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DAS181 Treatment of Severe Lower Respiratory Tract Parainfluenza Virus Infection in Immunocompromised Patients: A Phase 2 Randomized, Placebo-Controlled Study

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Background. There are no antiviral therapies for parainfluenza virus (PIV) infections. DAS181, a sialidase fusion protein, has demonstrated activity in in vitro and in animal models of PIV.

Methods. Adult immunocompromised patients diagnosed with PIV lower respiratory tract infection (LRTI) who required oxygen supplementation were randomized 2:1 to nebulized DAS181 (4.5 mg/day) or matching placebo for up to 10 days. Randomization was stratified by need for mechanical ventilation (MV) or supplemental oxygen (SO). The primary endpoint was the proportion of patients reaching clinical stability survival (CSS) defined as returning to room air (RTRA), normalization of vital signs for at least 24 hours, and survival up to day 45 from enrollment.

Results. A total of 111 patients were randomized to DAS181 (n = 74) or placebo (n = 37). CSS was achieved by 45.0% DAS181-treated patients in the SO stratum compared with 31.0% for placebo ($P = .15$), whereas patients on MV had no benefit from DAS181. The proportion of patients achieving RTRA was numerically higher for SO stratum DAS181 patients (51.7%) compared with placebo (34.5%) at day 28 ($P = .17$). In a post hoc analysis of solid organ transplant, hematopoietic cell transplantation within 1 year, or chemotherapy within 1 year, more SO stratum patients achieved RTRA on DAS181 (51.8%) compared with placebo (15.8%) by day 28 ($P = .012$).

Conclusions. The primary endpoint was not met, but post hoc analysis of the RTRA component suggests DAS181 may have clinical activity in improving oxygenation in select severely immunocompromised patients with PIV LRTI who are not on mechanical ventilation.

Clinical Trials Registration. NCT01644877.

Key words. parainfluenza virus; immunocompromised; supplemental oxygen; lower respiratory tract infections; DAS181.

Parainfluenza viruses (PIVs) frequently cause respiratory illnesses in the immunocompromised population. Studies have described the cumulative incidence of PIV infection to be as high as 17.9% during the first 100 days after hematopoietic cell transplantation (HCT) and 5.3% after lung transplantation [1, 2]. PIV infections may progress from upper tract infection to lower respiratory tract infection (LRTI) in 18%–44% of cases [3, 4].

Mortality following PIV-associated pneumonia has been observed in 17%–55% of allogeneic HCT recipients following myeloablative conditioning [5, 6]. This high mortality resulting from PIV is unique to the severely immunocompromised population. In retrospective analyses, neither aerosolized ribavirin nor intravenous immunoglobulin led to improved outcome of PIV LRTI or a reduction in viral titers [7, 8].

DAS181 is an inhaled sialidase with catalytic domain and amphiregulin glycosaminoglycan-binding sequence fusion protein [9]. The sialidase of DAS181 cleaves sialic acids from host respiratory epithelial receptors, thus preventing the attachment and entry of viruses that use 2,6- or 2,3-linked terminal sialic acids to infect respiratory cells, such as PIV and influenza viruses. The amphiregulin glycosaminoglycan-binding sequence improves retention on cell surfaces. DAS181 has shown PIV antiviral activity in multiple cell lines, human airway epithelium models, and animal models [10, 11]. The emergency use of DAS181 in immunocompromised patients with severe PIV respiratory illness has been reported [12, 13].

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This study was designed to examine the clinical efficacy and safety profile of DAS181 in an immunocompromised population with severe PIV LRTI who required supplemental oxygen or mechanical ventilation. The requirement for supplemental oxygen is a risk factor for poor prognosis in these patients [6, 14]. Specifically, a study of 544 HCT patients found that both LRTI and use of supplemental oxygen were significant risk factors for overall death and pulmonary-related death [14]. Therefore, the reversal of the need for supplemental oxygen is likely to be of clinical benefit to hypoxic patients in this population.

METHODS

Study Population

Immunocompromised patients met at least 1 of the following criteria: (1) autologous or allogeneic HCT; (2) lung or lung–heart transplantation; or (3) treatment with chemotherapy for hematologic or solid tumor malignancies. Patients with PIV LTRI who were ≥ 12 years of age, currently on invasive mechanical ventilation (MV stratum) or at least 1 of the following: requiring ≥ 2 liters per minute of supplemental oxygen (SO stratum) therapy or noninvasive ventilation (continuous positive airway pressure or bilevel positive airway pressure) were eligible for this study if their alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase levels were <3× the upper limit of normal and total bilirubin was <2× the upper limit of normal.

Patients were excluded for the following reasons: (1) psychiatric or cognitive illness or recreational drug/alcohol use that would affect patient safety or compliance; (2) any significant finding in the patient's medical history or physical examination that, in the opinion of the investigator, would affect patient safety or compliance with the dosing schedule; (3) patients with a low chance of survival during the first 10 days of treatment, as determined by the investigator; (4) patients treated with oral, aerosolized, or intravenous ribavirin for the PIV infection (a 48-hour washout period before randomization was allowed for patients treated with ribavirin; ribavirin used for viral coinfections was allowed); (5) patients receiving any other investigational drug; and (6) patients with a history of allergic reactions to lactose.

PIV LRTI Confirmation

Confirmed PIV at screening was performed at the local site by 1 of the following methods using any sample type; (1) a respiratory virus panel, which was a multiplex polymerase chain reaction test for most subjects; (2) direct fluorescent antibody; or (3) qualitative/quantitative reverse transcriptase-polymerase chain reaction test.

Patients in the MV stratum had confirmed PIV LRTI within 7 days of screening by 1 of the following: (1) PIV detection in bronchoalveolar lavage; (2) PIV detection in biopsy; or (3) PIV detection in a respiratory sample (eg, nasopharyngeal swab), along with new or worsening pulmonary infiltrates or radiographic findings of bronchiolitis, pneumonitis on chest X-ray, or computed tomography temporally associated with the PIV diagnosis.

PIV LRTI was confirmed for patients in the SO stratum within 7 days of screening by meeting the criteria for having both: (1) a new or worsening of a pulmonary infiltrates or radiographic findings of bronchiolitis, pneumonitis on chest X-ray or computed tomography temporally associated with a diagnosis of PIV infection; and (2) at least 1 PIV sign or symptom excluding hypoxia (eg, cough, wheezing, rhonchi, rales, dyspnea).

Study Design and Interventions

Participants were randomly assigned 2:1 to either DAS181 or matched placebo administered daily by nebulized oral inhalation for up to 10 consecutive days (Figure 1). A total of 3.5 mL of reconstituted solution containing placebo or 4.5 mg of DAS181 was administered by Aeroneb Solo nebulizers (Aerogen, Ireland) via either mouthpiece (facemask acceptable if mouthpiece not tolerated) for subjects on supplemental oxygen or via the endotracheal tube of mechanically ventilated patients. Permuted block randomization was balanced centrally and stratified by the need for MV at the time of randomization.

Patients who clinically improved and met their institution's criteria for hospital discharge before completing the 10-day treatment course could return to the institution for the remaining treatment.

All patients were followed for the 45-day study period or until death or withdrawal from the study. All patients were required to complete safety, efficacy, and pharmacokinetic assessments through day 10. All patients, whether hospitalized or discharged, were required to return to the hospital for assessments on days 14 and 28. Hospitalized patients had additional assessments required on days 11, 12, 13, 21, and 35. A final survival assessment occurred at day 45, which was conducted via phone for discharged patients.

Efficacy and Safety Evaluations

Efficacy Endpoints

The primary efficacy evaluation used a composite endpoint, clinical stability survival (CSS; Figure 1), based on clinical stability criteria modified from Halm et al [15], and survival. Clinical stability survival was defined as the day subjects achieved clinical stability and if they remained alive at day 45. Clinical stability was defined as maintaining the following parameters for 24 continuous hours: weaned to room air with saturation of peripheral oxygen on room air ≥ 92%, respiratory rate on room air ≤ 24 breaths/min, heart rate ≤ 100 beats/min, and systolic blood pressure ≥ 90 mm Hg. Secondary clinical efficacy endpoints included achieving clinical stability, all-cause mortality, and hospital discharge.

A primary endpoint of mortality at day 45 was initially selected and sample size was determined by previous publications with

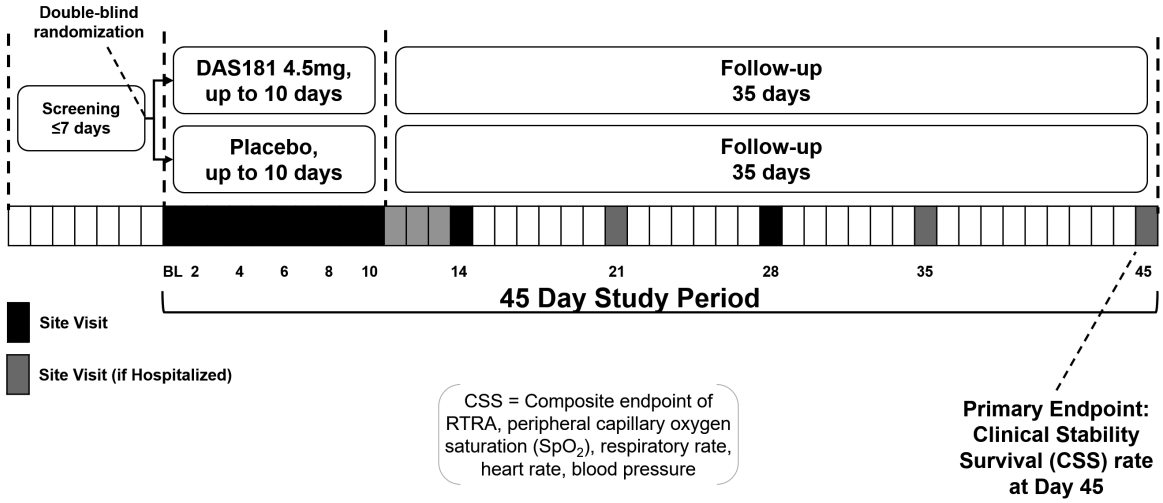

Figure 1. Clinical trial design timeline. Abbreviation: RTRA, return to room air.

high mortality rates. A protocol amendment changed the primary endpoint from mortality to CCS because of observed low overall mortality during trial enrollment.

Safety and Exploratory Endpoints

Adverse event (AE) reporting, clinical laboratory test results, vital signs, electrocardiography, and oxygen saturation levels were assessed. Each AE was mapped to a system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1. A treatment-emergent adverse event was defined as one with a start date and time, which occurred after the date and time of the first study drug administration through the last follow-up visit (day 45). Exploratory endpoints included changes in hospitalization status, intensive care unit stay, Apache III scores, chest imaging, graft versus host disease, pulmonary function, symptom severity, and co-infections. PIV viral load, viral shedding, viral resistance, pharmacokinetics, and immunogenicity were assessed from all patients at selected time points (data not shown).

Post Hoc Analyses

It was observed that improved CSS was due mainly to the improvement of pulmonary function as measured by return to room air (RTRA); thus, additional analyses were conducted post hoc on this factor. RTRA was defined as the day when supplemental oxygen support was removed from a patient and no further oxygen supplementation was required throughout the remainder of the observation period. At each specified time point, patients were considered RTRA failures if they: (1) died by any cause; (2) remained on supplemental oxygen; (3) achieved RTRA but subsequently required supplemental oxygen for more than 24 consecutive hours; or (4) withdrew from the study. Patients who achieved RTRA before first dose were excluded from all RTRA endpoint analyses.

Patients were stratified by solid organ transplant (SOT) or the timing of their HCT or chemotherapy. Patients that had HCT or chemotherapy within 1 year before treatment, and all SOT patients, were included in a subgroup deemed severely immunocompromised. The remaining patients that had HCT or chemotherapy longer than 1 year before treatment were deemed mildly immunocompromised [14].

Statistical Analysis

Efficacy data were analyzed for the modified intent-to-treat (mITT) population (all randomized patients who met all eligibility criteria and received at least 1 dose of study medication). Safety data were summarized for all randomized patients who received at least 1 dose of study medication. Categorical data were compared using Fisher's exact test, including treatment groups for CSS or RTRA efficacy proportions, and AE or severe AE (SAE) incidence analyses. Time-to-event data were analyzed using Kaplan–Meier estimator and groups compared using log-rank tests.

Study Conduct

This study was conducted in the United States from June 2014 until September 2016 and sponsored by Ansun Biopharma, Inc. Procedures for study approval and informed consent were followed in accordance with the ethical standards of the central and local sites' institutional review boards and with the principles of the Helsinki Declaration.

RESULTS

Patient Population

A total of 116 patients were consented to participate and were screened, and 111 patients were randomized to DAS181 (n = 74) or placebo (n = 37) (Figure 2); 1 patient randomized to placebo died before receiving any study treatment. One patient was

excluded from the mITT data set for not meeting the supplemental oxygen requirement for the inclusion criteria. No children aged 12–18 years old were enrolled. Seventy-one subjects completed the 45-day observation period. In 39 subjects, early termination of the study was due to death in 32 and withdrawal from the trial in 7 subjects. Three of the withdrawn subjects achieved RTRA and 3 subsequently died. All but 2 protocol deviations were considered minor. One patient did not meet inclusion criteria (not on oxygen at consent/randomization). The second patient received placebo and was alive at day 40 but was counted as a death in all endpoint analyses because the subject rolled over to the open-label study and was counted as RTRA failure in the post hoc analyses.

Table 1 presents baseline characteristics. The most common underlying cause for immunocompromised status for both DAS181 and placebo was HCT (n = 64), followed by hematological malignancy/solid tumor patients on chemotherapy (n = 39), and lung transplant recipients (n = 7). Three subjects in the DAS181 group received aerosolized ribavirin (1 for respiratory syncytial virus coinfection and 1 for worsening respiratory status, which were allowed by protocol, and 1 subject received ribavirin for PIV after stopping study drug at 6 doses, which was considered a minor protocol deviation).

A total of 68 subjects (61.8%) received the full 10-day treatment course; 91 subjects (82.7%) received at least 7 days of treatment. Early discontinuation of study drug for 27 of 42 subjects (64.3%) correlated with discharge for 12 subjects, death within 2 days of treatment discontinuation for another 12 subjects, and early RTRA for the remaining 3 subjects.

Efficacy Analyses

Clinical Stability Survival

In the mITT population, 29/74 (39.2%) of patients on DAS181 compared with 11/35 (31.4%) of patients on placebo reached CSS by day 45 (P = .29, Table 2). In the SO stratum, 27/60 (45.0%) of patients on DAS181 versus 9/29 (31.0%) on placebo reached CSS by day 45 (P = .15), whereas in the MV stratum, 2/14 (14.3%) of patients on DAS181 versus 2/6 (33.3%) on placebo reached CSS by day 45 (P = .94).

Analysis of the time to CSS in the SO stratum demonstrated a trend of reduced time to CSS for patients on DAS181 when compared with placebo (P = .15, Figure 3A). At day 19 (median for DAS181 with 50% of patients reached CSS), only 22% of patients on placebo reached CSS. There was no difference in the mechanical ventilation stratum between DAS181 and placebo for time to CSS analysis (Figure 3B). In addition, no significant difference between DAS181 and placebo was observed for CS and hospital discharge analyses (data not shown).

Safety Analysis

Mortality

There were 35 deaths from any cause by day 45 in the safety population, including 24/74 (32%) deaths in DAS181 arm and 11/36 (31%) in the placebo arm (Supplementary Table 1).

Treatment-emergent Adverse Events

Treatment-emergent AEs of at least 10% incidence in either group full analysis set (FAS) are shown in Table 3. DAS181-emergent AEs that showed a difference from the placebo-treated group were

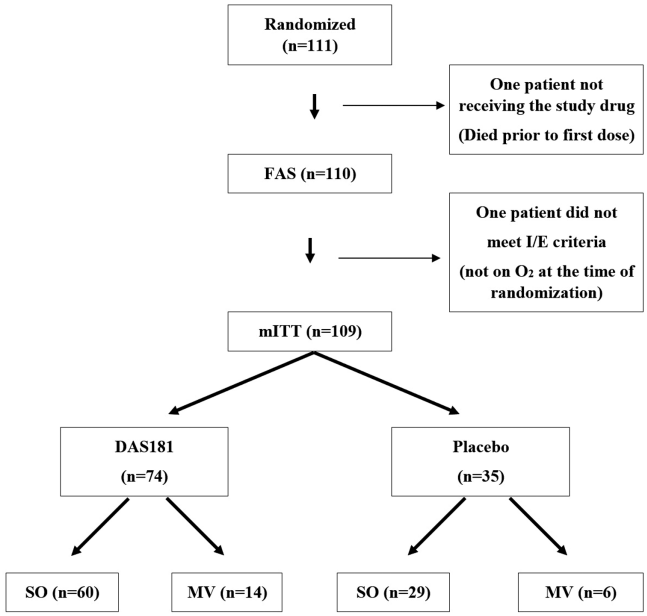

Figure 2. Patient population. A total of 111 patients were randomized to DAS181 or placebo treatment groups. The FAS consisted of 110 randomized patients that received at least 1 dose of study drug (DAS181, n = 74; placebo, n = 36). The mITT data set was 109 patients because of the exclusion of 1 patient that did not meet all inclusion criteria. Abbreviations: I/E, inclusion/exclusion criteria; FAS, full analysis set; mITT, modified intent-to-treat; MV, mechanically ventilated; SO, supplemental oxygen.

Table 1. Summary of Patients' Demographic and Baseline Characteristics (Full Analysis Set)

	Mechanical Ventilation		NIPPV/O_2 (SO)		Total	
Characteristics	DAS181 (N = 14)	Placebo (N = 6)	DAS181 (N = 60)	Placebo (N = 30)	DAS181 (N = 74)	Placebo (N = 36)
Median age, y (range)	50 (24–74)	61.5 (31–67)	57.5 (19–85)	55.5 (18–77)	57.0 (19–85)	57.0 (18–77)
Male gender, n (%)	10 (71.4)	5 (83.3)	31 (51.7)	18 (60.0)	41 (55.4)	23 (63.9)
Race, n (%)						
White	12 (85.7)	5 (83.3)	51 (85.0)	27 (90.0)	63 (85.1)	32 (88.9)
African American	2 (14.3)	0 (0)	6 (10.0)	2 (6.7)	8 (10.8)	2 (5.6)
Asian American	0 (0)	1 (16.7)	3 (5.0)	0 (0)	3 (4.1)	1 (2.8)
Decline to answer	0 (0)	0 (0)	0 (0)	1 (3.3)	0 (0)	1 (2.8)
Oxygen therapy, n (%)						
Mechanical ventilation	14 (100)	6 (100)	0 (0)	0 (0)	14 (18.9)	6 (16.7)
NIPPV	0 (0)	0 (0)	4 (6.7)	0 (0)	4 (5.4)	0 (0)
≥2 L supplemental oxygen, n (%)	0 (0)	0 (0)	56 (93.3)	30 (100)	56 (75.7)	30 (83.3)
Underlying disease, n (%)						
AML	2 (14.3)	2 (33.3)	17 (28.3)	8 (26.7)	19 (25.7)	10 (27.8)
NHL	1 (7.1)	1 (16.7)	8 (13.3)	3 (10/0)	9 (12.2)	4 (11.1)
Multiple myeloma	3 (21.4)	1 (16.7)	4 (6.7)	3 (10.0)	7 (9.5)	4 (11.1)
ALL	2 (14.3)	0 (0)	5 (8.3)	3 (10.0)	7 (9.5)	3 (8.3)
MDS	0 (0)	1 (16.7)	6 (10.0)	3 (10.0)	6 (8.1)	4 (11.1)
Others	5 (35.7)	0 (0)	16 (26.7)	9 (30.0)	21 (28.4)	9 (25.0)
Subgroups, n (%)						
Severely immunocompromised	13 (92.9)	6 (100)	51 (85.0)	19 (63.3)	64 (86.5)	25 (69.4)
SOT	2 (14.3)	0 (0)	3 (5.0)	2 (6.7)	5 (6.8)	2 (5.6)
HCT < 1 y	4 (28.6)	2 (33.3)	31 (51.7)	8 (26.7)	35 (47.3)	10 (27.8)
HM on chemotherapy < 1 y	7 (50.0)	3 (50.0)	13 (21.7)	8 (26.7)	20 (27.0)	11 (30.6)
ST on chemotherapy < 1 y	0 (0)	1 (16.7)	4 (6.7)	1 (3.3)	4 (5.4)	2 (5.6)
Mildly immunocompromised	1 (7.1)	0 (0)	9 (15.0)	11 (36.7)	10 (13.5)	11 (30.6)
HCT > 1 y	0 (0)	0 (0)	8 (13.3)	11 (36.7)	8 (10.8)	11 (30.6)
HM > 1 y	0 (0)	0 (0)	1 (1.7)	0 (0)	1 (1.4)	0 (0)
ST > 1 y	1 (7.1)	0 (0)	0 (0)	0 (0)	1 (1.4)	0 (0)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; HCT, hematopoietic cell transplantation; HM, hematologic malignancy; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NIPPV, noninvasive positive pressure ventilation; PPV, positive pressure ventilation; SOT, solid organ transplant; ST, solid tumor.

vomiting, pyrexia, and hypotension. Furthermore, no acute respiratory AEs such as bronchospasm or mechanical airway obstruction were associated with drug administration to MV subjects. Additional information on most commonly reported treatment-emergent AEs is presented in Supplementary Table 2.

Serious Adverse Events

Most commonly reported SAEs are shown in Supplementary Table 3. The majority of SAEs were assessed as not related to study drug. Two patients, both in the DAS181/SO stratum, experienced SAEs assessed as related to the study drug. One SAE was a grade 3 increase in alanine aminotransferase and aspartate aminotransferase and the other was a grade 2 change in mental status; both resolved shortly after discontinuation of study drug.

Post Hoc Analyses

Return to Room Air

Analysis performed for the time to RTRA in the SO stratum for DAS181 compared with placebo (Figure 4) showed that 50% of DAS181 reached RTRA by day 17.5 compared with placebo, in which < 50% of the patients achieved RTRA during the 45-day observation period ($P = .35$). At day 17.5 (median for DAS181), only 31% of placebo had reached RTRA.

Table 2. Proportion of Patients Achieving CSS at Day 45 (mITT Population, Primary Efficacy Analysis)

	NIPPV/O_2 (SO)		Mechanical Ventilation		Total	
Statistics	DAS181 (N = 60)	Placebo (N = 29)	DAS181 (N = 14)	Placebo (N = 6)	DAS181 (N = 74)	Placebo (N = 35)
Achieved CSS, n (%) [95% CI estimates]	27 (45.0) [38.74–51.26]	9 (31.0) [23.24–38.82]	2 (14.3) [7.87–20.70]	2 (33.3) [15.55–51.11]	29 (39.2) [33.76–44.62]	11 (31.4) [24.29–38.57]
Fisher exact *P* value	.1520		.9391		.2854	

Abbreviations: CI, confidence interval; CSS, clinical stability survival; mITT, modified intent-to-treat; NIPPV, noninvasive positive pressure ventilation; SO, supplemental oxygen.

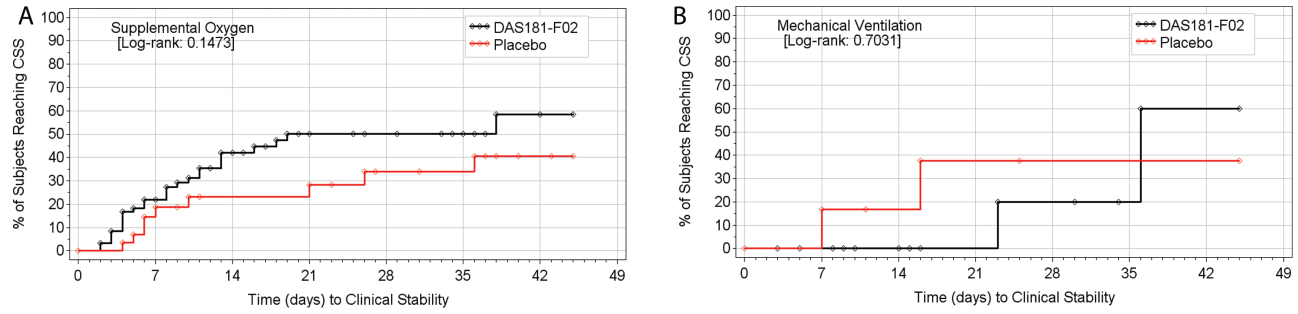

Figure 3. Time to clinical stability survival (SO and MV strata, mITT population). (*A*) Subjects within the NIPPV/O_2 supplemental oxygen stratum. (*B*) Subjects within the mechanical ventilation stratum. Abbreviations: mITT, modified intent-to-treat; MV, mechanically ventilated; NIPPV, noninvasive positive pressure ventilation; SO, supplemental oxygen.

Subgroup Analysis

Identification of Patients That Received Benefit From DAS181 Treatment

This clinical trial enrolled patients that were immunocompromised as defined by having HCT, SOT, or chemotherapy for solid tumor or hematologic malignancy. However, most severe PIV infections occur within the first year following HCT [14]. The SO group was divided into patients that received HCT or chemotherapy within 1 year before enrollment on the study or lung or lung–heart transplantation at any time (severely

Table 3. Adverse Events With Incidence of at Least 10% by System Organ Class (Full Analysis Set)

	DAS181 (n = 74)	Placebo (n = 36)	*P* Value
At least 1 treatment-emergent AE, n (%)	69 (93.2)	35 (97.2)	
Respiratory, thoracic, and mediastinal disorders	36 (48.6)	18 (50.0)	1.000
Respiratory failure	13 (17.6)	5 (13.9)	.786
Hypoxia	4 (5.4)	4 (11.1)	.434
Epistaxis	2 (2.7)	4 (11.1)	.088
Gastrointestinal disorders	39 (52.7)	14 (38.9)	.223
Diarrhea	16 (21.6)	6 (16.7)	.619
Nausea	11 (14.9)	2 (5.6)	.215
Constipation	6 (8.1)	4 (11.1)	.726
Vomiting	8 (10.8)	0 (0.0)	.051
Infections and infestations	35 (47.3)	18 (50.0)	.841
Pneumonia	9 (12.2)	6 (16.7)	.560
Metabolism and nutrition disorders	30 (40.5)	15 (41.7)	1.000
Hypokalemia	8 (10.8)	4 (11.1)	1.000
Investigations	34 (45.9)	10 (27.8)	.097
Blood alkaline phosphatase increased	13 (17.6)	2 (5.6)	.137
Aspartate aminotransferase increased	10 (13.5)	3 (8.3)	.540
Alanine aminotransferase increased	8 (10.8)	4 (11.1)	1.000
Blood lactate dehydrogenase increased	6 (8.1)	4 (11.1)	.726
General disorders and administration site conditions	26 (35.1)	16 (44.4)	.405
Pyrexia	9 (12.2)	0 (0.0)	.029
Renal and urinary disorders	20 (27.0)	6 (16.7)	.339
Psychiatric disorders	13 (17.6)	11 (30.6)	.143
Insomnia	3 (4.1)	4 (11.1)	.213
Vascular disorders	21 (28.4)	3 (8.3)	.025
Hypotension	15 (20.3)	2 (5.6)	.052
Blood and lymphatic system disorders	18 (24.3)	4 (11.1)	.131
Skin and subcutaneous tissue disorders	12 (16.2)	9 (25.0)	.306
Cardiac disorders	11 (14.9)	6 (16.7)	.786
Injury, poisoning and procedural complications	8 (10.8)	6 (16.7)	.380
Nervous system disorders	9 (12.2)	4 (11.1)	1.000
Eye disorders	7 (9.5)	5 (13.9)	.523
Musculoskeletal and connective tissue disorders	5 (6.8)	7 (19.4)	.056

Abbreviation: AE, adverse event.

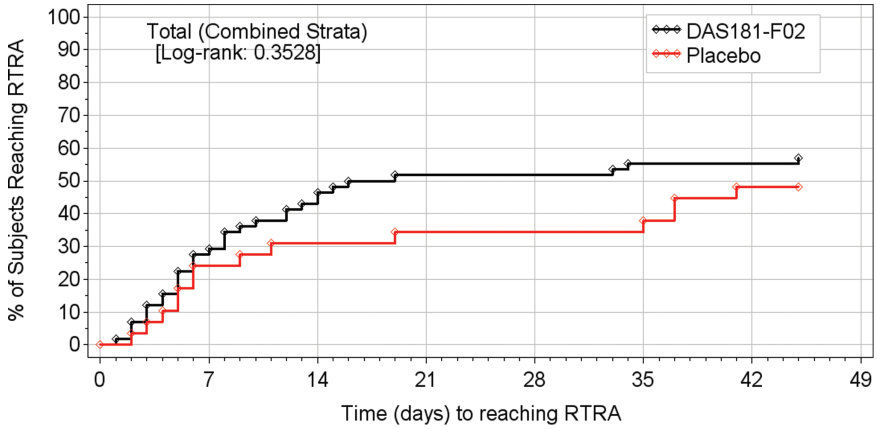

Figure 4. Time to subject RTRA (SO stratum, mITT population). Time to subject return to room air for DAS181 and placebo groups showing a trend toward improved time to RTRA with DAS181 treatment. Two patients were excluded from this analysis because they had achieved RTRA before receiving the first treatment dose. Abbreviations: mITT, modified intent-to-treat; RTRA, return to room air; SO, supplemental oxygen.

immunocompromised patients, n = 68) and patients that had received HCT or chemotherapy more than 1 year before enrollment (mildly immunocompromised patients, n = 19) (Figure 5). Of note, the MV group was not analyzed based on time from transplant because 19 of 20 MV subjects (95%) were severely immunocompromised.

RTRA in the Severely Immunocompromised Subgroup

In the severely immunocompromised SO subgroup, more patients on DAS181 treatment were RTRA when compared with patients on placebo (51.0% on DAS181 vs. 15.8% on placebo) at day 28, a time point of maximum difference between DAS181 and placebo (P = .0124; Table 4). In addition, the subanalysis of severely immunocompromised patients on DAS181 in the SO subgroup demonstrated a trend for a reduced time to RTRA when compared with placebo (P = .0615, Figure 6).

Forced Expiratory Volume Percent Predicted in the Severely Immunocompromised Subgroup

In the SO group, as expected from improved RTRA, DAS181 treatment significantly improved pulmonary function as measured by forced expiratory volume percent (FEV1%) predicted at multiple time points including days 3, 6, and 7 and greatest at day 14 (P = .0015) (Figure 7A), particularly for the severely immunocompromised subgroup in which placebo patients did not show sustained improvement by day 14 (Figure 7B).

DISCUSSION

This phase 2 clinical trial studied clinical stability survival at day 45 as the primary endpoint. Although the primary endpoint was not met, we found a trend toward improvement in DAS181-treated patients in the SO stratum. When analyzed separately in a post hoc analysis, improvement of FEV1%

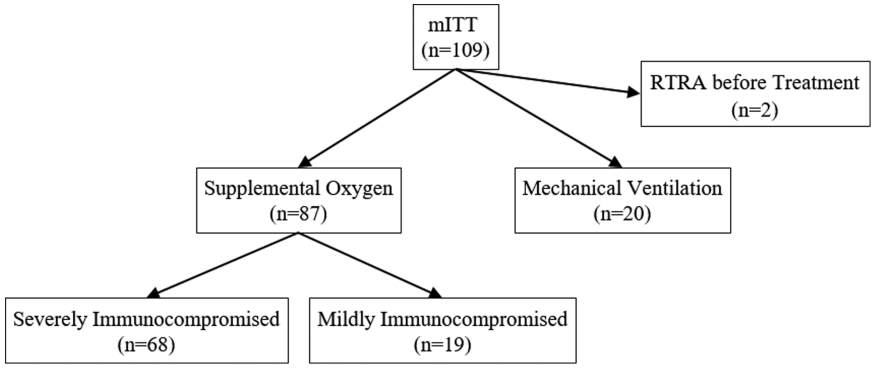

Figure 5. Strata and subgroup populations. Strata and subgroups for analysis of treatment effect using RTRA endpoint. Two patients that achieved RTRA before receiving treatment are not evaluable for this endpoint. Both of these patients were contained within the SO stratum and were removed for all RTRA and related endpoint analyses. The SO stratum consists of 2 subgroups: severely immunocompromised and mildly immunocompromised. Abbreviations: mITT, modified intent-to-treat; RTRA, return to room air; SO, supplemental oxygen.

Table 4. Proportion of Strata and Subgroup Return to Room Air at Day 28 (mITT Population)[a]

			Day 28			
Group	Statistic	N	DAS181	Placebo	Effect Size, %	*P* Value[b]
All patients	Returned to room air, n (%)	107	31/72 (43.1)	12/35 (34.3)	8.8	.4095
NIPPV/O_2 (SO) patients	Returned to room air, n (%)	87	30/58 (51.7)	10/29 (34.5)	17.2	.1718
MV patients	Returned to room air, n (%)	20	1/14 (7.1)	2/6 (33.3)	−26.2	.2018
Severely immunocompromised SO	Returned to room air, n (%)	68	25/49 (51.0)	3/19 (15.8)	35.2	.0124
Mildly immunocompromised SO	Returned to room air, n (%)	19	5/9 (55.6)	7/10 (70.0)	−14.4	.6499

Abbreviations: mITT, modified intent-to-treat; MV, mechanically ventilated; NIPPV, noninvasive positive pressure ventilation; SO, supplemental oxygen.
[a]Two patients returned to room air before being dosed and were excluded from this analysis.
[b]Fisher exact test.

predicted and a trend of improved RTRA proportion for patients on the DAS181 arm was observed for the SO stratum; this was supported by time to RTRA analysis. DAS181 was well tolerated with a comparable safety profile to placebo treatment.

In a post hoc analysis of a subgroup of severely immunocompromised patients in the SO stratum, significant benefit from DAS181 treatment as determined by RTRA proportion at day 28 and a borderline significance for time to RTRA were observed (P = .0124 and P = .0615, respectively). Therefore, potential treatment benefit was observed in severely immunocompromised patients with mild to moderate hypoxia that were at risk for progressive disease and prolonged hospitalization. On the other hand, we excluded patients with a low chance of survival during the first 10 days of treatment; therefore, a potential selection bias could favor a positive result.

Weaning off from supplemental oxygen represents a clinically meaningful clinical outcome for patients with respiratory viral infection. Given that enrolled patients suffered from severe lower respiratory tract infection and began treatment on supplemental oxygen, being able to RTRA and maintain adequate oxygenation indicates substantial improvement in their overall PIV-related disease. This is critically important because pulmonary impairment after respiratory viral infections has been shown to be associated with increased mortality [16].

In retrospect, it is not unexpected that analysis of RTRA provides a clearer assessment than CSS because the CSS endpoint includes several factors, such as heart rate and blood pressure, which may not be reliable indicators of improvement after respiratory viral infection. RTRA is likely the most direct measurement of meaningful clinical improvement after PIV LRTI. One caveat concerning RTRA endpoint is that patients with a preexisting requirement for supplemental oxygen due to underlying diseases would not achieve RTRA because of their preexisting conditions.

There was no observed improvement in the MV stratum. Whether earlier therapy of PIV LRTI would have affected our findings needs to be determined in future trials; it may be more favorable to treat patients on SO before requirement of MV. Moreover, the small sample size of patients on MV could have precluded any determination of clinical benefit.

In summary, RTRA serves as a clinical meaningful endpoint for DAS181 in clinical trials for PIV infections. Resolution of supplemental oxygen (RTRA) and improvement of FEV1% predicted after DAS181 treatment in severely immunocompromised patients with PIV LRTI suggests possible clinical activity in severely immunocompromised patients with PIV LRTI not on MV. A phase 3 trial (NCT03808922) is currently ongoing to confirm the findings of this phase 2 PIV trial.

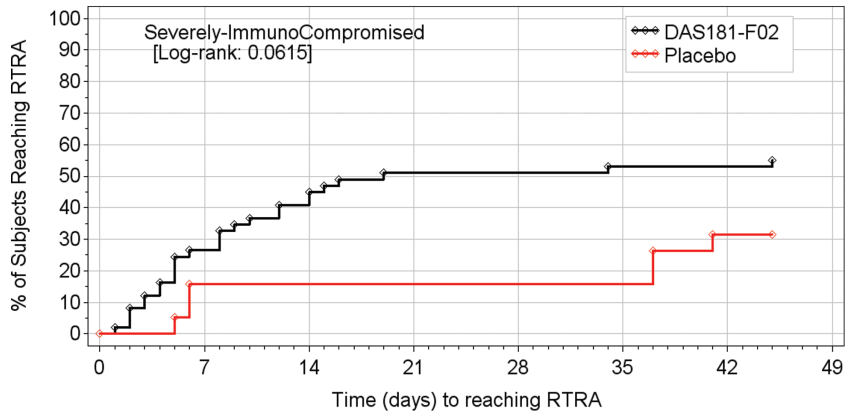

Figure 6. Time to subject RTRA (SO stratum, severely immunocompromised patient subgroup, N = 68). Abbreviations: RTRA, return to room air; SO, supplemental oxygen.

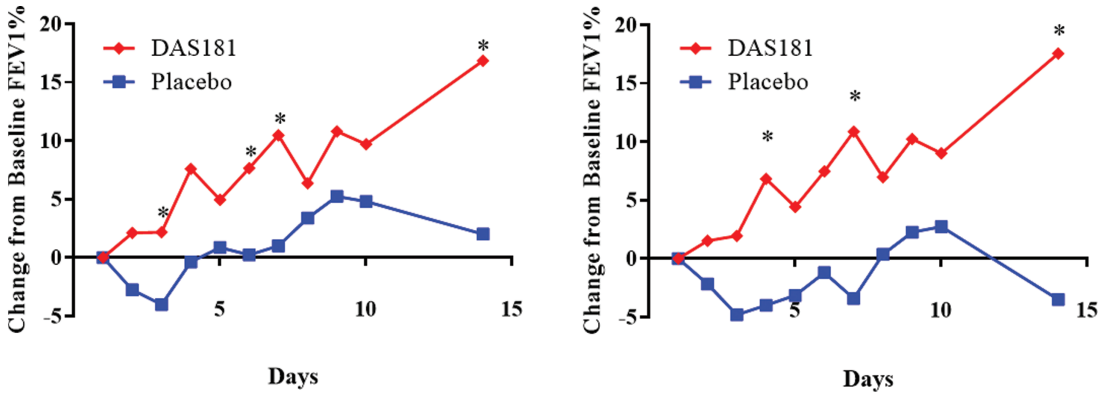

Figure 7. Absolute change from baseline FEV1% predicted. Subjects had FEV1% predicted determined daily for 10 days starting at treatment day 1, and at day 14 posttreatment. (*A*) SO strata patients. (*B*) Severely immunocompromised SO subgroup. *$P < .05$. Abbreviations: FEV1%, forced expiratory volume percent; SO, supplemental oxygen.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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