Zelicapavir Reduces Symptom Duration and Hospitalization in a Randomized, Double-Blind, Placebo-Controlled, International Phase 2 Trial

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Disclosure to Learners

Financial Relationships with “ineligible companies” within the past 24 months:

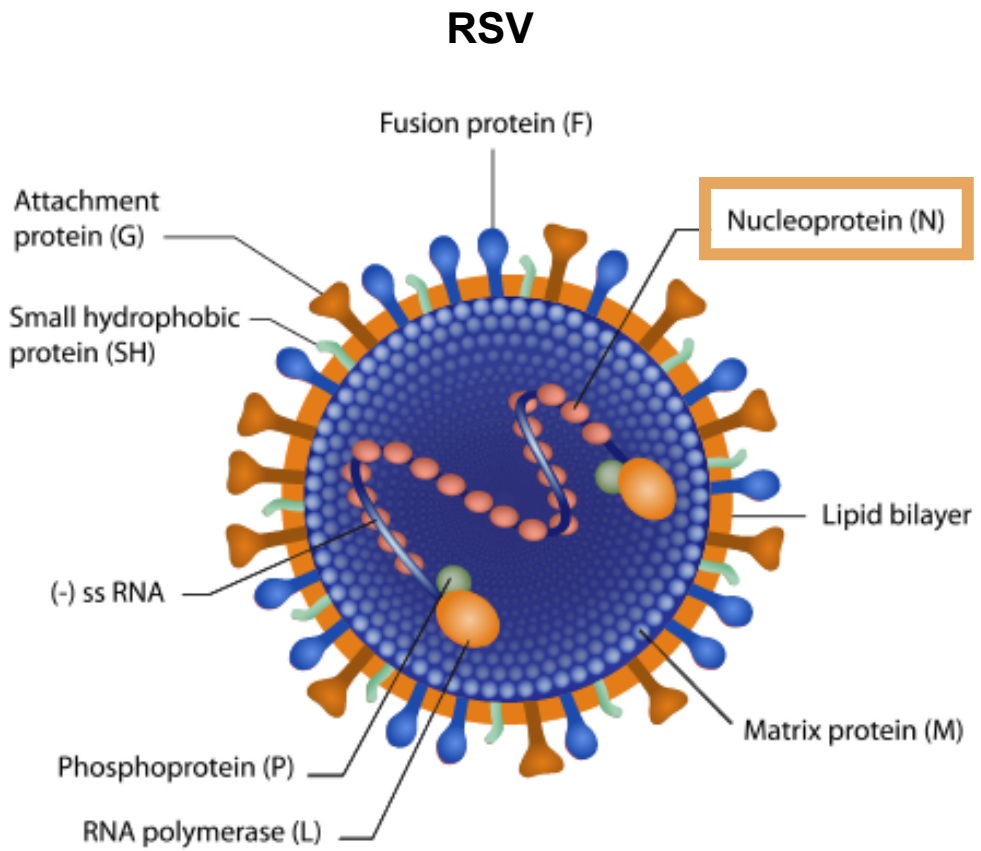
Company name, type of relationship:

Enanta Pharmaceuticals, Employee, Stock holder

Vertex Pharmaceuticals, Former Employee, Stock holder

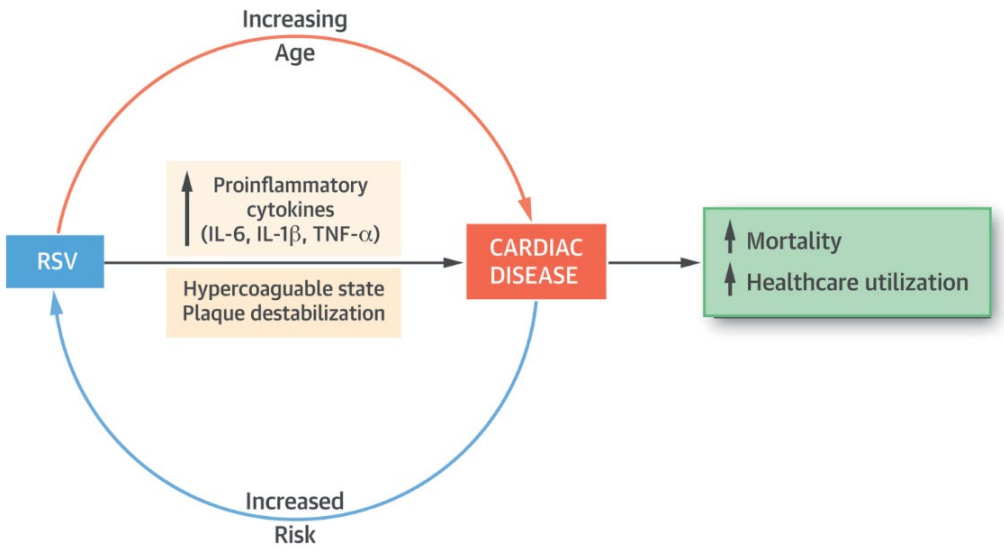
Zelicapavir (EDP-938):
N-Protein Inhibitor for RSV

- N-inhibitor in clinical development for RSV
  - Replication inhibitor: shuts down the production of new virions (vs. fusion inhibitors that block viral entry)
- Granted Fast Track designation by the FDA
- Strong preclinical profile
  - Nanomolar potency against RSV-A and RSV-B
  - Antiviral potency across all clinical isolates tested
  - High barrier to resistance
  - Synergistic activity and no cross-resistance with other drug mechanisms (e.g. L-inhibitors)
- Favorable safety and efficacy profile in clinical studies
  - Challenge study showed reduction in viral load and clinical symptoms
  - Pediatric study showed reduction in viral load and clinical symptoms
  - Well-tolerated in more than 700 people dosed



Respiratory Syncytial Virus Disease:
Effects in CHF and COPD Patients

- **Congestive Heart Failure**
  - A recent study showed that, among those with RSV infection, CHF hospitalizations were associated with higher odds of in-hospital mortality, septic shock, acute respiratory failure. Also had longer length of stay and higher costs.

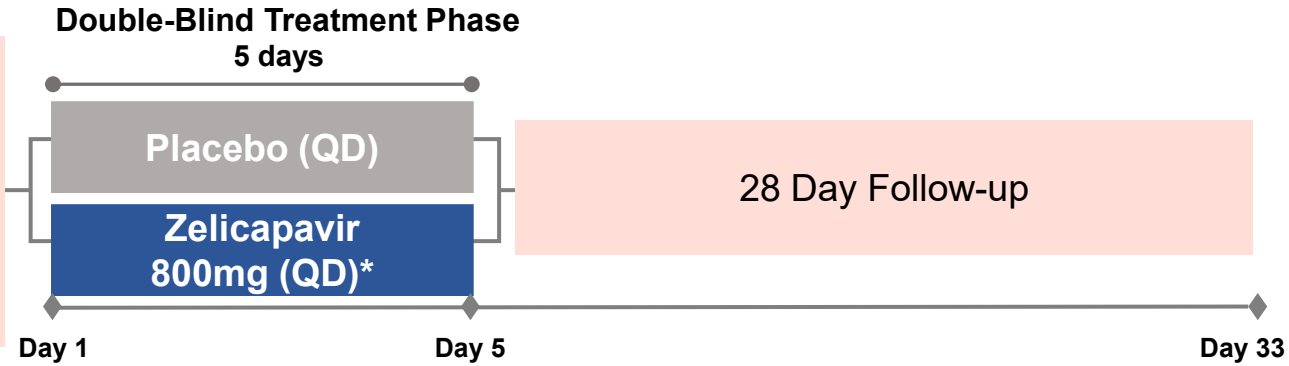


- **Chronic Obstructive Pulmonary Disease**
  - A case-control study of 11887 patients showed that RSV hospitalization was associated with new COPD exacerbation for up to 7 wks after admission.
  - A recent review evaluated the prevalence of COPD among RSV-infected adults, RSV-related hospitalizations from 40 studies.
    - The adjusted incidence rate ratio for hospitalization was 9.6-9.7/100,000 for those with COPD.
    - Complications of RSV infection for those with COPD included new COPD exacerbation, ICU admission, mechanical ventilation &, overall, severe clinical outcomes.

Patil, J Clin Med. 2026; 15(3):990. Ivey. J Am Coll Cardiol. 2018;71:1574. Liang, JAMA Network Open. 2026; 9(2). Penders, Curr Allergy Asthma Rep.2025. 25, 14.

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Design & Objectives

186 adults with at least one of the following:
- COPD
- Congestive heart failure
- Asthma
- Age ≥65



- Patients enrolled within 72 hours of RSV symptom onset
- Patients whose only high-risk criterion of either age 65-74 or asthma were capped at 20% of the total

Safety Population***		Efficacy Population***		HR3 Population	
All patients who received study drug		All patients in safety population PCR positive for RSV		All patients in efficacy population with CHF, COPD, or age ≥75	
Zelicapavir (N=121)	Placebo (N=65)	Zelicapavir (N=115)	Placebo (N=60)	Zelicapavir (N=92)	Placebo (N=50)

- **Primary Objective:** Time to resolution** of RSV LRTD symptoms (RiiQ™ symptom scale)
  - Shortness of Breath
  - Wheezing
  - Coughing
  - Coughing up Phlegm
- **Secondary Objectives:** PROs, MAVs, virology, antibiotic use, bronchodilator use, corticosteroid use, hospitalization, ICU, mechanical ventilation, all cause mortality, PK & safety

First proof-of-concept Phase 2 high-risk adult outpatient study with positive clinical signal

*Equivalent to 600mg suspension dosage form used in challenge study; **Resolution: all symptoms mild or absent; ***One patient randomized to zelicapavir was treated with placebo in error. Data for this patient are in the placebo group for safety analyses and zelicapavir group for efficacy analyses.
CHF, congestive heart failure; COPD: chronic obstructive pulmonary disease; LRTD: lower respiratory tract disease; PCR: polymerase chain reaction; PROs: patient reported outcomes; MAVs: medically attended visits; ICU: intensive care unit; PK: pharmacokinetics; QD: once-daily

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Baseline Characteristics (Safety & HR3 Population)

- Baseline characteristics were balanced across treatment groups
- Majority of patients (~2/3) enrolled within 48 hours of symptom onset prior to randomization

Description	Safety Population		HR3 Population*	
	Zelicapavir (N=121)	Placebo (N=65)	Zelicapavir (N=92)	Placebo (N=50)
Age: Years – Median (Min, Max)	71 (29, 97)	72 (24, 96)	73 (29, 97)	73 (36, 96)
Sex: Female – n (%)	74 (61.2)	49 (75.4)	52 (56.5)	38 (76.0)
Race: White – n (%)	101 (83.5)	57 (87.7)	79 (85.9)	45 (90.0)
Did Not Receive RSV Vaccination – n (%)	120 (99.2)	64 (98.5)	91 (98.9)	49 (98.0)
Duration of RSV Symptoms Prior to Randomization ≤ 48 hours	78 (64.5)	42 (64.6)	58 (63.0)	32 (64.0)
CHF – n (%)	27 (22.3)	8 (12.3)	26 (28.3)	8 (16.0)
COPD – n (%)	45 (37.2)	25 (38.5)	43 (46.7)	24 (48.0)
Total RSV RiiQ Symptom Score – n	120	64	91	49
Mean (SD)	1.50 (0.507)	1.46 (0.479)	1.46 (0.484)	1.46 (0.445)
RSV Viral Load by RT-qPCR – n	112	58	88	47
Mean (SD) – $\log_{10}$ copies/mL	5.31 (1.958)	5.36 (2.174)	4.99 (2.065)	5.28 (2.160)

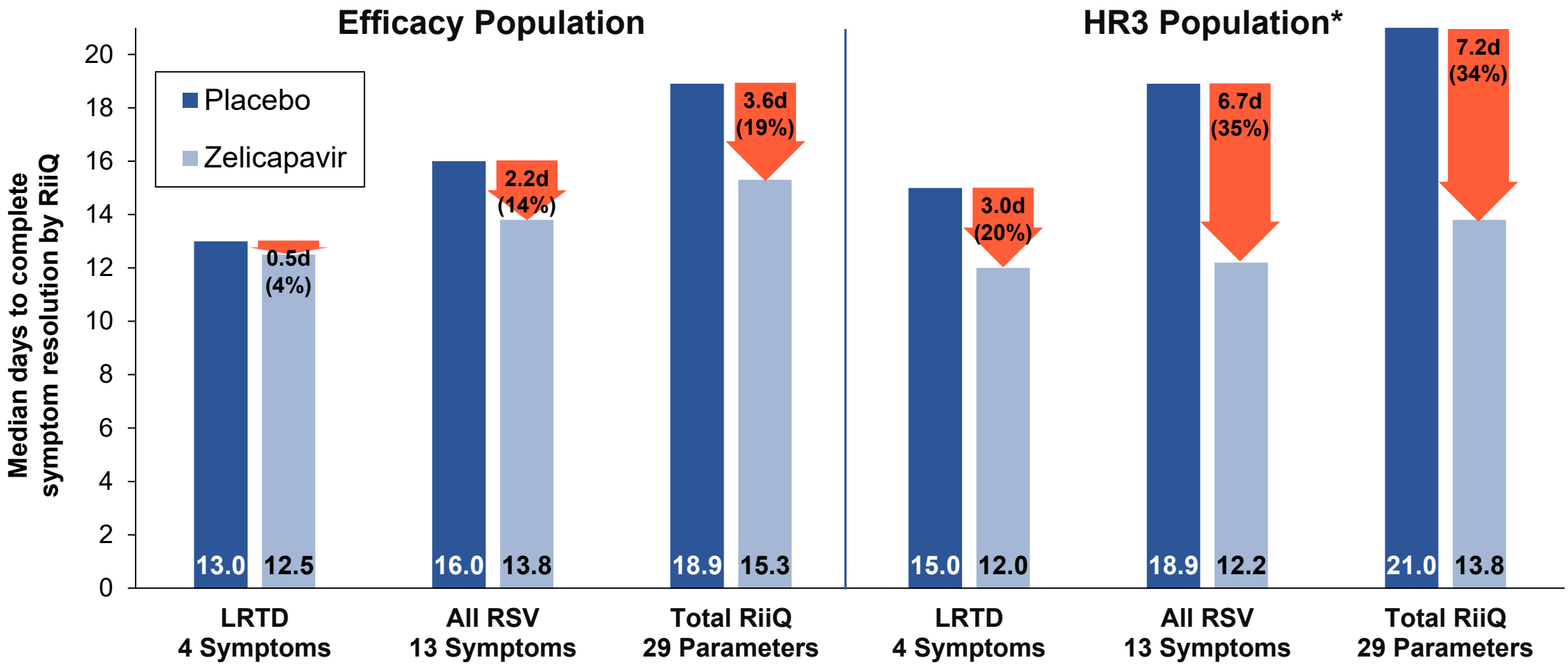
*HR3 Population = Patients with CHF, COPD, or age ≥75

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Favorable Safety Profile

- Adverse events (AEs) were similar between zelicapavir dosing groups and placebo
- No AEs led to treatment discontinuation or study withdrawal in zelicapavir group

Description, n (%)	Zelicapavir (N=121)	Placebo (N=65)
Treatment emergent AEs (TEAEs)	27 (22.3)	16 (24.6)
Study drug related TEAEs	7 (5.8)	3 (4.6)
Grade 3 or higher TEAEs	1 (0.8)	5 (7.7)
Serious TEAEs	2 (1.7)	4 (6.2)
TEAEs leading to **study drug discontinuation**	0	1 (1.5)
TEAEs leading to **study withdrawal**	0	2 (3.1)
TEAEs leading to **death**	0	1 (1.5)

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Faster Time to Complete Symptom Resolution Across Multiple RiiQ™ Measures



*HR3 Population: Patients with CHF, COPD, or age ≥75; LRTD: lower respiratory tract disease

Time to Complete Resolution of All RSV Symptoms:
CHF and COPD (Efficacy Population)

- Faster time to complete resolution of all RSV symptoms in CHF and COPD populations

	CHF		COPD	
	Zelicapavir (n=26)	**Placebo** (n=8)	**Zelicapavir** (n=43)	**Placebo** (n=24)
Complete Resolution of All RSV Symptoms				
Resolved – n (%)	20 (76.9)	6 (75.0)	32 (74.4)	19 (79.2)
Not Resolved or Censored – n (%)	6 (23.1)	2 (25.0)	11 (25.6)	5 (20.8)
Median Time to Complete Resolution of All RSV Symptoms – Days (95% CI)	11.6 (8.0, 17.7)	19.0 (5.0, NE)	13.0 (10.0, 16.1)	16.5 (9.0, 24.7)

Results showed 3.5 to 7.4 day improvement for patients treated with zelicapavir

Comparison was made irrespective of treatment discontinuation; subjects were censored at Day 33 if resolution was not achieved prior to study discontinuation, the use of prohibited medications, or death.
NE: not estimable

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Symptom Summary for Zelicapavir Compared to Placebo

Symptoms Measured by RiiQ™

- Faster time to complete resolution of all RSV symptoms to absent
  - Symptom reduction of ~one week in the HR3 population for all 13 RSV symptoms and total RiiQ
  - Time to complete resolution in CHF population: 11.6 vs 19.0 days
  - Time to complete resolution in COPD population: 13.0 vs 16.5 days
- No effect on time to resolution of RSV symptoms to mild, including primary endpoint (time to resolution of LRTD subset of symptoms to mild in the efficacy population)
- Improvement in RSV 13-symptom score* in HR3 population
  - Day 9 (p=0.0403) and Day 14 (p=0.0247)

Symptom Resolution Measured by PGI-S

- 2-day faster median time to improvement in efficacy (p=0.0446) and HR3 population (p=0.0465)

*post-hoc analysis
RiiQ: Respiratory Infection Intensity and Impact Questionnaire; PGI-S: Patient Global Impression of Severity; HR3 Population: Patients with CHF, COPD, or age ≥75; LRTD: lower respiratory tract disease

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Hospitalization and Death Endpoints

- Lower hospitalizations for patients treated with zelicapavir

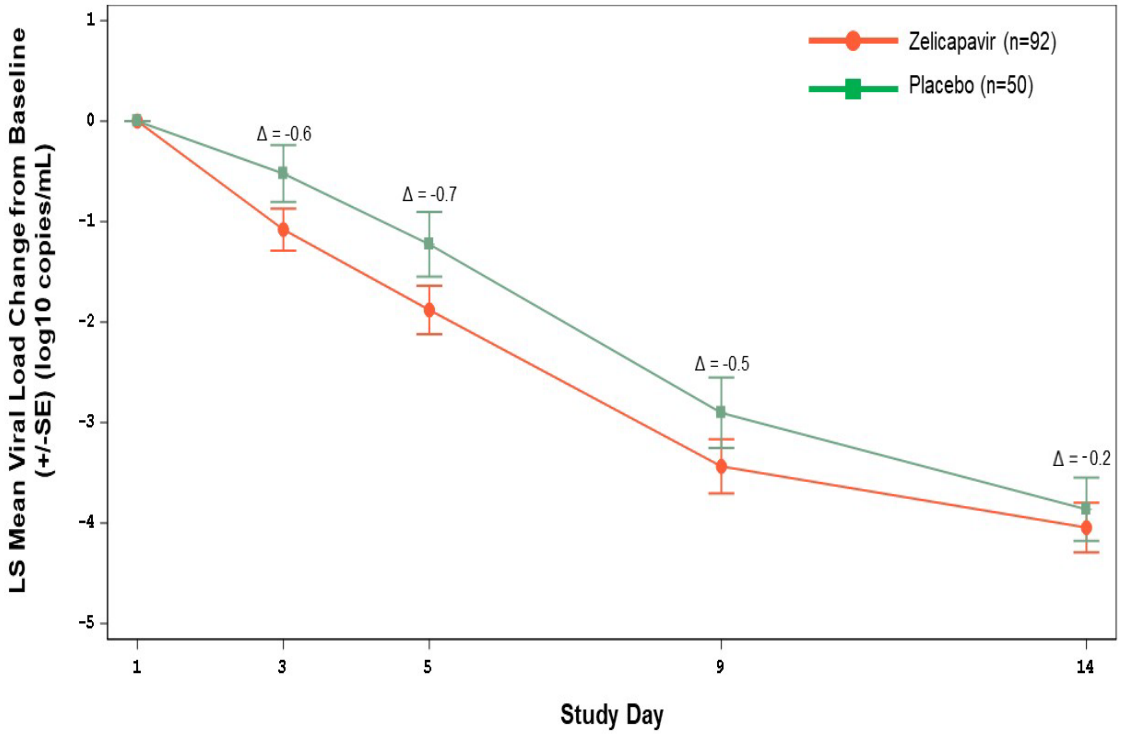
	Zelicapavir	Placebo
All-cause-hospitalizations	1.7% (2/115)	5.0% (3/60)
RSV-associated hospitalizations • Blinded investigator attribution	0% (0/115)	5.0% (3/60)

- One death on placebo; no deaths on zelicapavir

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Virology Results for Zelicapavir Compared to Placebo

- **Larger viral load decline at end of treatment (Day 5)**
  - Efficacy Population: 0.6 log
  - HR3 population: 0.7 log
- **Greater proportion of patients with undetectable viral load at the end of treatment**
  - Efficacy Population: 23.5% (27/115) vs 10.0% (6/60) (p=0.0198)
  - HR3 Population: 23.9% (22/92) vs 10.0% (5/50) (p=0.0292)
- **Faster median time to undetectable viral load**
  - Efficacy Population: 4 days
  - HR3 Population: 5 days

RSV PCR viral load decline of **0.7 log** for HR3 population at the end of treatment



Zelicapavir Phase 2b RSV High-Risk Adult Study:
Pharmacokinetics

- Zelicapavir target exposures were achieved and were consistent with exposures observed in previously treated subjects
- Mean predose (C_{trough}) concentrations were 1100 and 1141 ng/mL on Days 3 and 5, respectively

Visit	n	Mean	% CV
Day 3	101	1100	79
Day 5	104	1141	65

- Mean C_{trough} concentrations were 55-fold and 57-fold higher than the *in vitro* EC_{90} (20 ng/mL) for RSV M37, on Days 3 and 5 respectively

Zelicapavir Phase 2b RSV High-Risk Adult Study:
Conclusions

- Zelicapavir demonstrated compelling results on multiple clinically meaningful endpoints measuring different aspects of RSV disease
  - ✓ Up to one week improvement in complete symptom resolution in the HR3 population
    - ✓ 3.5 to 7.4 day symptom improvement in COPD and CHF populations
  - ✓ Statistically significant improvement in PGI-S
  - ✓ Lower hospitalizations
- Robust antiviral effect
- Favorable safety profile

Data support advancement of zelicapavir into Phase 3 study of high-risk adults

RiiQ: Respiratory Infection Intensity and Impact Questionnaire; PGI-S: Patient Global Impression of Severity