

S-337395, a novel L-protein inhibitor of respiratory syncytial virus demonstrates dose-dependent antiviral activity in a human challenge study



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Conclusions:

- S-337395, a novel L-protein inhibitor of respiratory syncytial virus was well tolerated and demonstrated dose-dependent anti-viral activity in this human challenge study.
- At 300 mg, S-337395 produced statistically significant reductions in viral load, infectious viral titers and clinical symptoms compared to placebo.
- These data are promising and support further development of S-337395 as a potential treatment for RSV infection.

Background:

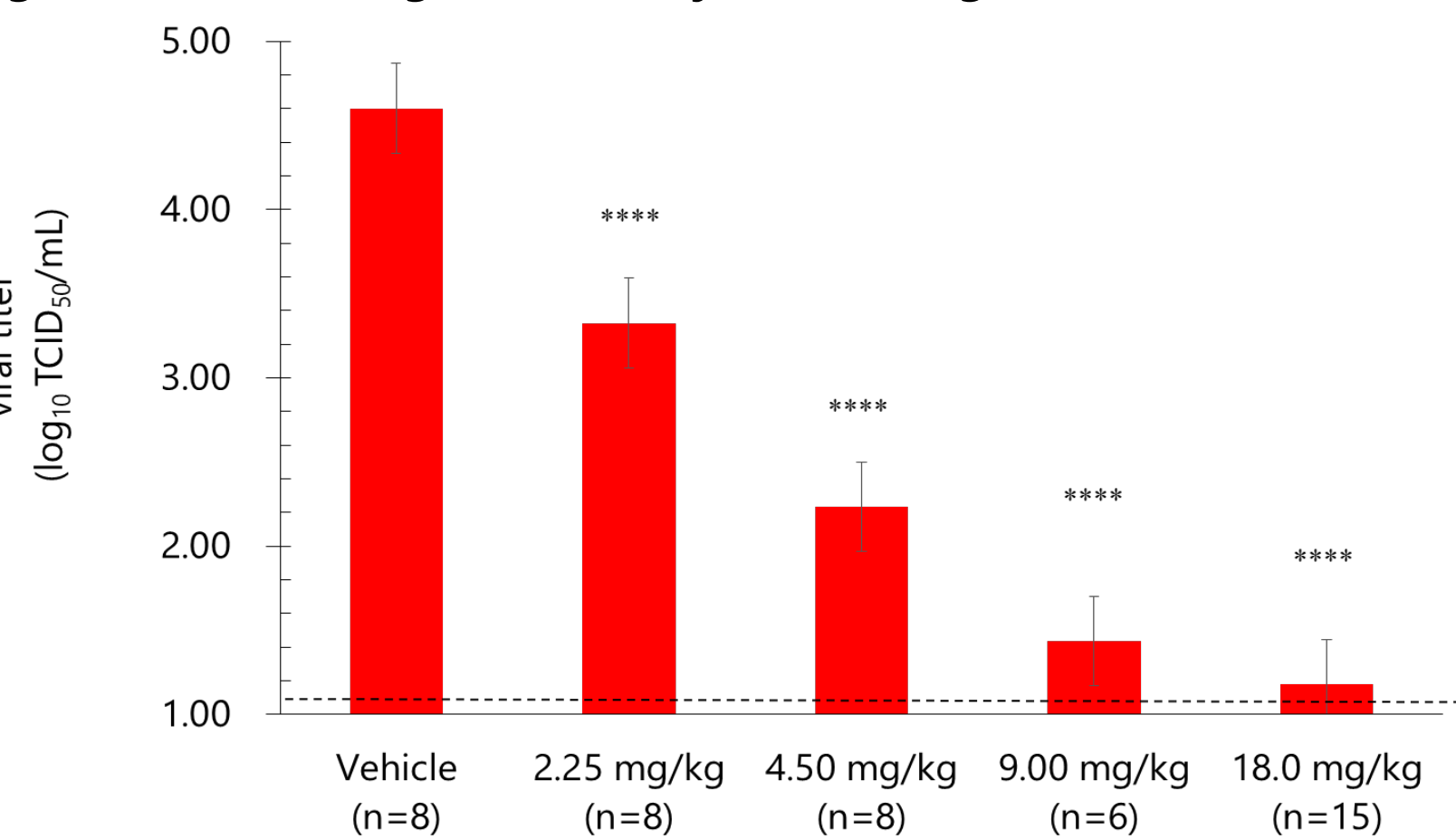
S-337395 is a novel Respiratory Syncytial Virus (RSV) L-protein inhibitor discovered by Shionogi & Co., Ltd. and UBE Corporation as a potential oral antiviral therapy against RSV infection. S-337395 has shown promise in *in vitro* and *in vivo* models (Table 1, Figure 1). In this study, we evaluated the efficacy of S-337395 against RSV in a human challenge model.

Table 1 S-337395 *in vitro* efficacy against RSV

Virus strain	Subtype	EC ₅₀ (nmol/L)
RSV A-2	A	1.49 ± 0.09
RSV A Memphis 37b	A	1.59 ± 0.13

HEp-2 cells, inhibitory effect against plaque formation
EC₅₀ values were expressed as mean ± SD.

Figure 1 Mouse lung titers at day 4 following administration of various doses of S-337395

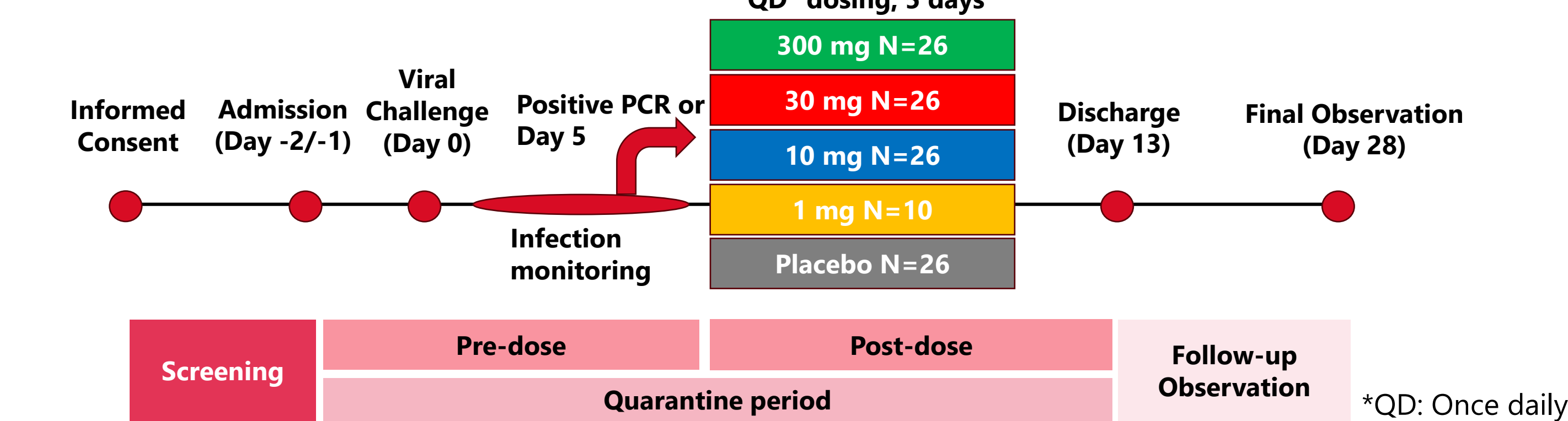


Mice: Female BALB/c, Virus: RSV A-2
Administration method: Oral administration twice daily for 4 days
S-337395 was administered 1 hour before virus infection.
Viral titers in lung homogenates were measured at day 4 following S-337395 administration.
Viral titers were expressed as mean ± SD.
Broken line represents the lower limit of quantification (1.10 log₁₀ TCID₅₀/mL).
**** p < 0.0001 vs vehicle by Dunnett's test

Methods:

This was a randomized, double-blind, placebo-controlled, parallel-group study to assess antiviral activity of S-337395 in an RSV human challenge model. Healthy individuals aged 18-55 years were eligible to participate. Participants were individually quarantined and later inoculated with RSV-A Memphis 37b on Day 0. Nasal washes were collected for diagnostic and virology assessments by PCR twice daily from Day 2 to Day 12, with final collection on Day 13 (Figure 2). On the day of RSV confirmed infection or Day 5, participants were randomized to receive either S-337395 (1, 10, 30, or 300 mg) or placebo once daily for 5 days. Participants with confirmed RSV infection by PCR at any time after inoculation were included in the intention-to-treat infected (ITT-I) set for efficacy analyses. Efficacy was assessed based on change in viral RNA load, infectious viral titer and clinical total symptom score area under the curve (AUC) from baseline (last non-missing observation prior to the administration of the first dose of study treatment) through Day 13. Safety was assessed in all treated participants. A subtherapeutic dose of 1 mg was used to assess dose response.

Figure 2 Study Design



Results:

Demographic data

A total of 114 participants were randomized, with 60 participants confirmed to have RSV infection (ITT-I analysis set: 6, 13, 11, and 9 participants in S-337395 1, 10, 30, and 300 mg respectively, and 21 participants in placebo group, Table 2).

Table 2 Demographic data (ITT-I Analysis Set)

Description	Statistics	Placebo (N=21)	1 mg (N=6)	10 mg (N=13)	30 mg (N=11)	300 mg (N=9)	All (N=60)
Sex							
Female	n (%)	5 (23.8)	2 (33.3)	7 (53.8)	2 (18.2)	1 (11.1)	17 (28.3)
Male	n (%)	16 (76.2)	4 (66.7)	6 (46.2)	9 (81.8)	8 (88.9)	43 (71.7)
Age							
Mean (SD)		25.24 (5.73)	30.17 (9.39)	26.69 (5.04)	30.45 (7.89)	26.33 (7.33)	27.17 (6.78)
Min, Max		18.0, 40.0	19.0, 43.0	19.0, 38.0	21.0, 49.0	20.0, 44.0	18.0, 49.0
Race							
Asian	n (%)	2 (9.5)	0 (0.0)	1 (7.7)	2 (18.2)	0 (0.0)	5 (8.3)
White	n (%)	15 (71.4)	6 (100.0)	10 (76.9)	8 (72.7)	8 (88.9)	47 (78.3)
Other	n (%)	4(19.0)	0 (0.0)	2 (15.4)	1 (9.1)	1 (11.1)	8 (13.3)

N is the number of subjects in each group.
n is the number of non-missing values for the corresponding variable or modality.
Percentages are based on the number of subjects without missing values in the ITT-I analysis set.

Safety profile

Among the 114 participants, treatment-emergent adverse events (TEAE) were reported in 29.5% (26/88) of S-337395 and 7.7% (2/26) of placebo participants. No serious adverse events, or discontinuations due to TEAE were reported in any group. No AEs related to the study drug were observed. Furthermore, no dose-dependent increase in frequency or severity of TEAE was observed. The most frequent TEAE was Upper Respiratory Tract Infection observed in 3 subjects; 1 in the placebo group, and 2 in the 300mg group.

Table 3 Summary of Adverse Events

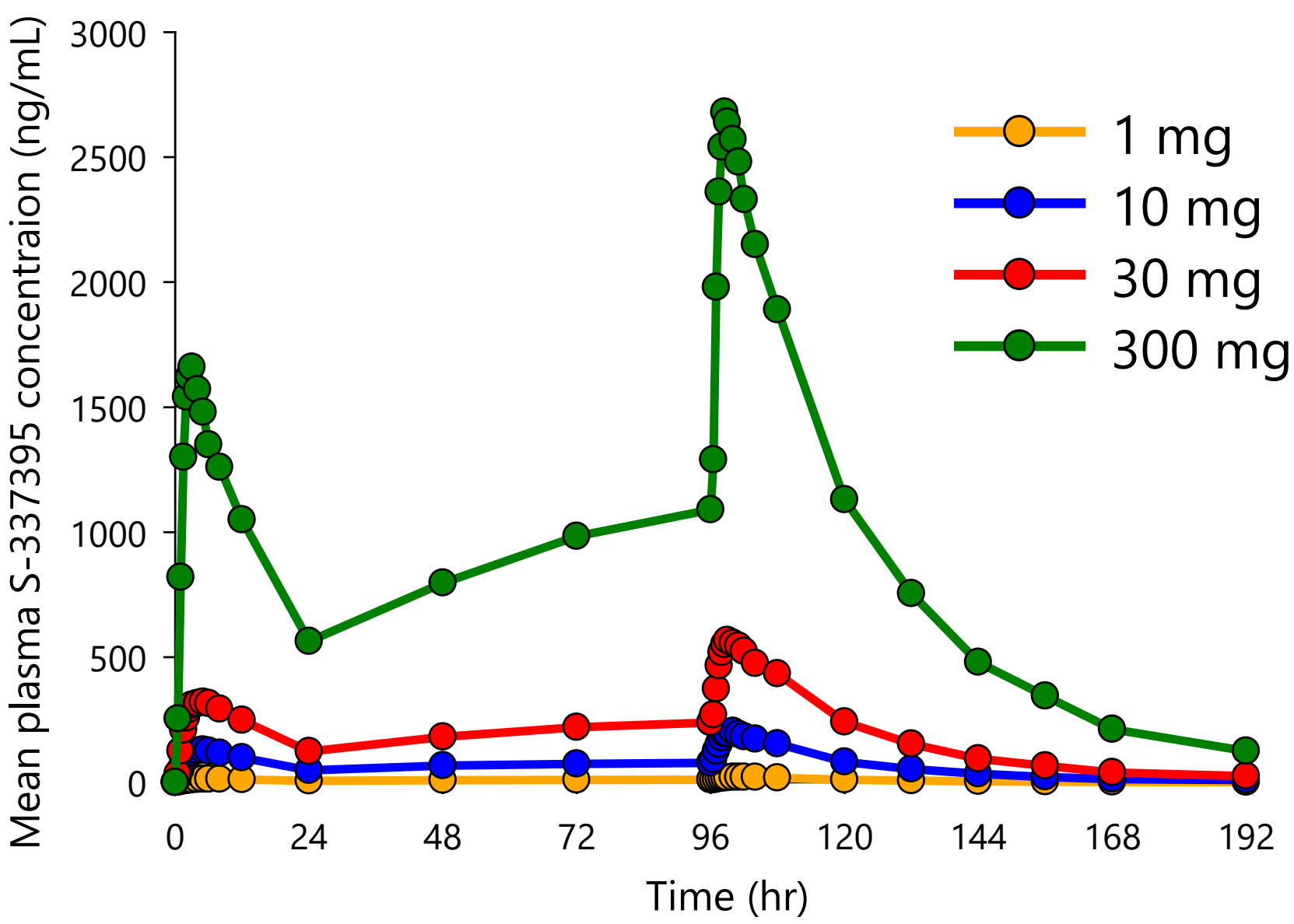
Description	Placebo (N=26)	1 mg (N=10)	10 mg (N=26)	30 mg (N=26)	300 mg (N=26)	All (N=114)
Any TEAEs	2 (7.7%) [2]	4 (40.0%) [5]	6 (23.1%) [8]	10 (38.5%) [10]	6 (23.1%) [6]	28 (24.6%) [30]
Drug related AEs	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]

N is the number of subjects in each group. TEAE: Treatment Emergent Adverse Event.
Presented: number of subjects (percentage of subjects) [number of events].

Pharmacokinetics:

S-337395 exposures increased with ascending doses.

Figure 3 Mean Plasma S-337395 Concentration Profiles



Efficacy:

RSV viral load AUC by qRT-PCR was significantly lower in 30 and 300 mg S-337395 groups compared to placebo (p=0.0004 and p<0.0001, respectively), with 300mg group showing an 88.9% reduction vs placebo (Table 4). A dose-dependent increase in viral load reduction was observed from 10 to 300mg (Figure 4). Infectious viral titer AUC was also significantly lower in 30 and 300 mg vs placebo (72.3% and 86.2% reduction respectively, both p<0.005, Figure 5). In addition, 300 mg showed a significantly lower AUC for clinical total symptom score with 78.2% reduction from placebo (p=0.021, Figure 6).

Table 4 VL-AUC measured by qRT-PCR (hours* Log₁₀ copies/mL)

Statistics	Placebo (N=21)	1 mg (N=6)	10 mg (N=13)	30 mg (N=11)	300 mg (N=9)
Mean (SD)	629.42 (468.48)	771.27 (449.97)	516.74 (444.56)	263.70 (258.64)	208.94 (195.22)
LSmeans	698.73	696.20	546.01	254.48	77.25
95% CI for LSmeans	[557.56 : 839.90]	[434.71 : 957.68]	[368.97 : 723.05]	[53.24 : 437.73]	[-140.14 : 294.64]
p-value*		0.9865	0.1798	0.0004	<0.0001
Reduction vs Placebo (%)		0.36	21.86	64.87	88.94

N is the number of subjects in each group. LSmeans: Least square means. CI: Confidence interval.
P-value are from ANCOVA with treatment group as main effect and the baseline value as a covariate.

Figure 4 Viral load measured by qRT-PCR mean values over time (ITT-I)

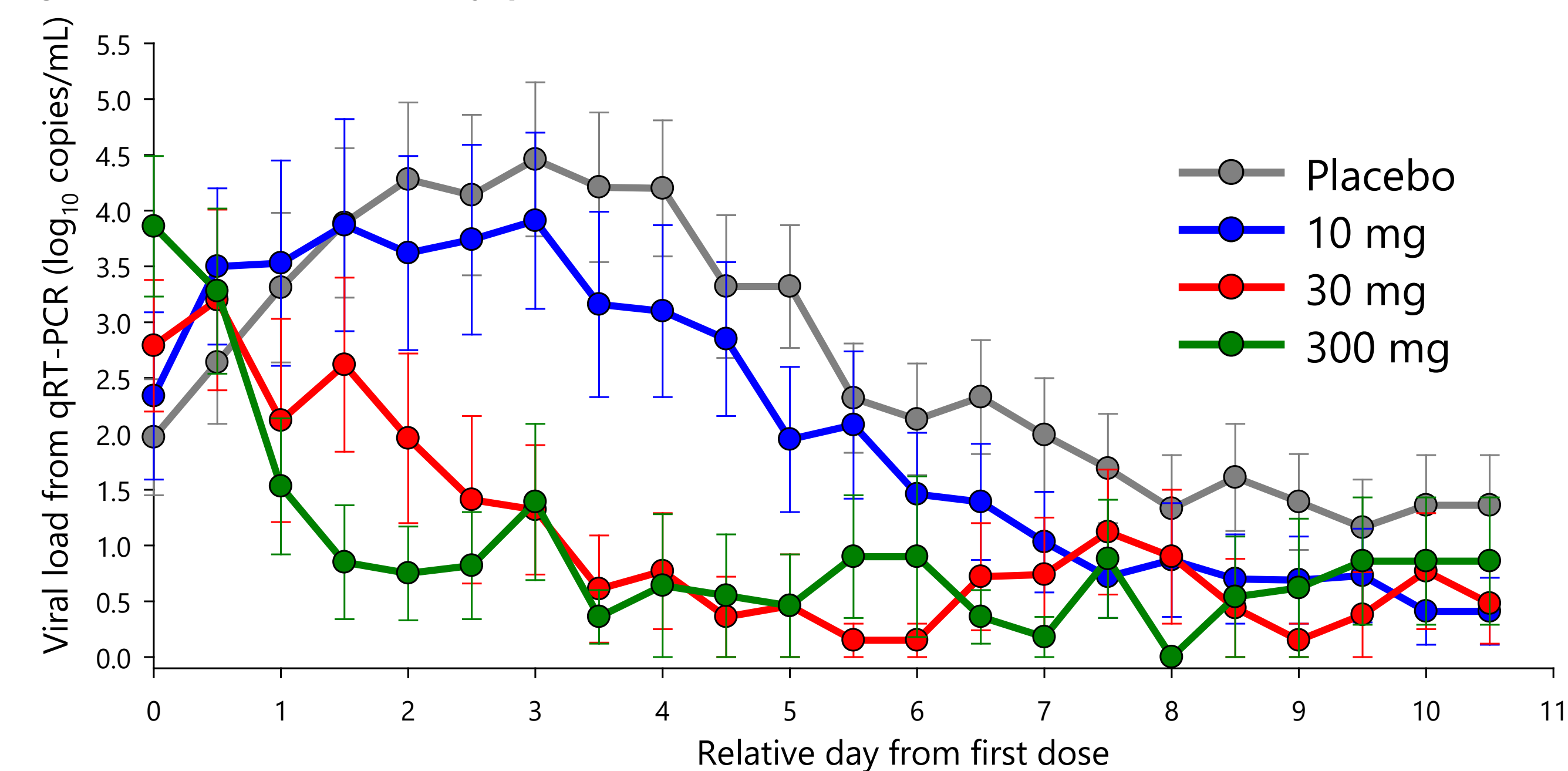


Figure 5 Viral load measured by viral culture mean values over time (ITT-I)

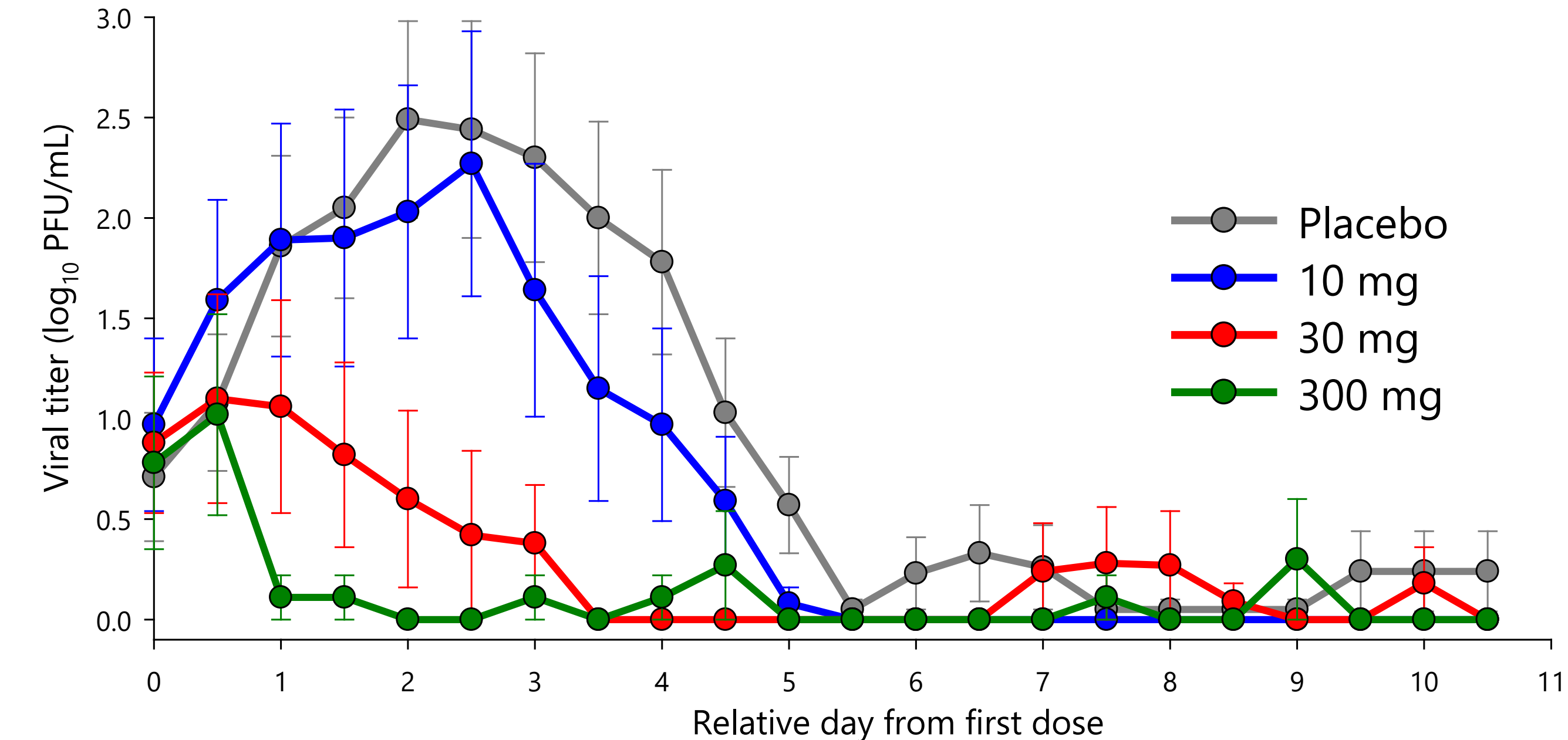
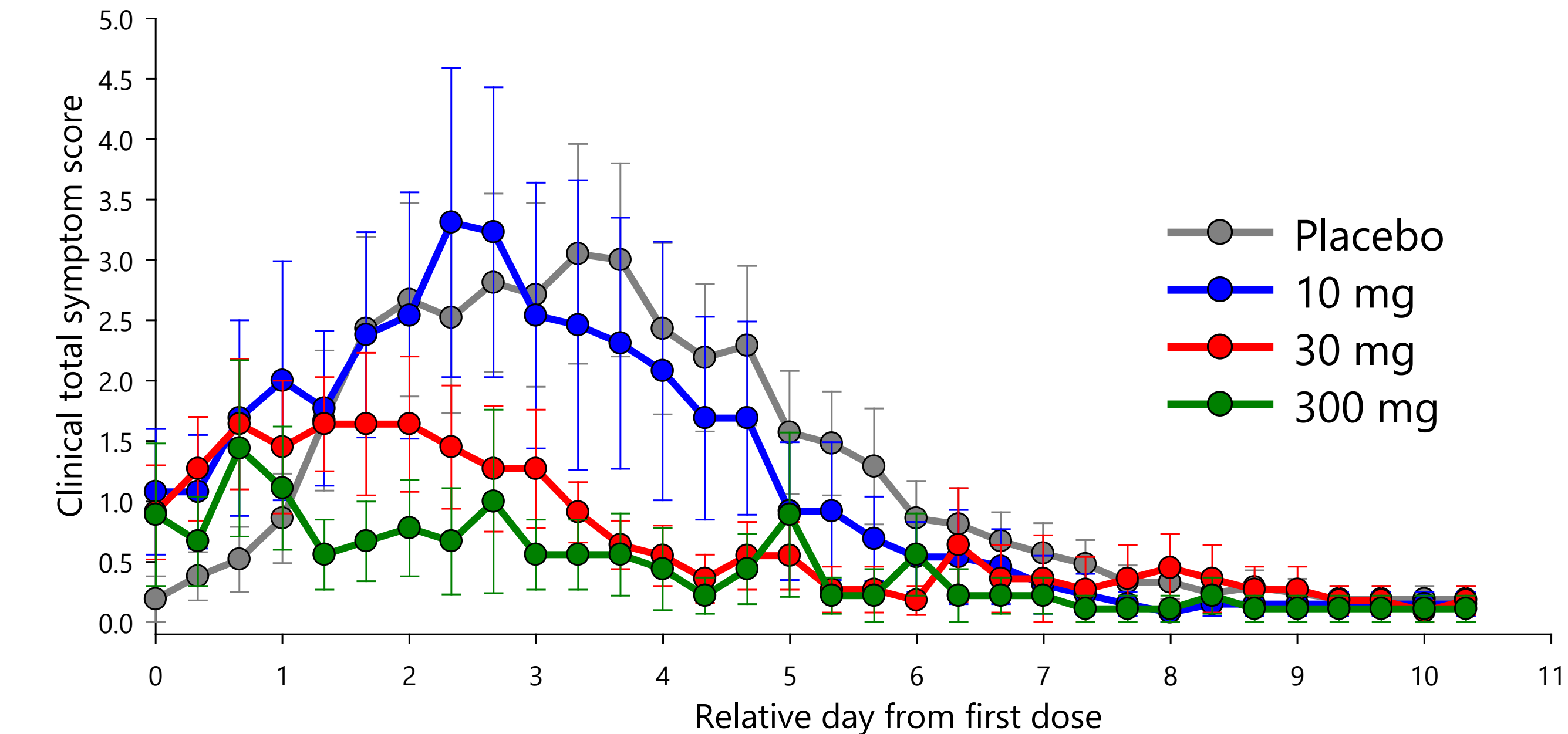


Figure 6 Total Symptom Score mean values over time (ITT-I)



Figures 4,5 & 6: Error bars represent standard error of the mean. Missing after discharge imputed by last observation.

Disclosures:

SB, TB, NK, YK, AY, YN, CD, TU are current or former employees of Shionogi & Co., Ltd. and may own stock and/or stock options in the company. BZD and NV are employees of hVivo services limited.

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