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A Pilot Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Explore the Antiviral Activity, Clinical Outcomes, Safety and Tolerability of Rilematovir at Two Dose Levels in Non-hospitalized Adults Infected with Respiratory Syncytial Virus (RSV)

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Introduction

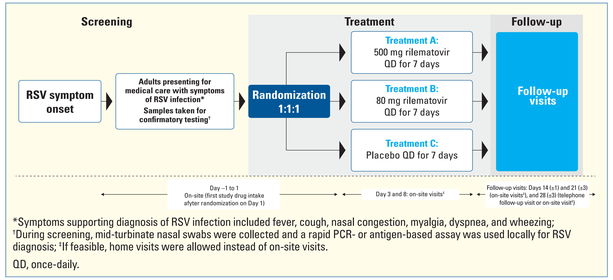
- Respiratory syncytial virus (RSV) causes a substantial burden in adults, including those in the community setting, and can be severe in certain at-risk groups, particularly older adults (aged ≥65 years), and those with underlying cardiovascular or pulmonary comorbidities such as congestive heart failure (CHF), asthma or chronic obstructive pulmonary disease (COPD).[1,2]
- Despite the high disease burden, there is a lack of efficacious direct-acting antiviral therapies to treat adults with RSV infection; management options are currently limited to supportive care.[3,4]
- Similarly to influenza, early initiation of antiviral treatment is important in patients with RSV infection as it may improve disease outcomes.[5,6]
- Rilematovir (JNJ-53718678) is an investigational RSV fusion inhibitor which has shown antiviral activity in healthy adults (aged 18–45 years) in an RSV human challenge study.[4]
- This study assessed the antiviral effect, clinical outcomes and safety of rilematovir in non-hospitalized adults with RSV infection.

Methods

Study Design

- This was a Phase 2a, randomized, double-blind, multicenter, placebo-controlled study in non-hospitalized adults with or without comorbidities aged ≥18 years with diagnosed RSV infection within 5 days of symptom onset (**Figure 1**).

Figure 1. Study Design.



*Symptoms supporting diagnosis of RSV infection included fever, cough, nasal congestion, myalgia, dyspnea, and wheezing;
†During screening, mid-turbinate nasal swabs were collected and a rapid PCR- or antigen-based assay was used locally for RSV diagnosis; ‡If feasible, home visits were allowed instead of on-site visits.

QD, once-daily.

Study Assessments

- The primary endpoint was the antiviral effect of rilematovir, as measured by nasal RSV viral load (VL) at a central laboratory using a qRT-PCR assay
  - Virologic parameters included RSV VL area under curve (AUC) from baseline through Day 3, Day 5, Day 8, and Day 14, and time to undetectable RSV VL.
- Clinical course of RSV infection was assessed by time to resolution (TTR) of Key RSV Symptoms as reported via the Respiratory Infection Intensity and Impact Questionnaire (RiiQ) or Respiratory Infection-Patient Reported Outcomes (RI-PRO) and time to return to usual activity (based on the RI-PRO)
  - The RiiQ Key RSV Symptoms (nasal congestion, sore throat, wheezing, short of breath, cough, cough with sputum and fatigue) were one-to-one mapped with the RI-PRO Key RSV Symptoms (congested/stuffy nose, sore/painful throat, trouble breathing, chest tightness, cough, cough with mucus or sputum and weak/tired).
- Safety and tolerability were also assessed throughout the study.

Statistical Analysis

- The primary population for the efficacy analyses was the intent-to-treat infected (ITT-i) set, defined as all randomized patients with central laboratory-confirmed RSV infection who received ≥1 dose of the study treatment
- Patients were stratified by duration of symptom onset before randomization (≤3 days vs >3 days to ≤5 days).
- For continuous variables, descriptive statistics (n, mean, standard deviation [SD], median) were provided.
- For categorical variables, frequency tables were presented.
- The RSV VL AUC over time (through Days 3, 5, 8, and 14) was assessed using a mixed effects model with repeated measurements including fixed categorical effects of treatment, symptoms onset (≤3 days vs >3 days before randomization), time and treatment-by-time interaction, as well as the continuous covariates of baseline $\log_{10}$ VL and baseline $\log_{10}$ VL by-time interaction.
- Time-to-event variables were analyzed and plotted using Kaplan-Meier (KM) analyses.
- Resolution of Key RSV Symptoms occurred when all 7 key items from either RI-PRO or RiiQ were scored as 0 (none/absent) or 1 (mild) for at least 24 hours.

Results

Baseline Characteristics

- Overall, 79 adult outpatients were screened, 72 were randomized and dosed, of whom 66 patients with centrally-confirmed RSV infection (ITT-i set) received rilematovir 80 mg (n=21), rilematovir 500 mg (n=23) or placebo (n=22).
- Most baseline demographics were similar among treatment groups (**Table 1**)
  - Risk factors for severe RSV disease (asthma, COPD, CHF, chronic renal failure (CRF) and age ≥65 years) were present in a higher proportion of patients in the rilematovir 500 mg group (52.2%) and placebo group (45.5%) compared with the rilematovir 80 mg group (19.0%)
  - Slight differences were also observed for age and sex: fewer older adults (aged ≥65 years) and fewer females were included in the rilematovir 80 mg group compared with the rilematovir 500 mg group and placebo group.

Table 1. Baseline Demographics and Disease Characteristics (selected).

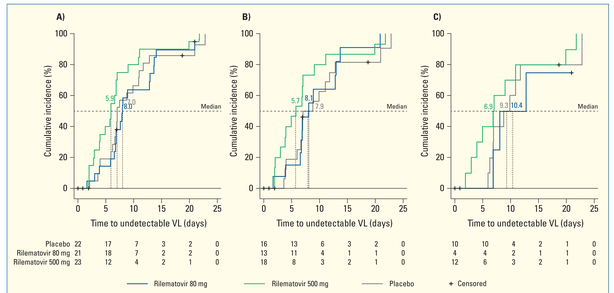
	Rilematovir 80 mg (n=21)	Rilematovir 500 mg (n=23)	Placebo (n=22)
Age, years			
Mean (SD)	45.9 (16.8)	51.3 (18.2)	59.5 (14.6)
Median	46.0	50.0	58.5
Age group, n (%)			
≥65 years	1 (4.8)	9 (39.1)	7 (31.8)
Sex, n (%)			
Female	8 (38.1)	12 (52.2)	13 (59.1)
Race, n (%)			
American Indian or Alaska Native	0	1 (4.3)	0
Asian	1 (4.8)	1 (4.3)	4 (18.2)
Black or African American	2 (9.5)	1 (4.3)	0
White	18 (85.7)	20 (87.0)	18 (81.8)
RSV subtype, n (%)			
A	8 (38.1)	9 (39.1)	4 (18.2)
B	13 (61.9)	14 (60.9)	18 (81.8)
Median RSV symptom duration prior to randomization, days (range)	3 (2; 5)	3 (1; 5)	3 (2;5)
RSV symptom onset group, n (%)			
≤3 days	13 (61.9)	18 (78.3)	16 (72.7)
>3 days	8 (38.1)	5 (21.7)	6 (27.3)
Baseline RSV VL ($\log_{10}$ copies/mL), mean (SD)	5.9 (1.7)	5.5 (1.8)	5.3 (1.7)
Symptom onset ≤3 days	5.3 (1.7)	5.6 (1.8)	5.4 (2.0)
Symptom onset >3 days to ≤5 days	6.8 (1.1)	5.3 (1.7)	5.0 (0.7)
Any risk factor for severe RSV, n (%)*			
No	17 (81.0)	11 (47.8)	12 (54.5)
Yes	4 (19.0)	12 (52.2)	10 (45.5)
Selected comorbidities associated with risk for severe RSV			)
Asthma	2 (9.5)	2 (8.7)	2 (9.1)
CAD	1 (4.8)	1 (4.3)	2 (9.1)
CHF	0	1 (4.3)	2 (9.1)
COPD	1 (4.8)	4 (17.4)	2 (9.1)

*Risk factors for severe RSV were defined as asthma, COPD, CHF, CRF and age ≥65 years.
CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; SD, standard deviation; VL, viral load.

Antiviral Activity

- There was no clear effect of rilematovir versus placebo on VL over time for both mean VL AUC and change from baseline analyses.
- In the overall population, the KM estimate of median time to first confirmed undetectable RSV VL was shorter for rilematovir 500 mg (5.9 days) compared with placebo (7.0 days) or rilematovir 80 mg (8.0 days) (**Figure 2A**)
  - In patients with symptom onset ≤3 days at initiation of treatment, a shorter median time to first undetectable RSV VL was observed for rilematovir 500 mg compared with placebo or rilematovir 80 mg (**Figure 2B**)
  - In patients with any risk factor for severe RSV (n=26), median time to undetectable RSV VL was shorter with rilematovir 500 mg (6.9 days) versus placebo (9.3 days) or rilematovir 80 mg (10.4 days) (**Figure 2C**).

Figure 2. Kaplan-Meier Estimate of Time to First Confirmed Undetectable RSV VL* (Days) in the A) Overall Population B) Patients with Symptom Onset ≤3 Days and C) Patients with Any Risk Factor for Severe RSV.

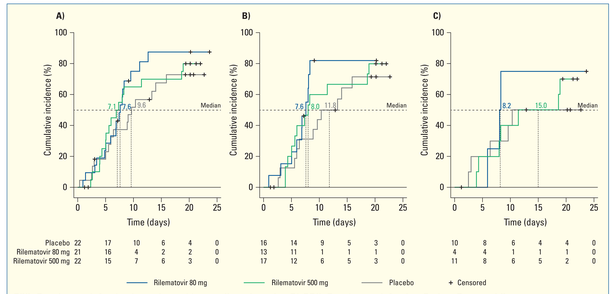


*Defined as the time to first post-baseline timepoint at which the virus is undetectable and confirmed by one consecutive undetectable assessment. All efficacy analyses were based on the ITT-i set.a
ITT-i, intent-to-treat infected; VL, viral load.

Clinical Course of RSV Infection

- There was a greater reduction from baseline in the patient-reported Key RSV Symptom score from Day 2 with rilematovir 80 mg versus placebo, and from Day 5 with rilematovir 500 mg versus placebo (data not shown).
- KM estimates for median TTR of Key RSV Symptoms (by RiiQ or RI-PRO) were shorter with rilematovir 80 mg (7.6 days) and 500 mg (7.1 days) versus placebo (9.6 days) (**Figure 3A**), and in patients with symptom onset ≤3 days (8.0 days and 7.6 days vs 11.8 days, respectively) (**Figure 3B**) i.e. a treatment effect of 26% and 32% reduction in TTR for rilematovir 500mg versus placebo, respectively.
- In patients with any risk factor for severe RSV, median KM estimates were shorter in the rilematovir 80 mg group (8.2 days) versus the rilematovir 500 mg group (15.0 days), but could not be calculated for the placebo group (**Figure 3C**).
- The KM estimate of the patient-reported median time to return to usual activity was shorter in the rilematovir 80 mg group (3.0 days) compared with the rilematovir 500 mg group (6.0 days), and the placebo group (5.6 days) [data not shown].

Figure 3. Time to Resolution of Key RSV Symptoms, Assessed by the RiiQ or RI-PRO in A) Overall Population B) Patients with Symptom Onset ≤3 Days and C) Patients with Any Risk Factor for Severe RSV.



RiiQ, Respiratory Infection Intensity and Impact Questionnaire; RI-PRO, Respiratory Infection-Patient Reported Outcomes; TTR, time to resolution.

Safety

- There were no serious adverse events (AEs) or deaths reported during the treatment or follow-up phase of the study.
- All treatment-emergent AEs (TEAEs) were Grade 1 (mild) or Grade 2 (moderate) in severity, except in one patient in the placebo group, who experienced Grade 3 bacterial infection
  - TEAEs leading to study treatment discontinuation were reported in two (8.3%) patients in the rilematovir 80 mg group, three (12.5%) patients in the rilematovir 500 mg groups, and one (4.2%) patient in the placebo group.
- The incidence of TEAEs was lower in the rilematovir 500 mg group (37.5%) compared with the rilematovir 80 mg group (75.0%) and the placebo group (62.5%)
  - Diarrhea was the most common TEAE, reported in 20.8% of rilematovir 500 mg recipients and 37.5% of patients in both the rilematovir 80 mg and placebo groups; all cases were mild and resolved during the study period.

Conclusions

- In adult outpatients, including those at high risk of severe disease, rilematovir demonstrated antiviral effect based on reduction in time to undetectability of nasal RSV VL and favorable impact on clinical course of RSV infection, and was generally safe and well tolerated
  - Shorter time to undetectable RSV VL was observed with rilematovir (500 mg) compared with placebo, with approximately 1 day reduction overall
  - Shorter TTR of Key RSV Symptoms was observed with rilematovir (80 mg and 500 mg) compared with placebo, with approximately 3 days reduction overall.
- Similar findings on antiviral effect were observed in the subgroup of patients with onset of symptoms ≤3 days at initiation of treatment.
- The sample size of patients with any risk factor for severe RSV was too small to make a reliable conclusion about the treatment effect of rilematovir in this group.
- This study provides proof-of-concept and warrants further investigation of rilematovir in RSV-positive non-hospitalized adults.

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