Zelicapavir (EDP-938) Antiviral Treatment is Associated with Shortened Duration of RSV Symptoms in a Randomized, Double-Blind, Placebo-Controlled, Clinical Trial in Children 28 Days to 36 Months of Age

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BACKGROUND

- Respiratory syncytial virus (RSV) presents a significant health challenge to pediatric populations in their first years of life[1,2]
- There remains an unmet need for effective and well-tolerated therapies for active RSV infections[3,4]
- Zelicapavir (EDP-938) is currently the only nucleoprotein inhibitor in development for the treatment of RSV infection[5]
  - Zelicapavir is highly specific for both RSV-A and RSV-B subtypes, inhibiting RSV at the post-entry replication step of the viral life cycle.[5] This mechanism of action differentiates zelicapavir from RSV fusion inhibitors, which block viral entry but allow viral replication within cells already infected[5,6]
- In a phase 2 trial of healthy adult patients challenged with RSV, zelicapavir reduced RSV viral load, total symptom score, and nasal discharge mucus weight compared with placebo, while maintaining a high barrier to resistance and a safety profile similar to placebo[7,8]

OBJECTIVE

- To evaluate symptom resolution after zelicapavir treatment in pediatric patients with RSV infection

METHODS

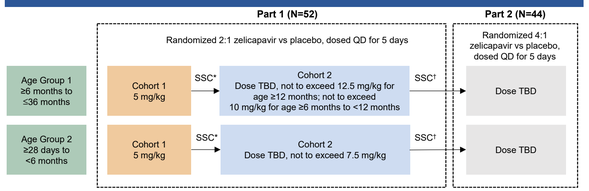
Study Design

- A phase 2, randomized, double-blind, placebo-controlled, two-part clinical trial (NCT04816721) (**Figure 1**)
- Study population: hospitalized and nonhospitalized pediatric patients with RSV infection 28 days to 36 months of age
  - The time from the first sign of respiratory infection onset to signing informed consent was ≤7 days for part 1 and ≤5 days for part 2
- Treatment
  - Part 1: 2:1 randomization to zelicapavir oral suspension (starting dose of 5 mg/kg) or placebo for 5 days
  - Part 2: 4:1 randomization to zelicapavir oral suspension (dose of 5 mg/kg for ≥28 days to <12 months; dose of 7.5 mg/kg for ≥12 to ≤36 months) or placebo

Endpoints and Assessments

- Overall primary efficacy endpoint: antiviral activity in the pooled population from parts 1 and 2
  - Antiviral activity was assessed by RSV RNA reverse-transcription quantitative polymerase chain reaction (RT-qPCR) performed on nasal swab samples obtained at baseline (day 1) and on days 3, 5, 9, and 14
- Part 1
  - Primary endpoint: pharmacokinetics (PK) and safety
  - Secondary endpoint: antiviral activity
- Part 2
  - Primary endpoint: antiviral activity
  - Secondary endpoint: PK and safety
- Exploratory endpoint: parent/guardian-reported Respiratory Syncytial Virus Network (ReSVinet)[9] Scale score
  - As there are no available validated symptom observer or clinical outcome assessment tools approved by regulatory agencies for evaluation of symptoms in pediatric patients with RSV infection, this clinical scoring scale, which has been used in prior investigations,[9,10] was used to assess and record respiratory status daily with an electronic device
- All data were summarized using descriptive statistics
- Efficacy population: all patients who received at least 1 full dose of zelicapavir or placebo
  - Modified intent-to-treat (mITT)-3 population (prespecified): all patients who received at least 1 full dose of zelicapavir or placebo and had onset of symptoms within 3 days before randomization
- Safety population: all patients who received any dose, including partial doses, of zelicapavir or placebo
- PK population: all patients who received at least 1 full dose of zelicapavir and had samples with quantifiable plasma levels

Figure 1. Study Design



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 study participants had been randomized in cohort 1 for each age group.
†SSC reviewed available blinded data when ≥6 study participants had been exposed to zelicapavir in cohort 2 for each age group.
QD, once daily; SSC, Study Steering Committee; TBD, to be determined.

RESULTS

Baseline Characteristics

- Overall, 96 patients were administered zelicapavir or placebo, including 52 patients in part 1 (zelicapavir, n=35; placebo, n=17), and 44 patients in part 2 (zelicapavir, n=34; placebo, n=10) (**Table 1**)
- Demographic and baseline characteristics were generally well balanced between the treatment groups
- Most (80.2%) patients were hospitalized at baseline
- Mean (SD) duration of RSV symptoms prior to randomization was 4.0 (1.6) days and 4.1 (1.8) days in the zelicapavir and placebo groups, respectively

Table 1. Demographic and Baseline Characteristics: Parts 1 and 2 Pooled (Safety Population)

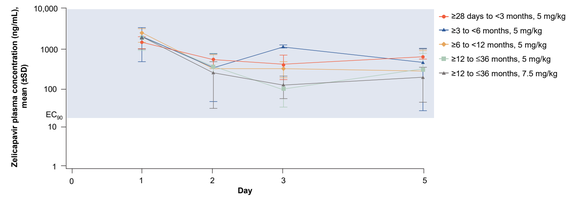
	Zelicapavir (n=70)	Placebo (n=26)*
Age, months, mean (SD)	10.4 (9.1)	10.7 (9.0)
Sex, female, n (%)	35 (50.0)	14 (53.8)
Race, white, n (%)	51 (72.9)	11 (42.3)
RSV viral load by RT-qPCR, log_{10} copies/mL		
n	63	23
Mean (SD)	6.60 (1.52)	6.19 (1.44)
Duration of symptoms prior to randomization, days, mean (SD)	4.0 (1.6)	4.1 (1.8)
Participants hospitalized at enrollment, n (%)	57 (81.4)	20 (76.9)

*One patient randomized to placebo was treated with zelicapavir in error.
RSV, respiratory syncytial virus; RT-qPCR, reverse-transcription quantitative polymerase chain reaction.

Pharmacokinetics

- All zelicapavir recipients achieved target drug exposure levels across all age groups and dosing cohorts (parts 1 and 2; **Figure 2**)
- Population PK analysis indicated that all patients achieved model-predicted exposures within the therapeutic range
  - Trough concentrations of zelicapavir exceeded the EC_{90} by 15-44 fold
- Based on the exposures achieved in part 1, the following doses were selected for part 2:
  - 5 mg/kg for patients aged ≥28 days to <12 months
  - 7.5 mg/kg for patients aged ≥12 to ≤36 months

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



Results shown on a semi-logarithmic scale. The exposure threshold for efficacy was 42.3 ng/mL. The exposure threshold for safety was 44,500 ng•hr/mL.
EC_{90} was established in primary human bronchial epithelial cells using RSV-A Memphis 37.[5]
EC_{90}, effective concentration at which there is a 90% decrease in viral replication; PK, pharmacokinetics; RSV-A, respiratory syncytial virus A.

Safety

- Zelicapavir was well tolerated, with a similar incidence of treatment-emergent adverse events (TEAEs) reported in the zelicapavir and placebo groups (**Table 2**)
- Most TEAEs were mild or moderate in severity
  - There were no grade 4 or 5 TEAEs in either group
- Drug-related TEAEs were reported by 6 (8.6%) patients who received zelicapavir, with diarrhea being the most common (n=4)
- None of the TEAEs led to treatment discontinuation or study withdrawal

Table 2. Treatment-Emergent Adverse Events (Safety Population)

n (%)	Zelicapavir (n=70)	Placebo (n=26)
Any TEAE	28 (40.0)	13 (50.0)
Any study drug–related TEAE	6 (8.6)	0
Any grade 3 or higher TEAE	2 (2.9)*	1 (3.8)†
Any serious TEAE	1 (1.4)‡	2 (7.7)¶
TEAEs occurring in >1 patient		
Diarrhea	7 (10.0)	1 (3.8)
Rash	3 (4.3)	1 (3.8)
Otitis media, acute	2 (2.9)	1 (3.8)
Eczema	2 (2.9)	1 (3.8)
Thrombocytosis	2 (2.9)	0
Nasopharyngitis	1 (1.4)	2 (7.7)

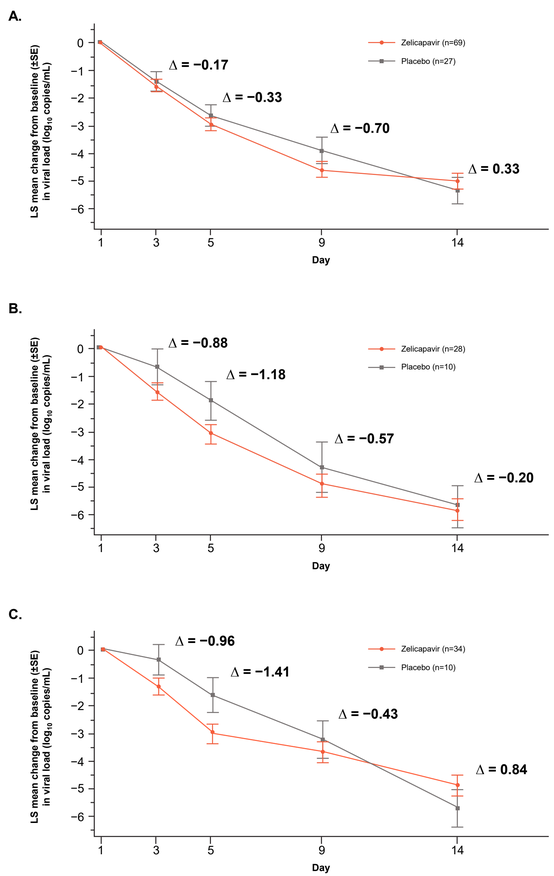
*Burn on hand on day 22, community-acquired pneumonia on day 22 (unrelated to study drug).
†Pleural effusion.
‡Community-acquired pneumonia on day 22 (unrelated to study drug).
¶Bronchiolitis, pleural effusion.
TEAE, treatment-emergent adverse event.

RESULTS (Cont.)

Antiviral Effect

- Change from baseline in viral load in all patients (parts 1 and 2 pooled population) showed numerically greater reductions in the zelicapavir group compared with the placebo group (**Figure 3A**)
  - The difference between the zelicapavir and placebo groups at day 5 was −0.33 log_{10} copies/mL
- A prespecified analysis of patients treated with zelicapavir or placebo randomized within 3 days of symptom onset (mITT-3 population), which represented ~40% (n=38/96) of the study population, showed that zelicapavir-treated patients had numerically greater reductions in viral load compared with those given placebo (**Figure 3B**)
  - The difference between the zelicapavir and placebo groups at day 5 was −1.18 log_{10} copies/mL
  - The reductions in viral load in the mITT-3 population were numerically greater than those in the pooled efficacy population, suggesting that patients are most likely to benefit from early treatment, underscoring the importance of prompt RSV diagnosis and intervention
- In part 2, in which the primary endpoint was antiviral activity, reductions in viral load from baseline were numerically greater in the zelicapavir group compared with the placebo group (**Figure 3C**)
  - The difference between the zelicapavir and placebo groups at day 5 was −1.41 log_{10} copies/mL

Figure 3. LS Mean Change from Baseline in Viral Load Measured by RT-qPCR for (A) Pooled Analysis, (B) Prespecified mITT-3 Population,* and (C) Part 2



*Prespecified mITT-3 population: Patients randomized within 3 days of symptom onset.
LS, least squares; mITT, modified intent-to-treat; RT-qPCR, reverse-transcription quantitative polymerase chain reaction.

RESULTS (Cont.)

ReSVinet Scale Symptom Resolution

- In the protocol-specified analysis, no difference was observed between zelicapavir and placebo in time to resolution of symptoms (defined as the first of two consecutive timepoints with mild or absent symptoms), assessed by the ReSVinet Scale (**Table 3**)
  - In an ad hoc analysis, the estimated median time to **complete** resolution of symptoms (defined as the first of two consecutive timepoints with symptoms absent and the patient not hospitalized) was reduced by 1.61 days with zelicapavir vs placebo
  - The estimated median time to **sustained** resolution (defined as the first of two consecutive timepoints with symptoms absent, symptoms remaining absent, and the patient not hospitalized) was reduced by 3.69 days with zelicapavir vs placebo

Table 3. ReSVinet Scale Parent/Guardian-Reported Time to Symptom Resolution (Pooled Population)

Symptom Resolution	Zelicapavir (n=69)	Placebo (n=27)
Median time to symptom resolution* (protocol-defined) (95% CI)	2.99 days (2.03-3.80)	2.72 days (1.01-4.07)
	Difference: 0.27 days	
Median time to complete resolution† (ad hoc) (95% CI)	6.99 days (5.89-8.00)	8.60 days (5.00-11.99)
	Difference: −1.61 days	
Median time to sustained resolution§ (ad hoc) (95% CI)	6.99 days (6.02-8.24)	10.68 days (5.15-13.03)
	Difference: −3.69 days	

*All 7 symptoms were mild or absent.
†All 7 symptoms were absent and patient was not hospitalized.
‡All 7 symptoms were absent, remained absent, and patient was not hospitalized.
ReSVinet, Respiratory Syncytial Virus Network.

CONCLUSIONS

- This clinical trial is the first successful evaluation of a direct-acting antiviral (replication inhibitor) in children
- Zelicapavir's safety profile in children was similar to placebo
- Target zelicapavir PK exposures were achieved in all subjects
- A greater antiviral effect of zelicapavir was observed in a prespecified analysis of patients who initiated treatment early in the course of infection (within 3 days of presenting with symptoms)
- Analysis of study data demonstrated that symptoms improved faster with zelicapavir treatment
  - In an ad hoc analysis, zelicapavir treatment was associated with a 1.61-day reduction in time to complete resolution and a 3.69-day reduction in time to sustained resolution of RSV-related symptoms compared with placebo, assessed by parent/guardian-reported ReSVinet Scale score
- These results support the continued development of zelicapavir for the treatment of pediatric RSV infection

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DISCLOSURES AND ACKNOWLEDGMENT

- All authors are employees of and hold stock in Enanta Pharmaceuticals, Inc.
- The study was funded by Enanta Pharmaceuticals, Inc.
- Medical writing assistance was provided by Syneos Health and was supported by Enanta Pharmaceuticals, Inc.