A Pilot Trial of Thymalfasin (Tα1) to Treat Hospitalized Patients with Hypoxemia and Lymphocytopenia due to COVID-19 Infection

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ClinicalTrials.gov Identifier: NCT04487444

Running Title: Efficacy and safety of Tα1 in COVID-19

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Abbreviations: ACE2: Angiotensin Converting Enzyme 2, AKI: Acute Kidney Injury, COVID-19: Coronavirus Disease 2019, CTCAE: Common Terminology Criteria for Adverse Events, ICU: Intensive Care Unit, IL: Interleukin, IMV: Invasive Mechanical Ventilation, IQR: Interquartile Range, KDIGO: Kidney Disease Improving Global Outcomes, PCR: Polymerase Chain Reaction, SAE: Serious Adverse Events, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, SHR: Subdistribution Hazard Ratio, SpO_2: Oxygen Saturation, Tα1: Thymosin-α-1, USA: United States of America, WHO: World Health Organization

Abstract

Background: Thymosin-α-1 (Tα1) may be a treatment option for COVID-19, but efficacy and safety data remain limited.

Methods: Prospective, open-label, randomized trial assessing preliminary efficacy and safety of thymalfasin (synthetic form of Tα1), compared with standard of care, among hospitalized patients with hypoxemia and lymphocytopenia due to COVID-19.

Results: 49 patients were included in this analysis. Compared with control patients, the incidence of clinical recovery was higher for treated patients with either baseline low flow oxygen (subdistribution hazard ratio [SHR]: 1.48; 95% CI: 0.68 – 3.25) or baseline high flow oxygen (SHR: 1.28; 95% CI: 0.35 – 4.63), although neither were significant. Among patients with baseline low flow oxygen, treated patients, compared with control patients, had an average difference of 3.84 times more $CD4^+$ T cells on Day 5 than on Day 1 ($p = 0.0113$). Nine serious adverse events among treated patients were deemed not related to Tα1.

Conclusion: Tα1 increases $CD4^+$ T cell count among patients with baseline low flow oxygen support faster than standard of care and may have a role in the management of hospitalized patients with hypoxemia and lymphocytopenia due to COVID-19.

Keywords: Thymalfasin, Thymosin Alpha 1, COVID-19, Efficacy, Safety, Hypoxemia, Lymphocytopenia, Lymphopenia

1. Background

More than 60% of patients with coronavirus disease 2019 (COVID-19) develop some degree of lymphocytopenia [1–3] caused by pathophysiological mechanisms, such as T cell apoptosis and exhaustion mediated by both ACE2-independent infection of activated $CD4^+$ T cells [4–6] and cytokine dysregulation [4,6–8]. Since lymphocytopenia is associated with severe COVID-19 infection [1,7,9], poor clinical outcomes [10,11], and possibly linked with persistent symptoms [12], restoration of lymphocytes may contribute to recovery among patients with COVID-19 and lymphocytopenia.

Thymosin-α-1 (Tα1), produced by the thymus, binds to toll-like receptors of dendritic cells [13], promotes T cell maturation into $CD4^+$ and $CD8^+$ T cells [14], modulates signaling of cytokines associated with inflammation, such as interleukin (IL)-1β and tumor necrosis factor α [15], and enhances the signaling of IL-2 and IL-10 [15,16]. Tα1 has yielded encouraging preliminary results in the treatment of malignancies [17], infectious diseases such as hepatitis B [18], and sepsis [19]. Notably, Tα1 is also associated with limiting severe acute respiratory syndrome disease progression [20]. Regarding Tα1 as a treatment option for COVID-19, comprehensive efficacy and safety data from randomized clinical trials [21] and observational studies [22–27] are limited.

The objective of this pilot Phase 2 trial was to provide a preliminary assessment of thymalfasin (the synthetic form of Tα1) as a treatment option among hospitalized patients with hypoxemia and lymphocytopenia due to COVID-19. In this manuscript, we discuss interim efficacy and safety findings, as well as trends in total lymphocyte count, $CD4^+$ T cell count, $CD8^+$ T cell count, and leukocyte count, following treatment with either Tα1 or standard of care alone.

2. Methods

2.1 Study Setting and Design

We recruited patients from two acute care hospitals, Rhode Island Hospital and The Miriam Hospital, located in Providence, Rhode Island, USA. The trial protocol was approved by the institutional review board (Lifespan IRB#412020) and was monitored by an independent data and safety monitoring board. Consecutive hospitalized patients starting September 10, 2020 who had a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test result were screened for eligibility. Enrolled patients provided informed consent, or if the patient could not provide consent, then the patient's legally authorized representative provided surrogate consent (NCT04487444, https://clinicaltrials.gov/ct2/show/NCT04487444).

2.2 Inclusion and Exclusion Criteria

Eligible participants were, at screening, patients $\geq$ 18 years old and admitted with (a) PCR-confirmed SARS-CoV-2 infection $\leq$ 4 days of enrollment, (b) hypoxemia, defined as either oxygen saturation (SpO_2) $\leq$ 93% on room air or requiring supplemental oxygen support, and (c) lymphocytopenia, defined as total lymphocyte count < 1.5 x 10^9/L [1].

Key exclusion criteria at screening were: (a) use of invasive mechanical ventilation (IMV), (b) multi-organ failure, (c) advanced malignancy receiving cytotoxic chemotherapy, (d) prior history of solid organ or bone marrow transplant, (e) use of hydroxychloroquine or other immunomodulatory medications not including standard of care treatments (e.g., dexamethasone) for COVID-19, (f) history of allergy or intolerance to Tα1, or (g) currently pregnant or breastfeeding.

2.3 Treatment Assignment

Patients were randomly assigned in a concealed 1:1 allocation ratio using the REDCap (Research Electronic Data Capture) randomization module [28]. Randomization of treatment assignment was ensured by creating the randomization table using the Python random module that implements pseudo-random number generators [29]. Patients in the treatment arm received standard of care plus thymalfasin subcutaneously at a daily dose of 1.6 mg in 1 mL of diluent starting the day of randomization (Day 1) for seven consecutive days or until death, hospital discharge, or withdrawal from the study. Patients who were randomized to the treatment arm and received at least one dose of thymalfasin were considered treated with Tα1 in this modified intent-to-treat population.

2.4 Assessments

2.4.1 Clinical Assessments

Ascertainment of medical history was conducted at screening. Use of concomitant medications, such as remdesivir, corticosteroids, baricitinib, and tocilizumab, along with clinical status data, such as intensive care unit (ICU) admission, supplemental oxygen support (e.g., low flow delivery system, high flow delivery system, or IMV), and survival, were collected on Days 1-7, 10, 14, and 28. Telephone interviews were conducted for patients discharged prior to the end of the follow up period. Concurrent use of remdesivir and corticosteroids at baseline were defined as having received at least one dose of respective medications within 24 hours of randomization.

2.4.2 Laboratory Assessments

Laboratory assessments including routine standard chemistry evaluations and complete blood count with white blood cell differential, along with T cell subsets, were collected, while patients

remained hospitalized, either as part of standard clinical care or according to our study schedule of events (Days 1, 3, 5, 7, 10, 14, and 28) if not collected as part of standard clinical care. Specifically, we collected data on aspartate transaminase (AST) level, alanine transaminase (ALT) level, bilirubin level, neutrophil count, and platelet count. Additionally, total lymphocyte count, with subset of $CD4^+$ and $CD8^+$ T cell counts, and leukocyte count were determined by flow cytometry using the BD FACSCanto System (Becton, Dickinson and Company, Franklin Lakes, NJ, USA).

2.5 Endpoints

Due to limited recruitment following the initial Omicron wave, we decided to present interim findings regarding the efficacy and safety of Tα1 as a treatment option for COVID-19, while aiming to enroll 80 participants in this trial. All enrolled patients up to May 25, 2022 are included in this analysis. The primary efficacy endpoint was time to clinical recovery, defined as the length of time for a patient to either (a) no longer require supplemental oxygen support and sustain SpO_2 on room air, or (b) improve SpO_2 above 93% without supplemental oxygen support if SpO_2 was $\leq$ 93% at room air at screening, within 28 days.

Secondary efficacy endpoints included 28-day incidence of both all-cause mortality and use of IMV. We also assessed the 28-day incidence of ICU admission among patients who were not admitted to the ICU on Day 1. Additionally, we assessed trends from Day 1 to Day 7 in (a) total lymphocyte count, (b) $CD4^+$ T cell count, (c) $CD8^+$ T cell count, and (d) leukocyte count.

To evaluate the safety of Tα1, we assessed the incidence of serious adverse events (SAE) and their relation to Tα1. We also assessed the severity of transaminitis, hyperbilirubinemia, neutropenia, and thrombocytopenia, as defined and graded by the Common Terminology Criteria

for Adverse Events (CTCAE) v5.0 [30]. The severity of incident acute kidney injury (AKI) cases was graded based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which categorizes AKI cases into one of three severity grades contingent on serum creatinine level increase from baseline [31]. Also, to further assess the safety and tolerability of Tα1, we prospectively monitored patients following Tα1 administration to report and manage any adverse reactions such as irritation, redness, discomfort, or allergic reactions.

2.6 Statistical Analysis

Continuous variables were represented as medians with interquartile ranges (IQR). Univariate tests of association between treatment assignment and baseline demographic and health characteristics were performed using Wilcoxon rank sum tests for continuous variables and Pearson's Chi-square test for independence for categorical variables.

Due to a significant difference in baseline high flow oxygen support between treatment arms and the clinical merit of stratifying by baseline oxygen support due to relevance in clinical outcomes, as seen in larger trials in this population [32–35], all efficacy endpoint analyses were stratified by baseline oxygen support. To analyze the time to clinical recovery, we used the Fine and Gray competing risk regression model [36] with death as a competing risk to present subdistribution hazard ratios (SHR) with 95% confidence intervals (95% CI). The subdistribution hazard ratio allows us to assess the direction of the treatment effect on incidence of clinical recovery in the presence of death as a competing risk [37]. Moreover, the cumulative incidence function of clinical recovery for both treatment arms was estimated using Aalen-Johansen estimator and compared using Gray's Test for equality, with rho equal to 0 [38]. Additionally, incidence of all-cause mortality, IMV use, and ICU admission were assessed using Pearson's Chi-square test for independence. Also, for each specific cell count, we first performed

independent Student's *t* tests to assess differences between treatment arms in both average absolute cell count (on Days 1, 3, 5, and 7) and average rate of change (on Days 3, 5, and 7, using Day 1 as reference). Then, we implemented individual mixed effects models to predict, from Day 1 to Day 7, daily average absolute cell count and daily average rate of change for both treatment arms. Day of collection was used as the continuous independent covariate, and predictive cubic growth curves with 95% CI were plotted**.**

We also conducted a sensitivity analysis in which we utilized an inverse probability weighted competing risk regression analysis [39] to adjust for baseline oxygen support by predicting the propensity of treatment based on a patient's baseline low flow or high flow oxygen support status.

The incidence and severity of AKI, transaminitis, hyperbilirubinemia, neutropenia, and thrombocytopenia between treatment arms were evaluated by Pearson's Chi-square test for independence. Analyses were performed and plots were produced using either Stata, version 17.0 (Stata Corporation, College Station, TX, USA) or R language [40]. Significance was set at $\alpha = 0.05$.

3. Results

A total of 53 patients consented to enroll, and as shown in our patient disposition flowchart in **Figure 1**, four patients were excluded from analysis. Specifically, one patient withdrew consent prior to randomization, one patient in the control arm withdrew consent immediately following randomization, one patient in the control arm was lost to follow up after Day 1, and one patient died after randomization but before receiving the first dose of Tα1. As a result, 49 patients were included in the analysis, with 23/49 (47%) patients in the treatment arm and 26/49 (53%) patients in the control arm.

3.1 Baseline Characteristics

Most baseline demographic, health, and clinical characteristics were comparable between both treatment arms (**Table 1**). The median age of patients in the Tα1 arm was 64 years (IQR: 49 – 80) and the median age of patients in the control arm was 57 years (IQR: 49 – 68). Women comprised 9/23 (39%) patients treated with Tα1 and 11/26 (42%) control patients. Overall, 34/49 (69%) enrolled patients were Non-Hispanic White, and 8/49 (16%) enrolled patients identified either as Non-Hispanic Black or Hispanic/Latinx.

All patients required supplemental oxygen support at baseline. Notably, a greater proportion of patients who required higher supplemental oxygenation, suggestive of greater respiratory distress, were treated with Tα1. Specifically, 15/23 (65%) patients treated with Tα1 required baseline high flow oxygen support, while 8/26 (31%) control patients required baseline high flow oxygen support.

3.2 Primary Efficacy Endpoint

Primary efficacy endpoint results for the entire cohort and stratified by baseline oxygen support are presented in **Table 2**. Overall, 14/23 (61%) patients in the Tα1 arm and 17/26 (65%) patients in the control arm recovered within 28 days, and 3/23 (13%) patients in the Tα1 arm died, compared with 4/26 (15%) patients in the control arm.

After accounting for death as a competing risk, the unadjusted competing risk analysis showed that the incidence of clinical recovery was lower among patients in the Tα1 arm (SHR: 0.80; 95% CI: 0.42 – 1.55) compared with patients in the control arm, although this was not statistically significant, and patients treated with Tα1 were more likely to require higher supplemental oxygenation at baseline.

Among patients with baseline low flow oxygen support, 8/8 (100%) patients in the Tα1 arm and 14/18 (78%) patients in the control arm recovered within 28 days. After accounting for death as a competing risk, we found that the incidence of clinical recovery (**Figure 2A**) was higher among patients treated with Tα1 (SHR: 1.48; 95% CI: 0.68 – 3.25) compared with control patients, although this was also not statistically significant. Among patients with baseline high flow oxygen support, 6/15 (40%) patients in the Tα1 arm and 3/8 (38%) patients in the control arm recovered within 28 days. Similarly, we found that the incidence of clinical recovery (**Figure 2B**) was higher among patients treated with Tα1 (SHR: 1.28; 95% CI: 0.35 – 4.63) compared with control patients, although, again, this was not statistically significant. After adjusting for baseline oxygen support, we found that the incidence of clinical recovery was higher among patients treated with Tα1 (SHR: 1.40; 95% CI: 0.72 – 2.72) compared with control patients, although this was not significant.

3.3 Secondary Efficacy Endpoints

Secondary efficacy endpoints regarding the incidence of all-cause mortality, IMV use, and ICU admission were not statistically different between treatment arms, irrespective of baseline oxygen support (**Table 2**). In terms of mortality, among patients with baseline low flow oxygen support, 0/8 patients in the Tα1 arm died, while 2/18 (11%) patients in the control arm died. Among patients with baseline high flow oxygen support, 3/15 (20%) patients in the Tα1 arm died, while 2/8 (25%) patients in the control arm died.

In terms of IMV use, among patients with baseline low flow oxygen support, no patients in either treatment arm required IMV throughout the study period. Among patients with baseline high flow oxygen support, 1/15 (7%) patients in the Tα1 arm required IMV, while 2/8 (25%) patients in the control arm required IMV. In terms of ICU admission, among patients with

baseline low flow oxygen support, 1/8 (13%) patients in the Tα1 arm were admitted to the ICU, while 0/18 patients in the control arm were admitted to the ICU. Among patients with baseline high flow oxygen support, 6/13 (46%) patients in the Tα1 arm were admitted to the ICU, while 2/4 (50%) patients in the control arm were admitted to the ICU.

3.3.1 Time Trend Analyses

Absolute and relative increases in total lymphocyte count (**Figure S1**), $CD4^+$ T cell (**Figure S2**), $CD8^+$ T cell count (**Figure S3**), and leukocyte count (**Figure S4**) were generally comparable between treatment arms irrespective of baseline oxygen support. Notably, we found that among patients with baseline low flow oxygen, treated patients, compared with control patients, had an average difference of 3.84 times more $CD4^+$ T cells on Day 5 than on Day 1 ($p = 0.0113$; **Table S1**). Moreover, mixed effect modeling demonstrated that treated patients, compared with control patients, had greater average $CD4^+$ T cell ratios on Days 4, 5, and 6 than on Day 1, respectively, as indicated by the non-overlapping confidence intervals (**Figure 3**).

3.4. Safety Endpoints

Overall, ten patients experienced a total number of 18 SAE. For each treatment arm, the SAE with respect to organ system are presented in **Table 3.** Among patients in the Tα1 arm, four patients experienced a total of nine SAE and none of them were deemed related to Tα1 (**Table S3**).

Incidence of AKI, transaminitis, and hyperbilirubinemia classified as either Grade 1, Grade 2, or Grade 3 adverse events, respectively, were similar between treatment arms, while cases of neutropenia and thrombocytopenia classified as either Grade 1 or Grade 2, respectively, were also similar between treatment arms (**Table 4**). Notably, there were four cases of Grade 1

AKI between both treatment arms, with 3/4 (75%) of the cases reported among patients in the Tα1 arm, although this was not a statistically significant difference. Importantly, most patients among both treatment arms did not develop AKI, transaminitis, hyperbilirubinemia, neutropenia, or thrombocytopenia. Moreover, no events of irritation, pain, discomfort, or allergic reactions were reported after Tα1 administration.

4. Discussion

In this pilot trial, we assessed the efficacy and safety of Tα1 among hospitalized patients with hypoxemia and lymphocytopenia due to COVID-19. After stratifying and adjusting, respectively, for baseline oxygen support, the incidence of clinical recovery was higher among patients in the Tα1 arm compared with patients in the control arm, although all analyses were not statistically significant. Also, upward trends in total lymphocyte count, $CD4^+$ T cell count, $CD8^+$ T cell count, and leukocyte count within a week were generally comparable between treatment arms, but Tα1 increased $CD4^+$ T cell count for patients with baseline low flow oxygen support faster than standard of care alone. Clinical trial data reported while our manuscript was under review found that Tα1 is associated with reduced mortality, improvement in the WHO 8-point ordinal scale, and an increase in both $CD4^+$ T cell and $CD8^+$ T cell counts [21]. Of note, the Shetty *et al.* study was not restricted to patients with lymphocytopenia, and treatment regimen was defined as a 7-day course of 1.6 mg of Tα1 in which moderately ill patients received Tα1 four times a day and severely ill patients received Tα1 six times a day. Overall, our study along with the Shetty *et al.* [21] report and other observational findings [22,23] indicate that Tα1 is well tolerated and primed for a larger study in patients with hypoxemia and lymphocytopenia due to COVID-19.

Observational studies have found that Tα1 is associated with both greater [24,26] and reduced [22,23] likelihood of death, as well as both greater [26] and reduced [22] likelihood of

IMV use among severe patients with COVID-19. Taken in their totality, the observational efficacy findings regarding clinical outcomes following treatment with Tα1 are limited due to unmeasured confounding and non-standardized rationale for initiation and duration of Tα1 intervention. Tα1 has also been assessed as a prophylactic agent for COVID-19 among medical staff, but no significant effect was observed [27].

Observational studies [22,41,42] have also assessed the effect of Tα1 on restoring both total lymphocyte count and T cell count in patients with COVID-19. For instance, Yu *et al.* analyzed a small cohort of 25 severe and critical patients with COVID-19 and found a larger increase in lymphocyte count for patients treated with Tα1 compared with control patients [41]. In another retrospective study, Liu *et al.* analyzed 34 severe patients with COVID-19 and found that daily Tα1 administration increases both $CD4^+$ and $CD8^+$ T cell count among patients with counts less than 0.650 x 10^9/L and 0.400 x 10^9/L, respectively, at admission [22]. Of note, the study by Liu *et al.* is limited by lack of comparison group and by restricting analysis to patients who were hospitalized for ten days.

$CD4^+$ T cells are critical to establishing protective immunity against SARS-CoV-2 by promoting production and maturation of neutralizing antibodies [43–45], as well as regulating $CD8^+$ T cells to eliminate virally-infected cells [45]. Importantly, a coordinated humoral and cellular immune response is associated with mild disease [46,47] and patient recovery [48] following COVID-19 infection. We found that all patients with baseline low flow oxygen support who were treated with Tα1 recovered within 28 days. Notably, Tα1 increased $CD4^+$ T cell count among patients with baseline low flow oxygen support faster than standard of care. Thus, the effect of Tα1 on T cell restoration may be modified by disease severity and may contribute to patient recovery. Analogous to monoclonal antibodies [49] and oral agents [50] that

have demonstrated efficacy in earlier stages of COVID-19 infection, the effect of Tα1 may be limited to patients with hypoxemia and lymphocytopenia before they require high flow oxygen.

Irritation, redness, and discomfort at the site of injection are the most common reported adverse reactions following Tα1 administration [14]. Liu *et al.* did not observe any adverse reactions among 76 patients with severe COVID-19 treated with Tα1 [22]. Similarly, irritation, redness, discomfort, or allergic reactions were not observed among our cohort of patients treated with Tα1, and the incidence and severity of AKI, transaminitis, hyperbilirubinemia, neutropenia, and thrombocytopenia were comparable between treatment arms. Moreover, both treatment arms in our study experienced the same number of SAE, and none of the SAE among treated patients were deemed related to Tα1, which is similar to safety data from Shetty *et al*. [21].

Regarding study limitations, the non-blinded study design and patient enrollment limited to a single study center are important considerations. The small sample size of our trial is also a limitation, which resulted in underrepresentation of racial/ethnic groups and contributed to differential baseline oxygen support between treatment arms. Additionally, all patients received corticosteroids, so we could not discern the confounding effect of corticosteroid use on cell counts. Another important consideration is that findings from the *post hoc* analyses should be interpreted with caution because stratification by baseline oxygen support was not planned *a priori.* Nevertheless, our aim was to offer a preliminary assessment of Tα1 as a treatment option for COVID-19. Moving forward, larger placebo-controlled clinical trials with standardized Tα1 dosing regimens and more comprehensive follow-up protocols, including consistent collection of blood samples throughout entire study periods, are needed to definitively assess the efficacy and safety of Tα1, as well to appropriately describe trends in total lymphocyte count, $CD4^+$ T cell

count, $CD8^+$ T cell count, and leukocyte count in patients with hypoxemia and lymphocytopenia due to COVID-19.

5. Conclusion

Data from our randomized pilot trial offer a first preliminary assessment of the clinical efficacy and safety of Tα1 among hospitalized patients with hypoxemia and lymphocytopenia due to COVID-19. We found that Tα1 is safe and tolerable and increases $CD4^+$ T cell count among patients. Research from larger studies is encouraged to further assess the clinical benefit of Tα1 in managing COVID-19.

Funding Source: This work was supported by SciClone Pharmaceuticals, Inc.

Conflict of Interest: The authors declare that they have no relevant conflict of interest.

Author Contributions: Conceptualization: EM, FS; methodology: EM, FS, GB; formal analysis: GB, FS, EKM; investigation: all authors; data curation: FS, EKM, GB; writing original draft: GB, FS; writing review & editing: all authors; visualization: GB, FS

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1 Table 1: Baseline Demographic, Health, and Clinical Characteristics by Treatment Arm

	Total N=49	**Tα1** N=23	**Control** N=26	***P*-Value**
Age				0.28
[IQR]	58 [49 - 74]	64 [49 - 80]	57 [49 - 68]	
Patient Sex				0.82
Female	20 (41%)	9 (39%)	11 (42%)	
Male	29 (59%)	14 (61%)	15 (58%)	
Race/Ethnicity				0.11
Hispanic or Latinx	4 (8%)	1 (4%)	3 (12%)	
Non-Hispanic Black	4 (8%)	4 (17%)	0 (0%)	
Non-Hispanic White	34 (69%)	14 (61%)	20 (77%)	
Other / Unknown	7 (14%)	4 (17%)	3 (12%)	
COVID-19 Vaccination*				0.40
Not Fully Vaccinated	39 (80%)	20 (87%)	19 (73%)	
Fully Vaccinated	10 (20%)	3 (13%)	7 (27%)	
Oxygen Support				0.02
Low Flow	26 (53%)	8 (35%)	18 (69%)	
High Flow	23 (47%)	15 (65%)	8 (31%)	
ICU Admission Status				0.48
Not in ICU	43 (88%)	21 (91%)	22 (85%)	
In ICU	6 (12%)	2 (9%)	4 (15%)	
Corticosteroid Use°				-
Yes	49 (100%)	23 (100%)	26 (100%)	
Remdesivir Use°				0.898
No	5 (8%)	2 (9%)	2 (8%)	
Yes	45 (92%)	21 (91%)	24 (92%)	

Heart Disease	7 (14%)	2 (9%)	5 (19%)	0.29
Pulmonary circulation disorders	4 (8%)	1 (4%)	3 (12%)	0.36
Peripheral vascular disorders	7 (14%)	4 (17%)	3 (12%)	0.56
Hypertension	24 (49%)	12 (52%)	12 (46%)	0.67
Chronic pulmonary disease	15 (31%)	5 (22%)	10 (38%)	0.20
Diabetes	13 (27%)	8 (35%)	5 (19%)	0.22
Hypothyroidism	3 (6%)	0 (0%)	3 (12%)	0.093
Renal failure	1 (2%)	0 (0%)	1 (4%)	0.34
Liver disease	3 (6%)	1 (4%)	2 (8%)	0.63
Solid tumor without metastasis	1 (2%)	1 (4%)	0 (0%)	0.28
Coagulopathy	3 (6%)	2 (9%)	1 (4%)	0.48
Obesity	21 (43%)	12 (52%)	9 (35%)	0.22

Values displayed are N(%), unless otherwise specified. Abbreviations: COVID-19: Coronavirus disease 2019; ICU: Intensive Care Unit. *A patient was considered Fully Vaccinated against COVID-19 if their date of enrollment was $\geq$ 14 days after their 2nd mRNA vaccine dose or $\geq$ 14 days after their Johnson & Johnson vaccine. All patients who did not meet this definition were considered Not Fully Vaccinated. ° Concurrent use of remdesivir and corticosteroids at baseline were defined as having received at least one dose of respective medications within 24 hours of randomization.

Table 2: Efficacy Endpoints for Overall Patients and by Baseline Oxygen Support

Overall	Tα1 N = 23	Control N = 26	SHR (95% CI)	*P*-Value
Clinical Recovery°	14/23 (61%)	17/26 (65%)	0.80 (0.42 – 1.55)	0.516
Mortality	3/23 (13%)	4/26 (15%)	-	0.815
IMV	1/23 (4%)	2/26 (8%)	-	0.626
ICU Admission*	7/21 (33%)	2/22 (9%)	-	0.051
Low Flow Oxygen	Tα1 N = 8	Control N =18	SHR (95% CI)	*P*-Value
Clinical Recovery	8/8 (100%)	14/18 (78%)	1.48 (0.68 – 3.25)	0.326
Mortality	0/8 (0%)	2/18 (11%)	-	0.326
IMV	0/8 (0%)	0/18 (0%)	-	-
ICU Admission*	1/8 (13%)	0/18 (0%)	-	0.126
High Flow Oxygen	Tα1 N = 15	Control N = 8	SHR (95% CI)	*P*-Value
Clinical Recovery	6/15 (40%)	3/8 (38%)	1.28 (0.35 – 4.63)	0.707
Mortality	3/15 (20%)	2/8 (25%)	-	0.782
IMV	1/15 (7%)	2/8 (25%)	-	0.200
ICU Admission*	6/13 (46%)	2/4 (50%)	-	0.893

Abbreviations: ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; SHR: Subdistribution Hazard Ratio. ° Unadjusted Fine and Gray competing risk analysis for overall patients does not adjust for

1 difference in baseline oxygen support between treatment arms,* Incidence of ICU admission was

2 assessed among patients who were not admitted to the ICU on Day 1.

1 Table 3: Incidence of Serious Adverse Events by Treatment Arm

	Tα1	Control
Cardiovascular	Thromboembolism (2) - Deep Vein Thrombosis (1) - Pulmonary Embolism (1)	Non-ST Elevation Myocardial Infarction (1)
Hematologic	Epistaxis (1)	
Infection/Infestation	Sepsis (2) Superimposed Bacterial Pneumonia (1)	Sepsis (1)
Neurological		Brain Stem Herniation due to Left Frontal Brain Lesion (1)
Pulmonary	Respiratory Failure (3)	Respiratory Failure (5)
Renal		Renal Failure (1)

2 (N) indicates the number of patients who experienced the specific type of serious adverse event.

1 Table 4: Abnormal Laboratory Values by Treatment Arm

	Total N = 49	Tα1 N = 23	Control N = 26	*P*-Value
AST				0.91
Grade 1	6 (12%)	3 (13%)	3 (12%)	
No Increase	42 (88%)	20 (87%)	22 (88%)	
ALT				0.57
Grade 1	10 (21%)	4 (17%)	6 (24%)	
No Increase	38 (79%)	19 (83%)	19 (76%)	
Bilirubin				0.59
Grade 1	2 (4%)	1 (4%)	1 (4%)	
Grade 2	1 (2%)	0 (0%)	1 (4%)	
Grade 3	1 (2%)	0 (0%)	1 (4%)	
No Increase	44 (92%)	22 (96%)	22 (88%)	
AKI				0.70
Grade 1	4 (8%)	3 (13%)	1 (4%)	
Grade 2	2 (4%)	1 (4%)	1 (4%)	
Grade 3	2 (4%)	1 (4%)	1 (4%)	
No AKI	41 (84%)	18 (78%)	23 (88%)	
Neutrophil				0.45
Grade 1	6 (12%)	2 (9%)	4 (16%)	
Grade 2	1 (2%)	1 (4%)	0 (0%)	
No Decrease	41 (85%)	20 (87%)	21 (84%)	
Platelets				0.68
Grade 1	11 (23%)	4 (17%)	7 (28%)	
Grade 2	2 (4%)	1 (4%)	1 (4%)	
No Decrease	35 (73%)	18 (78%)	17 (68%)	

Values displayed are N(%). Abbreviations: AKI: Acute kidney injury; ALT: Alanine transaminase; AST: Aspartate transaminase. AKI cases were graded using the KDIGO criteria. Abnormal laboratory values were graded using the CTCAE v5.0.

Figure Legends

Figure 1: Patient disposition flow chart.

Figure 2: Cumulative incidence function of clinical recovery among patients with baseline low flow (2A) and high flow (2B) oxygen support. The cumulative incidence function estimates the probability of a patient recovering using the Aalen-Johansen estimator. At each time point, the number at risk represents the number of patients not lost to follow-up, alive, and yet to experience clinical recovery. Gray's test for equality compares cumulative incidence functions to assess the null hypothesis that the cumulative incidence functions are similar.

Figure 3: Daily average relative increase in $CD4^+$ T cell count among patients with baseline low flow oxygen support. The daily average relative increase was defined as the average ratio between the daily $CD4^+$ T cell count and the $CD4^+$ T cell count at baseline (Day 1).

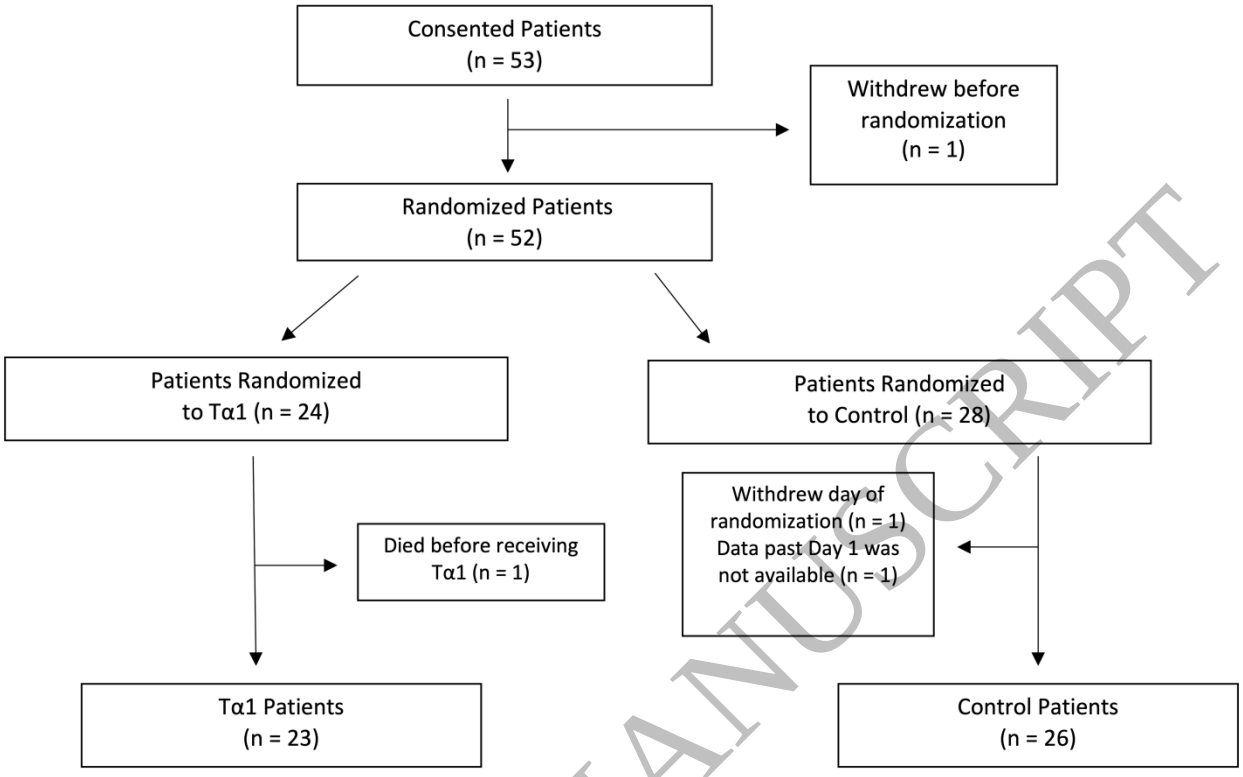

Figure 1
216x134 mm (.50 x DPI)

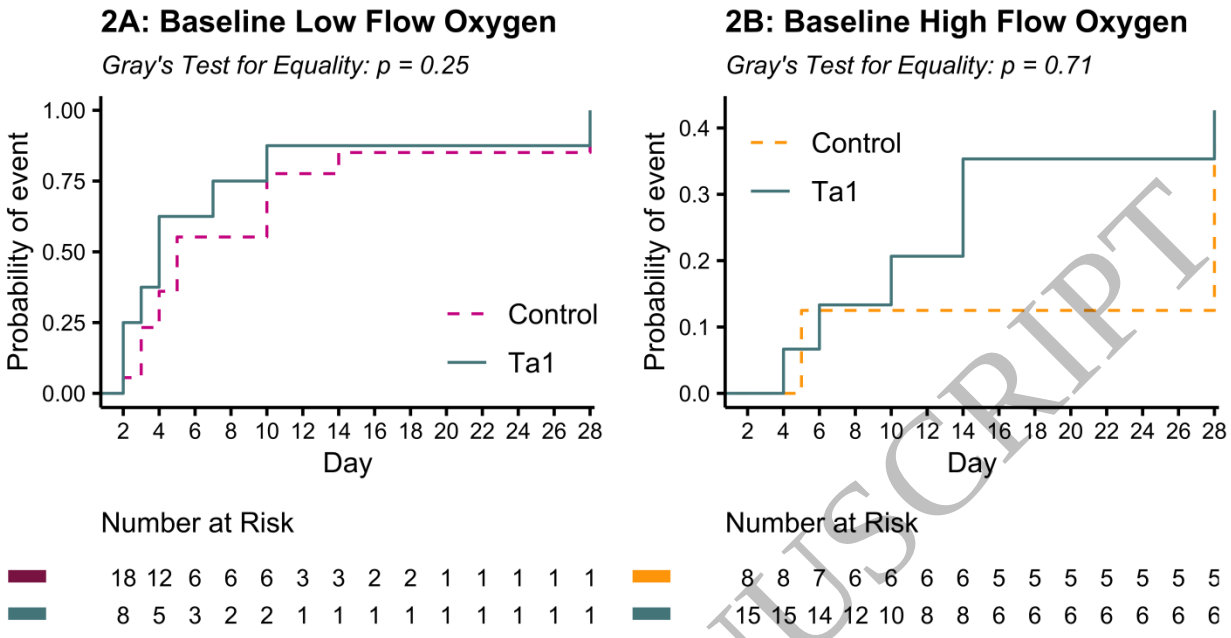

Figure 2
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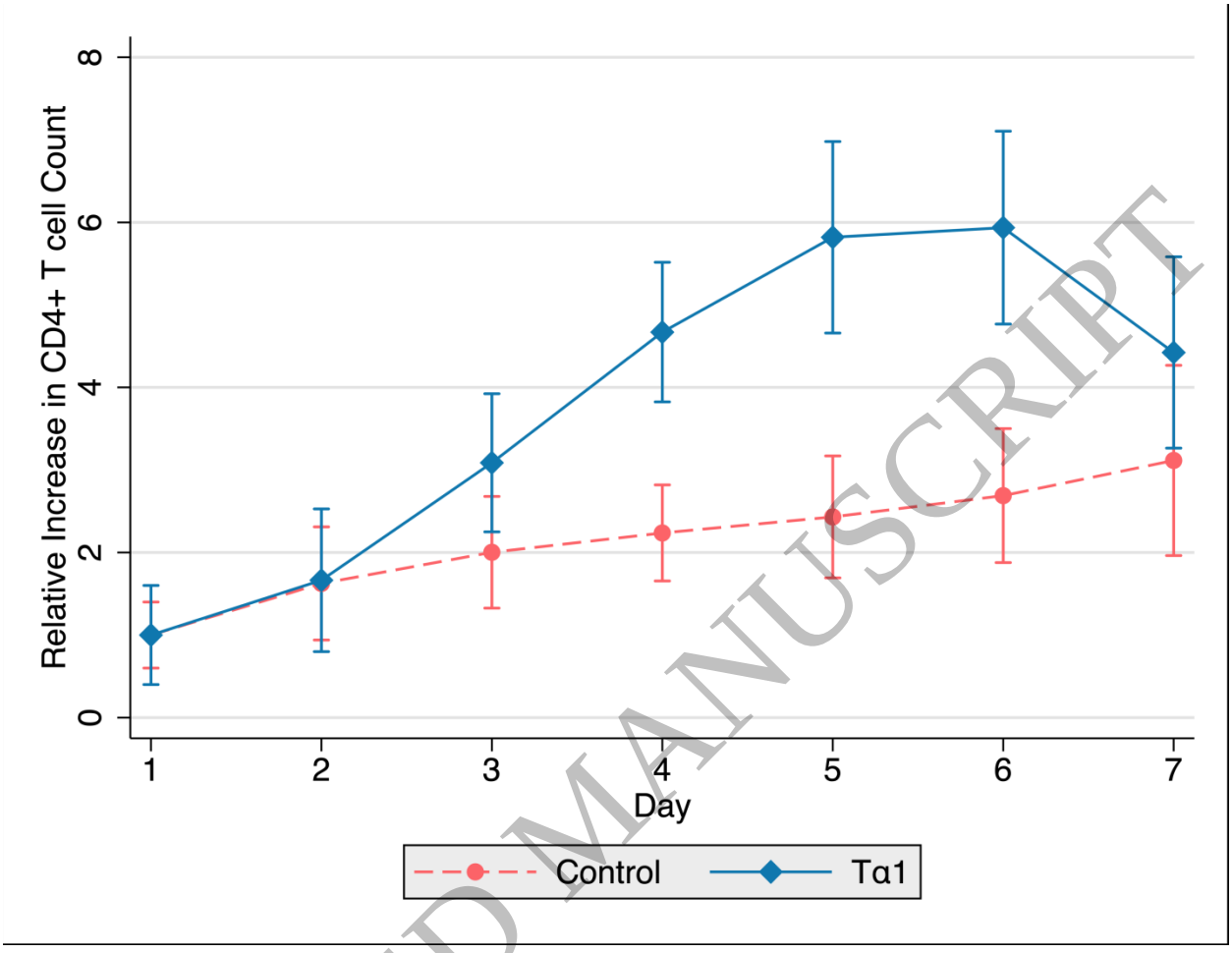

Figure 3
216x166 mm (.50 x DPI)