EDP-323, a First-in-Class, Oral RSV L-Protein Inhibitor Reduces Disease Severity (Respiratory Mucus Production) and Accelerates Viral Clearance in a Human Viral Challenge Study

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BACKGROUND AND OBJECTIVE

Background

- There is a significant unmet need for respiratory syncytial virus (RSV) antiviral therapies despite availability of prophylaxis[1]
  - Antivirals are complementary to effective preventive vaccines and monoclonal antibodies
- **EDP-323** is a first-in-class, non-nucleoside, direct-acting L-protein inhibitor in clinical development as an oral once-daily therapy (blocks viral replication and transcription)[2]
- Strong preclinical profile[2-4]
  - Picomolar in vitro potency against RSV-A and RSV-B[2]
  - Maintained in vitro antiviral effect when dosed ≤3 days post-infection. Fusion inhibitors activity ablated if dosed after infection[2,4]
  - Dose dependent reduction in viral load and symptoms in vivo (in prophylactic and therapeutic settings)[2,3]
  - High barrier to viral resistance compared to fusion inhibitors[4]
- A phase 1 study (NCT05587478) evaluated 7 daily oral doses up to 800 mg/dose[5]
  - Once-daily oral dosing supported by pharmacokinetic (PK) profile
  - Side effects and safety lab profile similar to placebo at all dose ranges
  - C_{24} (trough concentrations) of 200 mg and 600 mg dosing: 11- and 44-fold above in vitro protein-adjusted EC_{90}

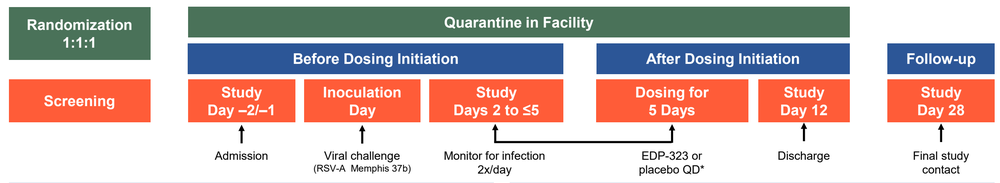
Objective

- The objective of this study was to evaluate PK, safety, and antiviral activity of multiple EDP-323 doses in an RSV challenge study of healthy adults

METHODS

- Randomized, double-blind, placebo-controlled human viral challenge phase 2a study (NCT06170242)
- Population: healthy volunteers, 18-55 years, low serum RSV neutralizing antibody titer, weight ≥50 kg, BMI 18-35 kg/m^2

Figure 1. Study Design and Endpoints



Dosing QD for 5 days (N=141), followed for 28 days

- **EDP-323 high dose: 600 mg (N=47)**
- **EDP-323 low dose: 200 mg (600 mg loading dose on Day 1 followed by 200 mg for 4 days) (N=47)**
- **Placebo (N=47)**

Primary endpoint

- **VL AUC measured by qRT-PCR**

Selected secondary endpoints

- **PKs, safety profile, VL measured by qRT-PCR and viral culture, viral clearance, mucus weight, tissue use, and total symptom score**

*Dosing initiated 12 hours after +RSV test (qualitative RT-PCR) or Day 5, whichever was first.
AUC, area under the curve; PK, pharmacokinetic; QD, once daily; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; RSV, respiratory syncytial virus; VL, viral load.

- Twice-daily nasal washes and nasal mucus quantity were obtained from Days 2-12
- Antiviral activity was assessed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and by viral culture, which were performed using nasal washes

RESULTS

- After RSV challenge, participants were randomized and received EDP-323 200 mg (N=47), EDP-323 600 mg (N=47), or placebo (N=47) (safety population, N=141)
  - All participants in both EDP-323 arms completed the study
- Primary efficacy analysis: intent-to-treat infected (ITT-I) population comprised all randomized participants who received challenge virus and ≥1 dose of study drug, and with RSV infection confirmed by central lab RT-PCR
  - ITT-I population: EDP-323 200 mg, N=23; EDP-323 600 mg, N=26; placebo, N=30
- Demographics: balanced across study arms for age, sex, race, and baseline serum RSV neutralization antibody titer
- PK: EDP-323 mean trough plasma concentrations maintained at 16- to 35-fold above protein-adjusted EC_{90}[6]
- Safety: frequency of treatment-emergent adverse events (TEAEs) was similar across EDP-323 and placebo arms (**Table**)
  - No serious TEAEs, severe TEAEs, or TEAEs leading to treatment discontinuation/study withdrawal
  - TEAEs reflected usual RSV and quarantine-related patterns

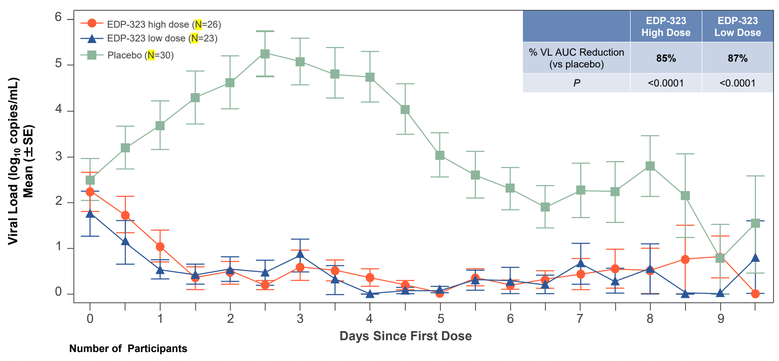
Table: Summary of Safety Outcomes (Safety Population)

	EDP-323 High Dose (N=47)	EDP-323 Low Dose (N=47)	Pooled EDP-323 (N=94)	Placebo (N=47)
Participants with any TEAE, n (%)	11 (23.4)	14 (29.8)	25 (26.6)	13 (27.7)
Any TEAE considered related to study drug, n (%)	1 (2.1)*	1 (2.1)*	2 (2.1)*	0 (0)
Participants with TEAEs graded at least moderate in severity, n (%)	1 (2.1)	1 (2.1)	2 (2.1)	2 (4.3)

*Grade 1/mild diarrhea.

Figure 2: Mean Viral Load Over Time and AUC by qRT-PCR (ITT-I Population)

- EDP=323 reduced mean viral load AUC by 85% (high dose) and 87% (low dose) vs placebo (*P* <0.0001; primary efficacy endpoint)



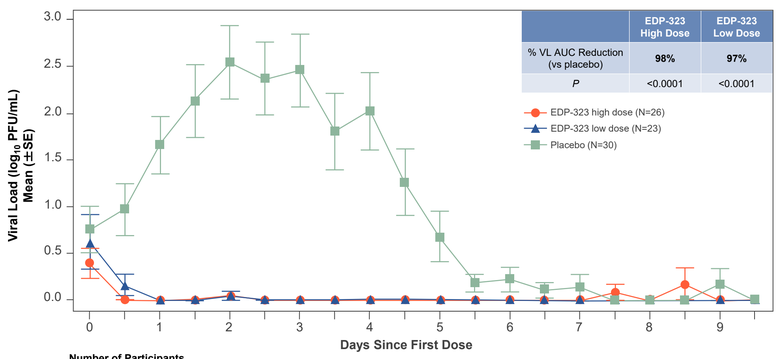
Number of Participants

EDP-323 high dose	26	26	26	26	26	26	26	26	26	26	26	26	26	15	12	10	6	4	1
EDP-323 low dose	23	23	23	23	23	23	23	23	23	23	23	23	23	17	16	10	5	4	2
Placebo	30	30	30	30	30	30	30	30	30	30	30	30	30	19	18	11	8	6	4

AUC, area under the curve; ITT-I, intent-to-treat infected; qRT-PCR: quantitative reverse transcription-polymerase chain reaction; VL, viral load.

Figure 3: Mean Viral Load Over Time and AUC by Viral Culture (ITT-I Population)

- EDP-323 reduced mean viral load AUC by 98% (high dose) and 97% (low dose) vs placebo (*P* <0.0001; secondary efficacy endpoint)



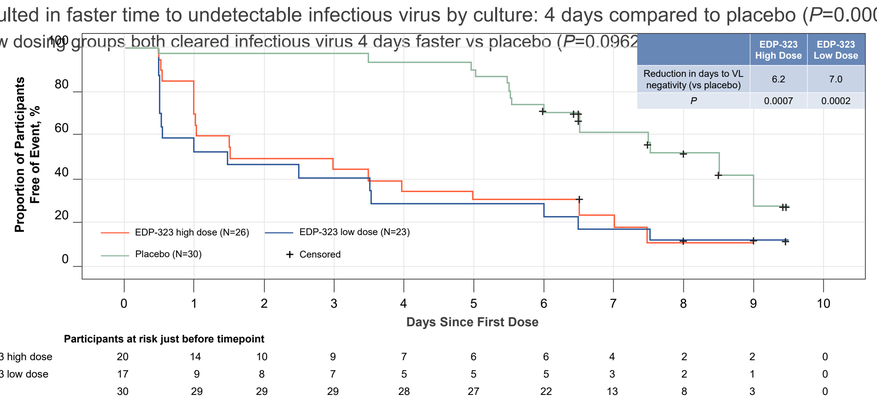
Number of Participants

EDP-323 high dose	26	26	26	26	26	26	26	26	26	26	26	26	26	15	12	10	6	4	1
EDP-323 low dose	23	23	23	23	23	23	23	23	23	23	23	23	23	17	16	10	5	4	2
Placebo	30	30	30	30	30	30	30	30	30	30	30	30	30	19	18	11	8	6	4

AUC, area under the curve; ITT-I, intent-to-treat infected; PFU, plaque-forming unit; VL, viral load.

Figure 4: Time to Viral Load Negativity by RT-PCR (ITT-I Population)

- EDP-323 resulted in faster time to undetectable viral load by RT-PCR: 6.2 days (high dose) and 7.0 days (low dose) compared to placebo (*P*=0.0007 and *P*=0.0002; secondary efficacy endpoint)
- EDP-323 resulted in faster time to undetectable infectious virus by culture: 4 days compared to placebo (*P*=0.0004)
  - High and low dosing groups both cleared infectious virus 4 days faster vs placebo (*P*=0.0962



Participants at risk just before timepoint

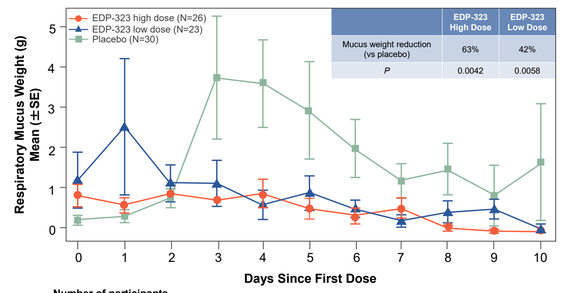
EDP-323 high dose	20	14	10	9	7	6	6	4	2	2	0
EDP-323 low dose	17	9	8	7	5	5	5	3	2	1	0
Placebo	30	29	29	29	28	27	22	13	8	3	0

Event is defined as viral load negativity measured by qRT-PCR. Number of considered participants: 67.
ITT-I, intent-to-treat infected; qRT-PCR, quantitative reverse transcription polymerase chain reaction; VL, viral load.

RESULTS (Cont.)

Figure 5: Mean Weight of Respiratory Mucus Produced (ITT-I Population)

- EDP-323 groups produced 63% (high dose) and 42% (low dose) less mucus than the placebo group (*P*=0.0042 and *P*=0.0058; secondary efficacy endpoint)
  - Pooled EDP-323 groups produced 53% less mucus vs placebo (*P* <0.0001)



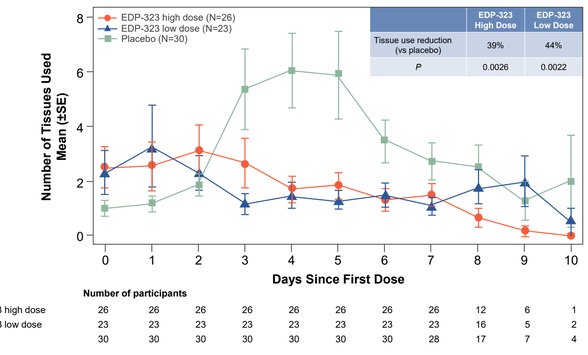
Number of participants

EDP-323 high dose	26	26	26	26	26	26	26	26	12	5	1
EDP-323 low dose	23	23	23	23	23	23	23	23	16	5	2
Placebo	30	30	30	30	30	30	30	28	16	7	4

ITT-I, intent-to-treat infected.

Figure 6: Mean Number of Tissues Used (ITT-I Population)

- EDP-323 groups used 39% (high dose) and 44% (low dose) fewer tissues than the placebo group (*P*=0.0026 and *P*=0.0022; secondary efficacy endpoint)
  - Pooled EDP-323 groups used 41% fewer tissues vs placebo (*P* <0.0001)



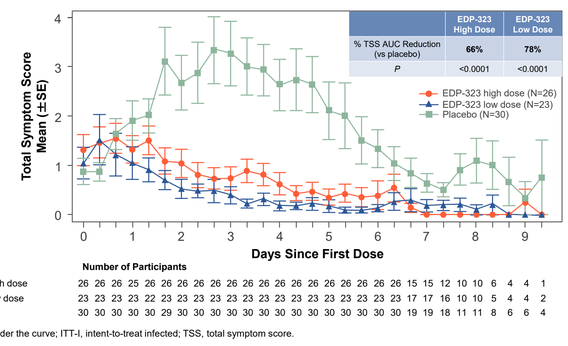
Number of participants

EDP-323 high dose	26	26	26	26	26	26	26	26	12	6	1
EDP-323 low dose	23	23	23	23	23	23	23	23	16	5	2
Placebo	30	30	30	30	30	30	30	28	17	7	4

ITT-I, intent-to-treat infected.

Figure 7: Mean Total Symptom Score (10 Symptoms) and AUC (ITT-I Population)

- EDP-323 reduced mean total symptom score AUC by 66% (high dose) and 78% (low dose) vs placebo (*P* <0.0001; secondary efficacy endpoint)
  - Pooled EDP-323 groups used 41% fewer tissues vs placebo (*P* <0.0001)



Number of Participants

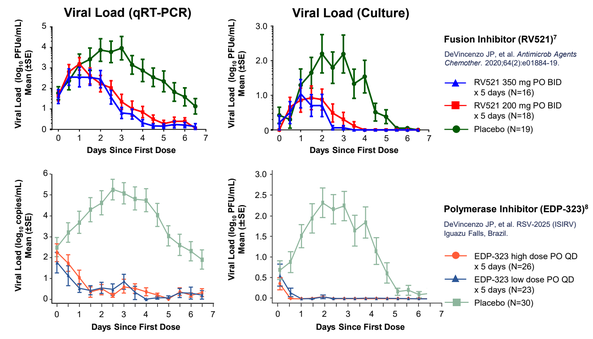
EDP-323 high dose	26	26	26	25	26	26	26	26	26	26	26	26	26	26	26	26	15	15	12	10	10	6	4	4	1
EDP-323 low dose	23	23	23	22	23	23	23	23	23	23	23	23	23	23	23	23	23	17	17	16	10	10	5	4	4	2
Placebo	30	30	30	30	30	29	30	30	30	30	30	30	30	30	30	30	30	30	19	19	18	11	11	8	6	6	4

AUC, area under the curve; ITT-I, intent-to-treat infected; TSS, total symptom score.

DISCUSSION & CONCLUSIONS

- **EDP-323** was well tolerated, with a safety profile similar to placebo
- Mean trough plasma concentrations were maintained at 16- to 35-fold above protein-adjusted EC_{90}
- Met primary endpoint with statistical significance at both dose levels compared with placebo
- Antiviral effect started rapidly after dosing, in contrast to that of fusion inhibitors (**Figure 8**)
- Met key secondary endpoints (viral load by qRT-PCR and viral culture, total symptom score) with statistical significance at both dose levels vs placebo
- Accelerated clearance of viral RNA and infectious virus vs placebo
- Reduced clinical disease severity relative to placebo was shown by both total symptom score and by respiratory mucus production, assessed by mucus weight and by number of tissues used
- Findings confirm the potential of EDP-323 as a once-daily oral treatment for RSV and support further clinical evaluation

Figure 8. Viral Dynamics in RSV Challenge Studies: Fusion vs Polymerase Inhibitors



BID, twice daily; PFU, plaque-forming unit equivalents; PO, oral; QD, daily; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

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- **JPDV**, **AA**, **SC**, and **STR** are employees of Enanta Pharmaceuticals and hold Enanta Pharmaceuticals stock; **BL**, **AM**, **JM**, and **AC** are employees of hVivo and hold hVivo stock.
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