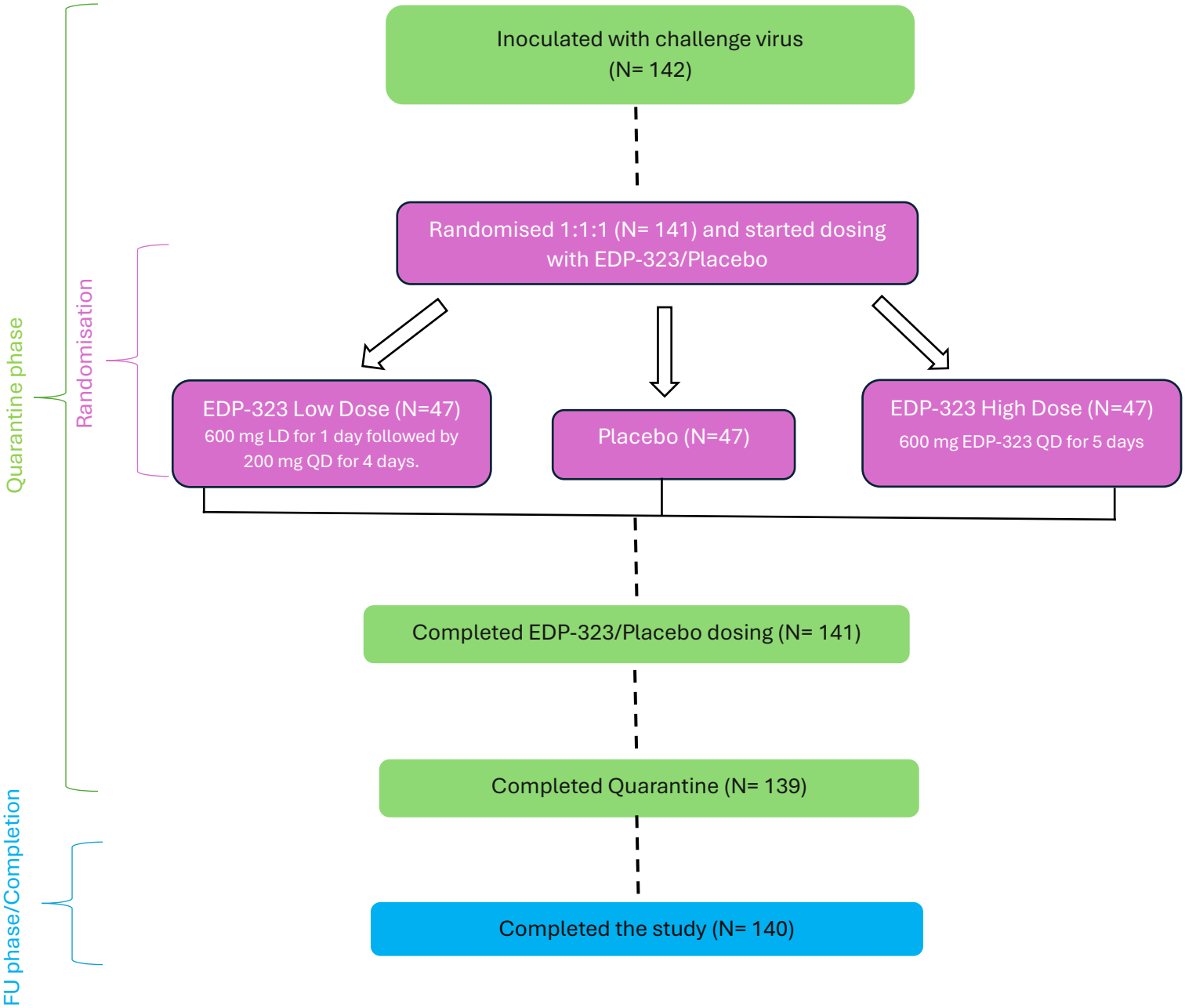
ETP-CST-001 Number of Participants (Planned and Analysed):

Planned:

- Protocol, Final v1.0, 23-June-2023: 114 participants were planned to be randomized 1:1:1 into 1 of 3 treatment groups (n=38 each) to receive EDP-323 (at 2 different doses) or placebo; the number of participants was planned to not exceed 125 dosed with EDP-323/placebo.
- Protocol Amendment, Final v2.0, 25-March-2024: 132 participants were planned to be randomized 1:1:1 into 1 of 3 treatment groups (n=44 each) to receive EDP-323 (at 2 different doses) or placebo; the number of participants was planned to not exceed 150 dosed with EDP-323/placebo.

Analysed:



Disposition of Participants:

In total, 142 participants were enrolled and inoculated with challenge virus of which 141 participants were randomized 1:1:1 into 1 of 3 treatment groups (EDP-323 high dose, EDP-323 low dose, and placebo groups; n=47 each) and completed IMP administration. One participant (1267229) was inoculated but was not randomized nor dosed. This participant self-discharged during quarantine on Day 4. Following a last telephone contact on Day 12 the participant was considered lost to follow-up.

All treated participants completed quarantine, except for 2 participants. One participant (1251060) in the placebo group self-discharged on Day 9 to attend to personal issues and was considered lost to follow-up after 3 telephone contacts made for missed Day 28 follow-up. One participant (1268979) in the EDP-323 high dose group self-discharged on Day 11 for family emergency reasons. This participant completed the Day 28 follow-up visit and was considered to have completed the study.

In total, 140 participants completed the study: 47 in EDP-323 high dose, 47 in the EDP-323 low dose, and 46 participants in the placebo group. Mean study duration was 31.02 days in the placebo group, 33.57 days in the EDP-323 high dose group, and 34.36 days in the EDP-323 low dose group.

Demographic and Other Baseline characteristics:

Overall, demographic characteristics were well balanced across the treatment groups. No notable differences were observed in age, ethnicity, BMI, or baseline RSV neutralization antibody concentrations between the EDP-323 groups and the placebo group. Participants were predominantly of not Hispanic or Latino ethnicity in all treatment groups. The proportion of females was slightly higher in the placebo group (40.4%) as compared with the EDP-323 groups (31.9 and 36.2%, in the EDP-323 high and low dose groups, respectively). Participants were predominantly White in all treatment groups. The EDP-323 low dose group had a higher proportion of Black or African American (14.9%) and Asian (6.4%) participants as compared with the other groups (6.4 and 4.3%, respectively, in the EDP-323 high dose group; 10.6 and 2.1%, respectively, in the placebo group). The proportion of White participants in the EDP-323 low dose group (74.5%) was lower as compared with the EDP-323 high dose group (83.0%) and the placebo group (80.9%). Since RSV viral loads and disease severity markers are not known to differ between these baseline demographic characteristics, the differences in sex and race are not expected to have impacted the study results.

Table 10-3: Demographics and BMI Data - Safety Analysis Set (Treated Participants)

Description	Statistics	EDP-323 High dose N=47	EDP-323 Low dose N=47	Pooled EDP-323 N=94	Placebo N=47	All N=141
	N'	47	47	94	47	141
	Missing	0	0	0	0	0
Sex	n (%) - Female	15 (31.9)	17 (36.2)	32 (34.0)	19 (40.4)	51 (36.2)
	n (%) - Male	32 (68.1)	30 (63.8)	62 (66.0)	28 (59.6)	90 (63.8)
Age (years)	Mean	29.09	27.62	28.35	27.91	28.21
	SD	6.372	5.980	6.190	6.223	6.182
	Median	28.00	26.00	27.00	27.00	27.00
	Q1, Q3	24.00, 33.00	24.00, 30.00	24.00, 32.00	23.00, 30.00	24.00, 31.00
	Min, Max	19.0, 44.0	18.0, 46.0	18.0, 46.0	19.0, 47.0	18.0, 47.0
Race	n (%) - White	39 (83.0)	35 (74.5)	74 (78.7)	38 (80.9)	112 (79.4)
	n (%) - Black or African American	3 (6.4)	7 (14.9)	10 (10.6)	5 (10.6)	15 (10.6)
	n (j%) - Asian	2 (4.3)	3. (6.4)	5 (5.3)	1 (2.1)	6 (4.3)
	n (%) - Other	3 (6.4)	2. (4.3)	5 (5.3)	3 (6.4)	8 (5.7)
Ethnicity	n (%) - Hispanic or Latino	1 (2.1)	2 (4.3)	3 (3.2)	1 (2.1)	4 (2.8)
	n (%) - not Hispanic or Latino	46 (97.9)	45 (95.7)	91 (96.8)	46 (97.9)	137 (97.2)

Notes:

- Percentages are calculated as n/N' and are based on the number of non-missing values in the safety treated set.
- The ALL column includes EDP-323 high dose, EDP-323 low dose, and placebo groups.

Efficacy:

The study's primary endpoint was reduction in Viral Load AUC as measured by RT-PCR compared to placebo. Treatment with EDP-323 high dose (600 mg QD for 5 days) or low dose (600 mg LD for 1 day followed by 200 mg QD for 4 days) after viral challenge with RSV-A Memphis 37b showed a statistically significant reduction of VL-AUC determined by qRT-PCR and by viral culture compared with placebo (p-values both <0.0001; α=0.05 2-sided). These PCR viral loads represented an 85% reduction in VL-AUC in the high dose vs placebo and an 87% reduction in VL-AUC in the low dose vs placebo. Similarly, these viral quantitative culture viral loads represented a 98% reduction in VL-AUC in the high dose vs placebo and a 97% reduction in VL-AUC in the low dose vs placebo. In contrast, between the EDP-323 low and high dose groups, VL-AUCs as measured by either qPCR or q Culture were not significantly different at the 5% 2-sided significance level for both qRT-PCR and viral culture methods. Sensitivity analyses using different populations and/or alternative definitions of AUC showed comparable results.

Figure 11-1: Mean Viral Load Determined by qRT-PCR over Time - ITT-I Analysis Set

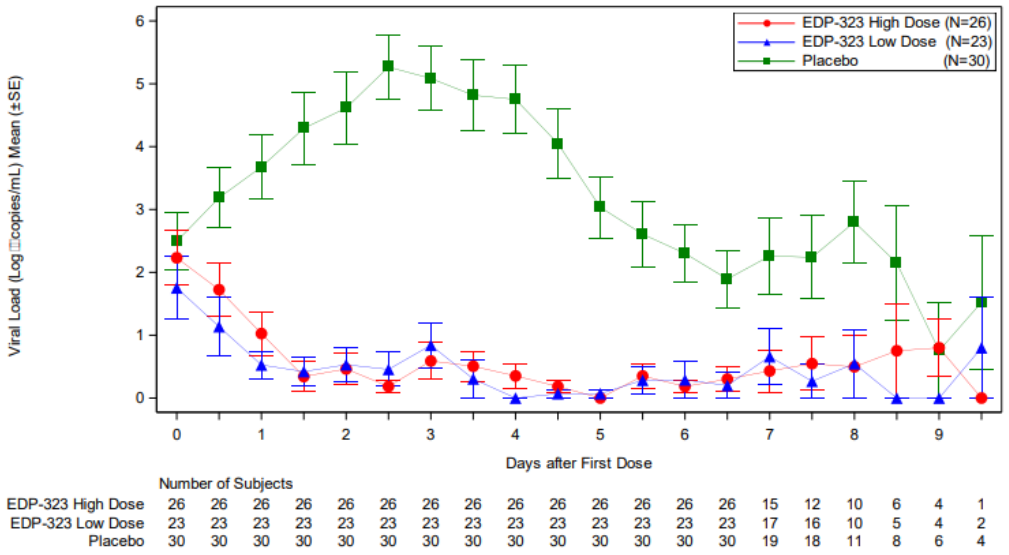


Table 11-1: VL-AUC Determined by qRT-PCR - ITT-I Analysis Set

VL-AUC (log_{10} copies/mL*hours)	EDP-323 High dose N=26	EDP-323 Low dose N=23	Pooled EDP-323 N=49	Placebo N=30
Mean (SD)	99.05 (133.325)	82.28 (158.033)	91.18 (144.140)	657.45 (396.743)
SE	26.15	32.95	20.59	72.44
%CV	134.60	192.06	158.08	60.35
Median	37.43	10.28	25.23	677.57
Q1, Q3	9.32, 150.66	0.00, 91.17	9.32, 97.20	312.94, 951.70
Min, Max	0.0, 514.8	0.0, 703.0	0.0, 703.0	9.6, 1375.8
Geometric mean[d]	25.13	15.82	20.25	453.51
GSD	8.31	7.99	8.08	3.16
Wilcoxon p-value[a]	<0.0001	<0.0001	<0.0001	
Difference in LS means[a]	-540.56	-523.12	-536.30	
95% CI for difference	-680.80, -400.33	-674.46, -371.78	-641.71, -430.89	
p-value[c]	<0.0001	<0.0001	<0.0001	
Wilcoxon p-value[b]	0.3966			
Difference in LS means[b]	-4.16			
95% CI for difference	-65.45, 57.13			
p-value[c]	0.8919			

ANCOVA=analysis of covariance; CI=confidence interval; CV=coefficient of variation; GSD=geometric standard deviation; IMP=investigational medicinal product; ITT-I=intent-to-treat infected; LLOD=lower limit of detection; LLOQ=lower limit of quantification; LS=least square; N=number of participants; Q1, Q3=first and third quartile; qRT-PCR=quantitative reverse transcriptase-polymerase chain reaction; SD=standard deviation; SE=standard error of the mean; VL-AUC=area under the viral load-time curve.

[a] Comparison of each active dose to placebo, and pooled EDP-323 to placebo.

[b] Comparison between active doses.

[c] P-values are from ANCOVA with treatment group as main effect and the baseline value as a covariate. The baseline value is defined as the qRT-PCR viral load value at the time of first dose of IMP.

[d] A constant of 1 was added to compute the geometric mean and GSD.

Notes:

- In case of value below the LLOQ, the qRT-PCR value used was 1.60 log_{10} copies/mL and in case of value below the LLOD, the qRT-PCR value used was 0 log_{10} copies/mL.
- For Participant 1251060 (placebo group) who discontinued the quarantine after the Day 9 a.m. assessment, viral load values were imputed to 0 from Day 9 p.m. to Day 12 a.m.

The VL-AUC determined by viral culture for the ITT-I analysis set showed a statistically significant reduction for both EDP-323 dosing regimens as well as for the pooled EDP-323 dosing regimens compared with the placebo group (p-value <0.0001; α=0.05 2-sided); the difference in LS means to placebo was -203.63 and -215.03 log10 PFU/mL*hours for the EDP-323 high and low dose group respectively, and -212.62 log10 PFU/mL*hours for the pooled EDP-323 groups.

The VL-AUC determined by viral culture was not significantly different between the EDP-323 low dose group and the EDP-323 high dose group at the 5% 2-sided significance level (p-value=0.8563); the difference in LS means between the high and low dose group was -0.40 log10 PFU/mL*hours.

The time to viral load negativity and time to first viral load negative slope, determined by qRT-PCR or viral culture, were generally shorter in both EDP-323 dose groups compared to placebo, and both were not significantly different between the EDP-323 dose groups. Viral loads dropped quickly after treatment with EDP-323 was initiated. The viral load slopes for both EDP-323 dosing regimens between first dose of IMP and approximately 12 hours, 1 day, or 2 days after IMP determined by qRT-PCR or viral culture were negative from the first evaluable time interval (approximately 12 hours) after IMP onwards and, in most cases, statistically significantly different from 0 indicating a decrease of viral load over time. This declining viral load in the EDP-323 groups contrasted with the viral load slopes in the placebo group being positive and (statistically significantly) different from 0 indicating that the viral load increased over time. No participants receiving EDP-323 developed a laboratory-confirmed RSV infection after beginning or after completing their 5-day dosing regimen. In contrast, 6 participants developed a laboratory-confirmed RSV infection after starting their 5-day regimen of placebo.

The TSS-AUC (based on 10 symptoms) showed a statistically significant reduction in TSS-AUC compared to placebo for both EDP-323 dosing regimens compared with the placebo group (p-value <0.0001; α=0.05 2-sided). The TSS-AUC was not significantly different between the EDP-323 low and high dose groups at the 5% 2-sided significance level. Sensitivity analyses using alternative definitions of AUC or using an SDC based on 11 symptoms showed comparable results. The total weight of mucoid secretions discharged from the nose and the total number of tissues used were statistically significantly lower for both EDP-323 dosing regimens as well as for the pooled EDP-323 dosing regimens compared with the placebo group (p-value=0.0042, 0.0058, and <0.0001, respectively, and p-value=0.0026, 0.0022, and <0.0001, respectively; α=0.052-sided).

Table 11-11: Total Symptom Score-AUC (10-items) - ITT-I Analysis Set

TSS-AUC (10-items) (score*hours)	EDP-323 High dose N=26	EDP-323 Low dose N=23	Pooled EDP-323 N=49	Placebo N=30
Mean (SD)	127.31 (149.221)	82.67 (100.412)	106.36 (129.325)	369.10 (330.397)
SE	29.26	20.94	18.48	60.32
%CV	117.21	121.46	121.60	89.51
Median	68.05	60.36	64.10	292.02
Q1, Q3	39.85, 167.57	0.00, 127.98	19.58, 127.98	72.11, 703.45
Min, Max	0.0, 608.3	0.0, 418.3	0.0, 608.3	0.0, 1182.1
Geometric mean[d]	59.67	20.21	36.05	156.87
GSD	4.75	9.36	7.09	6.43
Wilcoxon p-value[a]	0.0080	0.0006	0.0003	
Difference in LS means[a]	-280.61	-301.15	-286.64	
95% CI for difference	-404.44, -156.77	-428.53, -173.76	-378.30, -194.98	
p-value[c]	<0.0001	<0.0001	<0.0001	
Wilcoxon p-value[b]	0.2279			
Difference in LS means[b]	30.76			
95% CI for difference	-27.25, 88.77			
p-value[c]	0.2914			

ANCOVA=analysis of covariance; CI=confidence interval; CV=coefficient of variation; GSD=geometric standard deviation; IMP=investigational medicinal product; ITT-I=intent-to-treat infected; LS=least square; N=number of participants; Q1, Q3=first and third quartile; SD=standard deviation; SE=standard error of the mean; TSS=total symptom score; TSS-AUC=area under the TSS-time curve.

[a] Comparison of each active dose to placebo, and pooled EDP-323 to placebo.

[b] Comparison between active doses.

[c] P-values are from ANCOVA with treatment group as main effect and the baseline value as a covariate. The baseline value is defined as the TSS value at the time of first dose of IMP.

[d] A constant of 1 was added to compute the geometric mean and GSD.

Note: For Participant 1251060 (placebo group) who discontinued the quarantine after the Day 9 afternoon assessment, TSS values were imputed to 0 from Day 9 p.m. to Day 12 a.m.

Source: Refer to Table 14.2.3.1.1.1.

Figure 11-15: Mean Total Symptom Score (10-items) over Time – ITT-I Analysis Set

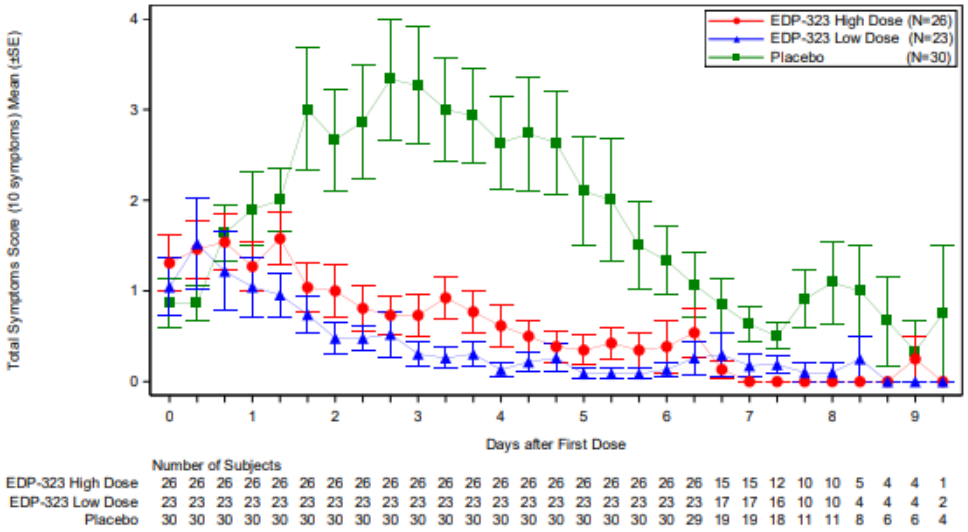


Table 11-13: Time to Peak Total Symptom Score (10-items) - ITT-I Analysis Set

Time to peak TSS (10-items)[e] (days)	EDP-323 High dose N=26	EDP-323 Low dose N=23	Pooled EDP-323 N=49	Placebo N=30
Mean (SD)	2.00 (2.403)	2.84 (3.125)	2.40 (2.768)	3.36 (2.065)
SE	0.47	0.65	0.40	0.38
%CV	120.03	109.96	115.52	61.51
Median	1.00	1.00	1.00	3.34
Q1, Q3	0.33, 3.00	0.33, 6.33	0.33, 3.34	1.68, 4.34
Min, Max	0.0, 9.0	0.0, 9.0	0.0, 9.0	0.0, 9.3
Geometric mean[d]	1.34	1.74	1.52	2.90
GSD	2.01	2.33	2.15	1.65
Wilcoxon p-value[a]	0.0023	0.1141	0.0056	
Difference in LS means[a]	-1.08	-0.38	-0.72	
95% CI for difference	-2.19, 0.03	-1.69, 0.92	-1.77, 0.33	
p-value[c]	0.0552	0.5599	0.1763	
Wilcoxon p-value[b]	0.5805			
Difference in LS means[b]	-0.61			
95% CI for difference	-2.01, 0.80			
p-value[c]	0.3879			

ANCOVA=analysis of covariance; CI=confidence interval; CV=coefficient of variation; GSD=geometric standard deviation; IMP=investigational medicinal product; ITT-I=intent-to-treat infected; LS=least square; N=number of participants; Q1, Q3=first and third quartile; SD=standard deviation; SE=standard error of the mean; TSS=total symptom score.

[a] Comparison of each active dose to placebo, and pooled EDP-323 to placebo.

[b] Comparison between active doses.

[c] P-values are from ANCOVA with treatment group as main effect and the baseline value as a covariate. The baseline value is defined as the TSS value at the time of first dose of IMP.

[d] A constant of 1 was added to compute the geometric mean and GSD.

[e] Time to peak TSS = Time of peak TSS – time of the nearest TSS assessment to the first dose of IMP.

Table 11-14: Time to Resolution from Peak Total Symptom Score (10-items) - ITT-I Analysis Set

Time to resolution from peak TSS (10-items)[e] (days)	EDP-323 High dose N=26	EDP-323 Low dose N=23	Pooled EDP-323 N=49	Placebo N=30
Participants with at least one TSS >0 – n (%)	24 (92.3)	16 (69.6)	40 (81.6)	28 (93.3)
Mean (SD)	2.16 (1.922)	2.58 (2.415)	2.33 (2.113)	2.93 (1.789)
SE	0.39	0.60	0.33	0.34
%CV	88.77	93.51	90.60	61.12
Median	1.51	2.02	1.67	3.00
Q1, Q3	0.65, 3.67	1.15, 2.33	0.83, 3.18	1.33, 4.50
Min, Max	0.0, 6.3	0.3, 8.7	0.0, 8.7	0.3, 5.7
Geometric mean[d]	1.66	2.05	1.81	2.48
GSD	1.82	1.74	1.79	1.69
Wilcoxon p-value[a]	0.0827	0.3291	0.0925	
Difference in LS means[a]	-1.04	-0.53	-0.84	
95% CI for difference	-1.97, -0.10	-1.81, 0.76	-1.77, 0.09	
p-value[c]	0.0307	0.4119	0.0752	
Wilcoxon p-value[b]	0.5254			
Difference in LS means[b]	-0.38			
95% CI for difference	-1.68, 0.93			
p-value[c]	0.5629			

ANCOVA=analysis of covariance; CI=confidence interval; CV=coefficient of variation; GSD=geometric standard deviation; IMP=investigational medicinal product; ITT-I=intent-to-treat infected; LS=least square; n/N=number of participants; Q1, Q3=first and third quartile; SD=standard deviation; SE=standard error of the mean; TSS=total symptom score.

[a] Comparison of each active dose to placebo, and pooled EDP-323 to placebo.

[b] Comparison between active doses.

[c] P-values are from ANCOVA with treatment group as main effect and the baseline value as a covariate. The baseline value is defined as the TSS value at the time of first dose of IMP.

[d] A constant of 1 was added to compute the geometric mean and GSD.

[e] Time to resolution from peak TSS = Time of the first 24-hour symptom-free time point - Time of peak TSS.

Safety:

Viral challenge with RSV-A Memphis 37b and subsequent treatment with EDP-323 high dose (600 mg QD for 5 days) or low dose (600 mg LD for 1 day followed by 200 mg QD for 4 days) was generally safe and well tolerated. No deaths, SAEs, or AEs of grade 3 or above were reported, and none of the AEs led to treatment discontinuation or permanent study discontinuation. The incidence of AEs, challenge-emergent adverse events (CEAEs), or treatment-emergent adverse events (TEAEs) was comparable between the EDP-323 groups and the placebo group. Most AEs were of mild intensity, not deemed related to the IMP, and were recovered/resolved by the end of the study.

No relevant changes from baseline to post-baseline visits, no apparent trends over time, and no notable differences between the treatment groups were observed for clinical laboratory parameters (haematology, biochemistry, and urinalysis), vital signs, temperature, electrocardiograms (ECGs), or physical examination results.

Table 12-2: Summary of Adverse Events – Enrolled Analysis Set/Safety Analysis Set (Treated Participants)

Description	EDP-323 High dose N=47	EDP-323 Low dose N=47	Pooled EDP-323 N=94	Placebo N=47
Any AE (Period 0 up to 3)[a]	13 (27.7%) [16]	15 (31.9%) [19]	28 (29.8%) [35]	15 (31.9%) [23]
Any CEAE overall	13 (27.7%) [16]	15 (31.9%) [18]	28 (29.8%) [34]	15 (31.9%) [22]
Any CEAE during Period 1	2 (4.3%) [2]	1 (2.1%) [1]	3 (3.2%) [3]	3 (6.4%) [3]
Any CEAE overall related to challenge virus	3 (6.4%) [3]	0	3 (3.2%) [3]	2 (4.3%) [2]
Any CEAE leading to study discontinuation during Period 1	0	0	0	0
Any serious CEAE during Period 1	0	0	0	0
AEs leading to death	0	0	0	0
Any TEAE overall	11 (23.4%) [14]	14 (29.8%) [17]	25 (26.6%) [31]	13 (27.7%) [19]
Any TEAE during Period 2	6 (12.8%) [6]	7 (14.9%) [8]	13 (13.8%) [14]	7 (14.9%) [8]
Any TEAE during Period 3	7 (14.9%) [8]	8 (17.0%) [9]	15 (16.0%) [17]	8 (17.0%) [11]
Any TEAE overall related to study treatment	1 (2.1%) [1]	1 (2.1%) [1]	2 (2.1%) [2]	0
Any TEAE during Period 2 related to study treatment	1 (2.1%) [1]	1 (2.1%) [1]	2 (2.1%) [1]	0
Any TEAE during Period 3 related to study treatment	0	0	0	0
Any TEAE during Period 2 leading to treatment discontinuation	0	0	0	0
Any TEAE leading to permanent study discontinuation	0	0	0	0
Any serious TEAE	0	0	0	0
Any TEAE with grade 3 or above	0	0	0	0

AE=adverse event; CEAE=challenge-emergent adverse event; IMP=investigational medicinal product; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants; TEAE=treatment-emergent adverse event.

[a] 2 AEs occurred prior to inoculation and are included in this category.

Notes:

- Presented: number of participants (percentage of participants) [number of events].
- AEs are coded using the MedDRA version 27.0.
- Percentages are based on the number of participants in the enrolled analysis set (CEAEs) or on the number of treated participants in the safety analysis set (TEAEs).
- Period 0: from admission at Day -2/-1 to just before challenge virus inoculation Day 0.
- Period 1: from challenge virus inoculation on Day 0 to just before first IMP dose between Day 1 and Day 5 (p.m.).
- Period 2: from first IMP dose between Day 1 and Day 5 (p.m.) to actual discharge from the quarantine unit.
- Period 3: from actual discharge from the quarantine unit to end-of-study visit.
- For Periods 2 and 3, all AEs are both TEAE and CEAE.

Pharmacokinetics

Following treatment with EDP-323 high dose (600 mg QD for 5 days) or low dose (600 mg LD for 1 day followed by 200 mg QD for 4 days) mean plasma concentrations for EDP-323 and the metabolites EP-038725 and EP-039082 were generally comparable between both EDP-323 dosing regimens after administration of the first EDP-323 dose, while following multiple dose administration of EDP-323, mean plasma concentrations for EDP-323 and metabolites were generally higher in the EDP-323 high dose group compared to low dose group.

Overall, the mean trough concentrations of EDP-323 were approximately 25- and 26-fold higher after the first dose compared to the protein adjusted EC90 value for EDP-323 (0.184 ng/mL) determined in vitro using 3D pHAEC-ALI, and approximately 35- and 16-fold higher after the last dose for the EDP-323 high and low dose groups, respectively.

Overall, the mean trough concentrations of EDP-323 were maintained at approximately 16- to 35-fold above the protein adjusted EC90 value after the last dose of EDP-323.

No linear correlations and no non-linear Emax relations were identified between RSV VL-AUC or TSS-AUC and plasma exposure of EDP-323 for any of the EDP-323 dosing regimens, which is consistent with robust efficacy at both dose levels.

Overall Conclusion:

Viral challenge with RSV-A Memphis 37b and subsequent treatment with EDP-323 for 5 days was generally safe and well tolerated with side effect profiles similar in general to placebo. Treatment with EDP-323 high dose (600 mg QD for 5 days) or low dose (600 mg LD for 1 day followed by 200 mg QD for 4 days) after viral challenge with RSV-A Memphis 37b significantly reduced RSV viral loads, clinical symptom scores, and the production of respiratory mucus, while no notable differences were observed between the EDP-323 dosing regimens. The timing of the onset of the reduction in RSV viral loads (as assessed by qRT-PCR and viral culture) was rapid, occurring between the baseline viral load pre-dose and the subsequent next nasal wash (within the very first ≈12 hours after first dose of EDP-323). Overall, the mean trough concentrations of EDP-323 were maintained at approximately 16- to 35-fold above the protein adjusted EC90 value 24 hours after the last dose of EDP-323. No linear correlations and no non-linear Emax relations were identified between RSV VL-AUC or TSS-AUC and plasma exposure of EDP-323 for any of the EDP-323 dosing regimens, which is consistent with robust efficacy at both dose levels generating plasma concentrations far-exceeding the EC-90 of RSV. These data support further clinical development of EDP-323.