| PK parameters | EDP-323 50 mg (fasted, $n=6$) | EDP-323 100 mg (fasted, $n=6$) | EDP-323 200 mg (fasted, $n=8$) | EDP-323 400 mg (fasted, $n=6$) | EDP-323 600 mg (fasted, $n=6$) | EDP-323 800 mg (fasted, $n=6$) |
|---|---|---|---|---|---|---|
| $AUC_{0\text{-inf}}$ (h•ng/mL) | 3050 (56.0) | 4000 (30.2) | 8480 (51.9) | 16,900 (33.3) | 22,600 (34.2) | 17,500 (39.6) |
| $C_{max}$ (ng/mL) | 216 (38.3) | 390 (23.8) | 583 (27.4) | 964 (27.3) | 1100 (31.5) | 965 (28.6) |
| $C_{24}$ (ng/mL) | 43 (76.4) | 53 (39.0) | 127 (56.8) | 252 (46.3) | 388 (27.4) | 291 (30.3) |
| $T_{max}$ (h) | 4.0 (2.0, 5.0) | 4.0 (2.0, 5.0) | 3.5 (2.0, 5.0) | 3.0 (3.0, 5.0) | 3.0 (2.0, 5.1) | 3.0 (1.0, 5.0) |
| $t_{1/2}$ (h) | 14.3 (30.3) | 12.4 (31.4) | 13.9 (52.0) | 12.9 (27.1) | 16.6 (39.0) | 13.1 (54.4) |
| $C_{L/F}$ (L/h) | 16.4 (56.0) | 25.0 (30.2) | 23.6 (51.9) | 23.7 (33.3) | 26.5 (34.2) | 45.6 (39.6) |
| $V_{d/F}$ (L) | 337 (51.8) | 448 (37.6) | 472 (45.0) | 441 (24.2) | 634 (26.4) | 860 (38.6) |

*Note:* Analysis was based on the PK set defined as all participants who received study drug with a measurable plasma concentration of the study drug. All parameters are presented as geometric mean (% GCV), except $T_{max}$, which is presented as median (minimum, maximum). Estimated using best-fit regression testing.
Abbreviations: % GCV, percent geometric coefficient of variation; $AUC_{0\text{-inf}}$, area under the plasma concentration vs. time curve between 0 to infinity; $C_{L/F}$, oral clearance; $C_{max}$, maximum plasma concentration; $C_{24}$, plasma concentration 24 h after dose; h, hours; PK, pharmacokinetic; $T_{max}$, time to maximum plasma concentration; $t_{1/2}$, terminal half-life; $V_{d/F}$, volume of distribution.

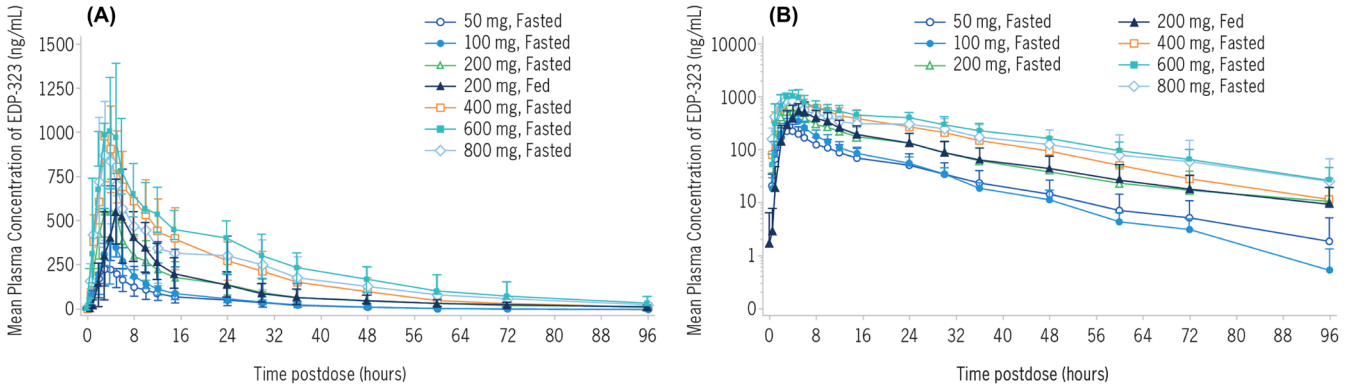



**FIGURE 2** | Mean EDP-323 plasma concentration vs. time following oral administration of single doses on a linear scale (A) and log scale (B). Analysis was based on the PK set defined as all participants who received the study drug with a measurable plasma concentration of the study drug. PK, pharmacokinetic.

**TABLE 4** | Plasma PK parameters following oral administration of multiple doses of EDP-323 over 7 days.

| PK parameters | EDP-323 200 mg (fed, $n=6$) | EDP-323 400 mg (fed, $n=6$) | EDP-323 600 mg (fed, $n=6$) | EDP-323 800 mg (fed, $n=6$) |
|---|---|---|---|---|
| Day 1 | | | | |
| $AUC_{0\text{-tau}}$ (h•ng/mL) | 5830 (54.5) | 13,900 (33.3) | 18,800 (34.6) | 20,900 (33.4) |
| $C_{max}$ (ng/mL) | 765 (40.7) | 1550 (41.3) | 2200 (39.7) | 2560 (33.0) |
| $C_{24}$ (ng/mL) | 89.5 (78.1) | 342 (46.0) | 468 (45.4) | 363 (41.0) |
| $T_{max}$ (h) | 5.0 (3.0, 5.1) | 5.0 (4.3, 5.0) | 4.5 (2.0, 5.0) | 4.5 (3.0, 5.0) |
| Day 7 | | | | |
| $AUC_{0\text{-tau}}$ (h•ng/mL) | 8970 (33.2) | 20,700 (33.6) | 28,300 (36.8) | 27,600 (35.1) |
| $C_{max}$ (ng/mL) | 983 (28.6) | 1900 (39.4) | 3000 (26.0) | 3040 (20.4) |
| $C_{24}$ (ng/mL) | 160 (52.1) | 507 (44.3) | 628 (58.8) | 548 (43.6) |
| $T_{max}$ (h) | 5.0 (3.0, 5.0) | 5.0 (3.0, 6.1) | 4.0 (3.0, 5.0) | 4.5 (4.0, 5.0) |
| $t_{1/2}$ (h) | 10.8 (16.3) | 14.3 (13.2) | 15.4 (26.2) | 11.7 (21.4) |
| AI | 1.54 (40.2) | 1.49 (7.9) | 1.51 (12.0) | 1.32 (15.8) |

*Note:* Analysis was based on the PK set defined as all participants who received study drug with a measurable plasma concentration of the study drug. All parameters are presented as geometric mean (percent geometric coefficient of variation [% GCV]), except $T_{max}$, which is presented as median (minimum, maximum). Estimated using best-fit regression testing.

Abbreviations: AI, accumulation index (ratio); $AUC_{0\text{-inf}}$, area under the plasma concentration vs. time curve between 0 to infinity; $C_{24}$, plasma concentration 24 h after dose; $C_{L/F}$, oral clearance; $C_{max}$, maximum plasma concentrationh, hours; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; $T_{max}$, time to maximum plasma concentration; $V_{d/F}$, volume of distribution.

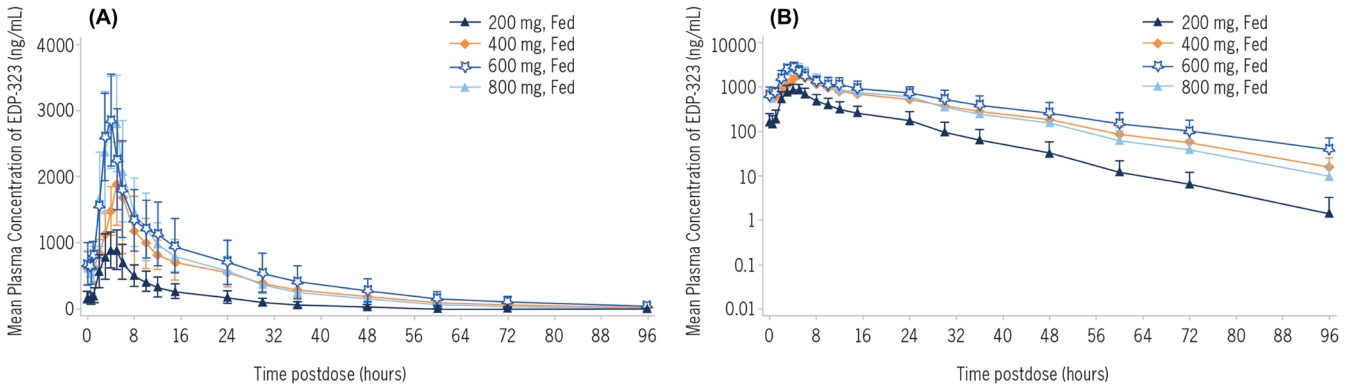



**FIGURE 3** | Mean EDP-323 plasma concentration vs. time on Day 7 following oral administration of multiple doses on a linear scale (A) and log scale (B). Analysis was based on the PK set defined as all participants who received the study drug with a measurable plasma concentration of the study drug. PK, pharmacokinetic.

MAD phase, plasma PK parameters for EDP-323 metabolites followed similar trends to those for EDP-323, with comparable AUC, $C_{max}$, $T_{max}$, and $t_{1/2}$ (Table S6). Overall, clinical metabolite levels are comparable to preclinical levels. The metabolites are not virologically active.

## 4 | Discussion

In this phase 1 study, single ascending doses and multiple ascending doses of EDP-323 up to 800 mg were generally well tolerated in healthy adult participants. EDP-323 demonstrated time-linear pharmacokinetics supporting once-daily oral dosing and no food effect. The number of TEAEs occurring among EDP-323 cohorts during the SAD and MAD phases was low ($n = 17$); all TEAEs were mild or moderate in severity, and most were considered unlikely or not related to study drug. Apart from 1 participant (from the SAD-FE 200 mg cohort) who discontinued treatment after developing syncope (deemed unlikely related to study drug), no other discontinuations occurred in either the SAD or MAD phase.

Administration of single and multiple ascending doses of EDP-323 resulted in increased plasma exposure of EDP-323 up to 600 mg in fasted and fed participants. The EDP-323 800 mg dose did not result in an increase in plasma exposure in the SAD or MAD phase, with exposures being similar to those at lower doses. Plasma exposure (AUC and $C_{max}$) was similar in the fasted and fed participants in the SAD-FE cohort, indicating no food effect.

In the SAD phase, EDP-323 AUC increased with increasing doses up to 600 mg. The plasma exposure observed in participants receiving the 800 mg EDP-323 dose was lower than in those receiving the 600 mg dose and similar to those receiving the 400 mg dose. Given that the geometric mean $t_{1/2}$ ranged from 12.4 to 16.6 h and appeared to be independent of dose, the trend in AUC and associated exposure saturation might be attributed to lower relative bioavailability and lower solubility at higher doses. Urinary excretion of EDP-323 was minimal (highest measurement of Fe [%], 0.237%), indicating that urine is a minor elimination pathway.

In the MAD phase, steady state was achieved by Day 3 with slight accumulation of EDP-323 (ranging from 1.32- to 1.54-fold). Elimination of EDP-323 was generally independent of dose, food, and frequency of administration, as the range of geometric mean $t_{1/2}$ estimates for the SAD phase (12.4–16.6 h) and for the MAD phase Day 7 (10.8–15.4 h) was similar.

Nonpharmaceutical interventions, such as infection prevention, control techniques, and education, are the first line of defense against RSV, but these approaches have not been sufficient to reduce the overall disease burden [26]. The current pharmaceutical landscape for RSV involves mainly vaccination efforts and prophylactics, such as palivizumab or nirsevimab-alip, for high-risk infants [26, 34, 35]. Antiviral therapies specific to RSV or with an RSV indication are currently unavailable. The limited therapies for RSV are not widely available to people who are not at high risk, and come with challenges relating to route of administration, high toxicity, and high cost, with only modest benefits [36, 37]. While these therapies are predominantly available for hospitalized patients, the burden of medically attended RSV in the outpatient setting is still substantially high [37]. There remains a necessity for a safe and effective RSV antiviral treatment for nonhospitalized patients, irrespective of their susceptibility, that is easy to administer and has convenient dosing.

EDP-323 is a promising candidate for the treatment of RSV that may help address some of these challenges. In this study, EDP-323 demonstrated safety and tolerability in healthy adult participants. PK analyses indicate EDP-323 is rapidly absorbed, with a half-life appropriate for once-daily dosing. EDP-323 plasma exposure was similar in the fed and fasted state, indicating EDP-323 can be administered without regard to food intake. EDP-323 administered once daily for 7 days resulted in steady state $C_{24}$ concentrations 11- to 44-fold greater than the protein-adjusted $EC_{90}$ (0.3 nM) determined using pHAEC grown in a 3-dimensional cell culture system against both RSV-A and -B strains [38].

EDP-323, a non-nucleoside RSV replication inhibitor, compares favorably with RSV fusion inhibitors currently in clinical development as it retains in vitro viral potency even when initiated up to 72 h after infection [29]. In contrast, fusion inhibitors work to block viral entry into cells and maintain potency only if initiated before infection [39]. This property may allow maintenance of clinical efficacy if EDP-323 is initiated after disease onset in human RSV infections.

While in vitro resistance profiling of EDP-323 identified resistance mutations localized to the capping domain of the L protein, no mutations were generated when EDP-323 was dosed at 50-fold $EC_{50}$ or above despite multiple attempts [29]. This barrier to resistance differs from that observed with fusion inhibitors, which have been observed to develop rapid resistance in vitro even when dosed 100-fold above their $EC_{50}$. Additionally, resistance to fusion inhibitors has been observed during treatment [40, 41]. Furthermore, EDP-323 shows no cross-resistance to fusion inhibitors or RSV preventative monoclonal antibodies (palivizumab) [33].

In addition to our study's PK and safety findings, EDP-323 shows promising properties for treating RSV clinically, including favorable penetration into lung alveolar macrophages [28]. RSV infection of these cells contributes to detrimental pro-inflammatory lung pathology in humans [42]. EDP-323 uniquely maintains potency and efficacy even when dosed 3 days post-infection in a 3D primary human airway epithelial cell system [29]. Additionally, EDP-323 has been shown to reduce host proinflammatory protein cascades in mice [29]. EDP-323 also demonstrates good lung tissue penetration, the exclusive site of RSV replication in humans [28]. EDP-323 lung to plasma ratio was 1.5 (mouse) and 0.8 (rat). The tissue/plasma ratio in rat lung alveolar macrophages (AMs) was 3.7 [28]. The data highlight favorable tissue distribution of EDP-323 in lungs and AM, which are the sites for RSV replication [28, 43]. The mechanism of action of EDP-323 in inhibiting L polymerase may also provide scope for continued research into combination therapies, which have been successfully applied for other antiviral treatments [44].

The outcomes of this study have established a foundation for further research into the safety and efficacy of EDP-323 against

RSV. A phase 2 human challenge study (NCT06170242) has been successfully completed, the results of which will be presented at an upcoming medical conference.

## 5 | Limitations

Although this study provides insights into the safety and pharmacokinetics of EDP-323, the study was performed in a relatively small number of healthy participants. Additional studies are needed to evaluate the safety, PK, and clinical effects of EDP-323 in individuals infected with RSV and in more susceptible populations, such as elderly adults and children.

## 6 | Conclusions

In this first-in-human study, oral EDP-323 was well tolerated in healthy adult participants over a broad range of single and multiple doses up to 800 mg once daily for 7 days. There were no apparent dose-related trends in the incidence or severity of TEAEs in either the SAD or MAD phase. EDP-323 was rapidly absorbed, and a dose-dependent increase in exposure was observed with single and multiple doses. EDP-323 exhibited PK characteristics supporting once-daily oral dosing, and exposures were not impacted by food. EDP-323 doses ranging from 200 mg to 800 mg once daily resulted in multiples up to 44-fold above the protein-adjusted $EC_{90}$ for both the RSV-A and RSV-B strains, indicating the potential for EDP-323 to be a highly potent antiviral treatment for human RSV infections [31].

### Author Contributions

K.E., J.D., and M.H.J.R. wrote the manuscript; A.A., K.E., and S.T.R. designed the research; A.A., K.E., J.D., and S.T.R. analyzed the data.


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### Disclosure

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### Conflicts of Interest

All authors are currently employees of and hold stock in Enanta Pharmaceuticals Inc., Watertown, MA.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.