A phase 2, randomized, double-blind, placebo-controlled trial of presatovir for the treatment of respiratory syncytial virus upper respiratory tract infection in hematopoietic-cell transplant recipients

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Summary

Presatovir treatment was safe but did not improve viral or clinical outcomes in hematopoietic-cell transplant recipients with respiratory syncytial virus upper respiratory tract infection. Exploratory analyses suggest clinical benefit in hematopoietic-cell transplant patients with lymphopenia at presentation.

Abstract

Background: Hematopoietic-cell transplant (HCT) recipients are at risk for severe respiratory syncytial virus (RSV) infection. We evaluated the RSV fusion inhibitor presatovir in a randomized, double-blind phase 2 trial in HCT recipients with RSV upper respiratory tract infection (URTI).

Methods: Patients were randomized, stratified by lymphopenia (<200/μL) and ribavirin use, to receive oral presatovir 200 mg or placebo on days 1, 5, 9, 13, and 17, and followed through day 28. The coprimary efficacy endpoints were time-weighted average change in nasal RSV viral load between days 1 and 9, and proportion of patients developing lower respiratory tract complications (LRTC) through day 28.

Results: From January 23, 2015, to June 16, 2017, 189 patients were randomized (96 presatovir, 93 placebo). Presatovir vs placebo treatment did not significantly affect (prespecified $\alpha = 0.01$) time-weighted average decline in RSV viral load from day 1 to 9 (treatment difference: −0.33 $\log_{10}$ copies/mL; 95% CI: −0.64, −0.02 $\log_{10}$ copies/mL; p = 0.040) or progression to LRTC (11.2% vs 19.5%; odds ratio [95% CI], 0.50 [0.22, 1.18]; p = 0.11). In post hoc analysis among patients with lymphopenia, presatovir vs placebo treatment decreased LRTC development by day 28 (2/15 [13.3%] vs 9/14 [64.3%], p = 0.008). Adverse events were similar for patients receiving presatovir vs placebo.

Conclusions: Presatovir had a favorable safety profile in adult HCT recipients with RSV but did not achieve the coprimary endpoints. Exploratory analyses suggest an antiviral effect among patients with lymphopenia.

Keywords: presatovir, respiratory syncytial virus, hematopoietic cell transplant

Clinical trials registration: www.clinicaltrials.gov, NCT02254408; EudraCT, #2014-002474-36

Introduction

Adult recipients of autologous or allogeneic hematopoietic-cell transplants (HCT) are at high risk for respiratory syncytial virus (RSV) infection and associated morbidity and mortality. Up to 17% of HCT recipients may develop RSV infection [1-7], of whom 17% to 84% progress from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) [2, 3, 5, 7-14]. Progression to LRTI often requires hospitalization, during which oxygen supplementation and intensive care may be required; RSV LRTI is associated with increased mortality, ranging from 6% to 35% [2, 4, 8, 9, 15-20]. Survivors of respiratory viral infection after HCT may have long-term airflow decline [15, 21].

Currently, there are no effective vaccines or approved antiviral agents for RSV infection in HCT recipients. Aerosolized ribavirin (Virazole®) is approved for treatment of RSV infection in young children but is not used in general pediatric practice because of efficacy and tolerability concerns and the complexity of the required specialized aerosol delivery system [22-24]. A randomized, placebo-controlled trial of aerosolized ribavirin attempted in HCT recipients recruited only 14 subjects in 5 years due to slow accrual [25]. Epidemiologic studies and a single-center retrospective analysis suggest ribavirin-based therapy has some efficacy for preventing RSV-associated morbidity or mortality in high-risk HCT recipients [6, 14, 18]. However, these results are from uncontrolled retrospective studies and ribavirin benefit remains unconfirmed. Thus, there remains a significant unmet medical need for safe, convenient, and effective treatments for RSV infection.

Presatovir (GS-5806) is an oral RSV fusion inhibitor with potent and selective anti-RSV activity in vitro and a terminal half-life of ~34 hours [26]. When tested in a human challenge study of healthy volunteers, presatovir reduced RSV viral load and severity of clinical disease [26]. In the current study, we evaluated presatovir safety, tolerability, and efficacy among HCT recipients with RSV URTI.

Patients and methods

Patients and study design

This phase 2, randomized, double-blind, placebo-controlled, 2-group, parallel study recruited allogeneic or autologous HCT recipients with positive local RSV test results, 18 to 75 years of age, from 43 centers in 9 countries (**Appendix**). Patients with new or worsening respiratory symptoms for ≤7 days, diagnosed with RSV infection of the upper respiratory tract for ≤6 days, and without new abnormalities on a chest X-ray obtained <48 hours from start of study treatment, were eligible to participate. Patients with specified documented respiratory virus coinfection within 7 days from start of study treatment or other significant respiratory or systemic infection were excluded. Full eligibility criteria are provided in **Supplemental methods**.

This study followed International Conference on Harmonisation requirements and the principles of the Declaration of Helsinki, and was approved by local ethics committees. Written informed consent was obtained from patients or legally responsible representatives. Protocol amendments and Data Monitoring Committee activities are described in **Supplemental methods.** The trial was registered at ClinicalTrials.gov (NCT02254408) and EudraCT (2014-002474-36) before enrolment began.

Randomization and masking

Patients were randomized (1:1) to receive presatovir or placebo, stratified centrally by lymphopenia (lymphocyte count <200 cells/mm^3 within 6 days of screening) and prescribed use of ribavirin by any route of administration at randomization. Study treatment assignment was provided by an interactive web response system (Bracket Global, Wayne, PA, USA). Patients, all study staff, and study sponsor were blinded to study treatment. Allocation was concealed by use of presatovir and placebo tablets identical in appearance.

Procedures

Patients received presatovir 200 mg (4 × 50 mg tablets) or placebo orally or by nasogastric tube during study visits on days 1, 5, 9, 13, and 17 (± 24 hours), and were followed through study day 28. Based on human pharmacokinetic and pharmacodynamic studies [26], this regimen was predicted to provide plasma concentrations >4-fold over requirements to inhibit replication of >95% of tested RSV isolates. Patients with detectable RSV by reverse transcription quantitative polymerase chain reaction (RT-qPCR) on day 22 could participate in an optional extended weekly follow-up through day 56. A detailed schedule of study assessments and procedures is provided in **Supplemental Table 1**.

Plasma pharmacokinetic methods are described in **Supplemental methods**. For virology assessments, bilateral intranasal swabs were obtained using mid-turbinate adult flocked swabs (Copan Diagnostics, Murrieta, CA, USA), at each study visit. Samples were analyzed using RT-qPCR to measure RSV viral load, RSV *F* gene sequencing to detect development of resistance, and a multiplex assay to identify respiratory viral coinfections. All nasal samples were analyzed at central laboratories; further methodological details are provided in **Supplemental methods.** Chest X-rays or computed tomography scans were performed per standard care in patients with suspected lower respiratory tract complications (LRTC). Imaging studies and results of local microbiology tests were collected for review by the endpoint adjudication committee (EAC).

Clinical safety assessments included vital signs, body weight, and oxygen saturation by pulse oximetry; laboratory safety assessments included complete blood cell counts and liver enzyme measurements. Cardiac safety was assessed via electrocardiograms and troponin testing (per US Food and Drug Administration [FDA] cardiac monitoring requirements) on days 1, 17, and 28. Additional safety assessments included evaluation of adverse events (AEs) and documentation of concomitant medications.

Outcomes

The coprimary endpoints were time-weighted average change in nasal RSV viral load measured by RT-qPCR ($\log_{10}$ copies/mL) between day 1 and day 9, and proportion of patients who developed LRTC—defined as primary RSV LRTI, secondary bacterial LRTI, lower respiratory tract infection due to unusual pathogens, or lower respiratory tract complication of unknown etiology—from day 1 through day 28. Development of LRTC was determined by an independent blinded EAC (details in **Supplemental methods**). The secondary efficacy endpoint was proportion of patients who

died or developed respiratory failure requiring invasive mechanical ventilation from day 1 to day 28. Safety was assessed from AEs, vital signs, electrocardiograms, and clinical laboratory test results.

Statistical analysis

Assuming a time-weighted average change in RSV viral load from day 1 to day 9 of −1 $\log_{10}$ copies/mL with standard deviation [SD] of 2 $\log_{10}$ and an LRTC event rate of 30% in patients receiving placebo, 100 patients per treatment group were planned to provide >80% power to detect a ≥1-$\log_{10}$ decrease in the first coprimary endpoint with a 2-sided α of 0.01 and >90% power to detect a ≥20% reduction in the second coprimary endpoint with a 2-sided α of 0.04 in patients receiving presatovir relative to placebo.

The efficacy population included patients who received ≥1 dose of presatovir with quantifiable nasal RSV viral load on day 1. The coprimary and secondary endpoints were analyzed in the efficacy population, in prespecified subgroups defined by the randomization stratification factors (lymphopenia and ribavirin use on day 1), and post hoc in subgroups defined by duration of RSV symptoms, hospitalization status, time after HCT, and graft-vs-host disease (GVHD) status on day 1. The safety population included patients who received ≥1 dose of presatovir.

The first coprimary analysis was performed by parametric analysis of covariance (ANCOVA) with baseline viral load and randomization stratification factors as covariates. The second coprimary analysis and secondary efficacy analysis were performed using 2-sided Cochran-Mantel-Haenszel tests stratified by lymphopenia (<200 cells/mm^3) and intent to use ribavirin at baseline. If the number of events was small, the Fisher exact method was applied. A fallback approach was employed to control the Type I error rate at 0.05 across the coprimary and secondary endpoints (details in **Supplemental methods**). Subgroup analyses were performed using the corresponding ANCOVA model for the first coprimary endpoint and the Fisher exact test with 95% confidence interval (CI) based on the Clopper-Pearson method for the second coprimary and secondary endpoints.

Results

Patients

From January 23, 2015, to June 16, 2017, 213 patients were screened for eligibility; 24 patients were excluded, the majority (n = 14) of whom did not have documented RSV infection of the upper respiratory tract. A total of 189 patients were randomized to study treatment (96 presatovir, 93 placebo), and 185 received ≥1 dose of study drug (95 presatovir, 90 placebo; **Figure 1**). The sponsor halted the study on September 20, 2017, before achieving the planned 200 subject enrollment, because an unplanned interim analysis before database lock by an unblinded team indicated results were unlikely to differ if enrollment was extended through another RSV season. Important protocol deviations are described in **Supplemental results** and **Supplemental Table 2**. Overall, 168 (90.8%) patients (88 presatovir, 80 placebo) completed study drug through day 17 (**Figure 1**).

Patient demographic and baseline clinical characteristics were generally well balanced between treatment groups except for hospitalization of a larger number of patients receiving presatovir compared with placebo at beginning of study treatment (43.2% vs 26.7%) (**Table 1**). The majority of treated patients (146/185, 78.9%) underwent allogeneic HCT, and 69/185 (37.3%) had

GVHD at baseline. Lymphopenia was noted in 29 (15.7%) patients, and 44 (23.8%) patients were treated with aerosolized or oral ribavirin at baseline (**Table 1**).

Efficacy

Figure 2A–B shows absolute RSV viral load and change from baseline at each study visit. Despite adequate plasma concentrations (**Supplemental results** and **Supplemental Table 3**), presatovir did not significantly (prespecified $\alpha = 0.01$) reduce time-weighted average change in RSV viral load from day 1 to day 9 compared with placebo (mean [SD], −1.26 [0.964] $\log_{10}$ copies/mL vs −0.91 [1.145] $\log_{10}$ copies/mL; treatment difference, −0.33 $\log_{10}$ copies/mL; 95% CI: −0.64, −0.02 $\log_{10}$ copies/mL; p = 0.040). Development of LRTC through day 28 is shown in **Figure 3**. Compared with placebo, presatovir did not significantly reduce the proportion of patients in the efficacy population who developed LRTC from day 1 through day 28 (10/89 [11.2%] on presatovir vs 17/87 [19.5%] on placebo, p = 0.11, $\alpha = 0.04$). The majority of LRTC events were adjudicated as unknown etiology (presatovir, 7/10 [70%]; placebo, 15/17 [88%]). Two events in each treatment arm were attributed to primary RSV LRTI, and 1 event in the presatovir arm was adjudicated as secondary bacterial infection. Sensitivity analyses are reported in **Supplemental results**. Death or respiratory failure requiring mechanical ventilation through day 28 occurred in 5/89 (5.6%) patients receiving presatovir and 5/87 (5.7%) patients receiving placebo (p = 0.98) (**Figure 4**).

In prespecified subgroup analyses, presatovir numerically decreased the proportion of patients who developed LRTC from day 1 through day 28 relative to placebo among patients with baseline lymphopenia (2/15 [13.3%] vs 9/14 [64.3%], p = 0.008) and those not receiving ribavirin (4/64 [6.3%] vs [12/68] 17.6%, p = 0.061) (**Table 2** and **Supplemental Tables 4** and **5**). Proportions of patients receiving presatovir vs placebo who developed LRTC were similar among patients without baseline lymphopenia and in patients without ribavirin use at baseline (**Supplemental Tables 4** and **5**). Overall, ribavirin use was higher among patients who developed LRTC (37.0%) vs those who did not (23.5%). Patients hospitalized at baseline had a numerically higher rate of LRTC relative to those who started treatment as outpatients (18/63 [28.6%] vs 9/113 [8.0%]), and hospitalization status was imbalanced between the presatovir and placebo arms at baseline. The effects of presatovir vs placebo treatment on time-weighted average change in viral load from day 1 to day 9 and occurrence of death or respiratory failure requiring mechanical ventilation through day 28 were similar between patients hospitalized or not hospitalized on day 1 (**Supplemental Table 6**). However, treatment with presatovir relative to placebo was associated with a 28% lower LRTC event rate among patients hospitalized on day 1 (**Table 2** and **Supplemental Table 6**). In other post hoc analyses, the proportion of patients who developed LRTC was numerically lower following presatovir vs placebo treatment among patients with shorter than median symptom duration (≤4 days) and ≤365 days since HCT (**Table 2** and **Supplemental Tables 6–9**). A post hoc multivariate Cox proportional hazard model for time to LRTC through day 28 in patients receiving presatovir vs placebo, adjusted for lymphopenia and ribavirin use on day 1, enrollment site, and hospitalization status on day 1, yielded an adjusted hazard ratio of 0.44 (95% CI: 0.19, 0.99; p = 0.091). Optional extended RSV monitoring and serologic responses are presented in **Supplemental results**. Patients with treatment-emergent substitutions in RSV F associated with presatovir resistance had numerically smaller change in time-weighted average RSV load, but not worse clinical outcomes, relative to those with wild-type F sequences; such substitutions occurred at significantly higher frequency in patients with vs without lymphopenia (**Supplemental results, Supplemental Tables 10–11)**.

Safety

Overall, AEs were reported in 76 (80%) patients receiving presatovir and 78 (86.7%) patients receiving placebo, while 18 (18.9%) patients receiving presatovir and 23 (25.6%) patients receiving placebo had SAEs. The most common AEs were diarrhea (15.8%), nausea (13.7%), and pyrexia (12.6%) in patients receiving presatovir; and diarrhea (15.6%), vomiting (13.3%), and nausea (11.1%) in patients receiving placebo (**Table 3**). Most grade 3 or 4 AEs and SAEs occurred less frequently in patients receiving presatovir except for pyrexia as an SAE in 4 (4.2%) patients and GVHD in the gastrointestinal tract as an SAE, grade 3 pyrexia, and grade 4 pneumonia in 2 (2.1%) patients each (**Supplemental Tables 12–13**). There was no imbalance in new electrocardiogram findings or troponin abnormalities between the 2 groups. Overall, 6 patients died during the study; 2 (2.1%) and 4 (4.4%) treated with presatovir and placebo, respectively. Two patients receiving presatovir died from gastrointestinal hemorrhage and pneumonia (1 each), and 4 patients receiving placebo died from LRTI, pneumonia, recurrent acute myeloid leukemia, and intracranial hemorrhage (1 each).

Discussion

This is the largest randomized, double blind, placebo-controlled clinical trial to date for treatment of allogeneic and autologous HCT recipients with RSV URTI. Presatovir treatment did not meet the coprimary endpoints of greater time-weighted average change in RSV viral load from day 1 to 9 and reduced development of LRTC through day 28, but was well tolerated with a comparable safety profile relative to placebo. In a post hoc analysis of patients with lymphopenia, the proportion who developed LRTC through day 28 was 51% lower following treatment with presatovir vs placebo; other post hoc analyses also indicated trends toward a treatment effect on LRTC. The results suggest lessons for design of future clinical trials of drugs for RSV or other respiratory viruses in transplant recipients or other immunocompromised patients.

Among healthy adults with established experimental RSV infection, presatovir vs placebo treatment significantly reduced RSV load and clinical severity [26]. The current study did not reproduce these findings, most likely because challenge study participants received presatovir at or before symptom onset, whereas current study patients were treated after a median of 4 days of symptoms. Exploratory analysis revealed trends toward reduced LRTC rates following presatovir vs placebo treatment of patients with median or shorter symptom duration (**Table 2**). Future studies of anti-RSV drugs, particularly fusion inhibitors, should explore whether earlier therapy improves treatment outcomes.

Some transplant centers treat RSV infection in immunocompromised patients with oral or aerosolized ribavirin despite lacking randomized clinical trial evidence [1]. Ribavirin use in RSV-infected HCT recipients, especially those with URTI, is associated with more favorable outcomes in retrospective studies [6, 8, 27]. In the current study, placebo-treated patients who received ribavirin had a higher LRTC progression rate compared with those who did not (26% vs 18%), and all patients who developed LRTC used ribavirin more frequently (37.0%) relative to those without progression (23.5%). As this was not a randomized controlled study of ribavirin treatment, these observations require confirmation.

The observed rate of LRTC was lower than the expected 30% used for sample size calculation, and day 28 mortality was very low (~3%) relative to previous retrospective studies [2, 7, 10], possibly due to recruitment of less severely ill patients who would not typically undergo RSV testing. Lymphopenia is a well-described risk factor for LRTC in RSV-infected HCT recipients [9, 12, 14, 28], as observed in the current study (64% vs 11% in placebo-treated patients with vs without lymphopenia). Treatment with presatovir reduced development of LRTC in patients with lymphopenia—a surrogate marker of impaired T cell or humoral immunity—possibly because robust immune responses masked treatment effect by improving outcomes regardless of treatment. Furthermore, lymphopenia could influence respiratory immunopathology, providing better evidence of presatovir's antiviral efficacy.

Perhaps the most important question is whether all-cause LRTC rate is a clinically relevant endpoint, and if so, whether the observed trends are clinically meaningful. Respiratory failure and mortality are more clinically significant, but their rates in this study suggest the sample size required would be prohibitive, especially for HCT recipients. The current study endpoint of LRTC included multiple etiologies because RSV URTI may predispose patients to secondary infections—eg, by disrupting mucociliary function [29, 30]—so treatment could prevent secondary as well as primary LRTI. Furthermore, any LRTC is a clinically significant event that may prolong hospitalization, necessitate intensive clinical care (including empiric antimicrobial treatment), and, potentially, result in death. Only a minority of LRTC in this study were adjudicated as primary RSV LRTI—likely due to other etiologies as well as lack of lower respiratory tract samples for confirmation of RSV—underscoring the potential importance of nonviral pulmonary events in HCT recipients with RSV infection. Determining the cause of each LRTC event in a clinical trial, while ideal, requires invasive procedures (eg, bronchoscopy or lung biopsy) that could pose significant patient risk and are not globally mandated by the current clinical standard of care. Thus, radiographic confirmation corroborated by clinical data with central blinded adjudication, as used here, may be the best approach to classify LRTI. Whether the near-50% relative reduction in LRTC events is clinically meaningful, despite lacking statistical significance, is left to interpretation. The consistent trends toward a treatment effect in exploratory analyses need confirmation in future studies.

In summary, this study provided important lessons for design of future clinical trials of drugs for RSV and other respiratory virus infections in HCT recipients. Although the coprimary endpoints were not achieved, presatovir treatment was associated with trends toward antiviral effect and clinical benefit. Similar future trials should judiciously select suitable at-risk patients (ie, patients with lymphopenia, neutropenia, GVHD, or receiving corticosteroids) to maximize potential benefits. Because LRTC increases mortality risk, prompt diagnosis, early intervention for RSV URTI in high-risk patients, and effective antiviral agents are imperative to improve clinical outcomes.

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Potential conflicts of interest

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Table 1. Baseline Characteristics and Demographics (Safety Population)

	Patients given presatovir (n = 95)	Patients given placebo (n = 90)	Total (N = 185)
Age, years, median (min, max)	54 (22, 70)	53 (20, 75)	54 (20, 75)
Male sex at birth	55 (57.9)	55 (61.1)	110 (59.5)
Ethnic origin			
White	66 (69.5)	70 (77.8)	136 (73.5)
Asian	13 (13.7)	9 (10.0)	22 (11.9)
African American or African	6 (6.3)	3 (3.3)	9 (4.9)
Other	2 (2.1)	0	2 (1.1)
Not documented	8 (8.4)	8 (8.9)	16 (8.6)
Hispanic or Latino	8 (8.4)	6 (6.7)	14 (7.6)
Body mass index, kg/m^2, median (min, max)[a]	25.0 (13.6, 49.8)	24.3 (16.8, 46.0)	24.6 (13.6, 49.8)
Lymphopenia (<200 cells/μL) at randomization	15 (15.8)	14 (15.6)	29 (15.7)
Ribavirin use at randomization	25 (26.3)	19 (21.1)	44 (23.8)
Route of administration[b]			
Aerosolized	4/25 (16.0)	5/19 (26.3)	9/44 (20.5)
Oral	21/25 (84.0)	14/19 (73.7)	35/44 (79.5)
RSV type			
RSV A	44 (46.3)	43 (47.8)	87 (47.0)
RSV B	44 (46.3)	43 (47.8)	87 (47.0)
Both RSV A and RSV B	2 (2.1)	1 (1.1)	3 (1.6)
Undetectable	5 (5.3)	1 (1.1)	6 (3.2)
Missing	0	2 (2.2)	2 (1.1)
Nasal RSV virus load, log_{10} copies/mL[c], median (min, max)	7.00 (0.00, 8.51)	7.10 (0.00, 8.94)	7.00 (0.00, 8.94)
Respiratory symptom duration before day 1, days, median (min, max)	4 (1, 7)	4 (1, 10)[d]	4 (1, 10)
Oxygen saturation, %, median (min, max)	96 (87, 100)	96 (90, 100)	96 (87, 100)
Smoking history			
Never	52 (54.7)	52 (57.8)	104 (56.2)
Former	40 (42.1)	35 (38.9)	75 (40.5)
Current	3 (3.2)	3 (3.3)	6 (3.2)
Other respiratory viruses detected			
Rhinovirus or enterovirus	2 (2.1)	3 (3.3)	5 (2.7)
Adenovirus	1 (1.1)	1 (1.1)	2 (1.1)
Coronavirus 229E	0	3 (3.3)	3 (1.6)
Coronavirus HKU1	1 (1.1)	1 (1.1)	2 (1.1)
Coronavirus NL63	0	1 (1.1)	1 (0.5)
Coronavirus OC43	1 (1.1)	0	1 (0.5)
Parainfluenza 1	1 (1.1)	0	1 (0.5)
Parainfluenza 2	1 (1.1)	0	1 (0.5)
Hospitalized on day 1	41 (43.2)	24 (26.7)	65 (35.1)
Unplanned hospitalization	27 (65.9)	11 (45.8)	38 (58.5)
Planned hospitalization	14 (34.1)	13 (54.2)	27 (41.5)
Hospitalization related to RSV infection	24 (58.5)	8 (33.3)	32 (49.2)
Hospitalization days before day 1, median (min, max)	0 (0, 48)	0 (0, 75)	0 (0, 75)
Hematopoietic-cell transplant type			
Allogeneic HCT	72 (75.8)	74 (82.2)	146 (78.9)
Autologous HCT	23 (24.2)	16 (17.8)	39 (21.1)

Time from HCT to day 1, days, median (min, max)[e]	278 (2, 4000)	275 (1, 7538)	278 (1, 7538)
Underlying hematologic disease			
Acute leukemia	44 (46.3)	49 (54.4)	93 (50.3)
Myeloma	24 (25.3)	13 (14.4)	37 (20.0)
Lymphoma	11 (11.6)	14 (15.6)	25 (13.5)
Refractory anemia	1 (1.1)	0	1 (0.5)
Chronic lymphocytic leukemia	4 (4.2)	1 (1.1)	5 (2.7)
Other	15 (15.8)	13 (14.4)	28 (15.1)
Acute or chronic graft-vs-host disease			
Yes	33 (34.7)	36 (40.0)	69 (37.3)
No	37 (38.9)	37 (41.1)	74 (40.0)
Not applicable, autologous HCT	23 (24.2)	16 (17.8)	39 (21.1)
Unknown	2 (2.1)	1 (1.1)	3 (1.6)
HCT donor type			
Unrelated	44 (46.3)	35 (38.9)	79 (42.7)
Matched-related	24 (25.3)	32 (35.6)	56 (30.3)
Mismatched-related	3 (3.2)	6 (6.7)	9 (4.9)
Autologous	23 (24.2)	17 (18.9)	40 (21.6)
Unknown	1 (1.1)	0	1 (0.5)
Stem-cell source			
Peripheral blood	72 (75.8)	75 (83.3)	147 (79.5)
Bone marrow	11 (11.6)	8 (8.9)	19 (10.3)
Cord blood	7 (7.4)	5 (5.6)	12 (6.5)
Other	2 (2.1)	1 (1.1)	3 (1.6)
Unknown	3 (3.2)	1 (1.1)	4 (2.2)
Recipient CMV seropositive	57 (60.0)	60 (66.7)	117 (63.2)

Data are presented as n (%) unless otherwise noted.

[a]For this value, n = 94 for presatovir and n = 184 total.

[b]For this value, n = 10 for presatovir, n = 11 for placebo, and n = 21 total.

[c]For this value, n = 88 for placebo and n = 183 total.

[d]Protocol deviation related to onset of respiratory symptoms was recorded for 1 placebo-treated patient.

[e]For this value, n = 94 for presatovir and n = 184 total.

CMV, cytomegalovirus; HCT, hematopoietic cell transplant; RSV, respiratory syncytial virus.

Table 2. Post Hoc Analyses of LRTC Development Through Day 28 by Presence of Lymphopenia, Duration of Symptoms, Hospitalization Status, and Time After HCT at Day 1

Patients developing LRTC, n/N (%)	Presatovir	Placebo	Treatment difference (95% CI), %	Nominal p value[a]
Lymphopenia (<200 cells/μL)	2/15 (13.3)	9/14 (64.3)	−51.0 (−77.8, −13.1)	0.008
No ribavirin use	4/64 (6.3)	12/68 (17.6)	−11.4 (−28.1, 5.9)	0.061
Symptom duration ≤ median (4 days)[b]	5/48 (10.4)	13/49 (26.5)	−16.1 (−35.4, 3.4)	0.066
Hospitalized on day 1	7/39 (17.9)	11/24 (45.8)	−27.9 (−50.9, −2.4)	0.023
≤365 days after HCT	5/50 (10.0)	12/47 (25.5)	−15.5 (−34.8, 4.7)	0.061

Data for other efficacy endpoints and subgroups are provided in **Supplemental Tables 4–9**.

[a]p values were calculated using the Fisher exact test.

[b]The median duration of respiratory symptoms on day 1 in the efficacy population was 4 days.

CI, confidence interval; HCT, hematopoietic cell transplant; LRTC, lower respiratory tract complications.

Table 3. Adverse Events and Laboratory Abnormalities Reported in ≥4 Patients in a Treatment Group in the Safety Population

Adverse event	Presatovir (n = 95)	Placebo (n = 90)
Any adverse event	76 (80.0)	78 (86.7)
Serious adverse events	18 (18.9)	23 (25.6)
Grade ≥3 adverse events	22 (23.2)	21 (23.3)
Diarrhea	15 (15.8)	14 (15.6)
Nausea	13 (13.7)	10 (11.1)
Vomiting	11 (11.6)	12 (13.3)
Pyrexia	12 (12.6)	9 (10.0)
Decreased appetite	7 (7.4)	6 (6.7)
Epistaxis	9 (9.5)	3 (3.3)
Headache	5 (5.3)	7 (7.8)
Pneumonia	4 (4.2)	7 (7.8)
Acute kidney injury	3 (3.2)	7 (7.8)
Asthenia	3 (3.2)	7 (7.8)
Cough	6 (6.3)	4 (4.4)
Dizziness	7 (7.4)	3 (3.3)
Rash	4 (4.2)	5 (5.6)
Fatigue	4 (4.2)	4 (4.4)
Neutropenia	3 (3.2)	5 (5.6)
Abdominal pain	3 (3.2)	4 (4.4)
Dyspnea	3 (3.2)	4 (4.4)
Febrile neutropenia	2 (2.1)	5 (5.6)
Hypokalemia	4 (4.2)	3 (3.3)
Anemia	5 (5.3)	1 (1.1)
Insomnia	4 (4.2)	2 (2.2)
Edema peripheral	2 (2.1)	4 (4.4)
Dysgeusia	1 (1.1)	4 (4.4)
Fall	1 (1.1)	4 (4.4)
Fluid overload	4 (4.2)	1 (1.1)
Hypertension	4 (4.2)	1 (1.1)
Pain in extremity	4 (4.2)	1 (1.1)
Dysuria	4 (4.2)	0
Sinusitis	4 (4.2)	0

Data are shown as n (%).

Figure legends

Figure 1. Patient disposition from enrollment through analysis. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and URT, upper respiratory tract.

Figure 2. Nasal RSV viral load at each study visit in the efficacy population. Panel **A**) shows median nasal RSV viral load, and panel **B**) shows median change from baseline in nasal RSV viral load at each study visit in patients treated with presatovir (closed circles, solid line) vs placebo (open circles, dashed line). Error bars represent the interquartile range.

Figure 3. Development of LRTC in the efficacy population. LRTC rate at each study visit in patients treated with presatovir (solid line) vs placebo (dashed line) is shown.

Figure 4. Occurrence of death or respiratory failure requiring mechanical ventilation in the efficacy population. Event rate at each study visit in patients receiving presatovir (solid line) vs placebo (dashed line) is shown.

Figure 1

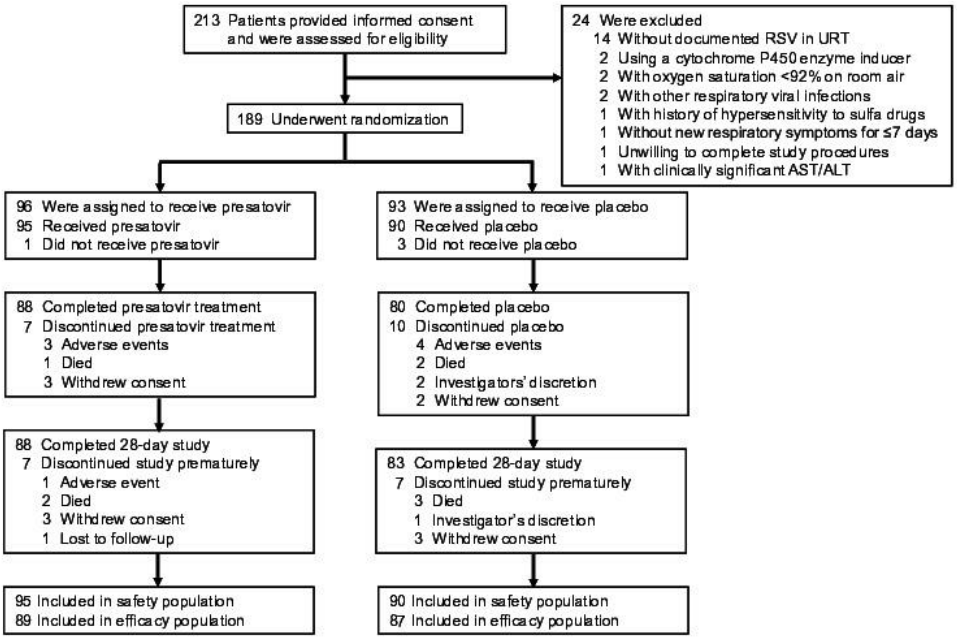


Figure 2

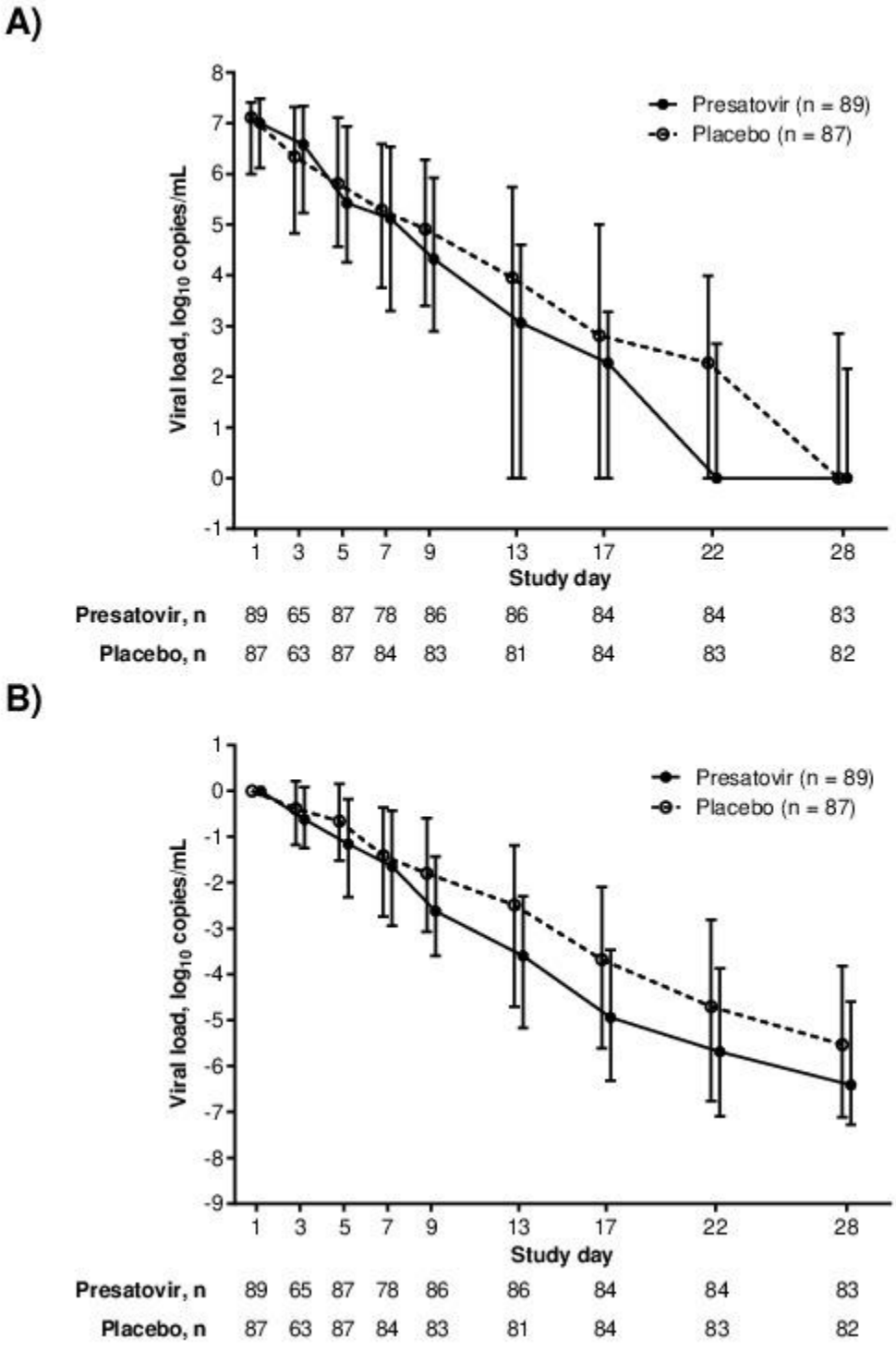
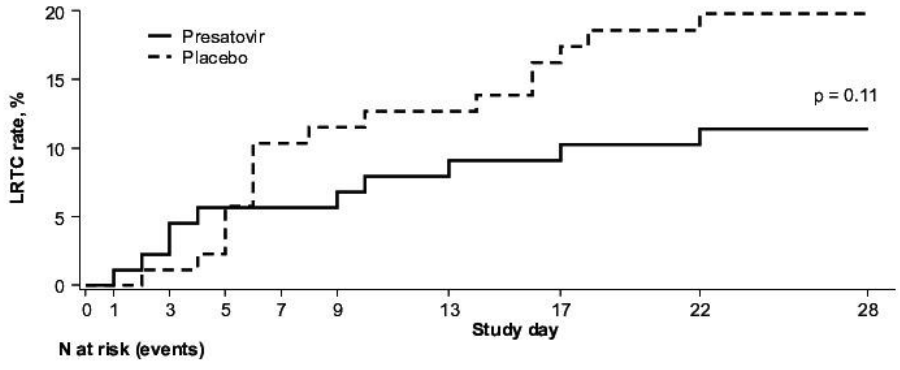


Figure 3



N at risk (events)										
Presatovir	89 (0)	89 (1)	86 (4)	83 (5)	83 (5)	83 (6)	80 (8)	79 (9)	77 (10)	76 (10)
Placebo	87 (0)	87 (0)	86 (1)	85 (5)	78 (9)	76 (10)	74 (11)	71 (15)	68 (17)	67 (17)

Figure 4