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From Chemistry to Cures

EDP-938, a Novel RSV N-inhibitor, Administered Once or Twice Daily was Safe and Demonstrated Robust Antiviral and Clinical Efficacy in a Healthy Volunteer Challenge Study

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DISCLOSURE

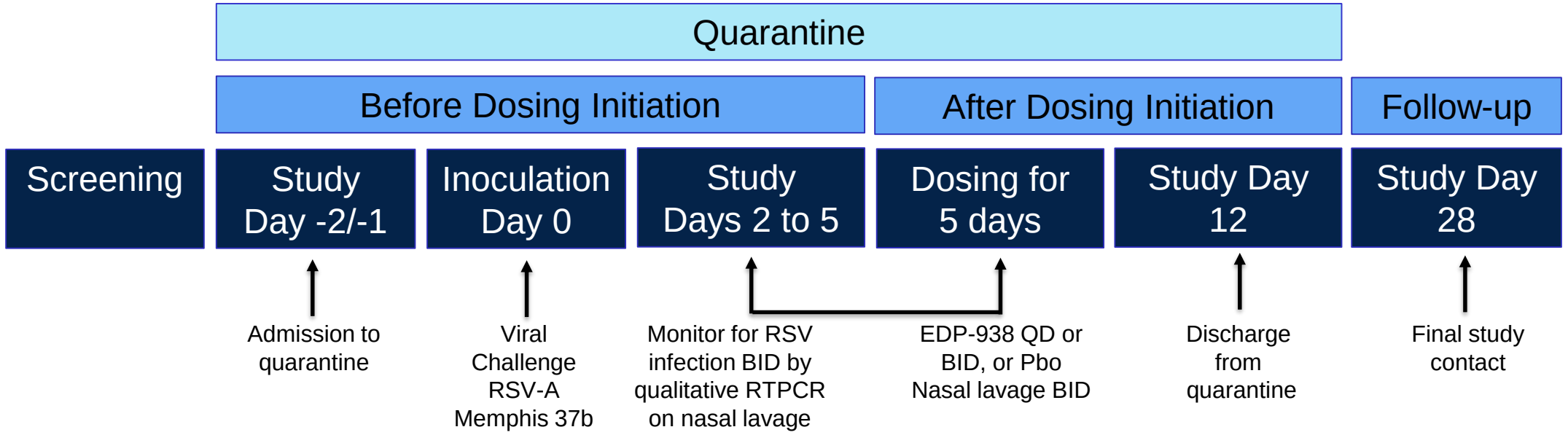
The presenter is an employee of Enanta Pharmaceuticals

BACKGROUND

- Respiratory Syncytial Virus (RSV) infection is associated with significant morbidity and mortality in infants, the elderly, and immunocompromised adults and is a condition for which there is currently no safe and highly effective therapy
- EDP-938 is a novel, potent RSV N-protein inhibitor, which is active *in vitro* against RSV A and B strains
  - EDP-938 reduced the RSV viral load by >4 $\log_{10}$ copies/mL in a preclinical primate infection model[1]
- In the Phase 1 first-in-human study, EDP-938 was observed to be generally safe and well tolerated at single doses up to 800 mg and multiple doses up to 600 mg once daily (QD) or 300 mg twice daily (BID) for 7 days and with mean trough exposures up to ≈30x higher than its *in vitro* EC_{90} for RSV[2]

1 M. H. J. Rhodin et.al, RSV18, 2 Ahmad A et al., 11th International Respiratory Syncytial Virus Symposium 2018

Design of EDP 938-101, a Phase 2a RSV Challenge Study



- Study drug dosing was initiated 12hrs after a +RSV test (qualitative RTPCR) or on Day 5 (PM), whichever was first
- EDP-938/placebo was administered as a blinded, oral suspension for 5 days in the 3 study arms:
  - EDP-938 600mg Q24h alternating with placebo Q24h or
  - EDP-938 500mg loading dose (LD), then 300mg BID or
  - Placebo BID

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METHODS

- Subjects were healthy male or female volunteers, 18-45 years, who had RSV antibody levels that were in lower 25th percentile of the reference population
  - **Primary Efficacy Endpoint**: RSV Viral Load (RTqPCR) area under the curve (AUC) measured in nasal lavage obtained every 12 hours
  - **Key Secondary Efficacy Endpoint**: Total Symptom Score (TSS) AUC assessed by 8 hourly subject diary entries
    - 10-point TSS assessments: runny nose, stuffy nose, sneezing, sore throat, earache, malaise/ tiredness, cough, shortness of breath, headache, muscle/ joint ache/ stiffness.
    - Symptoms were graded as absent (0), noticeable (1), bothersome (2) and interfering with activities (3)
  - **Other Secondary Endpoints**: Quantitative RSV culture AUC by Plaque Assay (nasal lavage) and Mucus Weight AUC assessed by daily tissue weights
- Additional assessments included Safety and PK

EDP 938-101 was Fully Powered to Evaluate the Predefined Efficacy Endpoints

- EDP 938-101 was fully powered for differences in both RSV viral load and total symptom score (TSS)
  - The study was designed with an 80% power to detect a 70% reduction with a two-sided alpha=0.05 and assuming an infection rate of 56% after inoculation
- The Intent-To-Treat Infected (ITT-I) population comprised all randomized subjects receiving challenge virus, ≥1 dose of study drug and with confirmed RSV infection by quantitative RTPCR
  - In the ITT-I population, end points were assessed from the 1st dose of study drug through Day 12

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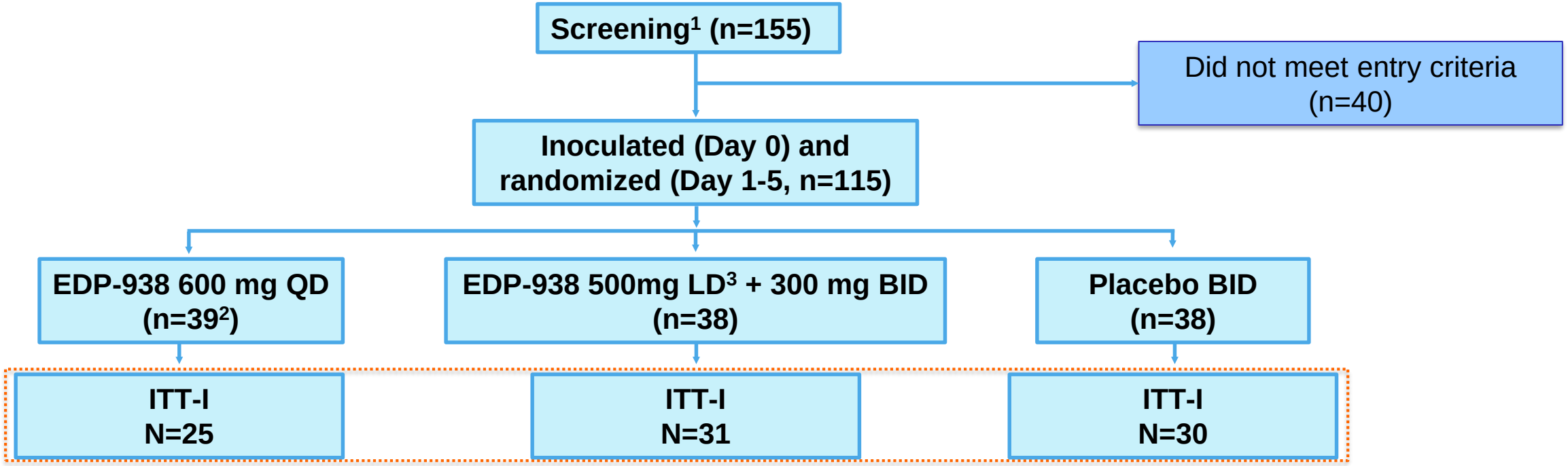
Results

EDP 938-101: Participant Disposition

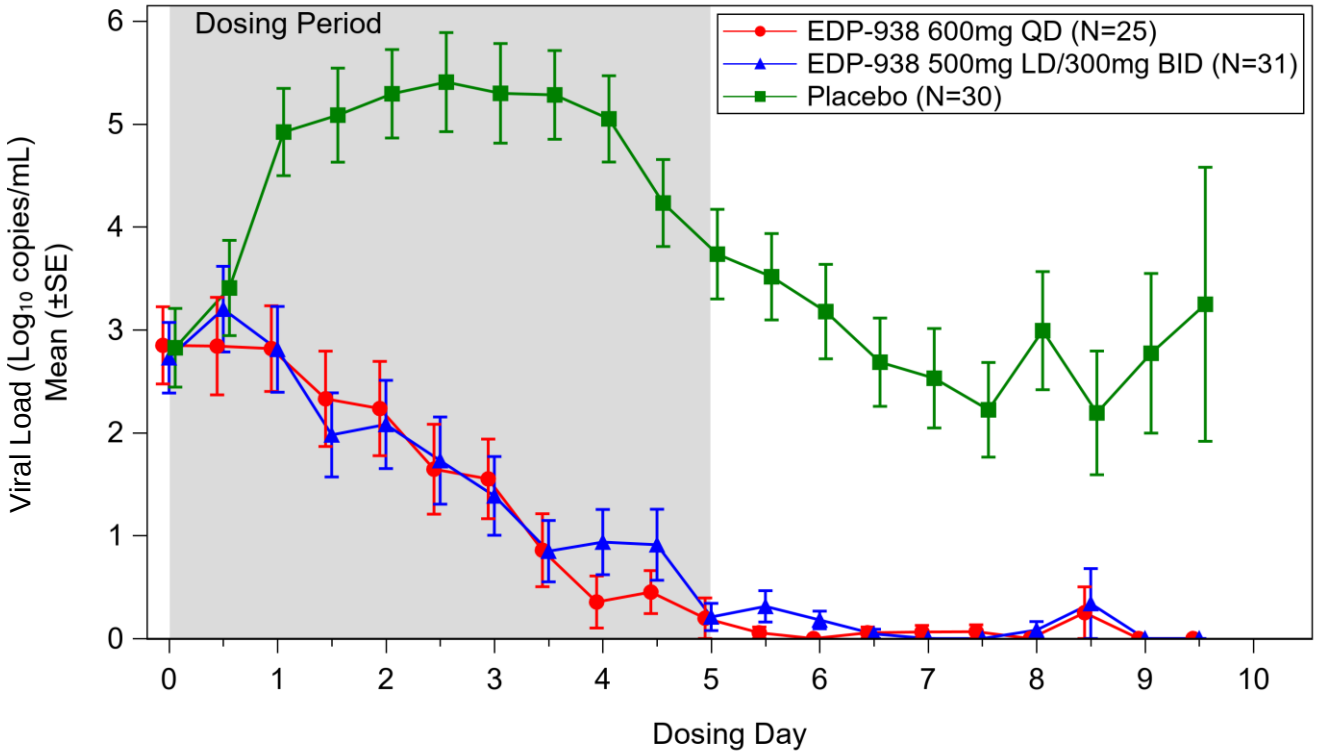


The **Intent-To-Treat Infected (ITT-I)** population comprises all randomized subjects receiving challenge virus, ≥1 dose of study drug and with confirmed RSV infection confirmed by RTqPCR

1. Screening Period is from Day -56 to Day -3
2. One subject was randomized but not dosed. This subject completed the quarantine period
3. LD=EDP-938 Loading Dose

RSV RNA Levels in Nasal Lavage by RTqPCR

Both EDP-938 Doses Demonstrated Highly Statistically Significant Reductions in RSV RNA Levels and with No Significant Difference in Outcome Between the Doses



	EDP-938 600 mg QD (n=25)	EDP-938 500 mg LD + 300 mg BID (n=31)	Placebo (n=30)
RSV Viral Load (RTqPCR) AUC mean (SD) (hrs x Log_{10} c/mL)	203.95 (173.50)	217.71 (217.55)	790.15 (408.80)
% Reduction (vs placebo)	**74.43%**	**71.46%**	
Absolute Reduction (vs placebo)	**-588.08**	**-564.63**	
P-value*	<0.001	<0.001	

*P-value represents comparison to Placebo

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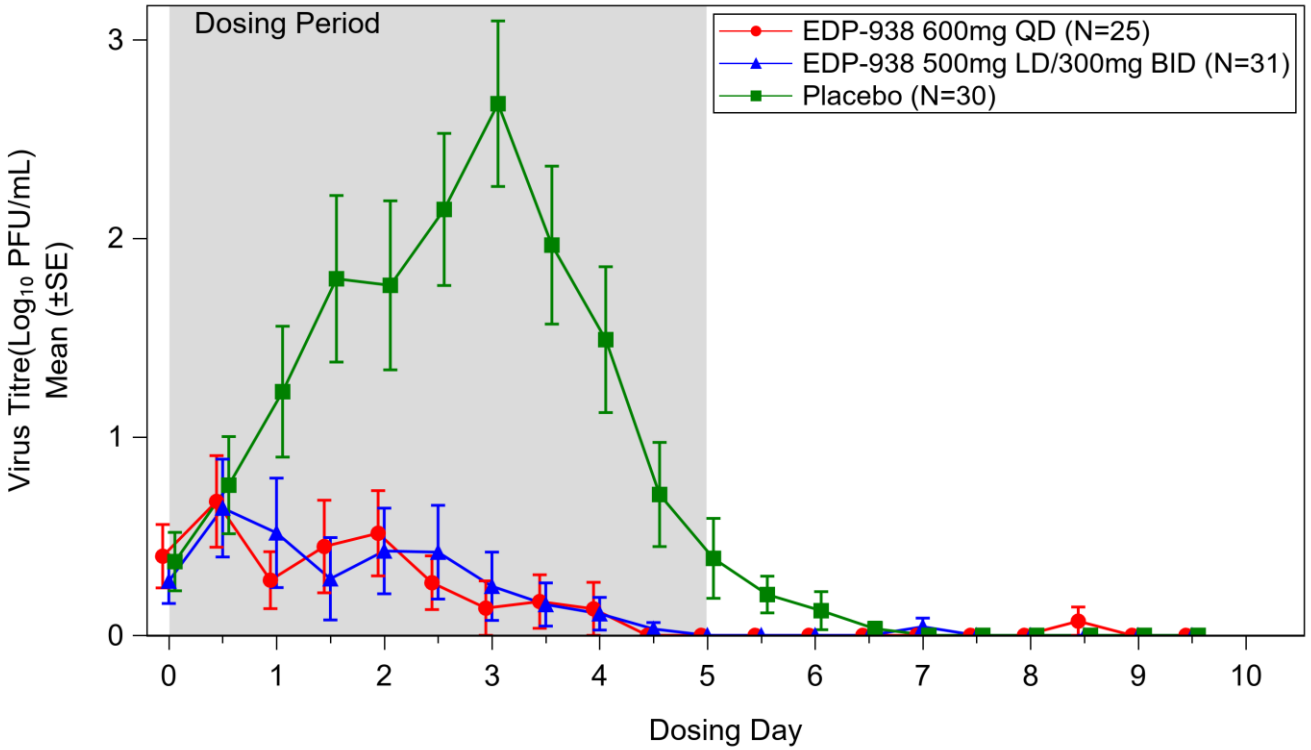
RSV Titre in Nasal Lavage by Quantitative Culture (Plaque Assay)

Both EDP-938 Doses Demonstrated Highly Statistically Significant Reductions in RSV Levels and with No Significant Difference in Outcome Between the Doses



	EDP-938 600 mg QD (n=25)	EDP-938 500 mg LD + 300 mg BID (n=31)	Placebo (n=30
RSV Titre Plaque Assay AUC mean (SD) (hrs x Log_{10} PFU/mL)	34.05 (63.58)	35.91 (78.04)	185.55 (161.71)
% Reduction (Vs placebo)	**82.53%**	**77.43%**	
Absolute Reduction (Vs placebo)	**-153.14**	**-143.67**	
P-value*	<0.001	<0.001	

*P-value represents comparison to Placebo

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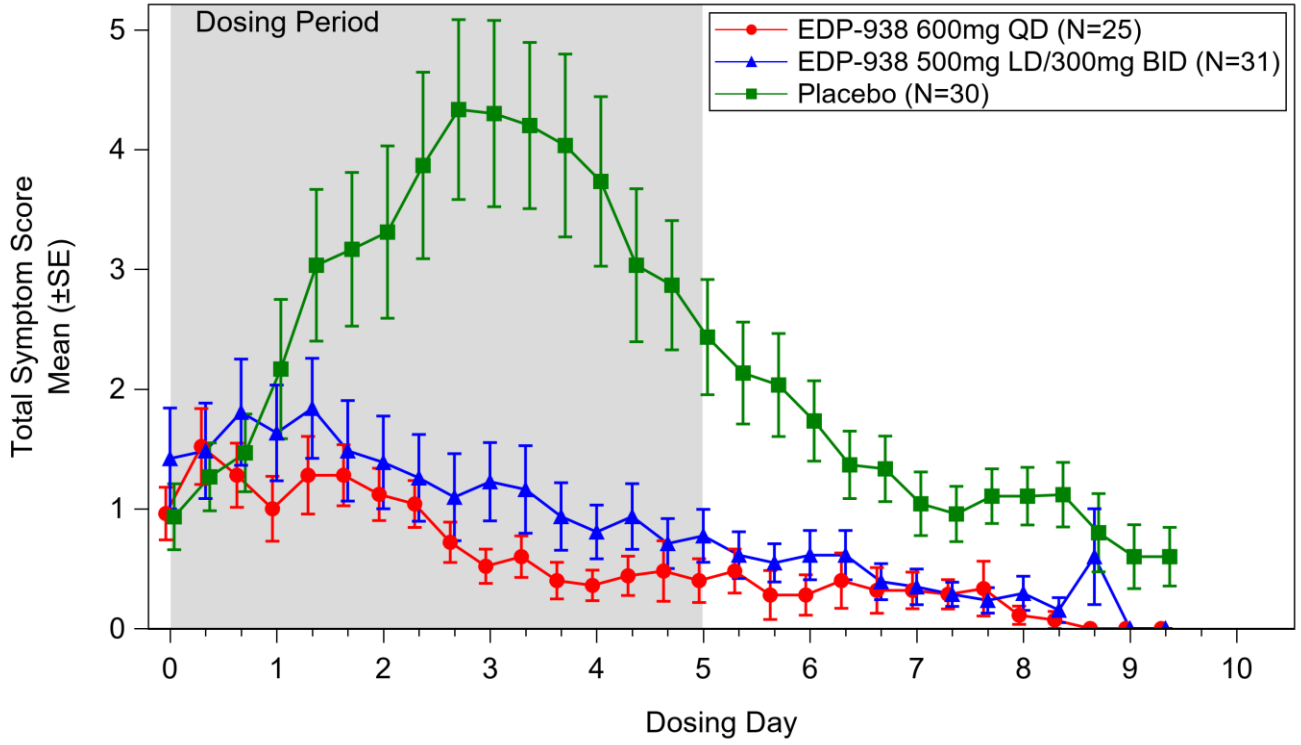
RSV Total Symptom Score (TSS)

Both EDP-938 Doses Demonstrated Highly Statistically Significant Attenuation of RSV Associated Symptoms and with No Significant Difference in Outcome Between the Doses



	EDP-938 600 mg QD (n=25)	EDP-938 500 mg LD + 300 mg BID (n=31)	Placebo (n=30)
TSS AUC mean (SD) (hours x Score)	124.47 (115.60)	181.75 (248.42)	478.75 (422.29)
% Reduction (Vs placebo)	**74.3%**	**68.2%**	
Absolute Reduction (Vs placebo)	**-355.91**	**-326.64**	
P-value*	<0.001	<0.001	

*P-value represents comparison to Placebo

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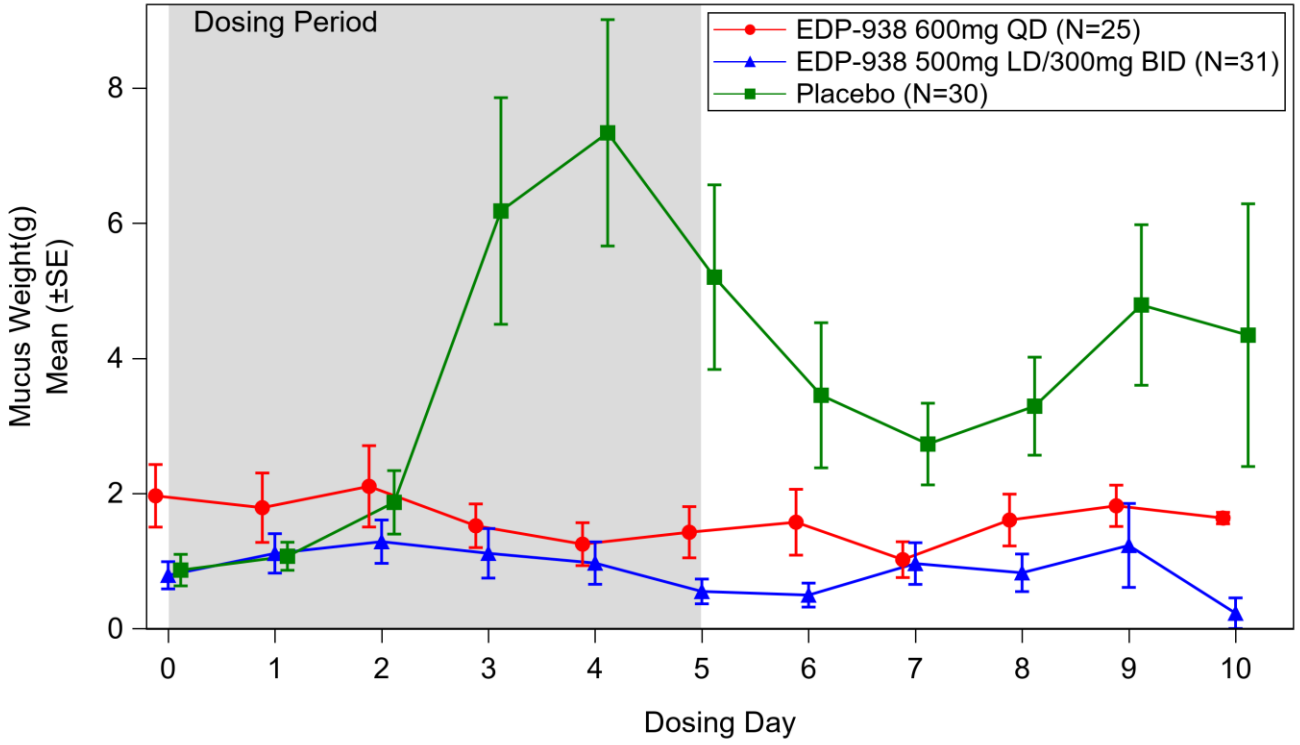
RSV Associated Mucus Production

Both EDP-938 Doses Markedly Attenuated Mucus Production and with No Significant Difference in Outcome Between the Doses



	EDP-938 600 mg QD (n=25)	EDP-938 500 mg LD + 300 mg BID (n=31)	Placebo (n=30
Nasal Mucus Total Weight (g) AUC Mean (SD)	12.965 (13.03)	7.428 (11.13)	33.416 (37.81)
% Reduction (versus placebo)	**72.06%**	**77.67%**	
Absolute Reduction (versus placebo)	**-24.081**	**-25.954**	
P-value*	<0.001	<0.001	

*P-value (ANCOVA) represents comparison to Placebo

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SAFETY OBSERVATIONS
EDP-938 was Generally Safe and Well-Tolerated

- Both EDP-938 dosing arms demonstrated favorable safety profiles, which were comparable to placebo over the 5 days of dosing through Day 28 of follow-up
  - Among EDP-938 recipients all AEs were mild expect for a single event of moderate dyspepsia in the BID arm and which resolved in follow-up
    - In the placebo arm, there were 3 AEs that were moderate in severity being headache (2) and hypoacusis (1) and which resolved in follow-up
  - There were no serious or severe AEs and no subject discontinued study drug
  - There were no clinically significant laboratory abnormalities in EDP-938 dosing groups compared to placebo

CONCLUSIONS
EDP-938 was Efficacious and Safe in the RSV Challenge Study

- In this Phase 2a RSV challenge study, the Primary and Key Secondary Efficacy Endpoints were achieved with high statistical significance at both dose levels, 600mg QD and 500mg LD + 300mg BID, over 5 days of dosing and with a favorable safety profile
- Specifically, EDP-938 demonstrated robust reductions in RSV viral load (by both RTqPCR and plaque assay), total symptom score and mucus weight
- These data support the further clinical evaluation of EDP-938 in populations at risk of severe RSV disease

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ACKNOWLEDGMENTS

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