EDP-323, a First-in-Class, Once-Daily, Oral Non-Nucleoside L-Protein, Replication Inhibitor Antiviral for the Treatment of RSV: Results From a Phase 2a Human Viral Challenge Study

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Presenter

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Disclosure of Relevant Financial Relationships and Acknowledgments

Disclosures

- **JPD, 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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EDP-323: First-in-Class, Oral, Once Daily, L-Protein Inhibitor for the Treatment of RSV Infection

- Significant unmet need for RSV antiviral therapies despite availability of prophylaxis[1]
  - Complementary to effective preventive vaccines and monoclonal antibodies
  - See late breaker poster #253, Huang et al – First in Pediatrics Phase 2 Trial of N-Targeting Antiviral, Zelicapavir
- **EDP-323**: first-in-class, non-nucleoside, direct-acting L-protein inhibitor in clinical development as an oral, once-daily therapy[2]
  - Blocks viral replication and transcription[2]
- Strong preclinical profile[2-4]
  - Picomolar in vitro potency against RSV-A and RSV-B[2]
  - Reduced viral load and disease dose dependently (prophylactically and therapeutically)[2,3]
- Phase 1 study evaluated 7 daily oral doses up to 800 mg/dose[5,6]
  - Once daily oral dosing supported by PK profile[5,6]
  - Side effects and safety lab profile similar to placebo at all dose ranges[5,6]
  - C_{24} (trough concentrations) of 200 mg and 600 mg dosing: 11- and 44-fold above in vitro protein-adjusted EC_{90}[5,6]

C_{24}, observed concentration at 24 hours after dose administration; EC_{90}, EC90, 90% effective concentration; PK, pharmacokinetic; RSV, respiratory syncytial virus.

1. Walsh E. N Engl J Med 2024;391:1155-1156. **2.** Rhodin MHJ, et al. Presented at: Discovery at Target: New Antivirals Conference. October 17-20, 2022. Boston, MA, US. **3.** Levene RE, et al. Presented at: 12th International RSV Symposium. September 29-October 2, 2022. Belfast, Northern Ireland, UK. **4.** Levene RE, et al. Presentation at: 13th International RSV Symposium. Poster #161. March 12-15, 2025. Iguazu Falls, Brazil. **5.** Mills K, et al. Presented at: European Scientific Working Group on Influenza (ESWI). 9th Influenza Conference 2023. September 17-20, 2023. Valencia, Spain. **6.** Mills K, et al. Manuscript submitted for publication to *Clin Trans Sci*. 2025.

Unique Properties of EDP-323 Mechanism of Action

Detailed in Poster #161: In Vitro Characterization of Respiratory Syncytial Virus Inhibitors

- EDP-323 maintained antiviral effect even when dosed up through 3 days post-infection in a 3D primary human airway epithelial cell system[1,4]
  - Antiviral effect of Fusion Inhibitors ablated if dosed shortly after infection[4]
- Development of antiviral resistance
  - Fusion inhibitors: low barrier to resistance; little impact to viral fitness[4]
  - EDP-323: higher barrier to resistance[4]
  - N inhibitor zelicapavir: highest barrier to resistance; viral fitness defects[4]
- Will these Mechanism of Action properties translate into outcome improvements in clinical trials?

*NCT05587478.
3-D, 3 dimensional; EC_{90}, 90% effective concentration; L, large; N, nucleoprotein; RNA, ribonucleic acid; RSV, respiratory syncytial virus.
1. Rhodin MHJ, et al. Presented at: Discovery at Target: New Antivirals Conference. October 17-20, 2022. Boston, MA, US. **2.** Mills K, et al. Presented at: European Scientific Working Group on Influenza (ESWI). 9th Influenza Conference 2023. September 17-20, 2023. Valencia, Spain. **3.** Mills K, et al. Manuscript submitted for publication to *Clin Trans Sci*. 2025. **4.** Levene RE, et al. Presentation at: 13th International RSV Symposium. March 12-15. Iguazu Falls, Brazil. **5.** Data on file, Enanta Pharmaceuticals.

Study Overview

Objective

- Evaluate the PK profile, safety, and antiviral activity of multiple doses of EDP-323 in a human RSV challenge study* among healthy adults[1]

Description

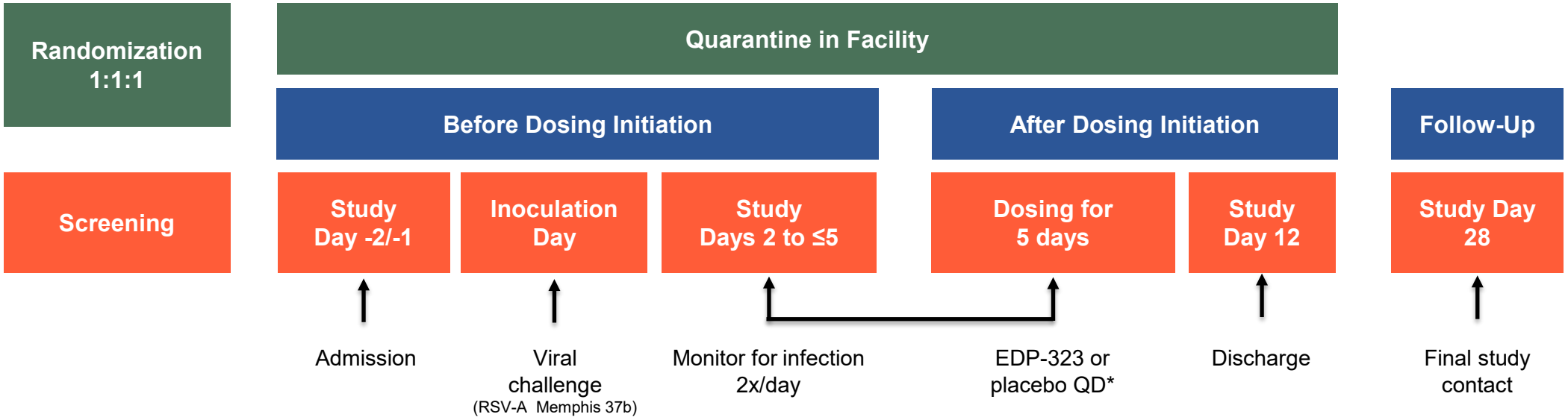
- Randomized, double-blind, placebo-controlled human viral challenge (RSV-A Memphis 37b strain) Phase 2a study†

Population

- Healthy, 18-55 years old, low serum RSV neutralizing antibody titer, weight ≥50 kg, BMI 18-35 kg/m^2

*RSV human challenge model mimics natural infection, allowing to evaluate safety/efficacy/immunogenicity of RSV therapeutics; utilized in the development of successful RSV vaccines.
†NCT06170242.
BMI, body mass index; PK, pharmacokinetic; RSV, respiratory syncytial virus.
1. DeVincenzo JP, et al. *Am J Respir Crit Care Med.* 2010;182(10):1305-1314.

Study Design and Endpoints



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

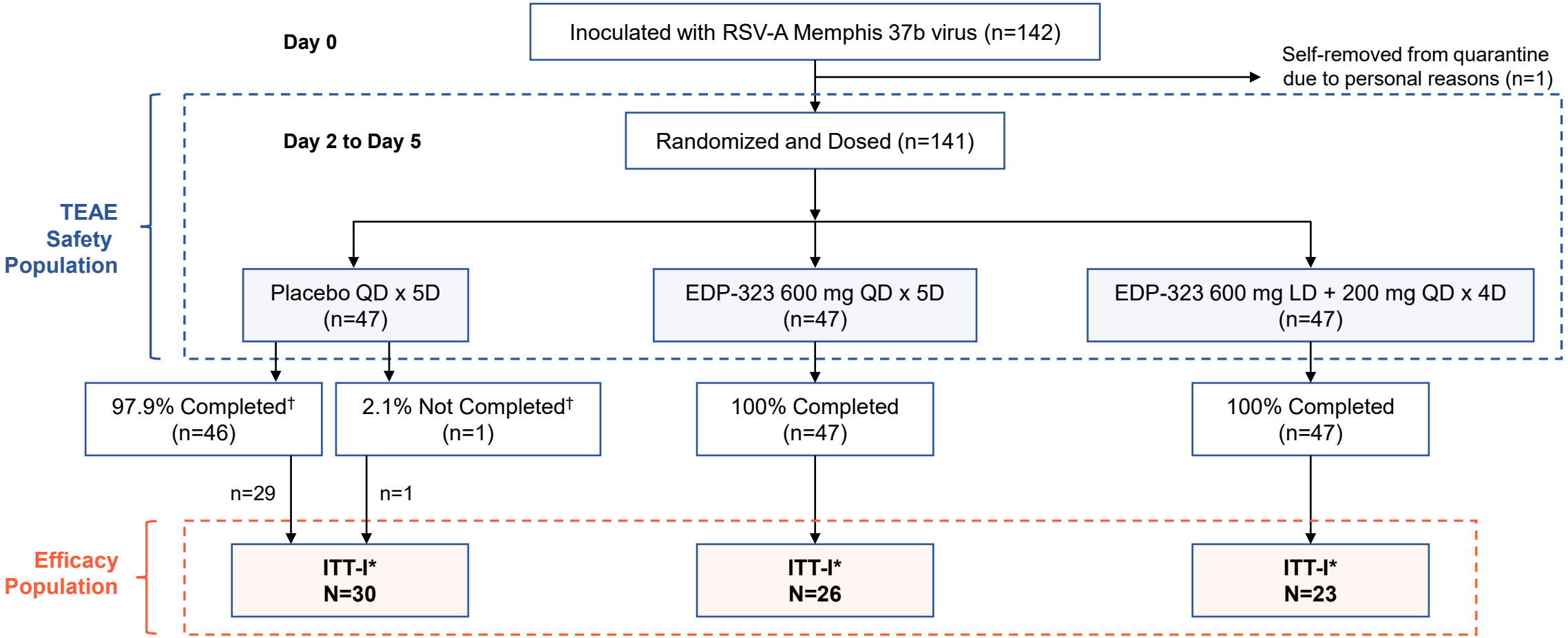
- **EDP-323 high dose: 600 mg (n=47)**
- **EDP-323 low dose: 200 mg (600 mg loading dose on Day 1 followed by 200 mg for 4 days) (n=47)**
- **Placebo (n=47)**

Please see Poster #153, Mills (Elmore) et al
PK and PK/PD Evaluation in RSV Human Challenge Study

- **Primary endpoint**
  - **Viral load AUC measured by qRT-PCR in nasal samples**
- **Selected secondary endpoints**
  - **PK profile**
  - **Safety profile**
  - **Reduction in viral load AUC measured by viral culture**
  - **Reduction in total symptom score AUC**

*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; RT-PCR, reverse transcription-polymerase chain reaction; RSV, respiratory syncytial virus.

Participant Disposition



†1 participant discontinued the study due to personal reasons on Day 9 after completing the full 5-day dosing period; data from this participant were used in analyses

***Primary efficacy analysis, intent-to-treat infected (ITT-I):** all randomized participants who received challenge virus and ≥1 dose of study drug, and with RSV infection confirmed by central lab RT-PCR (>1 sample time-points positive by RT-PCR or a single sample time-point positive by culture)

D, day; LD, loading dose; QD, once daily; RT-PCR, reverse transcription-polymerase chain reaction; RSV, respiratory syncytial virus; TEAE, treatment-emergent adverse event.

Summary of Demographics

- Demographics were balanced across study arms

	EDP-323 High Dose (n=47)	EDP-323 Low Dose (n=47)	Placebo (n=47)
Age, years, median (Q1, Q3)	28 (24, 33)	26 (24, 30)	27 (23, 30)
Sex, male, n (%)	32 (68.1)	30 (63.8)	28 (59.6)
Race, White, n (%)	39 (83.0)	35 (74.5)	38 (80.9)

Q, quartile.

Summary of PK and Safety Outcomes

PK - EDP-323 mean trough plasma concentrations were maintained at 16- to 35-fold above protein-adjusted EC_{90} against both RSV-A and RSV-B subtypes

- See Poster #153, Elmore et al – PK and PK/PD Evaluations of Human Viral Challenge Study

Safety - The frequency of TEAEs was similar across EDP-323 and placebo arms

- There were no serious TEAEs, severe AEs, or AEs leading to treatment discontinuation/ study withdrawal
- TEAEs reflected usual RSV and quarantine-related patterns

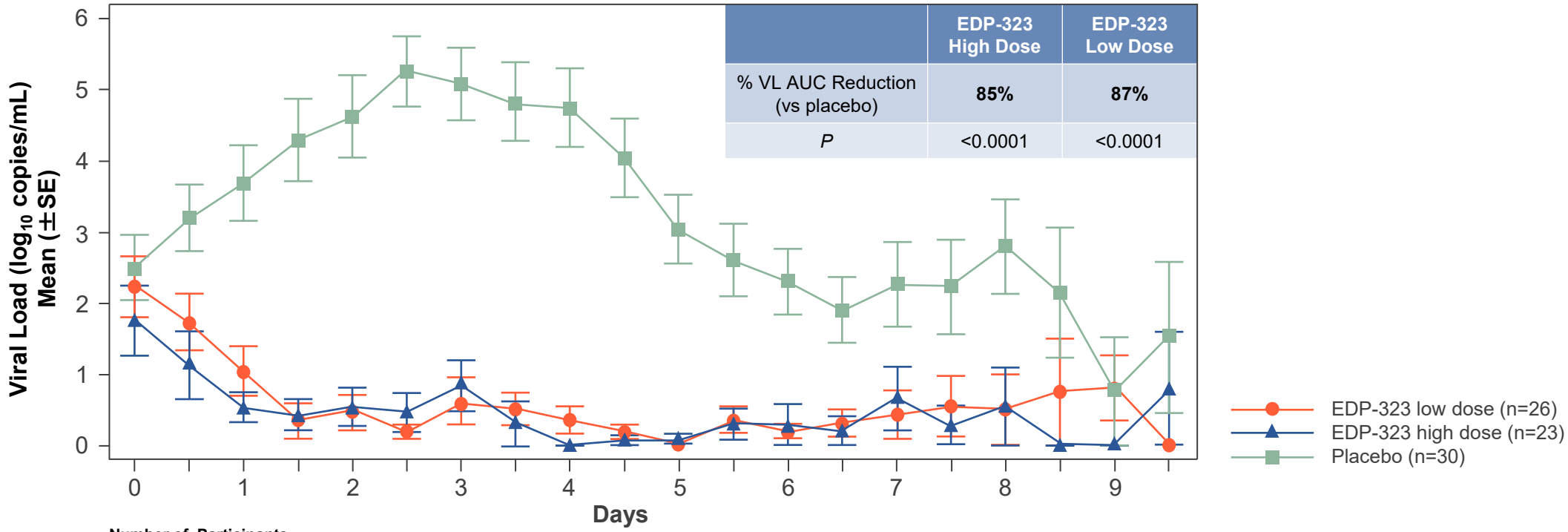
	EDP-323 High Dose (n=47)	EDP-323 Low Dose (n=47)	Pooled EDP-323 (N=94)	Placebo (n=47)
Participants with any TEAEs, n (%)	11 (23.4)	14 (29.8)	25 (26.6)	13 (27.7)
Any TEAEs considered related to study drug, n (%)	1 (2.1)*	1 (2.1)*	2 (2.1)*	0 (0)
Participants with TEAEs graded at least moderate in severity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

*Grade 1/mild diarrhea.
AE, adverse event; EC_{90}, 90% effective concentration; PK, pharmacokinetic; TEAE, treatment-emergent adverse event.

Mean Viral Load Over Time and AUC by qRT-PCR

Primary Efficacy Endpoint: AUC (ITT-I Population)

- EDP-323 showed 85% (high dose) and 87% (low dose) greater mean reductions in viral load AUC vs placebo (*P* <0.0001)
  - No statistically significant differences between the 2 EDP-323 dosing regimens



	EDP-323 High Dose	EDP-323 Low Dose
% VL AUC Reduction (vs placebo)	**85%**	**87%**
P	<0.0001	<0.0001

Number of Participants

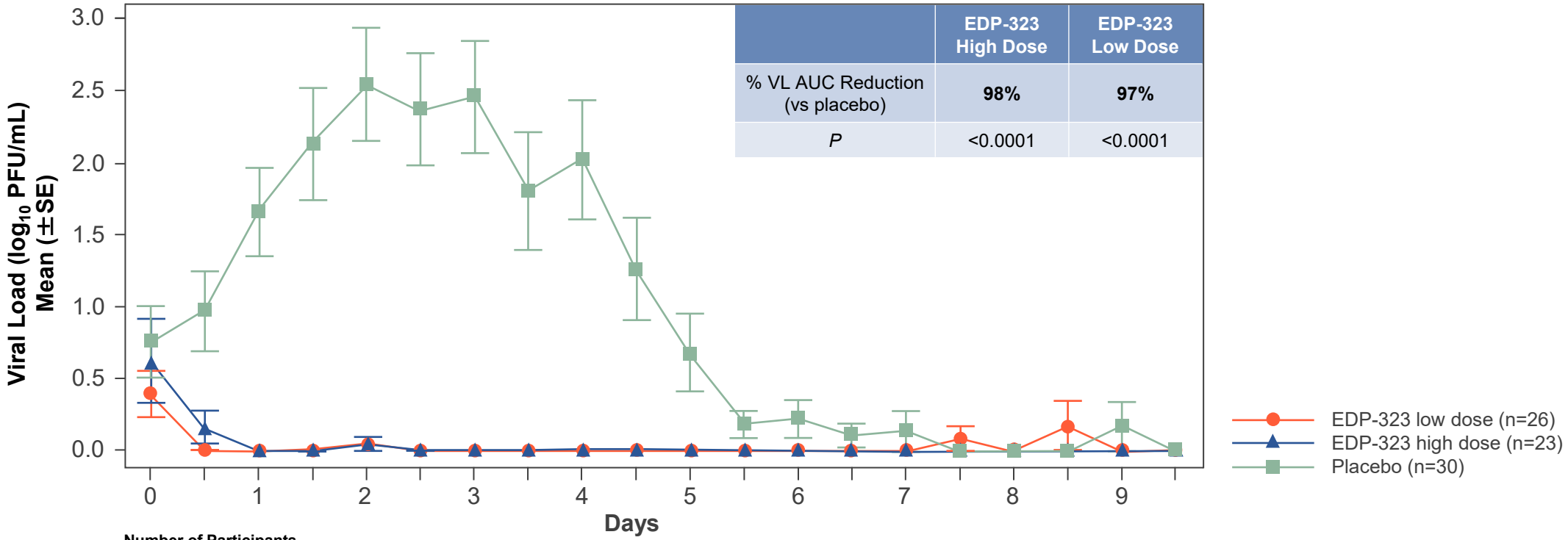
EDP-323 high dose	26	26	26	26	26	26	26	26	26	26	26	26	26	26	15	12	10	6	4	1
EDP-323 low dose	23	23	23	23	23	23	23	23	23	23	23	23	23	23	17	16	10	5	4	2
Placebo	30	30	30	30	30	30	30	30	30	30	30	30	30	30	19	18	11	8	6	4

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

Mean Viral Load Over Time and AUC by Viral Culture

Secondary Efficacy Endpoint: AUC (ITT-I Population)

- EDP-323 showed 98% (high dose) and 97% (low dose) greater mean reductions in viral load AUC vs placebo (*P* <0.0001)
  - No statistically significant differences between the 2 EDP-323 dosing regimens



	EDP-323 High Dose	EDP-323 Low Dose
% VL AUC Reduction (vs placebo)	**98%**	**97%**
P	<0.0001	<0.0001

Number of Participants

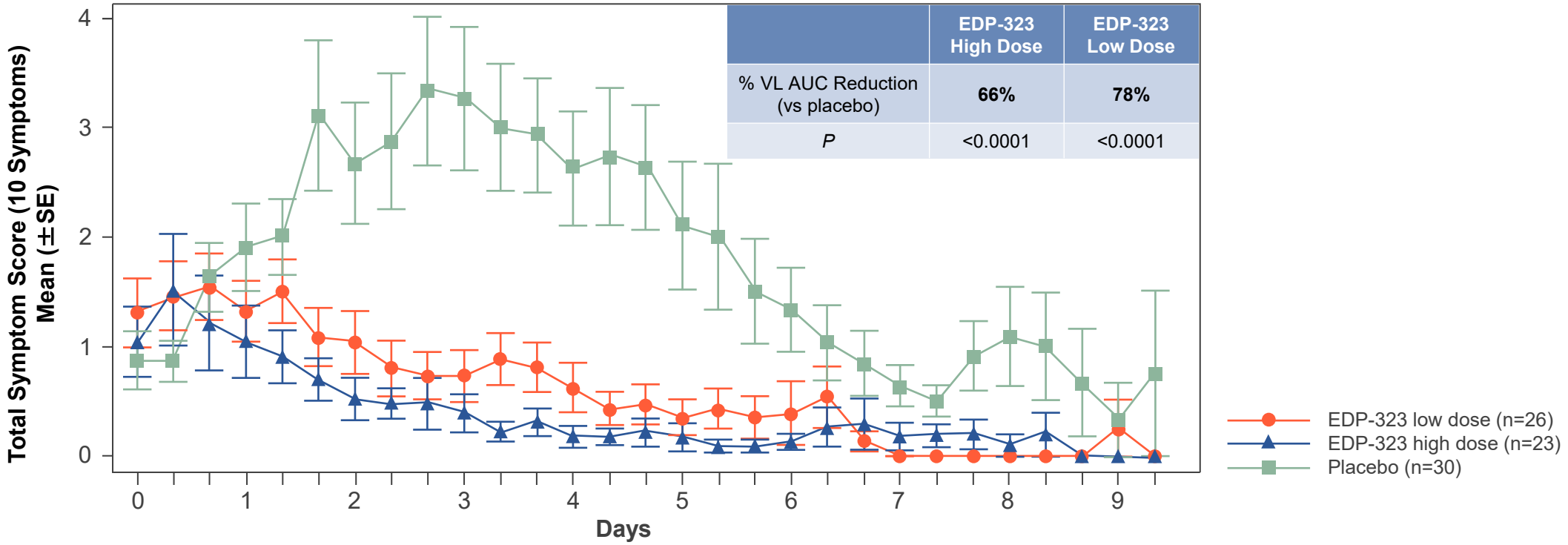
EDP-323 high dose	26	26	26	26	26	26	26	26	26	26	26	26	26	26	15	12	10	6	4	1
EDP-323 low dose	23	23	23	23	23	23	23	23	23	23	23	23	23	23	17	16	10	5	4	2
Placebo	30	30	30	30	30	30	30	30	30	30	30	30	30	30	19	18	11	8	6	4

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

Mean Total Symptom Score and AUC

Secondary Efficacy Endpoint: AUC (ITT-I Population)

- EDP-323 showed 66% (high dose) and 78% (low dose) greater mean reductions in total symptom score AUC vs placebo (*P* <0.0001)
  - No statistically significant differences between the 2 EDP-323 dosing regimens



	EDP-323 High Dose	EDP-323 Low Dose
% VL AUC Reduction (vs placebo)	**66%**	**78%**
P	<0.0001	<0.0001

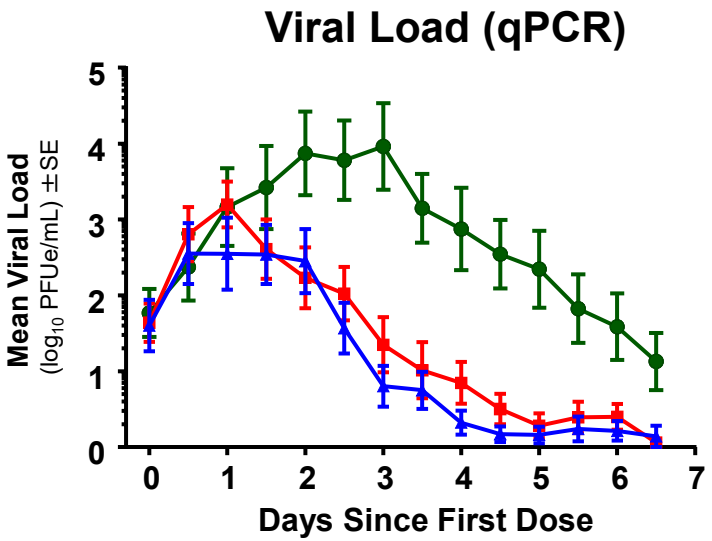
Number of Participants

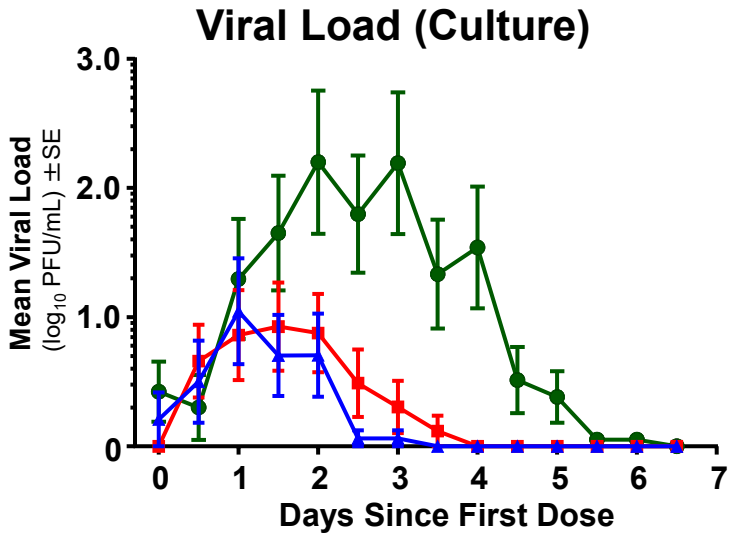
EDP-323 high dose	26	26	26	25	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	15	15	12	10	10	6	4	4	1
EDP-323 low dose	23	23	23	23	22	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	17	17	16	10	10	5	4	4	2
Placebo	30	30	30	30	30	29	30	30	30	30	30	30	30	30	30	30	30	30	30	30	19	19	18	11	11	8	6	6	4

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

Viral Dynamics in Human RSV Challenge Studies (Memphis-37b)

Fusion Inhibitor vs Polymerase Inhibitor

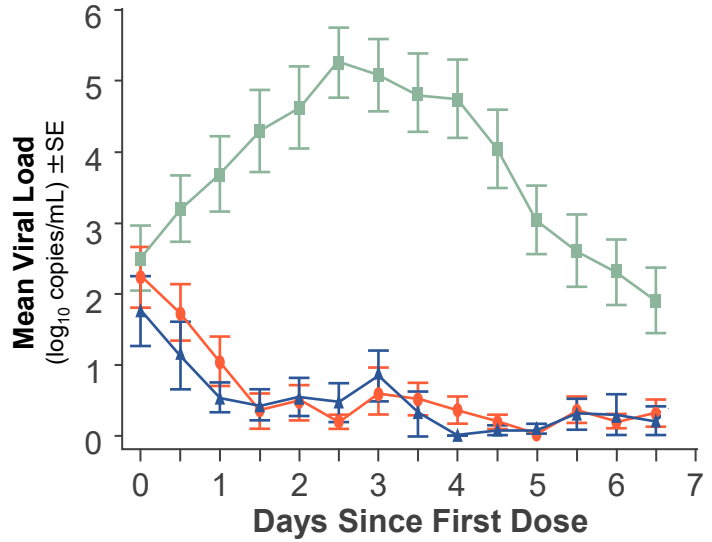


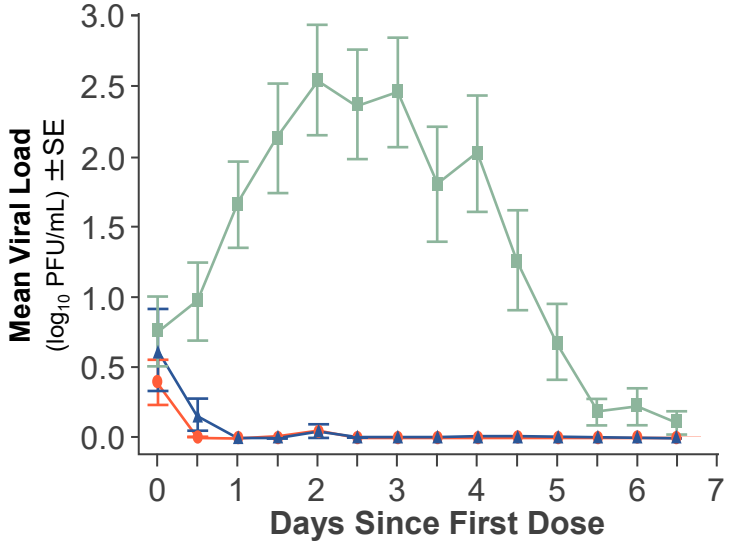


Fusion Inhibitor (RV521)

- RV521 350mg PO BID x 5 days (n=16)
- RV521 200mg PO BID x 5 days (n=18)
- Placebo (n=19)

DeVincenzo et al. Antimicrobial Agents and Chemotherapy. 2020;64(2):e01884-19; and DeVincenzo et al. ATS 2018.





Polymerase Inhibitor (EDP-323)

- EDP-323 low dose PO QD x 5 days (n=26)
- EDP-323 high dose PO QD x 5 days (n=23)
- Placebo (n=30)

DeVincenzo et al. RSV-2025 (ISIRV) Iguazu Falls, Brazil.

EDP-323 RSV Human Challenge Study

Conclusions

- Well tolerated with safety profile similar to placebo
- Mean trough plasma concentrations maintained at 16- to 35-fold above protein-adjusted EC_{90}
- Primary and key secondary endpoints achieved with statistical significance at both dose levels vs placebo

	EDP-323 Low Dose	EDP-323 High Dose	P*
qRT-PCR	87%	85%	<0.0001
Viral culture	97%	98%	<0.0001
Total symptom score	78%	66%	<0.0001

  - No statistically significant differences between the 2 dosing regimens

- Outcomes confirm the potential of EDP-323 as a once-daily oral treatment for RSV and support further clinical evaluation

P for both comparisons.
EC_{90}, 90% effective concentration; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; RSV, respiratory syncytial virus.

Poster Presentation: Zelicapavir for Treatment of RSV Infection in Young Children

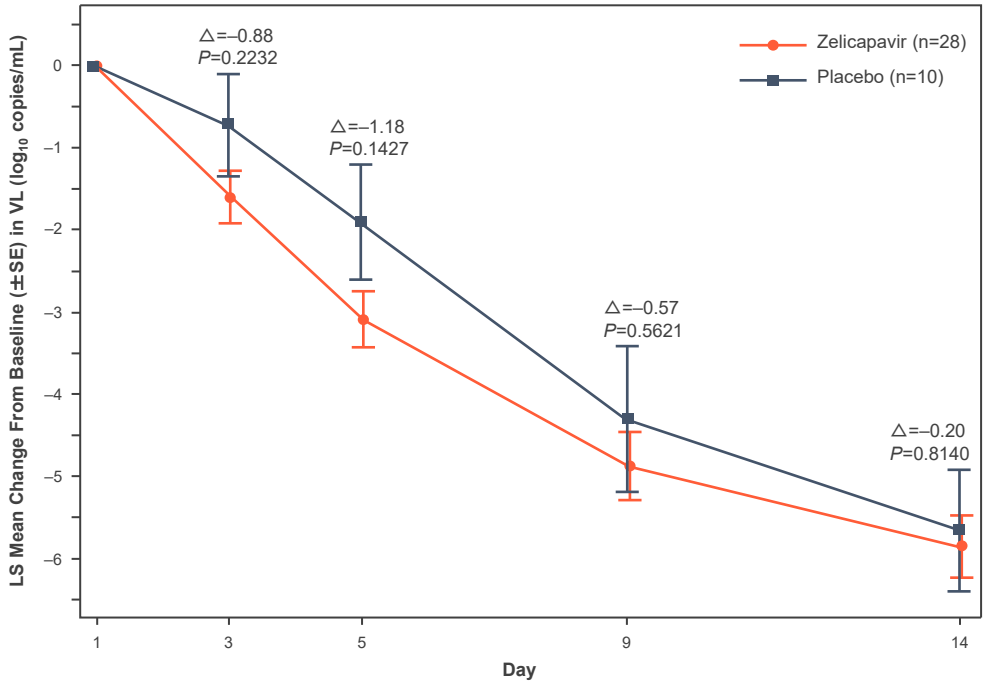
Enanta Pharmaceuticals

A Phase-2, Double-Blind, Placebo-Controlled, International Trial of Zelicapavir for Treatment of RSV Infection in Young Children

Stephen Huang, Christopher Harris, John P DeVincenzo, Alaa Ahmad, Shijie Chen, Taylor Ngo, Scott T Rottinghaus

- Late breaker poster **#253**
- Poster session: **RSV Monoclonal Antibodies and Antivirals**
  - Date: **Friday, March 14**
  - Time: **4:15 – 5:15 PM**
  - Location: **Pavillion C**

LS Mean Change (± SE) From Baseline in Viral Load in Prespecified mITT-3 Population* Measured by qRT-PCR



LS, least-squares; mITT, modified intent-to-treat; RESOLVE-P, Respiratory Observable Reported Outcome-Pediatric; qRT-PCR, quantitative reverse transcription polymerase chain reaction.
*Prespecified mITT-3 population: participants randomized within 3 days of symptom onset.

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Thank you!

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Backup Slides

DeVincenzo RSV-2025, Iguazu Falls, Brasil

Viral Dynamics after Fusion Inhibitor Antiviral Rx:

RV521 (Sisunatovir) Rx after RSV-A Memphis 37 human challenge

Enanta Pharmaceuticals

DeVincenzo et al. Antimicrobial Agents and Chemotherapy. 2020 64(2): e01884-19

qRTpPCR **Viral Culture**

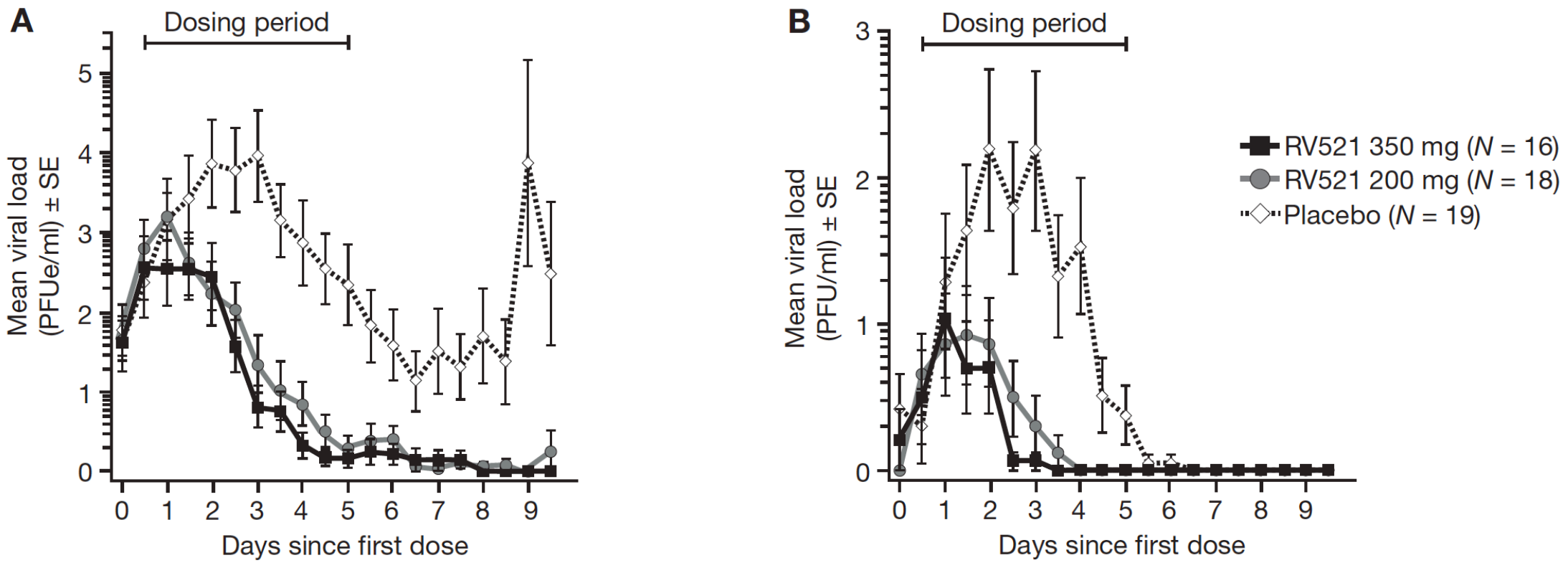

FIG 2 Mean viral load by nasal wash RT-qPCR (A) and by nasal wash quantitative culture (B) by day relative to dosing (ITT-I analysis set). Once RSV infection was confirmed (i.e., RSV RNA detected by qualitative integrated cycler PCR), subjects were assigned a randomization number; treatment was initiated 12 h (1 h) after the confirmatory RSV-positive nasal wash sample had been collected. Viral load (RT-qPCR) appeared to rebound after day 8.5 in the placebo arm. However, this apparent increase resulted from the staggered randomization of subjects (the mean viral load at day 9 was calculated from just four subjects, three of whom had consistently high viral loads throughout the study). ITT-I, intent-to-treat infected (all randomized subjects who received the challenge virus and at least one dose of study drug and met the criterion for laboratory-confirmed RSV infection [presence of viral shedding]); PFUe, PFU equivalents; RSV, respiratory syncytial virus; RT-qPCR, reverse transcriptase quantitative PCR; SE, standard error.