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A randomized controlled trial of presatovir for respiratory syncytial virus after lung transplant

Jens Gottlieb, MD,[a] Fernando Torres, MD,[b] Tarik Haddad, MD,[c] Gundeep Dhillon, MD, MPH,[d] Daniel F. Dilling, MD,[e] Christiane Knoop, MD, PhD,[f] Reinaldo Rampolla, MD,[g] Rajat Walia, MD,[h] Vivek Ahya, MD, MBA,[i] Romain Kessler, MD, PhD,[j] Marie Budev, DO, MPH,[k] Claus Neurohr, MD,[l] Allan R. Glanville, MBBS, MD,[m] Robert Jordan, PhD,[n] Danielle Porter, PhD,[n] Matt McKevitt, PhD,[n] Polina German, PharmD,[n] Ying Guo, PhD,[n] Jason W. Chien, MD, MS,[n] Timothy R. Watkins, MD, MSc,[n] and Martin R. Zamora, MD[o]

From the [a]Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany; [b]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; [c]Pulmonary Disease and Critical Care, Tampa General Hospital, Tampa, Florida; [d]Department of Medicine, Stanford University Medical Center, Stanford, California; [e]Division of Pulmonary and Critical Care, Loyola University Chicago, Stritch School of Medicine, Maywood, Illinois; [f]Department of Chest Medicine, Erasme University Hospital, Brussels, Belgium; [g]Lung Transplant Program, Cedars-Sinai, Los Angeles, California; [h]Pulmonary and Critical Care Section, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; [i]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; [j]Department of Respiratory Medicine and INSERM-UMR 1260 Regenerative NanoMedicine, University of Strasbourg, Strasbourg, France; [k]Department of Pulmonary Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; [l]Department of Internal Medicine, University of Munich, Munich, Germany; [m]Department of Thoracic Medicine, St. Vincent's Hospital, Darlinghurst, New South Wales, Australia; [n]Gilead Sciences, Inc., Foster City, California; and the [o]Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado at Denver Anschutz Medical Center, Aurora, Colorado.

KEYWORDS:
presatovir;
respiratory syncytial virus;
lung transplant;
RSV fusion inhibitor;
randomized controlled trial

BACKGROUND: Respiratory syncytial virus (RSV) infection in lung transplant recipients is associated with high morbidity. This study evaluated the RSV fusion inhibitor presatovir in RSV-infected lung transplant recipients.

METHODS: In this international Phase 2b, randomized, double-blind, placebo-controlled trial (NCT02534350), adult lung transplant recipients with symptomatic confirmed RSV infection for ≤7 days received oral presatovir 200 mg on day 1 and 100 mg daily on days 2 to 14, or placebo (2:1), with follow-up through day 28. There were 2 coprimary endpoints: time-weighted average change in nasal RSV load from day 1 to 7, calculated from nasal swabs, in the full analysis set ([FAS]; all patients who received study drug and had quantifiable baseline nasal RSV load) and time-weighted average change in nasal RSV load from day 1 to 7 in the subset of patients with pretreatment symptom duration at the median or shorter of the FAS. Secondary endpoints were changes in respiratory infection symptoms assessed using the Influenza Patient-Reported Outcomes questionnaire and lung function measured by spirometry.

Abbreviations: AE, adverse event; CARV, community-acquired respiratory virus; CI, confidence interval; FAS, full analysis set; FEV_1, forced expiratory volume in 1 second; FLU-PRO, Influenza Patient-Reported Outcome; IQR, interquartile range; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SAE, serious adverse event

Reprint requests: Martin R. Zamora, MD, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado at Denver Anschutz Medical Center, 12700 East 19th Ave, 9C03, Aurora, CO 80045.

E-mail address: marty.zamora@cuanschutz.edu

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RESULTS: Sixty-one patients were randomized, 40 received presatovir, 20 placebo, and 54 were included in efficacy analyses. Presatovir did not significantly improve the primary endpoint in the FAS (treatment difference [95% CI], 0.10 [−0.43, 0.63] $\log_{10}$ copies/ml; $p = 0.72$) or the shorter symptom-duration subgroup (−0.12 [−0.94, 0.69] $\log_{10}$ copies/ml; $p = 0.76$). Secondary endpoints were not different between presatovir and placebo groups. Presatovir was generally well tolerated.

CONCLUSIONS: Presatovir treatment did not significantly improve change in nasal RSV load, symptoms, or lung function in lung transplant recipients.

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Infection with respiratory syncytial virus (RSV) is of special concern in lung transplant recipients.[1] The estimated incidence of community-acquired respiratory virus (CARV) infections in lung transplant recipients is 15 to 50 cases per 100 patient-years, and RSV accounts for 19% of these infections (i.e., 2-10 per 100 patient-years).[2] In addition to the acute disease burden of respiratory infection, RSV and other CARV infections are linked to chronic lung allograft dysfunction, a major source of morbidity and mortality following lung transplantation.[1,3-5]

There is no approved treatment for RSV infection in adults, including after lung transplantation. Although ribavirin is used to treat RSV in lung transplant recipients and other immune-compromised adults, its efficacy is not established.[6-10] Though aerosolized ribavirin is approved for RSV treatment in hospitalized infants and young children with severe lower respiratory tract infections,[11,12] it is not recommended for routine management of RSV infection. Palivizumab is recommended for prophylaxis in children aged ≤24 months who are at high risk for severe RSV disease, but limited evidence is available for RSV treatment in children and immunocompromised adults.[13-15] Intravenous immunoglobulin (IVIG) is sometimes used for RSV treatment in lung transplant recipients[16,17]; however, there is insufficient evidence supporting association with improved clinical outcomes.

There is a continued unmet need for a specific treatment for RSV in lung transplant recipients and other adults at risk of severe RSV-related disease outcomes. Presatovir, a novel RSV fusion inhibitor, decreased RSV viral load and symptoms relative to placebo in a challenge study and had a favorable safety profile in healthy adults.[18-20] This study evaluated the short-term efficacy of presatovir on RSV viral load, RSV symptoms, and lung function. The study also confirmed presatovir pharmacokinetics and safety in lung transplant recipients.

Materials and methods

Study design and oversight

This was a Phase 2b, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 29 centers in 8 countries (Australia, Belgium, Canada, France, Germany, Netherlands, the UK, and the US) between December 2015 and September 2017. Patients were randomized (2:1 ratio), stratified by treatment with ribavirin (yes or no) and by use of palivizumab or IVIG (yes or no), to receive once daily presatovir 200 mg on day 1 (baseline) and 100 mg on days 2 to 14, orally or via nasogastric tube, or matching placebo. Randomization was performed via interactive web response system using a randomization schedule previously prepared by an independent biostatistician not involved in study conduct. Treatment assignment was blinded to study patients, investigational site personnel, and the sponsor. Patients were followed for a total of 28 days for the core randomized clinical trial. Patients completing the core trial could participate in an optional observational registry study for up to 48 weeks after day 28 (not included in this report). The study was conducted in accordance with the International Council for Harmonisation guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol, amendments, and other documents were approved by local independent ethics committees or institutional review boards before study initiation. All patients provided written informed consent before participating. The trial was registered with Clinicaltrials.gov (NCT02534350).

Patients

Adult patients who received a lung transplant >90 days prior to screening and who developed symptomatic RSV infection confirmed by polymerase chain reaction (PCR) testing ≤7 days before the baseline visit were eligible. Qualifying respiratory symptoms included any nasal congestion, earache, runny nose, cough, sore throat, shortness of breath, or wheezing. Patients with any transplants other than lung or heart and lung, including prior hematopoietic cell transplant, were excluded, as were those with rapidly deteriorating graft function as determined by the investigator, for any reason, prior to RSV infection. Patients with significant and confirmed respiratory coinfection ≤14 days before screening were excluded. Full eligibility criteria are provided in Supplementary Methods.

Outcomes and assessments

The primary efficacy outcome was time-weighted average change in nasal RSV viral load from baseline to day 7, by which time the majority of patients could be expected to have completed shedding virus. This was assessed as a coprimary endpoint among the full analysis set ([FAS], defined as patients who received ≥1 dose of study drug and who had a quantifiable baseline RSV nasal viral load) and also among the subset of the FAS who had duration of RSV symptoms at randomization that was less than or equal to the median value for the FAS. Secondary efficacy outcomes were change from baseline to day 7 in Influenza Patient-Reported Outcome (FLU-PRO) score[21] and change from baseline to day 28 in forced expiratory volume in 1 second (FEV_1; % predicted) value.

Nasal viral load was measured centrally by reverse transcription quantitative PCR by Viracor Eurofins (Lee's Summit, MO). Nasal swab specimens for viral load measurement were collected using a standardized procedure at study visits, and the FLU-PRO questionnaire was administered on days 1, 3, 5, 7, 9, 14, 21, and 28/last study visit (details in Supplementary Methods). Study visits from day 3 to day 21 could be conducted at home by home-trial-support nurses. Spirometry testing measurements were obtained and interpreted according to American Thoracic Society/European Respiratory Society guidance[22] at screening or day 1/baseline and day 28/end of study; patients also obtained handheld spirometry measurements at all study visits through day 28 (details in Supplementary Methods). Change in anti-RSV antibody titer was assessed from blood samples collected at baseline and day 28 (Supplementary Methods). Pharmacokinetic sampling was performed as described in the Supplementary Methods. Safety was assessed from adverse events (AEs) reporting and clinical laboratory tests. Additional safety assessments included vital signs, electrocardiography, cardiac-related tests, and monitoring concomitant medications. Safety events were assigned grades according to the Gilead Sciences, Inc., Grading Scale for Severity of AEs and Laboratory Abnormalities.

Statistical analysis

Efficacy analyses were performed using the FAS and the subset of FAS patients whose duration of RSV symptoms prior to first dose of study drug was ≤ median duration for the FAS population. Safety analyses included all patients who received ≥1 full dose of study drug. Coprimary and secondary efficacy endpoints were analyzed using parametric analysis of covariance with baseline values and stratification factors as covariates. The coprimary analyses were controlled at an overall type 1 error rate at the 2-sided 0.05 level using an appropriate α allocation numerically derived utilizing the inherent correlation between the test statistics (additional details of statistical analysis are included in Supplementary Methods). The α level for the overall FAS population was 0.04, and the α level for the subset of the FAS population with ≤ median symptom duration prior to first dose was 0.017. If the hypothesis for coprimary endpoints was rejected, sequential testing was performed for secondary endpoints based on the closed testing procedure. Patient characteristics were summarized descriptively. The number and percentage of patients experiencing AEs were summarized by treatment. Missing efficacy data due to premature discontinuation were not imputed, but missing intermediate viral load and FLU-PRO data were imputed using the trapezoidal rule for time-weighted average calculations. Missing baseline safety data were replaced with screening values when available.

Enrollment of 60 patients was estimated to provide ≥85% power to detect ≥1.2 and ≥1.5 $\log_{10}$ differences in the FAS population and the FAS population subset with median or shorter symptom duration, respectively. Details are provided in Supplementary Methods.

The sponsor performed an unplanned unblinding for 5 personnel on or after June 1, 2017, prior to planned unblinding on June 26, 2017. No changes were made to any of the preplanned statistical analyses for the primary or secondary endpoints after the unplanned unblinding.

Results

Patient disposition and baseline characteristics

In total, 111 lung transplant recipients with suspected RSV were screened; 61 were randomized; 60 received study drug and were included in safety analyses; and 54 were included in the FAS (Figure 1). The majority of patients were Caucasian (52/60; 87%), and 31/60 (52%) were male, with median age 58 years (25% quartile to 75% quartile [IQR], 51-65.5 years; range, 23-78 years). Patients had received lung transplant a median of 1,098 days (IQR, 570-1,776 days) prior and had median duration of symptoms of 6 days (IQR, 4-6 days; mean, 5 days; range, 1-8 days) before the first dose. Overall, 46/60 (77%) patients were planned to receive concomitant ribavirin for RSV treatment

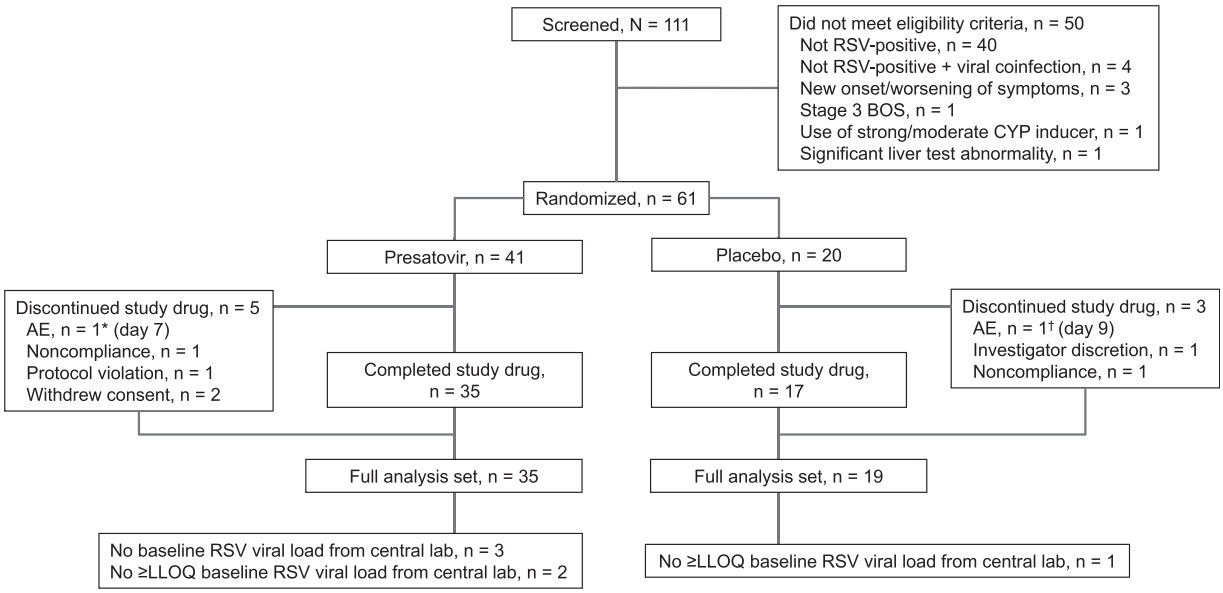

Figure 1 Patient disposition. *Patient discontinued study on day 7 due to diarrhea; †patient discontinued study on day 9 due to abdominal pain, nausea, and vomiting. AE, adverse event; BOS, bronchiolitis obliterans syndrome; CYP, cytochrome P450; LLOQ, lower limit of quantitation; RSV, respiratory syncytial virus.

and 18% to receive palivizumab or IVIG, and 42/60 (70%) patients actually received ribavirin (31/42 [74%], 10/42 [24%], and 1/42 [2%] by oral, aerosolized, and intravenous administration, respectively). Demographic traits, baseline characteristics, lung transplant indications, and immunosuppressant use were balanced across treatment arms (Table 1). Presatovir-treated patients had a longer time from lung transplant to first dose relative to placebo-treated patients (median [IQR], 40 [26-60] versus 22 [10-49] months) (Table 1). Among presatovir-treated patients, plasma presatovir concentrations obtained were >20-fold above the plasma protein binding-adjusted 95% maximal effective concentration for RSV through day 21 (Supplementary Results and Figure S1).

Efficacy analyses

Presatovir did not significantly decrease time-weighted average change in nasal RSV viral load from baseline to day 7, relative to placebo, in the FAS population (treatment difference: 0.10 $\log_{10}$ copies/ml; 95% confidence interval [CI], −0.43 to 0.63; $p = 0.72$) or among the subset of FAS patients whose duration of symptoms was at the median or shorter of the value for the complete FAS cohort (≤6 days; treatment difference: −0.12 $\log_{10}$ copies/ml; 95% CI, −0.94 to 0.69; $p = 0.76$). In the FAS population, presatovir, with or without ribavirin use at baseline, showed no significant decrease in time-weighted average change in nasal viral load: treatment difference with ribavirin, −0.11 $\log_{10}$ copies/ml (95% CI, −0.69 to 0.46; $p = 0.70$); treatment difference without ribavirin, 0.73 $\log_{10}$ copies/ml (95% CI, −0.75 to 2.21; $p = 0.29$). Median change in nasal RSV load from baseline (Figure 2A and 2B) and median absolute nasal viral load (Figure S2) were also similar between patients receiving presatovir versus placebo throughout the study.

No significant difference in time-weighted average change in FLU-PRO score from baseline to day 7 was observed between the presatovir and placebo treatment arms (treatment difference: 0.01; 95% CI, −0.12 to 0.15; nominal $p = 0.86$) (Figure 3 and Figure S3). Similarly, percent change in FEV_1(% predicted) from baseline to day 28 did not significantly differ between patients receiving presatovir versus placebo (treatment difference: −3.25; 95% CI, −15.58 to 9.08; nominal $p = 0.60$; Figure 4; handheld spirometry measurements shown in Figure S4). No significant treatment differences in the secondary endpoints were observed in the subgroup of patients whose duration of symptoms was at the median or shorter of the value in the FAS population (Table S1). Mean changes from baseline in RSV A and RSV B antibody titers were similar between patients receiving presatovir and placebo.

Safety analysis

AEs were similar regardless of presatovir or placebo treatment; 32/40 (80%) presatovir-treated patients reported ≥1 treatment-emergent AE compared with 17/20 (85%) placebo-treated patients. Overall, most AEs were mild to moderate in severity. Headache (13%), nausea (13%), dizziness (10%), fatigue (10%), and cough (10%) were the most frequently reported AEs following presatovir treatment (Table 2). Three (8%) patients receiving presatovir and 6 (30%) receiving placebo experienced AEs of Grade ≥3 in severity. The only Grade ≥3 AE reported by >1 patient in either treatment group was anemia, reported by 2 patients receiving presatovir (5%) and 2 receiving placebo (10%; Table 3). All 4 of these patients were also receiving ribavirin. Serious AEs (SAEs) occurred in 2 (5%) patients receiving presatovir and 4 (20%) receiving placebo. One patient each receiving presatovir had anemia and mental status change; SAEs in placebo-treated patients ($n = 1$ each) were hypoxemia, deep vein thrombosis, noncardiac chest pain, and combined hypoxemia, sepsis, and hypotension. No SAE was considered related to presatovir. One patient receiving presatovir and 1 patient receiving placebo discontinued study drug due to AEs of diarrhea at day 7 and combined abdominal pain, nausea, and vomiting at day 9, respectively. There were no deaths, and no patient required mechanical ventilation through day 28.

Grade ≥3 laboratory abnormalities occurred in 18 (46%) patients receiving presatovir and 5 (26%) receiving placebo (Table 4). The greatest difference was Grade 3 nonfasting hyperglycemia (glucose >250-500 mg/dl). Grade 3 increased fasting glucose was reported in 1 presatovir-treated versus 0 placebo-treated patients, and Grade 3 increased nonfasting glucose was reported in 6 presatovir-treated versus 0 placebo-treated patients. These abnormalities included 1 marked laboratory abnormality each of increased nonfasting glucose and increased fasting glucose in different patients, both of whom were missing baseline predose glucose measurements and had medical history of diabetes mellitus. The majority of patients with Grade 3 hyperglycemia had elevated glucose values at the day 1 predose assessment.

Discussion

In this multicenter study—among the largest randomized, double-blind, placebo-controlled clinical trials to date for treatment of lung transplant recipients with RSV infection—presatovir did not significantly improve measures of nasal RSV viral load relative to placebo, despite adequate plasma presatovir concentrations. Similarly, measures of symptom resolution (via FLU-PRO questionnaire) and change in lung function (assessed via FEV_1) did not significantly differ in patients receiving presatovir versus placebo. Presatovir was generally well tolerated in this population. These results are consistent with other studies of presatovir in high-risk adults infected with RSV.[23,24]

Although presatovir did not meet the efficacy endpoints, this and other recent studies demonstrate the feasibility of clinical trials in RSV-infected lung transplant recipients. The present study incorporated novel approaches, including the use of home nursing visits to perform nasal sampling and other clinical and safety assessments. Bringing the clinical trial to the participant facilitated enrollment of an

Table 1 Patient Demographics and Baseline Characteristics, Safety Analysis Set

Characteristic	Presatovir (n = 40)	Placebo (n = 20)
Age, years, mean (SD)	56 (13)	55 (14)
<65 years	25 (63)	15 (75)
Sex at birth		
Male	21 (52)	10 (50)
Race		
Asian	0	1 (5)
Black or African American	0	2 (10)
Native Hawaiian or Pacific Islander	1 (3)	0
Other/unknown	3 (8)	1 (5)
White	36 (90)	16 (80)
Bilateral lung transplant	33 (83)	17 (85)
Indication for transplant		
COPD/emphysema[a]	13 (33)	6 (30)
Cystic fibrosis/bronchiectasis	7 (17)	2 (10)
Interstitial/fibrotic lung disease	12 (30)	7 (35)
Pulmonary vascular disease	2 (5)	1 (5)
Other	6 (15)	4 (20)
Months from transplant to day 1, median (Q1, Q3)	40 (26, 60)	22 (10, 49)
Days symptomatic before day 1, median (Q1, Q3)	6 (4, 7)	5 (4, 6)
Baseline viral load, $\log_{10}$ copies/ml, mean (SD)	5.9 (2.1)	6.6 (2.1)
Median (Q1, Q3)	6.1 (4.7, 7.6)	7.3 (5.3, 8.0)
RSV subtype		
RSV A	19 (48)	4 (20)
RSV B	16 (40)	15 (75)
Undetectable	2 (5)	1 (5)
Missing	3 (8)	0
Immunosuppression		
Ciclosporin	2 (5)	1 (5)
Tacrolimus	38 (95)	19 (95)
Mycophenolate	24 (60)	12 (60)
Azathioprine	9 (23)	4 (20)
Sirolimus/everolimus	3 (8)	1 (5)
Corticosteroids, systemic	39 (98)	20 (100)
Intended treatment with ribavirin at randomization	31 (78)	15 (75)
Actual ribavirin treatment	28 (70)	14 (70)
Oral[b]	21 (75)	10 (71)
Aerosolized[b]	6 (21)	4 (29)
Intravenous[b]	1 (4)	0
Intended treatment with palivizumab or IVIG at randomization[c]	8 (20)	3 (15)
Hospitalized at baseline	11 (28)	4 (20)
Related to RSV infection[d]	10 (91)	4 (100)
Baseline FEV_1(% predicted), mean (SD)	64 (25)	62 (19)
Change from prior best measure, mean (SD)	−15 (−15)	−16 (−12)
Baseline FLU-PRO score, mean (SD)	2 (0.6)	2 (0.7)
Pre-existing chronic lung allograft dysfunction/BOS prior to screening	7 (18)	2 (10)
Pre-existing BOS prior to RSV infection	4 (10)	2 (10)
Grade 0p[e]	1 (25)	1 (50)
Grade ≥1[e]	3 (75)	1 (50)

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FLU-PRO, Influenza Patient-Reported Outcome; IVIG, intravenous immunoglobulin; Q1, first quartile; Q3, third quartile; RSV, respiratory syncytial virus; SD, standard deviation.

Data are shown as n (%) unless otherwise indicated.

[a]Includes 1 patient with alpha-1 antitrypsin deficiency.

[b]Shown as n (%) of patients who actually received ribavirin.

[c]One patient receiving presatovir received palivizumab and 1 different patient receiving presatovir received IVIG; 2 patients receiving placebo received both palivizumab and IVIG.

[d]Shown as n (%) of patients who were hospitalized at baseline.

[e]Percentage out of total patients with BOS, including Grade 0p.

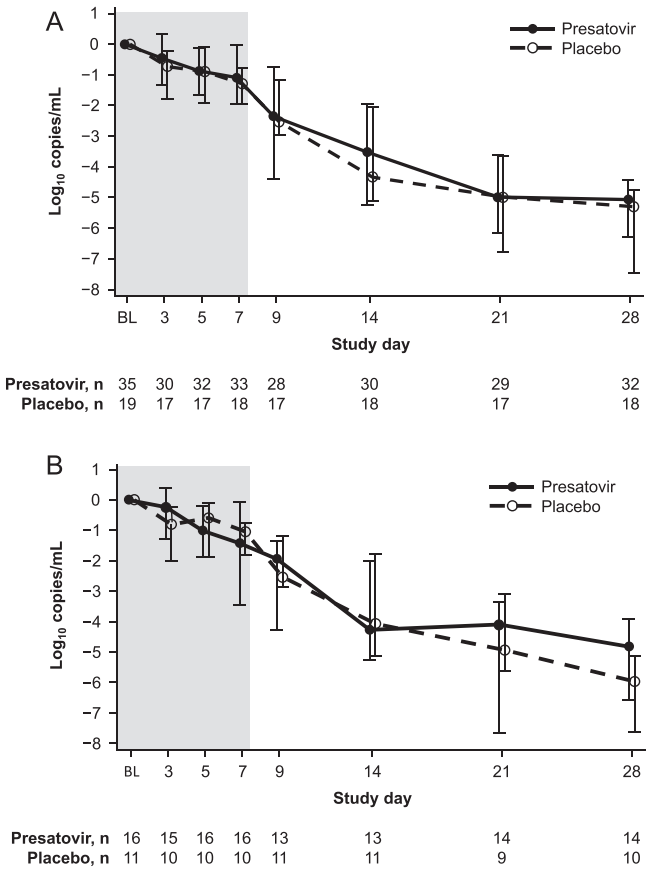

Figure 2 Median change from baseline to day 28 in (**A**) the full analysis set and (**B**) the subset of patients with median or shorter duration of symptoms before baseline. Error bars represent the 25% and 75% quartiles. Gray box represents assessment period for the coprimary endpoints. BL, baseline.

important population of patients who are often unable to participate in clinical studies due to the distance they reside from their central lung transplant center. Such research participation is imperative to improving outcomes for future generations of lung transplant patients.

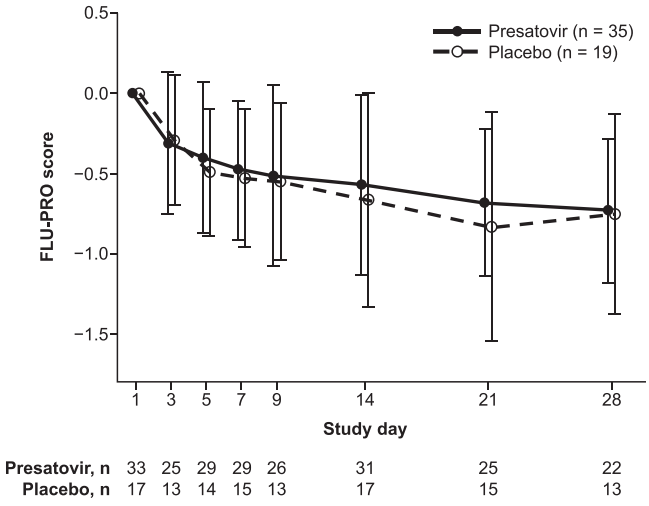

Figure 3 Median change in FLU-PRO score from baseline to day 28 in the full analysis set. Error bars represent the 25% and 75% quartiles. FLU-PRO, influenza patient-reported outcome.

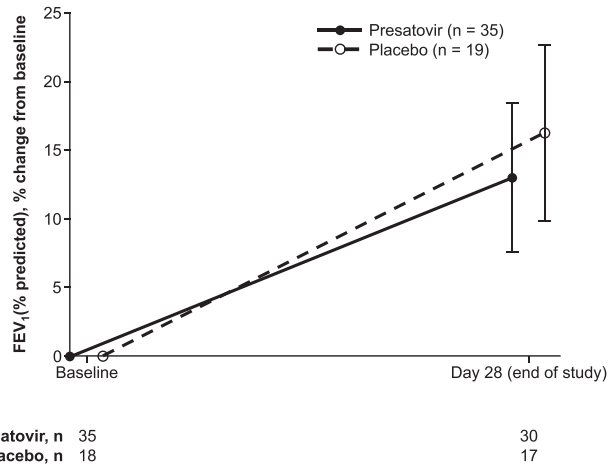

Figure 4 Mean % change in FEV_1(% predicted) from baseline to day 28 in the full analysis set. Error bars represent the standard deviation. FEV_1, forced expiratory volume in the first second.

Table 2 Treatment-Emergent Adverse Events Reported in ≥2 Patients

Preferred term	Presatovir (*n* = 40)	Placebo (*n* = 20)
Patients with any TEAE	32 (80)	17 (85)
Dizziness	4 (10)	5 (25)
Headache	5 (13)	4 (20)
Nausea	5 (13)	3 (15)
Fatigue	4 (10)	3 (15)
Anemia[a]	3 (8)	3 (15)
Diarrhea	2 (5)	4 (20)
Vomiting	3 (8)	3 (15)
Cough	4 (10)	0
Productive cough	2 (5)	2 (10)
Flatulence	2 (5)	1 (5)
FEV decreased	2 (5)	1 (5)
Tremor	2 (5)	1 (5)
Abdominal pain upper	1 (3)	1 (5)
Blood bicarbonate decreased	0	2 (10)
Confusional state	1 (3)	1 (5)
Deep vein thrombosis	0	2 (10)
Dehydration	1 (3)	1 (5)
Epistaxis	0	2 (10)
Hemoglobin decreased	2 (5)	0
Hypoxia	0	2 (10)
Insomnia	2 (5)	0
Leukopenia	2 (5)	0
Noncardiac chest pain	0	2 (10)
Palpitations	2 (5)	0
Pollakiuria	2 (5)	0
Pruritis	1 (3)	1 (5)
Sputum discolored	2 (5)	0
Urinary tract infection	1 (3)	1 (5)

FEV, forced expiratory volume; TEAE, treatment-emergent adverse event.

Data are shown as n (%).

[a]All 6 patients who experienced anemia (3 assigned to presatovir, 3 to placebo) were taking ribavirin.

Table 3 Grade ≥3 TEAEs, Safety Analysis Set

Preferred term	Presatovir (n = 40)	Placebo (n = 20)
Grade ≥3 TEAE	3 (8)	6 (30)
Anemia[a]	2 (5)	2 (10)
Nausea	1 (3)	1 (5)
Abdominal pain	0	1 (5)
Deep vein thrombosis	0	1 (5)
Hypotension	0	1 (5)
Hypoxia	0	1 (5)
Mental status changes	1 (3)	0
Noncardiac chest pain	0	1 (5)
Sepsis	0	1 (5)

Hb, hemoglobin; TEAE, treatment-emergent adverse event.

Data are shown as n (%).

Definitions of severity Grade 3 are anemia, Hb <7.5 g/dl; nausea, minimal oral intake for >48 hours or aggressive rehydration indicated; deep vein thrombosis, intervention indicated; hypotension, symptomatic with intravenous fluids indicated; hypoxia, pulse oximetry <90%; mental status changes, confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities; abdominal or noncardiac chest pain, causing inability to perform usual social and functional activities; sepsis, systemic antimicrobial treatment indicated and symptoms causing inability to perform usual social and functional activities or operative intervention other than simple incision and drainage indicated; septic shock is a Grade 4 infection event.

[a]All 4 patients who experienced Grade ≥3 anemia (2 assigned to presatovir, 2 to placebo) were taking ribavirin.

Several study design and patient population characteristics could have contributed to the failure of presatovir to meet the prespecified efficacy endpoints in this trial. Presatovir treatment may not be effective late in the disease course. The median duration of symptoms before the first dose of presatovir was 6 days (mean, 5 days). By contrast, healthy adults with established experimental RSV infections had reduced viral load and clinical symptom severity when treated with presatovir at or before RSV symptom onset in the Phase 2a RSV challenge study.[18] Similarly, the anti-influenza drugs, oseltamivir and baloxavir, are most effective when administered within 48 hours of symptom onset.[25-28] Acknowledging the potential for detecting an efficacy signal only when presatovir was used early after infection, the coprimary endpoint evaluated change in RSV load among the subset of the FAS whose duration of symptoms at baseline was at the median or shorter of the value for the overall population. No significant treatment effect was observed in this subpopulation, although this approach is limited by the accuracy of patient-reported symptom duration. As a fusion inhibitor, presatovir is best poised to interrupt the viral life cycle at an early stage and would not be expected to inhibit virus production in cells that are already infected. Therefore, presatovir's mechanism of action may offer only an incremental additive antiviral effect in symptomatic patients with a relatively intact immune system, in whom any potential benefit is masked as patients improve regardless of treatment. Alternatively, presatovir's potential treatment effect could be limited to more severely immunosuppressed populations in whom its antiviral effects become the predominant mechanism to inhibit and clear ongoing viral replication. This was suggested in a subgroup analysis of a recent Phase 2 randomized controlled trial examining presatovir efficacy in hematopoietic cell transplant recipients with isolated RSV upper respiratory tract infection and significant baseline lymphopenia (<200 cells/μl).[23] In contrast with the study of those with hematopoietic cell transplant, this trial enrolled patients regardless of RSV location in the respiratory tract (upper and lower), with the great majority not displaying the sort of immunocompromised state associated with significant lymphopenia at baseline (2 patients, both randomized to presatovir).

Table 4 Grade ≥3 Laboratory Abnormalities, Safety Analysis Set

	Presatovir (n = 40)[a]	Placebo (n = 20)[a]
Patients with ≥1 postbaseline value, n	39	19
Grade ≥3 laboratory abnormality	18 (46)	5 (26)
Grade 3	16 (41)	1 (5)
Grade 4	2 (5)	4 (21)
Grade ≥3 hematologic abnormalities		
Hemoglobin	8 (21)	3 (16)
Lymphocytes	4 (10)	3 (16)
Neutrophils, segmented	0	1 (5)
Grade ≥3 chemistry abnormalities		
Fasting glucose increased[b]	1 (6)	0
Nonfasting glucose increased[c]	6 (16)	0

Data are shown as n (%) unless otherwise indicated.

Definitions of severity Grade 3 are hemoglobin, <7.5 g/dl; lymphocytes, <500/mm^3; neutrophils, <750 mm^3; fasting glucose increased, >250 mg/dl; nonfasting glucose increased, >250 mg/dl. Not all laboratory abnormalities were reported as adverse events by the investigator.

[a]At least 1 postbaseline value available.

[b]Presatovir, n = 18; placebo, n = 10.

[c]Presatovir, n = 38; placebo, n = 19.

Another possible explanation is that the study endpoints may not reflect potential benefits of presatovir in lung transplant recipients. The FLU-PRO score, while the best validated symptom score available, has not been validated in patients with RSV. Additionally, the mean baseline FLU-PRO scores (Table 1) in both treatment groups were only approximately 2 on a scale of 0 to 4, suggesting absence of severe symptoms at baseline.[29] Although no change in FEV_1(% predicted) was detected after presatovir versus placebo treatment, this endpoint was only measured at randomization and day 28 and contained significant variability among patients, as expected in a study this size.

In conclusion, presatovir demonstrated safety but not efficacy for viral load reduction, symptom improvement, or prevention of lung function deterioration in lung transplant recipients infected with RSV. Although this study did not achieve its endpoints, it points to important considerations for design of future studies of antivirals in lung transplant recipients. Infection with CARVs, including RSV, remains a significant complication of lung transplantation and contributes to the relatively poor long-term survival of

recipients.[1,3-5] Effective therapies to prevent or mitigate these infections will address an important unmet need with potential to improve both short- and long-term clinical outcomes after lung transplantation.

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Authors' contributions

JG, TRW, and MZ contributed to the first draft of the manuscript. JG, FT, TH, GD, DD, CK, RR, RW, VA, RK, MB, CN, and ARG were study investigators. DP and RJ performed virology analyses. PG performed pharmacokinetic analyses. YG performed statistical analyses. All authors critically reviewed the manuscript, provided substantive comments, and approved the final draft for submission.

Data availability statement

Data are available on reasonable request. Anonymized individual patient data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use. The full data sharing policy for Gilead Sciences, Inc., can be found at https://www.gileadclinicaltrials.com/transparency-policy/.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2023.01.013.

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