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ORIGINAL RESEARCH

Consistent Effects of Early Remdesivir on Symptoms and Disease Progression Across At-Risk Outpatient Subgroups: Treatment Effect Heterogeneity in PINETREE Study

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ABSTRACT

Introduction: In the PINETREE study, early remdesivir treatment reduced risk of coronavirus disease 2019 (COVID-19)-related hospitalizations or all-cause death versus placebo by 87% by day 28 in high-risk, non-hospitalized patients. Here we report results of assessment of heterogeneity of treatment effect (HTE) of early outpatient remdesivir, focusing on time from symptom onset and number of baseline risk factors (RFs).

Methods: PINETREE was a double-blind, placebo-controlled trial of non-hospitalized

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patients with COVID-19 who were randomized within 7 days of symptom onset and had ≥ 1 RF for disease progression (age ≥ 60 years, obesity [body mass index ≥ 30], or certain coexisting medical conditions). Patients received remdesivir intravenously (200 mg on day 1 and 100 mg on days 2 and 3) or placebo.

Results: In this subgroup analysis, HTE of remdesivir by time from symptom onset at treatment initiation and number of baseline RFs was not detected. Treatment with remdesivir reduced COVID-19-related hospitalizations independent of stratification by time from symptom onset to randomization. Of patients enrolled ≤ 5 days from symptom onset, 1/201 (0.5%) receiving remdesivir and 9/194 (4.6%) receiving placebo were hospitalized (hazard ratio [HR] 0.10; 95% confidence interval [CI] 0.01–0.82). Of those enrolled at > 5 days from symptom onset, 1/78 (1.3%) receiving remdesivir and 6/89 (6.7%) receiving placebo were hospitalized (HR 0.19; 95% CI 0.02–1.61). Remdesivir was also effective in reducing COVID-19-related hospitalizations when stratified by number of baseline RFs for severe disease. Of patients with ≤ 2 RFs, 0/159 (0.0%) receiving remdesivir and 4/164 (2.4%) receiving placebo were hospitalized; of those with ≥ 3 RFs, 2/120 (1.7%) receiving remdesivir and 11/119 (9.2%) receiving placebo were hospitalized (HR 0.16; 95% CI 0.04–0.73).

Conclusions: In the outpatient setting, benefit of remdesivir initiated within 7 days of symptoms appeared to be consistent across patients with RFs. Therefore, it may be reasonable to broadly treat patients with remdesivir regardless of comorbidities.

Trial Registration: ClinicalTrials.gov number NCT04501952.

Keywords: Remdesivir; COVID-19; Outpatients; Antiviral; SARS-CoV-2; Coronavirus

Key Summary Points

In the PINETREE study, early remdesivir treatment reduced risk of COVID-19-related hospitalizations or all-cause death versus placebo by 87% by day 28 in high-risk, non-hospitalized patients.

In this subgroup analysis of PINETREE, we assessed the heterogeneity of treatment effect (HTE) of early outpatient remdesivir, focusing on time from symptom onset and number of baseline risk factors.

Treatment with remdesivir reduced COVID-19-related hospitalizations across stratification by time from symptom onset to randomization and by number of baseline risk factors for severe disease.

Among outpatients, efficacy of remdesivir is maintained across time from symptom onset prior to treatment or number of risk factors, suggesting that treatment with remdesivir may broadly benefit patients who meet eligibility criteria.

INTRODUCTION

Early treatment of acute respiratory viral infections improves clinical outcomes and reduces mortality, including in coronavirus disease 2019 (COVID-19) [1–4]. Medical comorbidities, such as obesity, hypertension, diabetes mellitus, and immunosuppression, have been associated with increased risk of worse COVID-19 outcomes [5–10], an association observed in both unvaccinated and vaccinated patients [11]. A higher overall comorbidity burden has also been associated with increased risk for poor outcomes from COVID-19 [12, 13].

Remdesivir, a direct-acting nucleotide prodrug inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase, improves clinical outcomes in patients hospitalized with

moderate-to-severe COVID-19 disease, as well as in non-hospitalized patients with mild-to-moderate COVID-19 with increased risk of disease progression [14–16]. The PINETREE study is a phase 3, randomized, double-blind, placebo-controlled trial of non-hospitalized patients with COVID-19 with symptom onset within the previous 7 days and with ≥ 1 risk factor for disease progression (age ≥ 60 years, obesity, or specified coexisting medical conditions placing them at increased risk of progression). This trial showed that remdesivir treatment reduced the risk for COVID-19-related hospitalizations or all-cause mortality compared to placebo by 87% through day 28 in these high-risk, non-hospitalized patients with COVID-19 [16]. Further, in a post hoc analysis, 36.1% of remdesivir-treated subjects had alleviation of symptoms by day 14, as opposed to 20.0% of placebo-treated patients. Whether these effects are consistent across subgroups is not known; it has been hypothesized that earlier treatment is better than later treatment. Here we report results of the assessment of treatment effect heterogeneity of early outpatient remdesivir, with a focus on time from symptom onset and number of baseline risk factors.

METHODS

The details of the PINETREE study design and main results have been previously published [16]. Briefly, non-hypoxemic outpatients ≥ 12 years of age with ≥ 1 risk factor for progression to severe COVID-19 who tested positive for SARS-CoV-2 were randomized to receive intravenous infusion of remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo. Eligible patients had ≥ 1 ongoing symptom consistent with COVID-19, with onset of the first symptom within 7 days before randomization and had SARS-CoV-2 infection confirmed by a diagnostic assay (either reverse transcriptase polymerase chain reaction [RT-PCR] or direct antigen) within 4 days before screening. The primary efficacy endpoint was a composite of COVID-19-related hospitalization or death from any cause by day 28; the primary safety endpoint was any adverse event. Secondary endpoints included the composite of COVID-19-related medically attended visits (MAVs) or death from any cause by days 14 and 28, COVID-19-related hospitalization by days 14 and 28, the time-weighted average change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7, and the time to alleviation of baseline COVID-19 symptoms (with alleviation defined as reduction to mild or absent symptoms) as compared with those reported on the baseline electronic COVID-19-adapted InFLUenza Patient-Reported Outcome (FLU-PRO) Plus questionnaire (Evidera, PPD; Bethesda, MD, USA) completed before the first infusion. The trial was approved by the institutional review board or ethics committee at each trial site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. Prior to trial procedures, adult patients provided written informed consent; patient assent and parental or guardian consent were obtained if patients were younger than 18 years of age.

The heterogeneity of the treatment effect of remdesivir by time from symptom onset at treatment initiation and by number of baseline risk factors was evaluated by pooling data from all treatment groups using the Cox proportional-hazards model adjusted for treatment and stratification factors for residence in a skilled nursing facility (yes or no), age (< 60 years or ≥ 60 years), and country (USA or outside the USA). Time from symptom onset at treatment initiation (≤ 3 and > 3 days; ≤ 5 and > 5 days; and as continuous variable) and number of risk factors (1–2 and ≥ 3; 1–3 and ≥ 4; and as continuous variable) were included in the model separately. Time from symptom onset at treatment initiation was defined as number of days to first dose (study day 1). The protocol required randomization within 7 days of symptom onset; due to a few patients with > 1 day between randomization and first dose, time from symptom onset to first dose may have exceeded 7 days. The test of heterogeneity was assessed as the *P* value of the treatment*factor interaction term for the relevant endpoint. Multiple testing correction was done using the Benjamini–Hochberg false discovery rate (FDR)

adjustment at an overall significance level of 0.05 [17].

Additional post hoc analyses were performed in clinically relevant subgroups to evaluate the effect of remdesivir treatment on COVID-19-related hospitalizations, COVID-19-related MAVs, symptom alleviation based on FLU-PRO Plus questionnaire (completed any time before or on the first day of treatment), and nasopharyngeal SARS-CoV-2 viral load, stratified by time from symptom onset at treatment initiation (≤ 5 and > 5 days) and by number of baseline risk factors (1–2 versus ≥ 3). The FLU-PRO Plus symptom questionnaire was first available on October 21, 2020 (1 month after the start of enrollment). SARS-CoV-2 viral load was defined as the number of copies of SARS-CoV-2 from nasopharyngeal swabs with the use of RT-qPCR assay. Sequencing was conducted at baseline and SARS-CoV-2 lineage was determined by Pangolin Software v.3.1.11 using whole genome consensus sequences [18]. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported for COVID-19-related hospitalizations, COVID-19-related MAVs, and symptom alleviation for each stratification group using a Cox proportional-hazards model with the same adjustments as stated above (residence in a skilled nursing facility [yes or no], age [< 60 years or ≥ 60 years], and country [USA or outside the USA]). Event rates and rate ratios were also reported. The time-weighted average change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 was assessed using analysis of covariance, with baseline viral load as a covariate. Subsequent to the clinical trial, antiviral activity of remdesivir against SARS-CoV-2 Omicron subvariant clinical isolates was assessed by nucleoprotein enzyme-linked immunoassay (ELISA) in A549-hACE2-TMPRSS2 cells [19].

RESULTS

The demographic and baseline clinical characteristics were balanced between the 2 groups (Table 1); details have been previously reported [16]. Specific to these subanalyses, there were no major differences between mean number of

Table 1 Demographics and clinical characteristics of patients[a,b]

Characteristic	Remdesivir (*N* = 279)	Placebo (*N* = 283)
Age (years), mean ± SD	50 ± 15	51 ± 15
Age category, *n* (%)		
≥ 60 years	83 (29.7)	87 (30.7)
< 18 years	3 (1.1)	5 (1.8)
Female, *n* (%)	131 (47.0)	138 (48.8)
Residence in the USA, *n* (%)	264 (94.6)	267 (94.3)
Race or ethnic group[c]		
White	228 (81.7)	224 (79.2)
Black	20 (7.2)	22 (7.8)
American Indian or Alaska Native	15 (5.4)	21 (7.4)
Asian, Native Hawaiian, or Pacific Islander	7 (2.5)	7 (2.5)
Hispanic or Latinx	123 (44.1)	112 (39.6)
Other	3 (1.1)	2 (0.7)
Body mass index, mean ± SD	31.2 ± 6.7	30.8 ± 5.8
Coexisting conditions, *n* (%)		
Diabetes mellitus	173 (62.0)	173 (61.1)
Obesity	154 (55.2)	156 (55.1)
Hypertension	138 (49.5)	130 (45.9)
Chronic lung disease	67 (24.0)	68 (24.0)
Current cancer	12 (4.3)	18 (6.4)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)
Immunocompromised	14 (5.0)	9 (3.2)
Chronic kidney disease, mild or moderate	7 (2.5)	11 (3.9)
Chronic liver disease	1 (0.4)	1 (0.4)
Residence in skilled nursing facility, *n* (%)	8 (2.9)	7 (2.5)
Median duration of symptoms before first infusion, IQR (days)	5 (3–6)	5 (4–6)
Median time since RT-PCR confirmation of SARS-CoV-2, IQR (days)	2 (1–3)	3 (1–4)
Mean SARS-CoV-2 RNA nasopharyngeal viral load, $\log_{10}$ copies/mL, mean ± SD	6.31 ± 1.75	6.28 ± 1.79

Table 1 continued

Characteristic	Remdesivir (N = 279)	Placebo (N = 283)
No. of patients in FLU-PRO data set	169	165
Mean no. of baseline symptoms[d]	10.2	9.7
Patients with first infusion ≤ 5 days from symptom onset, *n*	201	194
Patients with first infusion ≥ 6 days from symptom onset, *n*	78	89
Patients with 1–2 risk factors at baseline, *n*	159	164
Patients with ≥ 3 risk factors at baseline, *n*	120	119

IQR interquartile range, *RT-PCR* reverse-transcriptase polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *FLU-PRO* InFLUenza patient-reported outcome, *SD* standard deviation

[a]From [16] [*N Engl J Med*, Early remdesivir to prevent progression to severe Covid-19 in outpatients, R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty, M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators, 386, 305–315 Copyright © (2021) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society]

[b]Plus–minus values are mean ± SD

[c]Race and ethnic group were reported by the patients. Patients could have had > 1 race or ethnic group

[d]Baseline symptom is defined as baseline symptom score > 1 for all symptoms except loss of taste and smell. Loss of taste and smell is defined as with baseline symptom if baseline score is 1. For each subject, total number of baseline symptoms was computed and the mean across each subgroup in shown in this table

baseline symptoms, patients with first infusion within ≤ 5 days or > 5 days from symptom onset, and patients with 1–2 risk factors or ≥ 3 risk factors between the 2 groups (Table 1).

Lack of Heterogeneity of Treatment Effect

Heterogeneity of treatment effect of remdesivir by time from symptom onset at treatment initiation and number of baseline risk factors was not detected with all FDR-adjusted *P* values > 0.05 (Table 2). Across the Cox proportional-hazards models being tested with different clinical endpoints (COVID-19-related hospitalizations, COVID-19-related MAVs, and alleviation of symptoms), different stratifications of time from symptom onset at treatment initiation (≤ 3 and > 3 days; ≤ 5 and > 5 days; and as continuous variable), and different stratifications of number of risk factors (1–2 and ≥ 3; 1–3 and ≥ 4; and as continuous variable), the adjusted *P* values for the interaction between remdesivir treatment and time from symptom onset at treatment initiation and for the interaction between remdesivir treatment and number of baseline risk factors were not significant, except for a few approaches to stratification that created sparse cells and unreliable models. More specifically, for COVID-19-related hospitalizations, the adjusted *P* values for interaction are > 0.9, except for 2 stratifications with 0 events in 1 group (≤ 3 and > 3 days of time from symptom onset at treatment initiation and 1–2 and ≥ 3 baseline risk factors). Similarly, for COVID-19-related MAVs, the adjusted *P* values are > 0.3, except for 1 stratification with 0 events in 1 group (≤ 3 and > 3 days from symptom onset at treatment initiation). For symptom alleviation, the adjusted *P* values for interaction are > 0.9 for stratification by time from symptom onset at treatment initiation, and lower but still not significant (*P* value 0.08) for stratification by number of baseline risk factors (1–2 and ≥ 3).

Subgroup Analyses of COVID-19-Related Hospitalizations

Among patients receiving remdesivir (n = 201) or placebo (n = 194) within 5 days of symptom onset, 1 (0.5%) in the remdesivir group and 9 (4.6%) in the placebo group were hospitalized by day 28 (HR 0.10; 95% CI 0.01–0.82) (Fig. 1a). Among patients receiving remdesivir (n = 78) or

Table 2 Heterogeneity of treatment effect of remdesivir by time from symptom onset at treatment initiation and number of baseline risk factors and symptom alleviation

	Remdesivir	Placebo	FDR-adjusted *P* value for interaction
Hospitalizations			
Symptom onset time, days			Interaction between treatment and symptom onset time
≤ 3	0[a]/77	5/69	< 0.001
≥ 4	2/202	10/214	< 0.001
≤ 5	1/201	9/194	0.975
≥ 6	1/78	6/89	0.975
No. of risk factors			Interaction between treatment and no. of risk factors
1–2	0[a]/159	4/164	< 0.001
≥ 3	2/120	11/119	< 0.001
1–3	1/226	8/229	0.975
≥ 4	1/53	7/54	0.975
MAVs			
Symptom onset time, days			Interaction between treatment and symptom onset time
≤ 3	0[a]/77	6/69	< 0.001
≥ 4	4/202	15/214	< 0.001
≤ 5	1/201	14/194	0.328
≥ 6	3/78	7/89	0.328
No. of risk factors			Interaction between treatment and no. of risk factors
1–2	1/159	6/164	0.975
≥ 3	3/120	15/119	0.975
1–3	1/226	14/229	0.474
≥ 4	3/53	7/54	0.474
Symptom alleviation			
Symptom onset time, days			Interaction between treatment and no. of risk factors
≤ 3	17/41	9/40	0.975
≥ 4	44/128	24/125	0.975
≤ 5	45/123	24/120	0.975
≥ 6	16/46	9/45	0.975
No. of risk factors			Interaction between treatment and no. of risk factors
1–2	46/104	17/99	0.084
≥ 3	15/65	16/66	0.084
1–3	54/137	28/142	0.657
≥ 4	7/32	5/23	0.657

FDR false discovery rate, *MAV* medically attended visit

[a]After FDR adjustment, only subgroups labeled with [a] show significance, which is due to lack of events in these subgroups

placebo ($n = 89$) at > 5 days from symptom onset, 1 (1.3%) in the remdesivir group and 6 (6.7%) in the placebo group had a COVID-19-related hospitalization (HR 0.19; 95% CI 0.02–1.61) (Fig. 1b). Additionally, for patients receiving remdesivir ($n = 77$) or placebo ($n = 69$) within 3 days of symptom onset, 0 (0.0%) in the remdesivir group and 5 (7.2%) in the placebo group were hospitalized by day 28 (HR and *P* value were not calculable given the absence of events in the remdesivir arm). Among patients randomized to remdesivir ($n = 202$) and placebo ($n = 214$) at ≥ 4 days from symptom onset, 2 (1.0%) in the remdesivir group and 10 (4.7%) in the placebo group had a COVID-19-related hospitalization (HR 0.21; 95% CI 0.04–0.94) (see Table S1 in the supplementary material).

Of patients with 1–2 risk factors, no patients (0/159; 0.0%) receiving remdesivir and 4/164 (2.4%) receiving placebo had a COVID-19-related hospitalization; HR was not calculable (Fig. 2a). Of patients with ≥ 3 risk factors, 2/120 (1.7%) receiving remdesivir and 11/119 (9.2%) receiving placebo had COVID-19-related hospitalizations (HR 0.16; 95% CI 0.04–0.73) (Fig. 2b). Additional details are presented in Table S1 in the supplementary material.

Subgroup Analyses of COVID-19-Related MAVs

Among patients receiving remdesivir ($n = 201$) or placebo ($n = 194$) ≤ 5 days from symptom onset, 1 (0.5%) in the remdesivir group and 14 (7.2%) in the placebo group had MAVs (HR 0.07; 95% CI 0.01–0.52) (see Fig. S1A in the supplementary material). Among patients receiving remdesivir ($n = 78$) and placebo ($n = 89$) at > 5 days from symptom onset, 3 (3.8%) in the remdesivir group and 7 (7.9%) in the placebo group had MAVs (HR 0.44; 95% CI 0.11–1.77) (see Fig. S1B in the supplementary material). See Table S2 in the supplementary material for detailed results. Results for patients with COVID-19-related MAVs stratified by baseline number of risk factors demonstrated trends similar to outcomes for COVID-19 hospitalization alone and are available in Table S2 in the supplementary material. For example, for those with 1–2 risk factors, 1/159 (0.6%) receiving remdesivir and 6/164 (3.7%) receiving placebo had an MAV (HR 0.19; 95% CI 0.02–1.58) (see Fig. S2A in the supplementary material), whereas in patients with ≥ 3 risk factors, 3/120 (2.5%) receiving remdesivir and

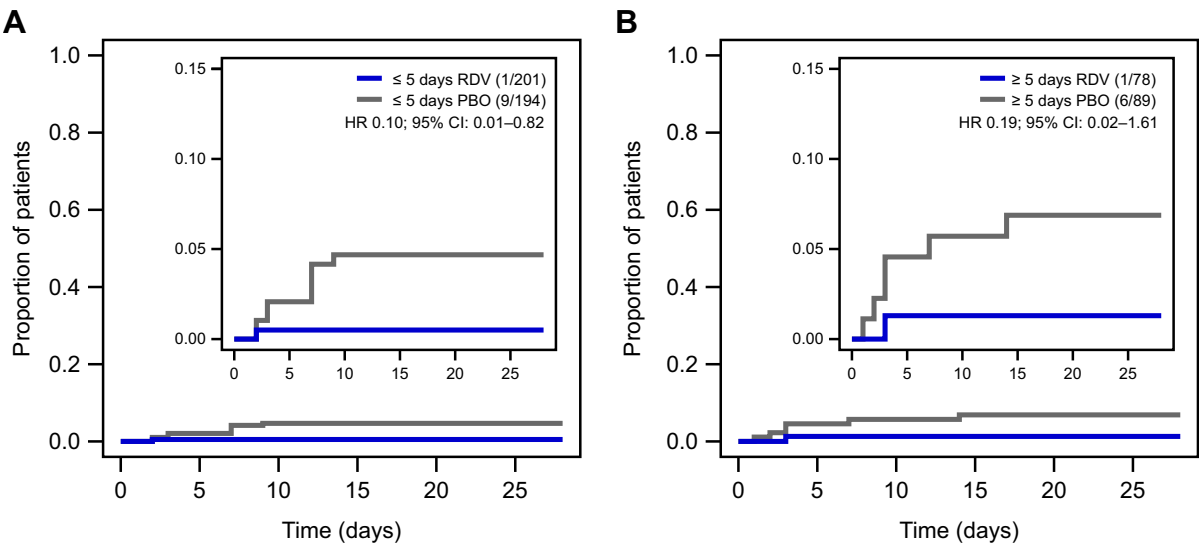

Fig. 1 COVID-19-related hospitalization stratified by time from symptom onset to infusion. Patients with **a** ≤ 5 days and **b** > 5 days between symptom onset and infusion. *COVID-19* coronavirus disease 2019, *RDV* remdesivir, *PBO* placebo, *HR* hazard ratio, *CI* confidence interval

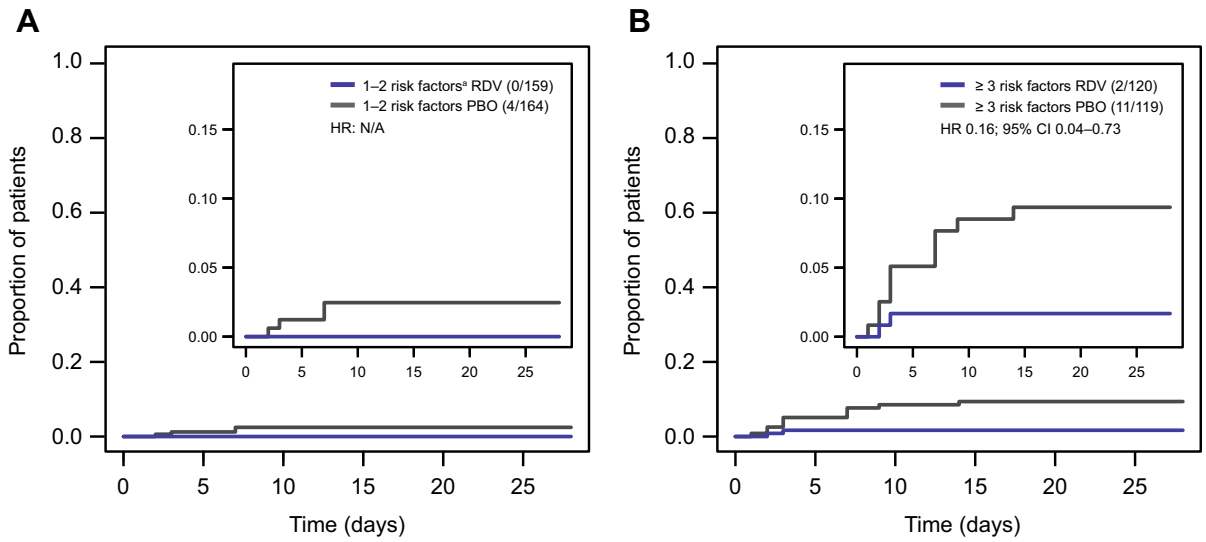

Fig. 2 COVID-19-related hospitalization stratified by risk factors. Patients with **a** 1–2 risk factors and **b** ≥ 3 risk factors. *COVID-19* coronavirus disease 2019, *RDV* remdesivir, *PBO* placebo, *HR* hazard ratio, *N/A* not applicable, *CI* confidence interval. [a]Including 1 subject without a risk factor

15/119 (12.6%) receiving placebo had an MAV (HR 0.18; 95% CI 0.05–0.63) (see Fig. S2B in the supplementary material).

Subgroup Analyses of Time to Alleviation of Symptoms

Among patients who received their first infusion within 5 days of symptom onset and completed the baseline FLU-PRO Plus questionnaire on the first day of study drug administration, symptom alleviation by day 14 was reported by 45/123 (36.6%) patients in the remdesivir arm and 24/120 (20.0%) patients in the placebo arm (rate ratio [RR] 1.90; 95% CI 1.16–3.13) (Fig. 3a). Among those who received the infusion after 5 days of symptom onset, symptom alleviation by day 14 was reported by 16/46 (34.8%) patients in the remdesivir arm and 9/45 (20.0%) in the placebo arm (RR 2.32; 95% CI 0.94–5.72) (Fig. 3b). When stratified according to number of risk factors at baseline, among those with 1–2 risk factors, 46/104 (44.2%) patients in the remdesivir arm and 17/99 (17.2%) patients in the placebo arm reported alleviation of symptoms by day 14 (RR 2.79; 95% CI 1.60–4.86) (Fig. 4a), whereas among those with ≥ 3 risk factors at baseline, 15/65 (23.1%) patients in the remdesivir arm and 16/66 (24.2%) patients in the placebo arm reported alleviation of symptoms (RR 0.99; 95% CI 0.49–2.00) (Fig. 4b). For additional details regarding time to alleviation of symptoms, see Table S3 in the supplementary material.

Subgroup Analyses of Nasopharyngeal SARS-CoV-2 Viral Load

The nasopharyngeal mean SARS-CoV-2 viral load reduction from baseline to day 7 was analyzed in the different subgroups, classified by their time from symptom onset to treatment and by the number of risk factors. Analyses of viral load in the nasopharynx stratified by time from symptom onset to treatment (≤ 5 days and > 5 days) and by number of risk factors (1–2 and ≥ 3) showed no significant differences between the mean nasopharyngeal SARS-CoV-2 viral load decrease from baseline to day 7 between patients receiving remdesivir and those receiving placebo (see Fig. S3 in the supplementary material).

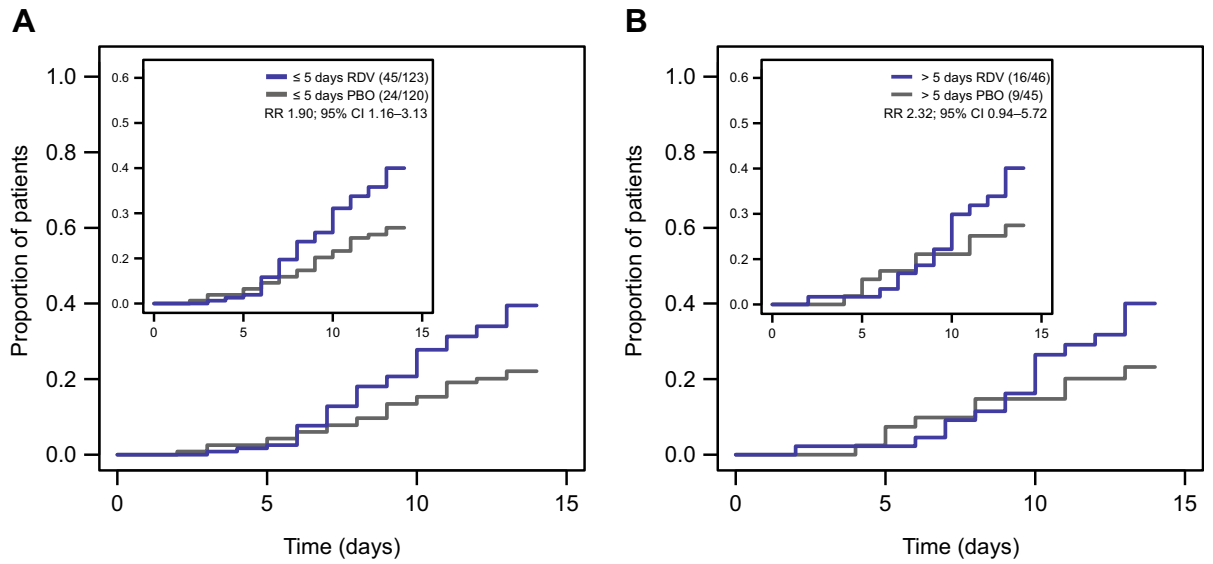

Fig. 3 Symptom alleviation stratified by time from symptom onset to infusion. Patients with **a** ≤ 5 days and **b** > 5 days between symptom onset and infusion. *RDV* remdesivir, *PBO* placebo, *RR* rate ratio, *CI* confidence interval

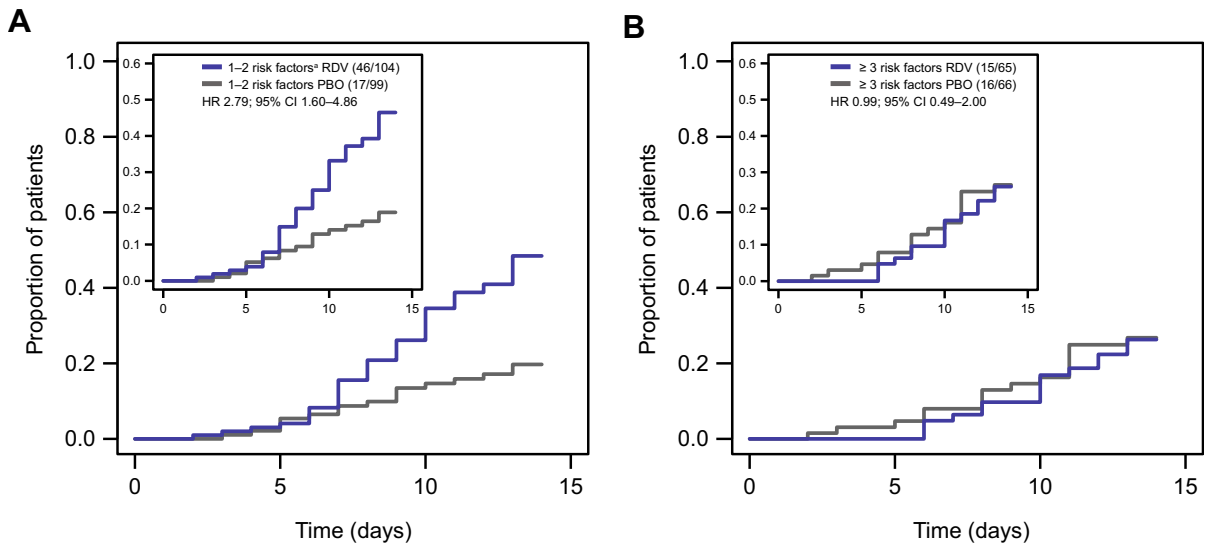

Fig. 4 Symptom alleviation stratified by risk factors. Patients with **a** 1–2 risk factors and **b** ≥ 3 risk factors. *RDV* remdesivir, *PBO* placebo, *HR* hazard ratio, *CI* confidence interval. [a]Including 1 subject without a risk factor

Contemporary SARS-CoV-2 Variants in the PINETREE Study and Antiviral Activity of Remdesivir Against Subsequently Emerged SARS-CoV-2 Omicron Subvariants

This study enrolled patients between September 2020 and April 2021 before the emergence of the Delta (B.1.617.2) variant. Baseline sequencing data were obtained for 256 of 562 participants. Of these, the most common SARS-CoV-2 variants were B.1.2, Alpha (B.1.1.7), and Epsilon (B.1.429) at 30.4%, 18.7%, and 8.9% of participants with baseline sequencing data, respectively. The variants Iota (B.1.526) and Gamma (P.1) were also observed but at a lower

frequency; ≤ 1.6% of participants with baseline sequencing (see Table S4 in the supplementary material). The antiviral activity of remdesivir against clinical isolates of SARS-CoV-2 variants of concern, including more recently emerged Omicron subvariants that were not yet extant at the time of the PINETREE study, have been determined. Remdesivir retained potent in vitro antiviral activity against the recent BA.2.12.1, BA.4.6, and BF.5 Omicron subvariants with mean remdesivir half-maximal effective concentration (EC_{50}) values ranging from 33 to 134 nM, representing 0.20- to 0.94-fold change compared with reference ancestral strain WA1 (see Table S5 in the supplementary material).

DISCUSSION

COVID-19 is an ongoing pandemic [5, 20] despite available vaccines, therapeutics, and public health measures to curtail infection, and is of concern especially in vulnerable patients. Test-and-treat strategies with remdesivir (and/or other antivirals) are important to protect vulnerable individuals, constituting a recent public health strategy to combat the epidemic in some countries [21]. Remdesivir is a well-tolerated parenteral therapeutic approved for treatment of hospitalized and non-hospitalized patients with COVID-19, with demonstrated effect in reduction of morbidity and mortality and a favorable tolerability and drug–drug interaction profile.

In the PINETREE study, non-hospitalized patients with COVID-19 who were at high risk for severe disease and received a 3-day course of remdesivir had an 87% lower risk of COVID-19-related hospitalization or death from any cause by day 28, an 81% lower risk of COVID-19-related MAVs or death from any cause by day 28, and among evaluable patients, demonstrated a faster time to symptom alleviation compared to patients who received placebo [16]. Numerically, risk reduction for hospitalization trended greater among those treated with remdesivir within 5 days of symptom onset (90%) compared to after 5 days symptom onset (81%). Subgroup analyses of symptom data showed a similar trend towards a higher magnitude of efficacy of remdesivir on symptom alleviation when administered earlier in the disease course, further supporting treatment initiation as early as feasible, while recognizing that efficacy remains if a delay to treatment occurs as a result of later patient presentation. Similar observations of early antiviral efficacy have been reported in studies of the 3CL protease inhibitor nirmatrelvir, administered as ritonavir-boosted nirmatrelvir, which was found to reduce the risk of hospitalization or death for high-risk individuals by 88% if given within 5 days of symptom onset [22]. Conversely, a phase 3 study of molnupiravir, an oral antiviral mutagen, reported that, in unvaccinated individuals, administration within 5 days of symptom onset resulted in only a 30% reduction in the composite of hospitalization or death compared with placebo [23], a result that is clinically equivocal given that no reduction in the frequency of COVID-19 hospitalizations or death were observed in an open-label, randomized, and much larger cohort of high-risk, vaccinated adults [24]. While the large majority of analyses of possible treatment effect heterogeneity, including the present analysis, lack sufficient power to support definitive difference, we find no evidence for treatment effect heterogeneity. This suggests that the clinical benefit of remdesivir was not restricted to any of the clinically relevant subgroups herein analyzed.

In the present subanalysis, remdesivir demonstrated efficacy for preventing COVID-19 hospitalization in patients regardless of baseline risk factor burden and was associated with symptom alleviation by day 14 in the entire cohort, and in the subgroup among those with ≤ 2 risk factors. Different measures of clinical efficacy may be most relevant to specific patient risk groups. The vast majority of COVID-19 hospitalizations in the study population (13/17 [76.5%]) occurred among patients with ≥ 3 risk factors; there were only 2 hospitalizations in the remdesivir arm among patients in this cohort (2/120), as compared to 11 in the placebo arm (11/119). These data are in line with our current understanding of COVID-19 disease progression and suggest patients with numerous (≥ 3) risk factors or comorbidities are not only at greater

risk for COVID-19 hospitalization but may also experience persistent symptoms over longer duration compared to those with fewer baseline risk factors [6–10, 25, 26]. Thus, different clinical metrics may be best suited to assessing efficacy in subgroups with different risk factors. For example, symptom alleviation may be most salient to those with fewer risk factors and a lower absolute event rate for hospitalization, whereas the hard clinical endpoint of progression to hospitalization may be most salient to those patients with higher numbers of risk factors.

Despite clinical improvement, no difference in nasopharyngeal SARS-CoV-2 viral load up to day 7 was observed in subgroup analyses. The SARS-CoV-2 viral load is expected to vary in different compartments of the respiratory tract, including the nasal cavity, nasopharynx, and pulmonary parenchyma, and according to viral tropism and/or disease progression. The viral load measured in the upper respiratory airway does not necessarily correlate with clinical severity of an infection in the lower respiratory tract for non-opsonizing antiviral therapies [27]. Consistent with this, macaques infected with SARS-CoV-2 and treated with remdesivir demonstrated reductions in the infectious viral titer in bronchoalveolar lavage samples and a reduced number of parenchymal lesions with remdesivir treatment; however, no reduction in nasal shedding was observed [28]. In humans, we are limited to sampling more accessible areas. However, on the basis of primate data, we can extrapolate that humans may demonstrate similar discordance between clinical treatment response to remdesivir and viral RNA copy number when comparing samples collected from the lower respiratory tract versus the upper respiratory tract and nasopharynx. Such factors may explain the discordance between convincing clinical efficacy despite an absence of treatment-related changes in the nasopharyngeal viral RNA copy number of patients in PINETREE. This also supports our prior conclusion that upper respiratory viral RNA copy number is not a useful surrogate for remdesivir efficacy [16], in contrast to its potential value as a surrogate for opsonizing therapies, such as neutralizing monoclonal antibodies [29–31].

A 3-day course of remdesivir provides a safe and effective treatment for non-hospitalized patients with COVID-19 and ≥ 1 risk factor for progression. These findings complement real-world analyses of patients with COVID-19 treated with remdesivir through outpatient infusions [32] and in at-home hospital units [33]. Given remdesivir's safety profile, outpatient and at-home administration of the drug are effective alternatives to conventional hospitalization for treating patients with non-severe COVID-19 in operationally compatible healthcare delivery systems. Although the current study was not powered to specifically assess remdesivir in long-term care residents, this population may also benefit given their access to nursing/infusion services, regular screening for early detection of SARS-CoV-2 infection, and likelihood of having multiple risk factors [34, 35].

A key limitation of these secondary analyses is that some subgroups had small numbers, limiting the security of inference. Importantly, PINETREE enrolled patients between September 2020 and April 2021 before the emergence of the B.1.617.2 (Delta) variant [16]. Fortunately, remdesivir retains potent in vitro antiviral activity against Delta and the original Omicron variant (B.1.1.529) [19], as well as subsequently emerging Omicron subvariants, including BA.2.12.1, BA.4.6, and BF.5 (see Table S5 in the supplementary material), supporting the continued efficacy of remdesivir for the treatment of COVID-19. Although PINETREE excluded patients who had received SARS-CoV-2 vaccines, the inclusion of vaccinated populations in real-world data sets affirms the ongoing clinical benefit of a 3-day intravenous course of early outpatient remdesivir.

CONCLUSIONS

In the outpatient setting for those infected with COVID-19, the benefit of remdesivir initiated within 7 days of symptom onset appeared to be consistent across patients with several risk factors. On the basis of this evidence, it is reasonable to provide broad access to early treatment with remdesivir for patients with ≥ 1 comorbidities.

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Compliance with Ethics Guidelines. The trial was approved by the institutional review board or ethics committee at each trial site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. Prior to trial procedures, adult patients provided written informed consent; patient assent and parental or guardian consent were obtained if patients were < 18 years of age.

Data Availability. Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting no conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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