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

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**Poster #253**

## 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 (N) inhibitor in development for the treatment of RSV
  - It is a potent, oral antiviral that prevents viral replication through its interaction with the nucleoprotein. This 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] (See poster #161)
- In a preclinical study, zelicapavir showed nanomolar potency against RSV-A and RSV-B subtypes, that 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[3,5,6] (See poster #161)

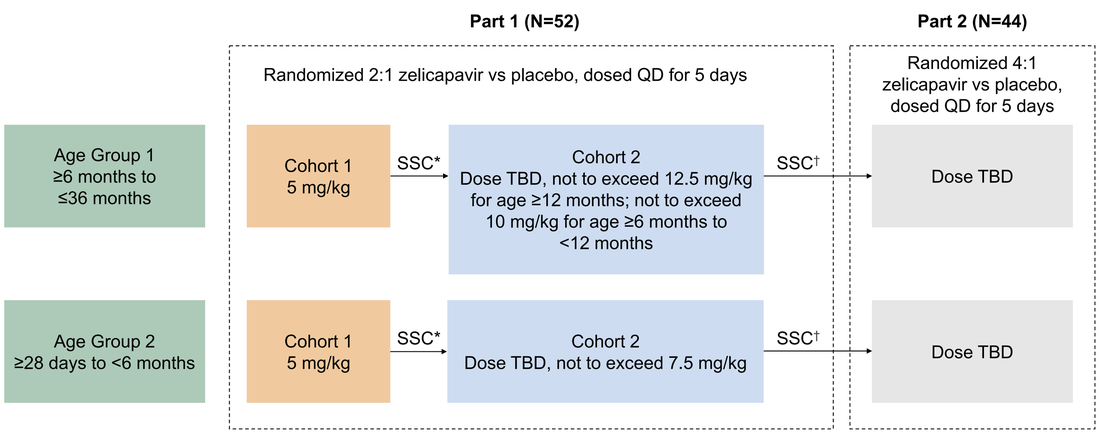
## OBJECTIVE

The objective of this study was to evaluate the 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
- Study design: shown in **Figure 1**

**Figure 1. Study Design**




QD, once daily; SSC, Study Steering Committee; TBD, to be determined.
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.

- 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
- 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) clinical scoring system responses were collected over time (exploratory endpoint)

## 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**

**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.

**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) |

TEAE, treatment-emergent adverse event.
*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.

- The incidence of treatment-emergent adverse events (TEAEs) was similar in the zelicapavir and placebo arms (**Table 2**)
  - There were no TEAEs that led to treatment discontinuation or study withdrawal

## RESULTS

- Target drug exposures similar to efficacious drug exposures in the Phase 2a viral 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 to the placebo arm (**Figure 2**)

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

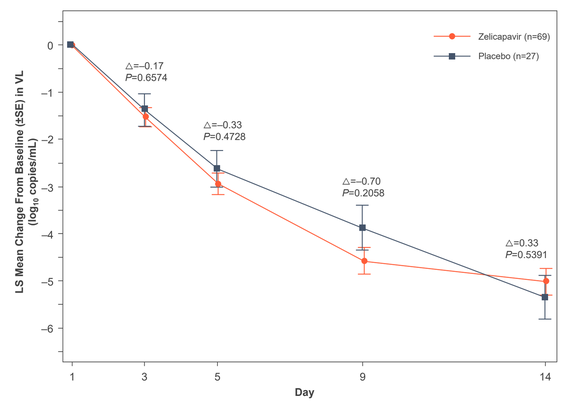
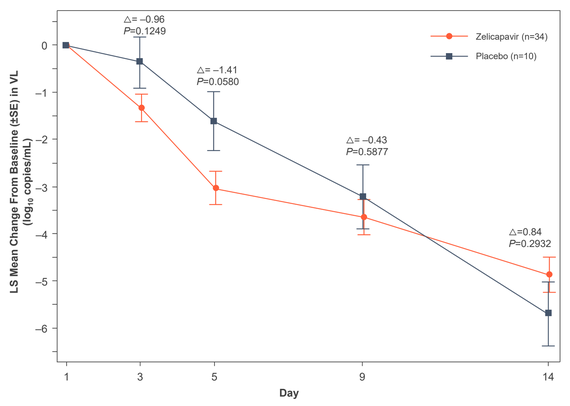



**Figure 3. LS Mean Change (± SE) From Baseline in Viral Load in Part 2 Measured by qRT-PCR**




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

- In the primary endpoint of Part 2, decreases from baseline in viral load were greater in the zelicapavir arm compared to 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
- A prespecified population comprising participants randomized within 3 days of symptom onset, which represents ~40% (n=38/96) of the study population, showed zelicapavir had greater reductions in viral load compared to 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 (± SE) From Baseline in Viral Load in Prespecified mITT-3 Population* Measured by qRT-PCR**

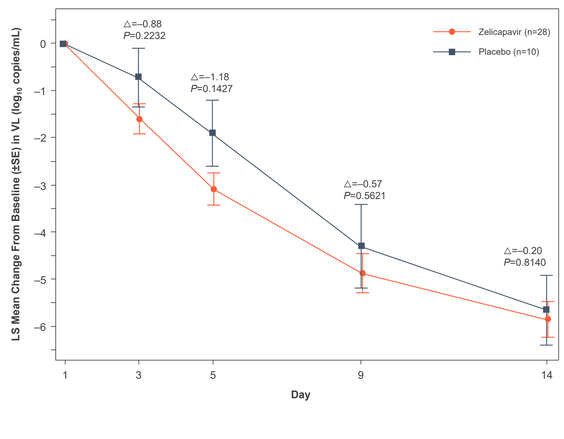
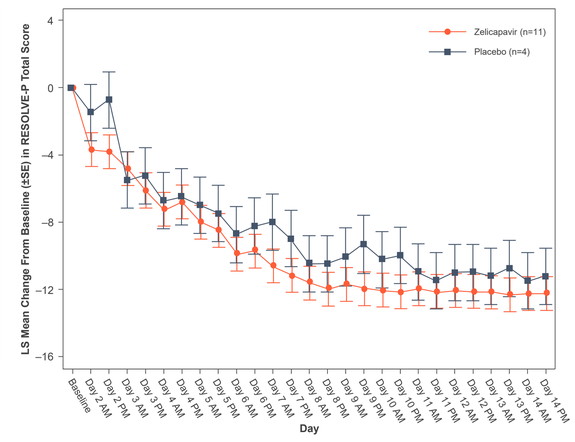



**Figure 5. Assessment of RSV Infection Clinical Course: LS Mean Change (± SE) From Baseline in RESOLVE-P Total Score (Part 2)**




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.

- 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 to placebo (**Figure 5**)

## 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 achieved target drug exposure levels across all age groups and dosing cohorts
- 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
- Together, the outcomes of this study support the continued development of zelicapavir for the treatment of RSV in pediatric patients

## REFERENCES

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## DISCLOSURES AND ACKNOWLEDGMENTS

- **SH**, **CH**, **JPD**, **AA**, **SC**, **TN**, and **STR** are employees of Enanta Pharmaceuticals and hold Enanta Pharmaceuticals stock
- Authors wish to thank the participants of this study and their families
- Under the direction of the authors, medical writing assistance was provided by Syneos Health Medical Communications, LLC, and supported by Enanta Pharmaceuticals