Antiviral Treatment of RSV in Children: Results of a Randomized, Double-Blind, Placebo-Controlled International Trial of Zelicapavir (EDP-938)

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BACKGROUND

- Despite availability of prophylaxis, there are no safe and effective therapies for the treatment of respiratory syncytial virus (RSV) infection in children and adults, resulting in a significant unmet need[1]
- Zelicapavir (EDP-938) is currently the only nucleoprotein inhibitor in development for the treatment of RSV
  - Potent, oral antiviral that prevents viral replication through its interaction with the nucleoprotein
  - Mechanism of action differentiates it from RSV fusion inhibitors, which block viral entry but do not inhibit viral replication in cells already infected[2,3]
- In preclinical studies, zelicapavir showed similar nanomolar potency against RSV-A and RSV-B subtypes, which was consistent against all clinical isolates tested, and potential for synergistic antiviral activity[2]
- Zelicapavir demonstrated a favorable safety, pharmacokinetic (PK), and drug-drug interaction profile in an extensive phase 1 program (NCTs: 03384823, 04498741, 04927793, 03755778, 03750383, and 04871724)[4]
- In a phase 2a viral challenge study comprising healthy adults infected with the RSV-A Memphis 37b subtype (NCT03691623), zelicapavir demonstrated a statistically significant reduction in viral load, total symptom score, and mucus weight; a safety profile similar to placebo without unexpected safety signals; and a high barrier to resistance[5,6]
  - All 4 dosing groups achieved statistically significant antiviral effect with no differences observed among groups
  - No PK/pharmacodynamic relationships were identified

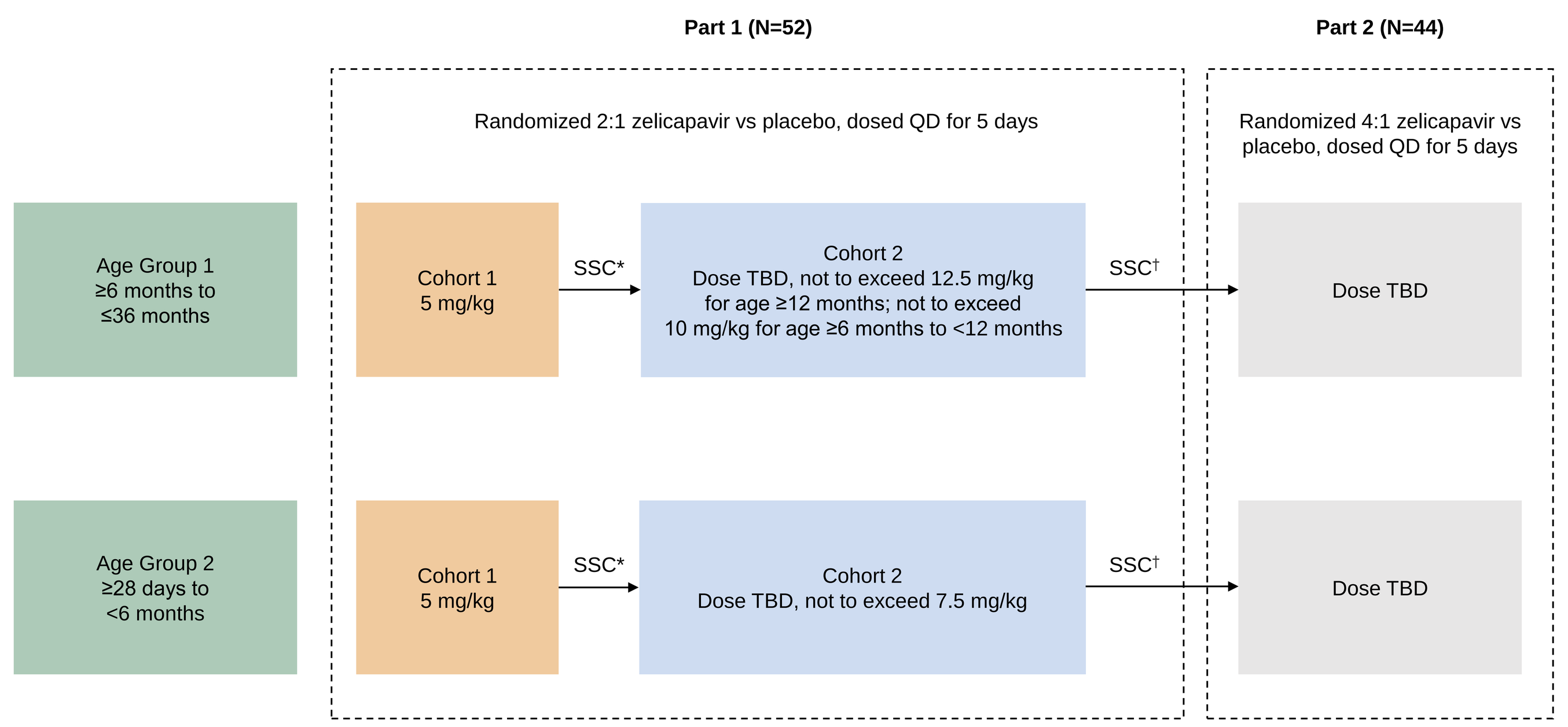
OBJECTIVE

- Evaluate PK profile, safety, and antiviral activity of zelicapavir in a pediatric population with RSV infection

METHODS

- Randomized, double-blind, placebo-controlled trial (NCT04816721)
- Study population: hospitalized or non-hospitalized infants and children aged 28 days to 36 months with RSV-associated respiratory tract infection who tested positive for RSV
- Starting doses were designed to achieve plasma C_{24} concentrations effective in the adult RSV challenge study, where plasma multiples approximately 14.5-40 times in vitro EC_{90} were achieved[5]
- Study design: shown in **Figure 1**

Figure 1. Study Design


Part 1 (N=52)
Part 2 (N=44)
Randomized 2:1 zelicapavir vs placebo, dosed QD for 5 days
Randomized 4:1 zelicapavir vs placebo, dosed QD for 5 days
Age Group 1 ≥6 months to ≤36 months
Cohort 1 5 mg/kg
SSC*
Cohort 2 Dose TBD, not to exceed 12.5 mg/kg for age ≥12 months; not to exceed 10 mg/kg for age ≥6 months to <12 months
SSC†
Dose TBD
Age Group 2 ≥28 days to <6 months
Cohort 1 5 mg/kg
SSC*
Cohort 2 Dose TBD, not to exceed 7.5 mg/kg
SSC†
Dose TBD

The SSC reviewed data from each cohort and determined dose selection and cohort progression in Parts 1 and 2.
*SSC reviewed available blinded data when ≥9 participants had been randomized in Cohort 1 for each age group.
†SSC reviewed available blinded data when ≥6 participants had been exposed to zelicapavir in Cohort 2 for each age group.
QD, once daily; SSC, Study Steering Committee; TBD, to be determined.

- Part 1 primary endpoint: safety and PK profile
- Part 2 primary endpoint: antiviral activity
- Overall primary efficacy endpoint: antiviral activity in the pooled population of Parts 1 and 2
- Zelicapavir plasma concentration was used to estimate the PK parameters using a population PK model. At the end of the study, PK data obtained from all groups were pooled for a population PK analysis
- Antiviral activity was assessed by RSV RNA quantitative reverse transcription polymerase chain reaction (qRT-PCR) performed on nasal swab samples obtained at baseline (Day 1), and Days 3, 5, 9, and 14
- ReSViNet (Respiratory Syncytial Virus Network) and RESOLVE-P (Respiratory Observable Reported Outcome-Pediatric), a proprietary tool designed to assess the severity of pediatric RSV infection over time) clinical scoring system responses were collected (exploratory endpoint)
- Safety population: participants who received any dose (including partial doses)
- PK population: participants who received 1 full dose and had blood samples with quantifiable plasma levels for PK estimations
- Efficacy population: participants who received 1 full dose and had ≥1 evaluable measurement while on treatment

RESULTS

- In Part 1 (N=52), 35 and 17 participants were randomized to the zelicapavir and placebo arms, respectively; 1 participant in the placebo arm received 5 days of zelicapavir in error (included in the zelicapavir arm for the safety population and in the placebo arm for the efficacy population). A total of 3 participants discontinued the study, 1 in the zelicapavir arm (discontinuation unrelated to study drug) and 2 in the placebo arm
- In Part 2 (N=44), 34 and 10 participants were randomized to the zelicapavir and placebo arms, respectively; all participants completed treatment
- Demographic and baseline characteristics of all participants (pooled Parts 1 and 2) are shown in **Table 1**
- The incidence of TEAEs was similar in zelicapavir and placebo arms (**Table 2**)
  - There were no TEAEs that led to treatment discontinuation or study withdrawal

Table 1. Demographic and Baseline Characteristics (Parts 1 and 2)

	Zelicapavir (N=70)	Placebo (N=26)
Age, months, mean (SD)	10.4 (9.06)	10.7 (9.04)
Sex, female, n (%)	35 (50.0)	14 (53.8)
Race, White, n (%)	51 (72.9)	11 (42.3)
RSV viral load by qRT-PCR (log_{10} copies/mL)		
n	63	23
Mean (SD)	6.60 (1.52)	6.19 (1.44)
Duration of symptoms prior to randomization, days, mean (SD)	4.0 (1.57)	4.1 (1.75)
Participants hospitalized at enrollment, n (%)	57 (81.4)	20 (76.9)

qRT-PCR, quantitative reverse transcription polymerase chain reaction; RSV, respiratory syncytial virus.

Table 2. Summary of Safety Outcomes (Parts 1 and 2; Safety Population)

	Zelicapavir (N=70)	Placebo (N=26)
Participants with		
Any TEAE, n (%)	28 (40.0)	13 (50.0)
Study drug–related TEAEs, n (%)	6 (8.6)	0 (0)
Grade 3 or higher TEAEs, n (%)	2 (2.9)*	1 (3.8)†
Serious TEAEs, n (%)	1 (1.4)§	2 (7.7)¶
TEAEs reported in >1 participant in either arm		
Diarrhea, n (%)	7 (10.0)	1 (3.8)
Rash, n (%)	3 (4.3)	1 (3.8)
Acute otitis media, n (%)	2 (2.9)	1 (3.8)
Eczema, n (%)	2 (2.9)	1 (3.8)
Thrombocytosis, n (%)	2 (2.9)	0 (0)
Nasopharyngitis, n (%)	1 (1.4)	2 (7.7)

*Burn on hand on Day 22, community-acquired pneumonia on Day 22 (unrelated to study drug).
†Pleural effusion.
§Community-acquired pneumonia on Day 22 (unrelated to study drug).
¶Bronchiolitis, pleural effusion.
TEAE, treatment-emergent adverse event.

- Target drug exposures similar to efficacious drug exposures in the adult RSV challenge study were achieved across all age groups and dosing cohorts (Parts 1 and 2)[5]
  - Exposure was similar across cohorts and all participants received a therapeutic dose
- Based on exposures achieved in Part 1, the following doses were selected for Part 2:
  - ≥28 days to <12 months: 5 mg/kg
  - ≥12 months to ≤36 months: 7.5 mg/kg

Virology

- Change from baseline in viral load in all participants (Parts 1 and 2 pooled population) showed a greater decline in the zelicapavir arm compared with the placebo arm (**Figure 2**)
  - Placebo-adjusted decreases were 0.17, 0.33, and 0.70 log_{10} copies/mL at Days 3, 5, and 9, respectively
- In the primary endpoint of Part 2, decreases from baseline in viral load were greater in the zelicapavir arm compared with the placebo arm (**Figure 3**)
  - Placebo-adjusted decreases were 0.96, 1.41, and 0.43 log_{10} copies/mL at Days 3, 5, and 9, respectively

Figure 2. LS Mean Change From Baseline in Viral Load for All Participants (Parts 1 and 2) Measured by qRT-PCR

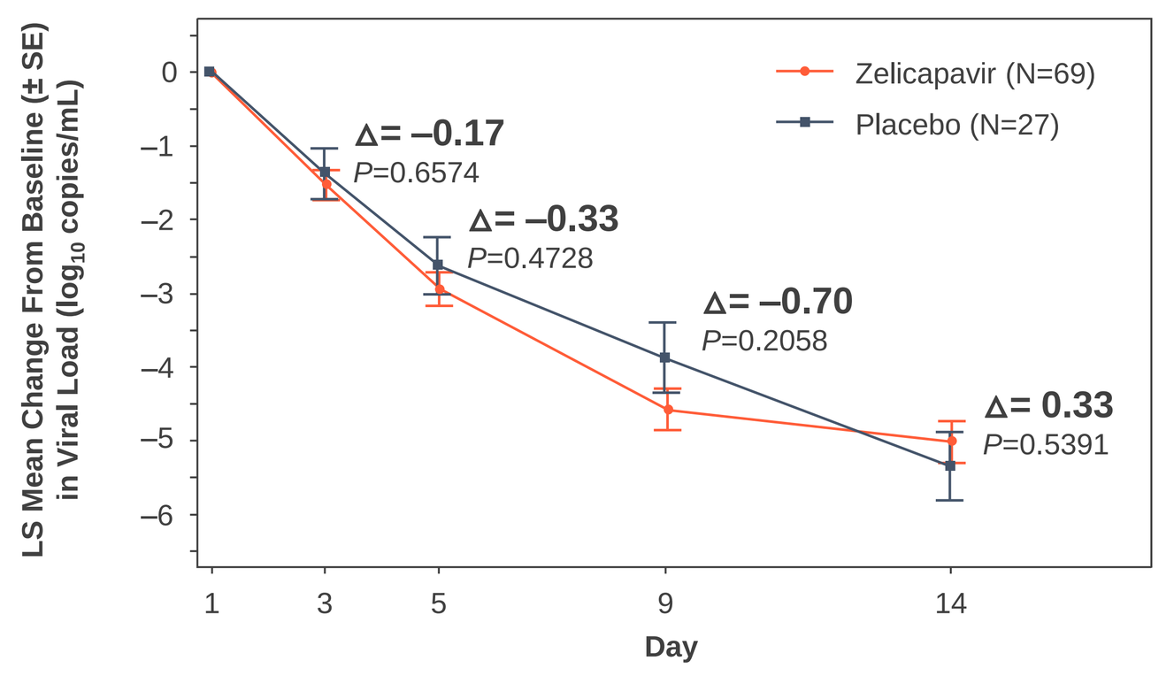
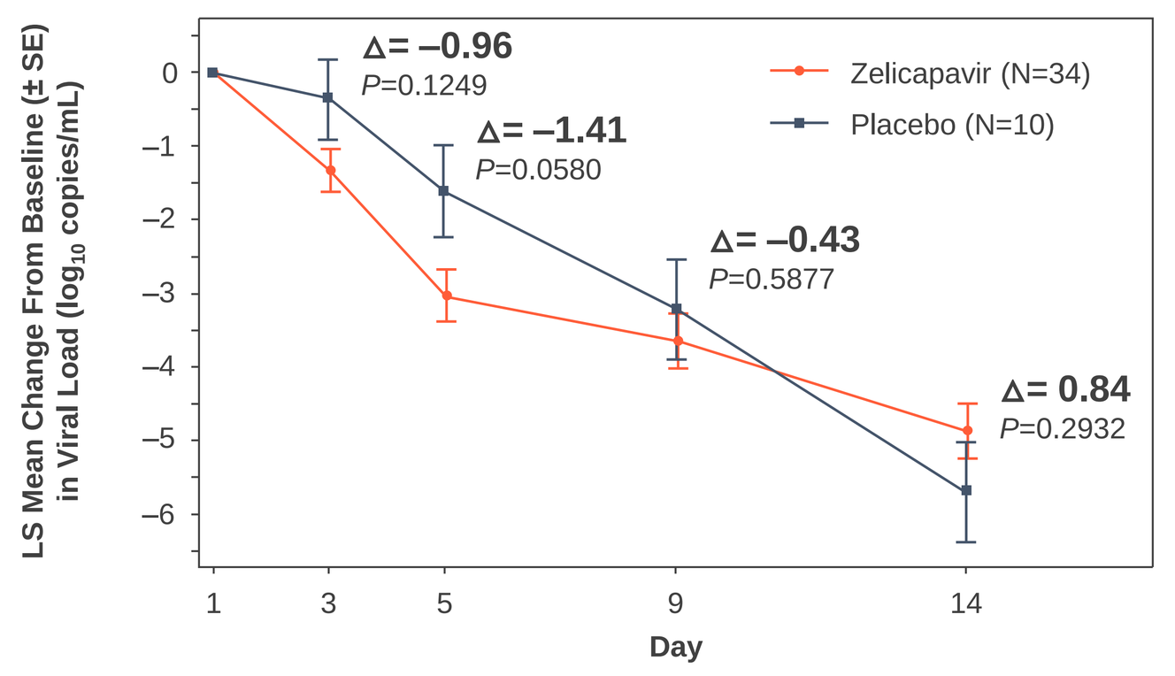


Figure 3. LS Mean Change From Baseline in Viral Load in Part 2 Measured by qRT-PCR



LS, least-squares; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

- A prespecified population comprising participants randomized within 3 days of symptom onset (modified intent-to-treat-3 [mITT-3] population), which represents ~40% (n=38/96) of the study population, showed zelicapavir had greater reductions in viral load compared with placebo (**Figure 4**)
  - Placebo-adjusted decreases were 0.88, 1.18, and 0.57 log_{10} copies/mL at Days 3, 5, and 9, respectively

Figure 4. LS Mean Change From Baseline in Viral Load in Prespecified mITT-3 Population* Measured by qRT-PCR

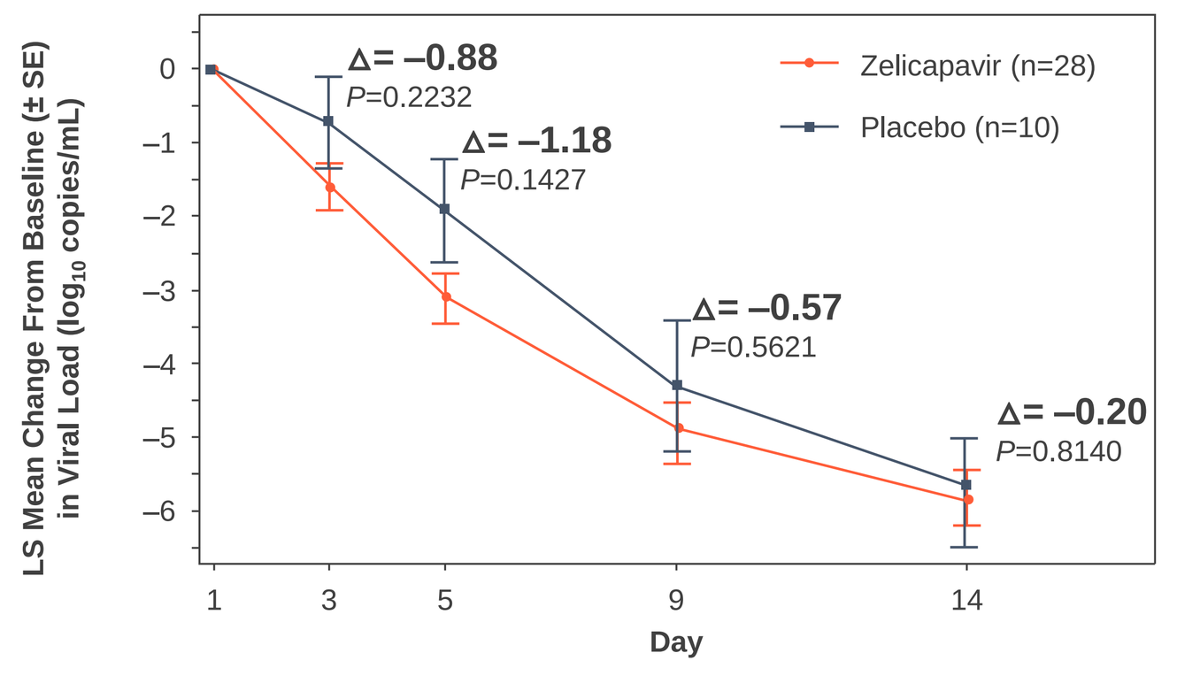
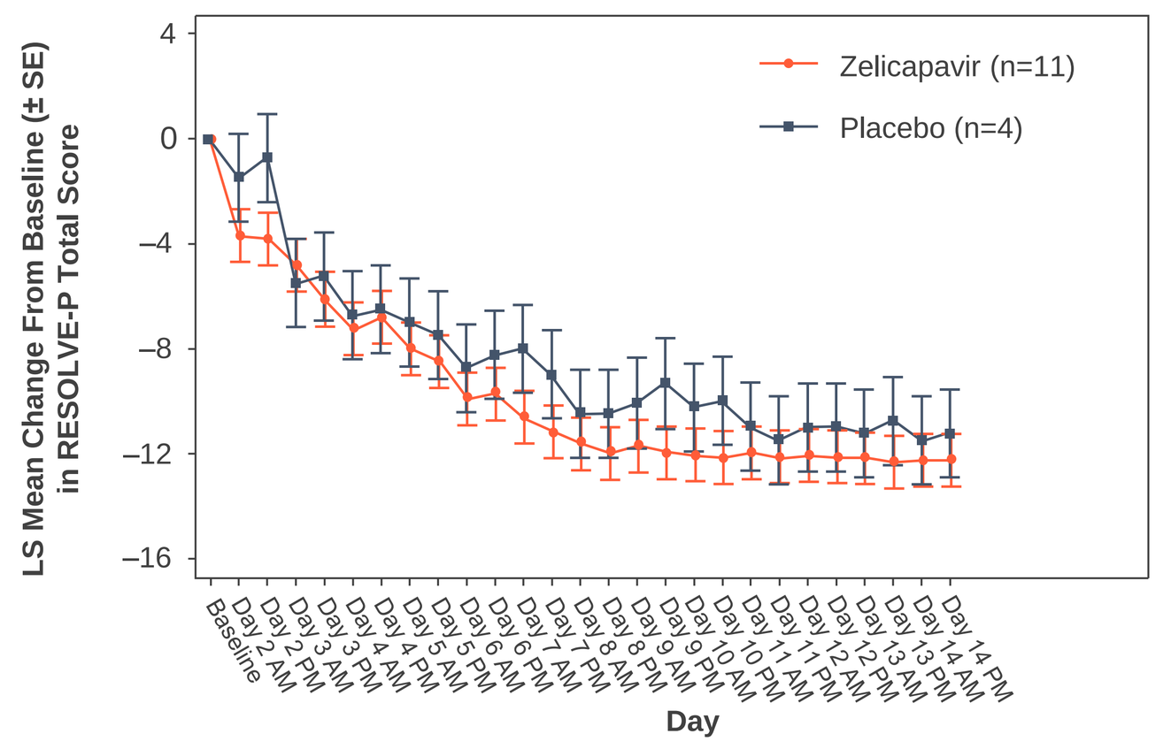


Figure 5. Assessment of RSV Infection Clinical Course: LS Mean Change From Baseline in RESOLVE-P Total Score (Part 2)



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

RESULTS (Cont.)

- Reductions in viral load AUC in zelicapavir recipients vs placebo were seen at all timepoints; baseline through Day 3 (−0.88), through Day 5 (−2.95), through Day 9 (−6.46), and through Day 14 (−8.39) log_{10} copies/mL*days in the mITT-3 population
- Overall, efficacy outcomes were similar regardless of age or inpatient vs outpatient setting of care
- The clinical course of the RSV infection was evaluated as an exploratory endpoint using the ReSViNet and RESOLVE-P clinical scoring systems
  - ReSViNet showed no apparent differences in signs/symptoms between the zelicapavir and placebo arms
  - RESOLVE-P, which became available at the end of the study, was assessed in a limited number of participants (n=15 [zelicapavir arm, n=11; placebo arm, n=4]). A trend toward greater sign/symptom reduction was observed with zelicapavir compared with placebo (**Figure 5**)
- A greater proportion of zelicapavir-treated participants had undetectable viral load at Days 5 and 9 vs placebo (**Figures 6 and 7**)

Figure 6. Proportion of All Participants With Undetectable RSV RNA Viral Load (Parts 1 and 2)

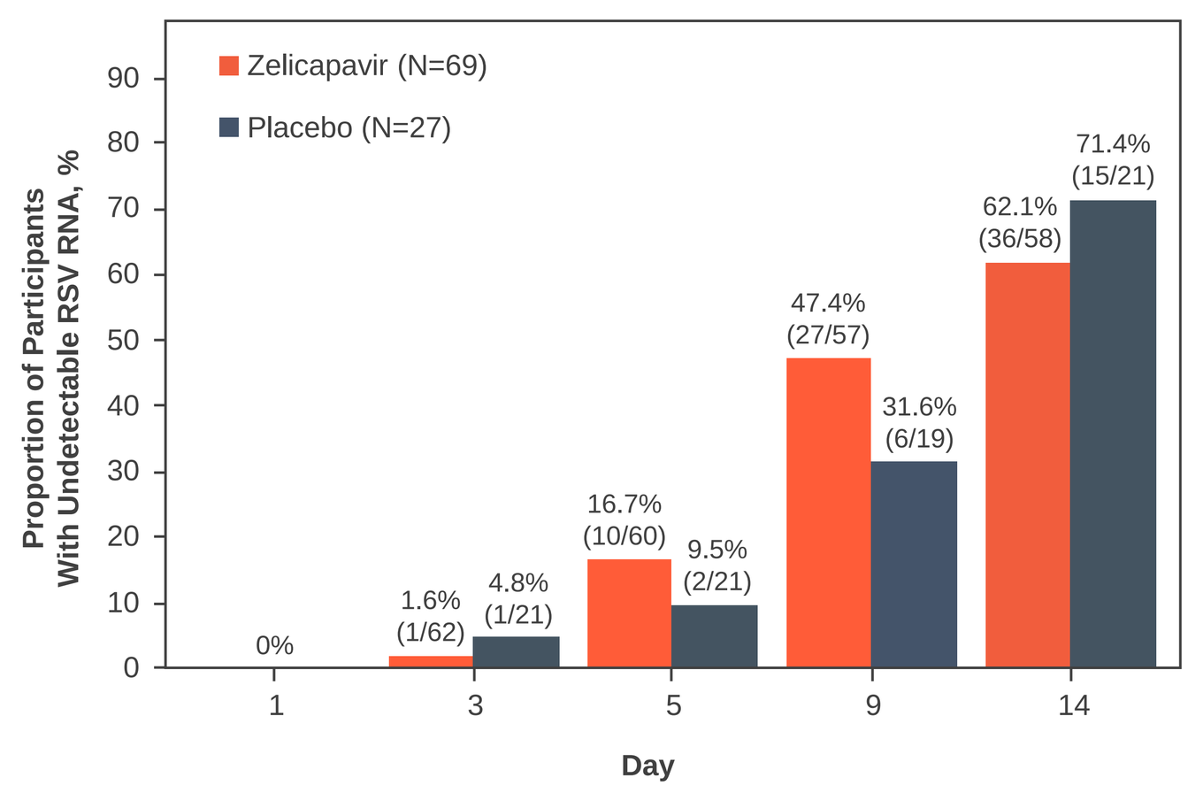
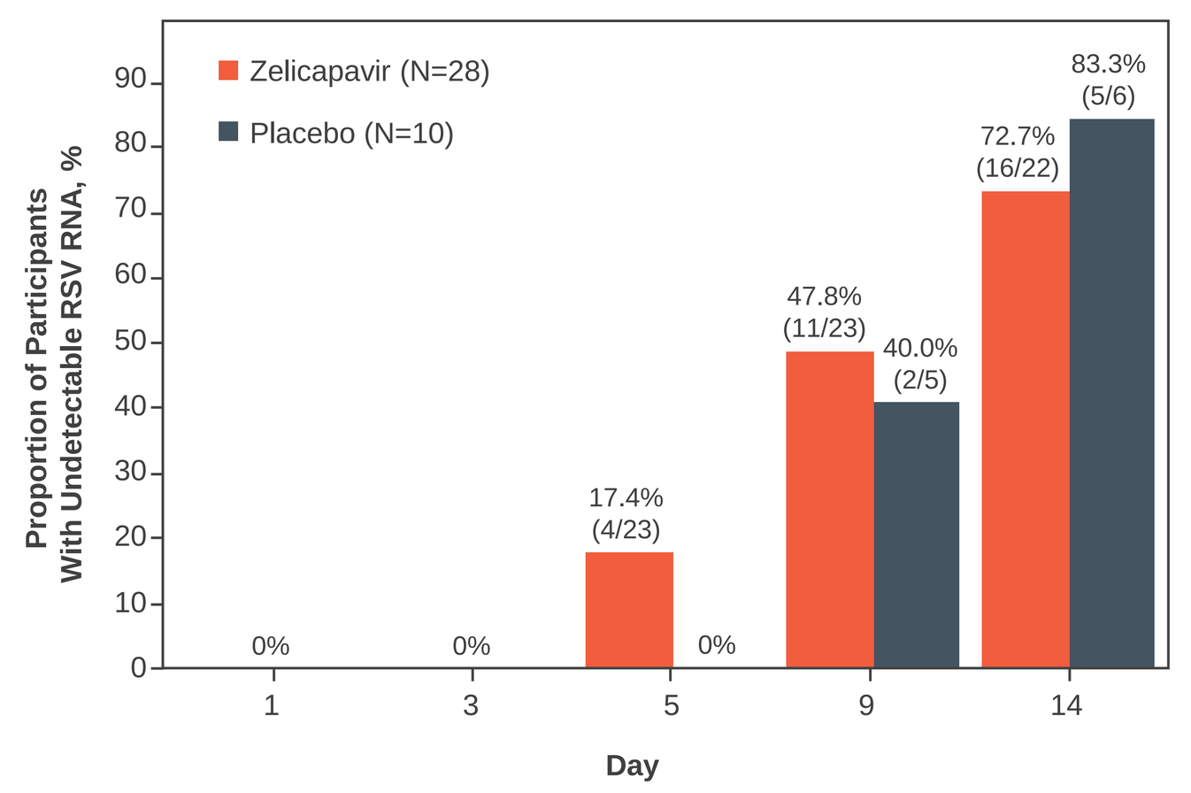


Figure 7. Proportion of Participants in Prespecified mITT-3 Population* With Undetectable RSV Viral Load (Parts 1 and 2)

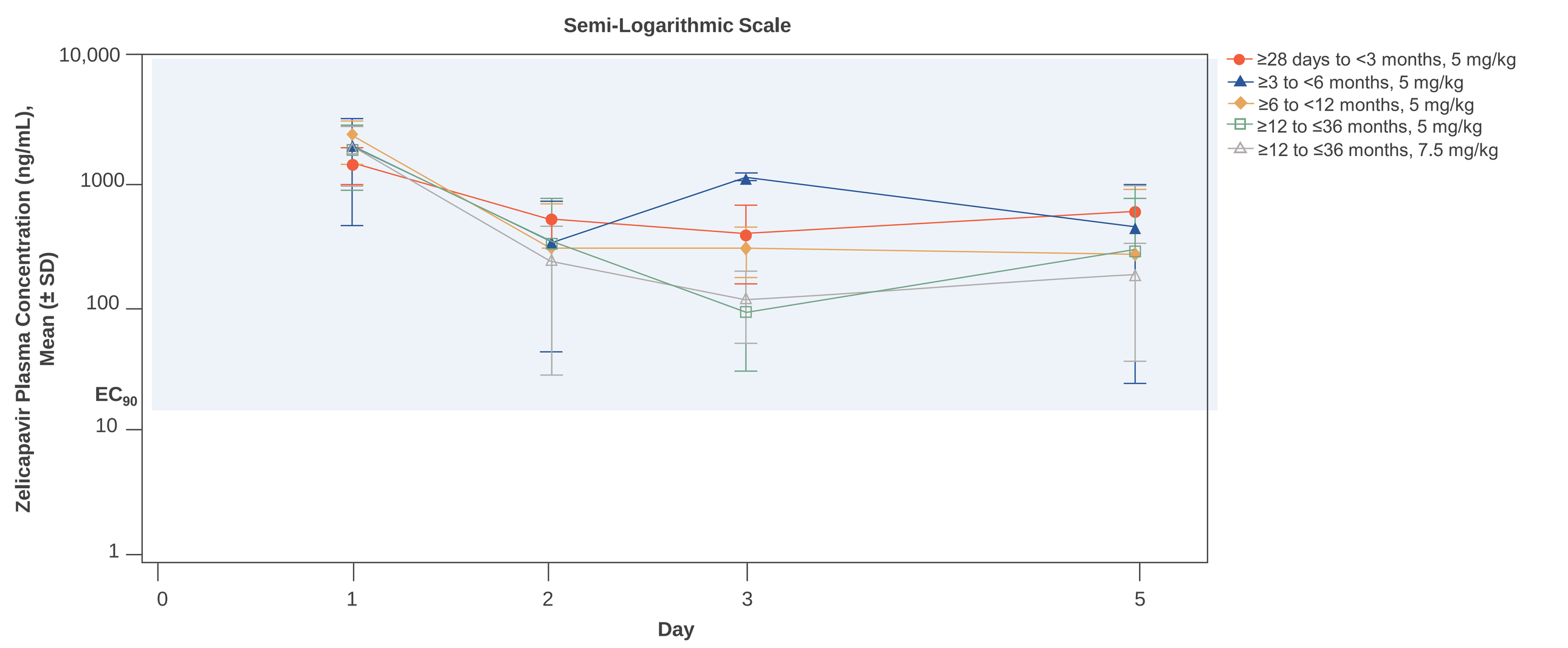


*Prespecified mITT-3 population: participants randomized within 3 days of symptom onset.
mITT, modified intent-to-treat; RSV, respiratory syncytial virus.

Population PK and exposure-response analyses

- Population PK analysis indicated that all participants had model-predicted exposures above the efficacy threshold defined as Day 1 C_{24} (trough) concentrations above 42.3 ng/mL and model-predicted Day 5 AUC to the end of the dosing period ($AUC_{0\text{-}tau}$) below the safety threshold of 44,500 ng*hr/mL (**Figure 8**)
- C_{24} concentrations exceeded the RSV EC_{90} by 15-44 times
  - EC_{90} was established in primary human bronchial epithelial cells using RSV-A Memphis 37 (same strain used in prior adult RSV challenge study)[5]

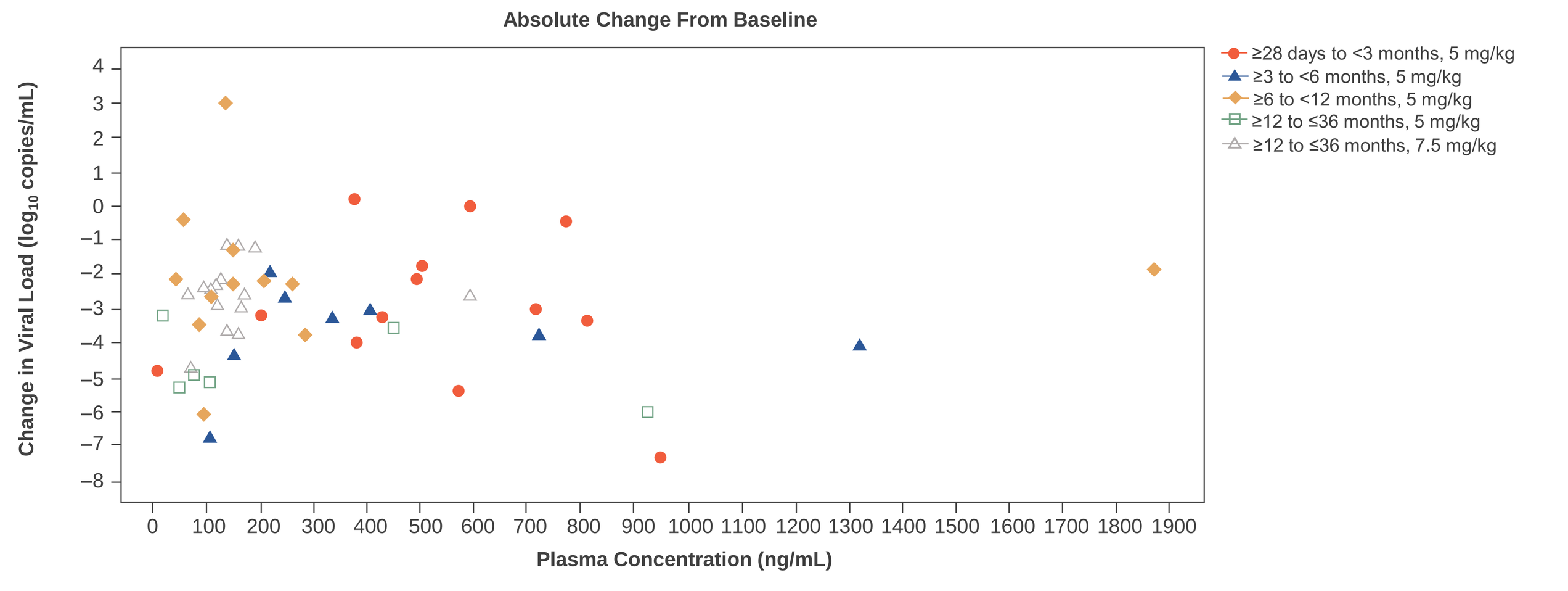
Figure 8. Mean Zelicapavir Plasma PK Concentration by Age Group (Parts 1 and 2; PK Population)



PK samples were collected postdose on Visit 1 and predose on Visits 3 and 5.
PK, pharmacokinetic.

- No apparent exposure-response correlations were observed between zelicapavir plasma concentrations and RNA viral load data or clinical symptoms assessed by ReSViNet and RESOLVE-P (**Figures 9 and 10**)

Figure 9. RNA Viral Load Change From Baseline and Zelicapavir Plasma Concentration Predose at Visit 5 (Parts 1 and 2; PK Population)

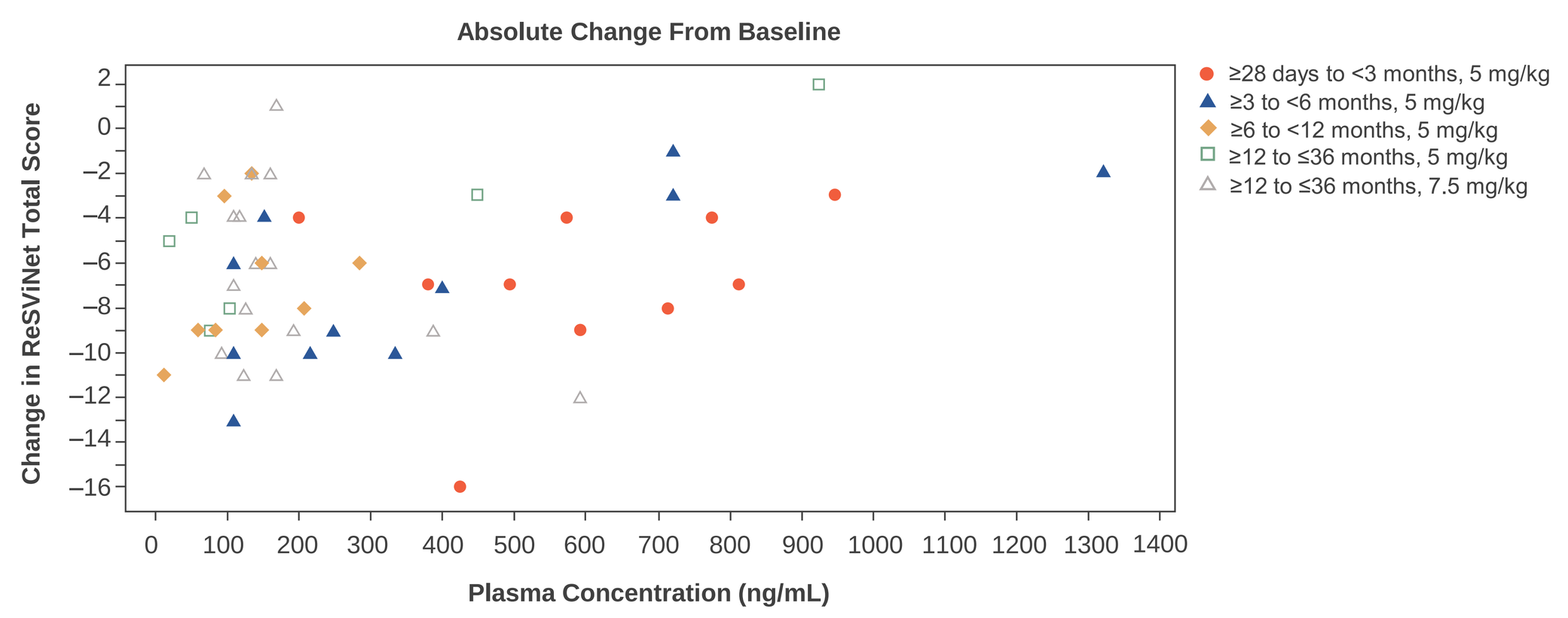


PK, pharmacokinetic.

RESULTS (Cont.)

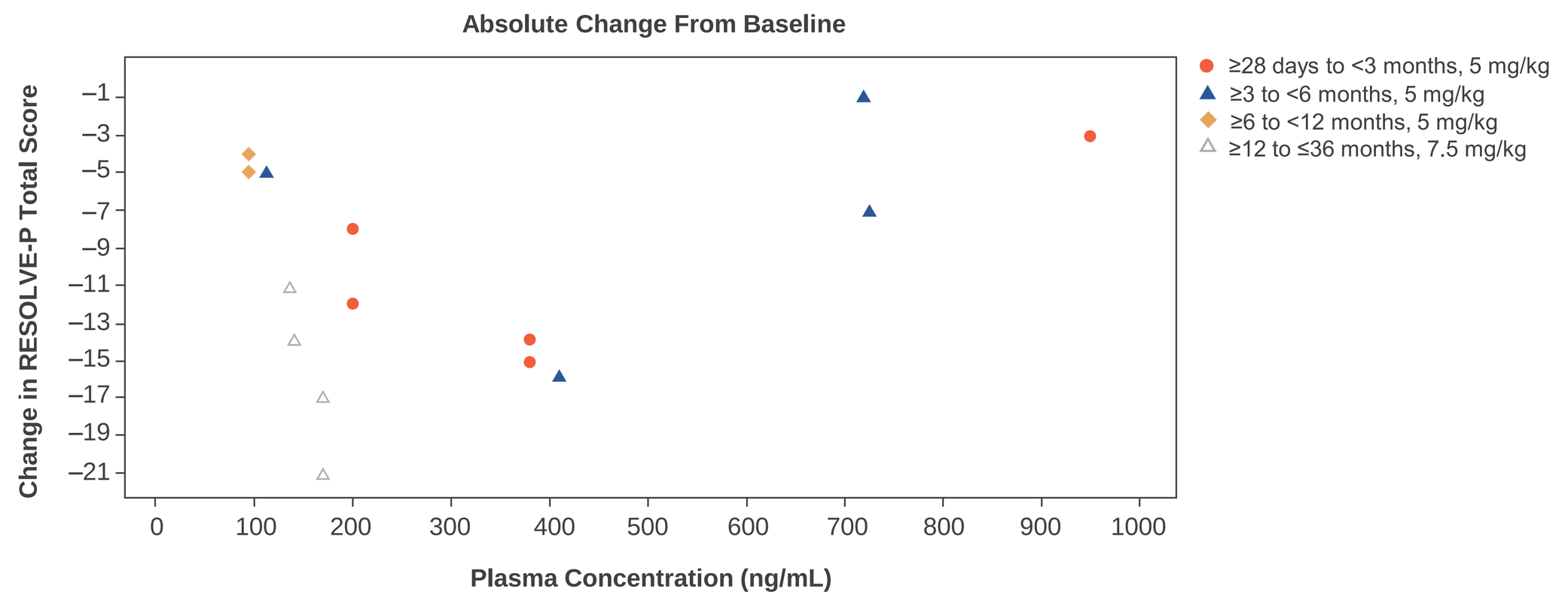
Figure 10. ReSViNet (Parts 1 and 2) and RESOLVE-P (Part 2) Total Score Change From Baseline and Zelicapavir Plasma Concentration Predose at Visit 5 (PK Population)

ReSViNet (Parts 1 and 2)



PK, pharmacokinetic; ReSViNet, Respiratory Syncytial Virus Network.

RESOLVE-P (Part 2)



PK, pharmacokinetic; RESOLVE-P, Respiratory Observable Reported Outcome-Pediatric.

CONCLUSIONS

- Zelicapavir was well tolerated, exhibited a similar safety profile to that of placebo, and was not associated with TEAEs leading to treatment discontinuation or study withdrawal
- Zelicapavir showed consistent antiviral effects for the primary and secondary virology endpoints
  - In the overall population, zelicapavir resulted in a viral load decline peaking at 0.7 log_{10} copies/mL at Day 9 vs placebo
  - In the primary endpoint of the virology-focused Part 2 of the study, zelicapavir resulted in a viral load drop of 1.41 log_{10} copies/mL at Day 5 vs placebo
  - In the prespecified population of participants treated within 3 days of symptom onset, zelicapavir resulted in a viral load drop of 1.18 log_{10} copies/mL at Day 5 vs placebo. Reductions in viral load AUC in zelicapavir recipients vs placebo were seen from baseline through all timepoints
  - A greater proportion of zelicapavir-treated participants had undetectable viral load at Days 5 and 9 vs placebo
- Zelicapavir achieved target drug exposure levels across all age groups and dosing cohorts
- In population PK analyses, all participants exhibited model-predicted exposures above the efficacy threshold
- There were no apparent exposure-response relationships for viral load or symptoms, consistent with the robust antiviral effect of zelicapavir at the exposures studied in this pediatric trial and in human challenge[5]
- Together, the outcomes of this study support the continued development of zelicapavir for the treatment of RSV in pediatric patients

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- **AA**, **JDV**, **SH**, **CH**, **CM**, **SC**, **TN**, and **SR** are employees of Enanta Pharmaceuticals, Inc. and hold Enanta Pharmaceuticals, Inc. stock
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