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Efzofitimod for the treatment of pulmonary sarcoidosis

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Steroid Taper

List of Abbreviations

Abbreviation or Specialist Term	Explanation
ADA	anti-drug antibody
AE	adverse event
ANCOVA	Analysis of Covariance
AUC	area under the curve
CI	confidence interval
CS	corticosteroid
D	day
DL_{co}%	percent-predicted diffusing capacity of the lungs for carbon monoxide
Efzofitimod	ATYR1923
ECG	electrocardiogram
EOS	end of study
FAS	Fatigue Assessment Scale
FVC%	percent-predicted forced vital capacity
GH	general health
HARS	histidyl-tRNA synthetase
HR	health-related
IRR	infusion-related reaction
IV	intravenous
KSQ	King's Sarcoidosis Questionnaire
L	Lung
LCQ	Leicester Cough Questionnaire
MCID	minimal clinically important differences
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed model for repeated measures
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or Specialist Term	Explanation
NRP2	neuropilin-2
Q4W	once every 4-weeks
PRO	patient reported outcome
QOL	quality of life
RCRM	random coefficient regression model
SAC BDI-TDI	Self-Administered Computerized Baseline and Transitional Dyspnea Indices
SAE	serious adverse event
SAT	Sarcoidosis Assessment Tool
SD	standard deviation
SoA	Schedule of Assessments
SOC	system organ class
TEAEs	treatment-emergent adverse events
W	week

Abstract

Background: Pulmonary sarcoidosis is characterized by the accumulation of immune cells that form granulomas affecting the lungs. Efzofitimod (ATYR1923), a novel immunomodulator, selectively binds neuropilin-2, which is upregulated on immune cells in response to lung inflammation.

Research Question*:* What is the tolerability, safety, and effect on outcomes from efzofitimod in pulmonary sarcoidosis?

Study Design and Methods:*:* A randomized, double-blind, placebo-controlled study evaluating multiple ascending doses of efzofitimod administered intravenously every four weeks for 24 weeks. Randomized patients (2:1) underwent a steroid taper to 5 mg/day by Week 8 or <5 mg/day after Week 16. The primary endpoint was the incidence of adverse events; secondary endpoints included steroid reduction, change in lung function, and patient-reported outcomes on health-related quality of life scales.

Results*:* Thirty-seven patients received at least one dose of study medication. Efzofitimod was well tolerated at all doses, with no new or unexpected adverse events and no dose-dependent adverse event incidence. Average daily steroid doses through end of study were 6.8, 6.5 and 5.6 mg for the 1, 3 and 5 mg/kg groups compared to 7.2 mg for placebo, resulting in a baseline-adjusted relative steroid reduction of 5%, 9% and 22%, respectively. Clinically meaningful improvements were achieved across several patient reported outcomes, several of which reached statistical significance in the 5 mg/kg dose arm. A dose-dependent but non-significant trend toward improved lung function was also observed for 3 and 5 mg/kg.

Interpretation*:* Efzofitimod was safe and well tolerated and associated with dose-dependent improvements of several clinically-relevant endpoints compared to placebo. The results of this study support further evaluation of efzofitimod in pulmonary sarcoidosis.

Clinical Trial Registration**:** ClinicalTrials.gov number, NCT03824392

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Sarcoidosis is a multisystem, granulomatous disorder that most commonly affects the lungs[1]. Patients often have organ-specific symptoms such as dyspnea and cough, but also suffer from a range of other disabling non-specific symptoms (e.g., fatigue) that have a major impact on quality of life (QOL). For patients with pulmonary sarcoidosis, the goal of treatment is to reduce the risk of death and/or permanent disability (danger) or to improve the patient's QOL[2], while secondarily managing the inflammation that may lead to pulmonary fibrosis and irreversible loss of lung function[3,4]. The consensus standard of care includes oral corticosteroids (CS) that act mainly by suppressing inflammatory genes[1,5]. Although CS therapy has been shown to stabilize or improve the disease, long-term CS use is associated with significant side effects, including substantial weight gain, development of insulin resistance, risk of infection[6] and impaired QOL[7]. Alternatives, such as immunosuppressive and cytotoxic agents (e.g., methotrexate) can be used; however, these therapies also have significant side effects and toxicities[8]. Hence, there is a need to find new and effective treatments for pulmonary sarcoidosis with fewer side effects and a positive impact on QOL.

Efzofitimod (ATYR1923) is a novel intravenous (IV) biologic immunomodulator composed of a splice variant of histidyl-tRNA synthetase (HARS)[9,10] that encodes the immunomodulatory domain that binds to the neuropilin-2 (NRP2) receptor protein[11]. NRP2 is a pleiotropic receptor[12] that is upregulated on the surface of activated immune cells responsible for inflammation and granuloma formation in the lungs of patients with pulmonary sarcoidosis[13]. Preclinical studies have shown that efzofitimod regulates immune responses[14-16] and significantly reduces lung fibrosis and inflammation[17,18]. Thus, efzofitimod may leverage a naturally occurring human immunomodulatory function to therapeutically control or balance the human immune system.

In healthy volunteers, single doses of efzofitimod (0.03 to 5 mg/kg) were well tolerated, with no significant safety concerns[19]. Efzofitimod pharmacokinetics were dose-proportional over the range of 0.03 to 5.0 mg/kg, with a mean half-life ranging from 167 to 242 hours (7 to 10 days), supporting once every 4-weeks (Q4W) dosing[19]. Here, we present the primary clinical data from the first investigation of efzofitimod in patients with pulmonary sarcoidosis, designed to evaluate the safety, tolerability, and preliminary efficacy in this patient population.

Methods

Trial Design and Procedures

Patients were 18 to 75 years of age, had a diagnosis of pulmonary sarcoidosis for ≥ 6 months according to the 1999 American Thoracic Society standards[20], and had evidence of parenchymal involvement. The full inclusion and exclusion criteria are provided in the online data supplement.

This was a randomized, double-blind, placebo-controlled multiple ascending dose study with 3 sequential dose cohorts with a 2:1 randomization (efzofitimod to placebo) in each cohort; the planned study size was 36 patients (ClinicalTrials.gov number, NCT03824392). Placebo subjects from each of the three cohorts were pooled when comparing safety and efficacy between placebo and efzofitimod. The treatment period consisted of 6 IV administrations of study drug (efzofitimod or placebo) once every 4-weeks for a total of 20 weeks (at D1 and Week [W]4, 8, 12, 16, and 20) with the final study assessments conducted at W24.

Safety and tolerability assessments consisted of evaluation of treatment emergent adverse events (TEAEs), physical examinations, vital signs and temperature, 12-lead ECGs, pulse oximetry, weight, immunogenicity, and clinical laboratory tests. Assessment of daily CS dose over the study period (D1-W24) and the number of patients who achieved the targeted tapered

dose of prednisone 5 mg/day (or equivalent) through W24 were also recorded. Pulmonary function tests including the percent-predicted forced vital capacity (FVC%) and percent-predicted diffusing capacity of the lungs for carbon monoxide (DL_{CO}%) were also performed. Patient-reported QOL was assessed by the Sarcoidosis Assessment Tool (SAT), the King's Sarcoidosis Questionnaire (KSQ), the Leicester Cough Questionnaire (LCQ), the Fatigue Assessment Scale (FAS), and the Self-Administered Computerized Baseline and Transitional Dyspnea Indices (SAC BDI-TDI). The schedule of assessments (SoA) is presented in the online data supplement (Table E1).

Starting on D15, patients began a taper (reduction) of CS from their starting dose of 10 to 25 mg/day of prednisone (or equivalent) to a target dose of 5 mg/day, which was to be completed on or before D50. The CS dose was to be tapered every 1 to 2 weeks, depending on the starting dose, with smaller incremental titrations allowed per the Investigator's judgment, as long as the patient reached the goal dose by D50. Patients were maintained at the target CS dose of 5 mg/day (or equivalent) through W24. Optional titrations in the CS dose to below 5 mg/day could occur after W16 if the Investigator determined further titration to be feasible. Patients who developed an acute worsening of sarcoidosis symptoms or who were unable to tolerate the taper were allowed to receive rescue treatment with higher CS doses per the site Investigators' clinical judgement; upon resolution of symptoms, the taper could be re-attempted per the Investigators' judgment.

Outcomes and Statistical Analysis

The primary endpoint was to evaluate the safety and tolerability of efzofitimod versus placebo in patients with pulmonary sarcoidosis. AEs were recorded from the date of informed consent and coded using the Medical Dictionary for Regulatory Activities (MedDRA), version

24.0. Treatment-emergent adverse events (TEAEs) were defined as any AE or worsening of an existing condition after initiation of the study drug through 30 days after the last study. The intensity of each AE was rated by the blinded Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. Please refer to the online data supplement for grading of AEs. The TEAEs were summarized by frequency of occurrence, number of patients experiencing the event, relationship to study medication, intensity and seriousness. Patients were closely monitored during study drug infusions and any AEs that occurred during or within 24 hours after study drug administration were captured as infusion related reactions (IRRs).

For the secondary outcome of potential CS-sparing effect of efzofitimod, the analysis included the time-adjusted area under the curve (AUC) from baseline to W24 for each patient and a corresponding AUC for the post-taper period (D51 through end of study [EOS]). The time-adjusted AUC approximates the average daily CS dose per patient over the respective time period. The development of anti-drug antibody (ADA) and Jo-1 Ab (antibodies that recognize HARS) was used to summarize immunogenicity.

Exploratory outcomes evaluated the change from baseline in lung function through W24. The change in PRO scores from baseline to W24 were also assessed; SAT: sarcoidosis-specific patient-reported outcomes of impact of disease and response to therapy[7]; KSQ: 29-item questionnaire related to general health (GH) and lung (L), (range: 1 – 100, higher numbers indicating better health[21]); LCQ: 19-item self-complete QOL measure of chronic cough (range: 3 – 21, higher numbers indicating better QOL[22]); FAS: 10 fatigue-related questions (range: 10 – 50, scores ≥22 are considered to represent substantial fatigue[23]); SAC BDI-TDI: graded

assessments of changes in the severity of dyspnea at baseline and at subsequent visits (range: 0 – 12, the lower the score the worse the severity of dyspnea[24]).

The primary analysis population (Safety Set) comprised all patients who received any amount of study drug and was based on the actual treatment received. The primary efficacy analysis was the modified intent to treat (mITT) population, defined as all randomized patients who received at least one administration of study drug.

Statistical analyses were performed in an exploratory manner to reflect the Phase 1/2 nature of the study. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables were summarized with the number and percentage (n, %) of patients within each classification. Any calculated p-values for exploratory variables were analyzed using either Analysis of Covariance (ANCOVA) or a mixed model for repeated measures (MMRM) with the results presented as the difference between active groups and placebo in the least-squares mean change.

Results

Baseline Characteristics and Patient Disposition

A total of 37 patients were randomized and received at least one dose of study drug: 12 to placebo and 8, 8, and 9 to the 1 mg/kg, 3 mg/kg and 5 mg/kg efzofitimod doses, respectively. Nine (24%) patients prematurely discontinued treatment, 6 due to coronavirus (COVID-19)-related restrictions (e.g., operational feasibility and site closures), 2 due to AEs, and 1 due to Investigator decision. Twenty-eight (76%) patients completed the study (Figure 1).

Baseline demographic characteristics were generally well balanced across the treatment groups. The mean (SD) age was 52.4 (10.1) years, with 54% female, 62% White, and 38% Black patients. Baseline disease characteristics, including pulmonary function, were similar across

treatment groups. Background CS use was generally comparable across treatment groups; of note, more patients in the placebo group were on concomitant immunomodulators compared to the efzofitimod treatment groups. Nearly all patients (36 [97%]) were receiving prednisone (one received methylprednisolone), with a mean (SD) daily steroid dose of 13.2 (4.4) mg/day, and 22 (59.5%) patients receiving 10 to <15 mg/day of prednisone equivalent dose. Demographics and disposition by treatment group are presented in Table 1.

Safety and Tolerability

There were no deaths or drug-related serious adverse events (SAEs) observed in the study. Overall, the proportion of patients with an AE was similar between the placebo and efzofitimod treatment groups, with no relationship between AE frequency and increased efzofitimod dose (Table 2). AEs within the respiratory system disorders system organ class (SOC) were most common and included, cough, wheezing, dyspnea, and upper respiratory tract infection (Table 2). These events were not dose-dependent, tended to be mild in severity and did not limit treatment duration. The high incidence of respiratory events across all treatment groups is expected in this patient population and aligns with the underlying disease.

During the treatment period, 4 (33%) patients in the placebo group and 4 (16%) patients receiving efzofitimod experienced grade 3 TEAEs. For placebo-treated patients, these events included urticaria, streptococcal sepsis, bradycardia, and worsening of pulmonary sarcoidosis. The relationship between sarcoidosis and study drug was designated as “unlikely related,” while urticaria was considered “related” to the study drug. One patient in the placebo arm experienced two grade 3 AEs (bradycardia and worsening pulmonary sarcoidosis) which were considered “unlikely” to be related to the study drug. In efzofitimod-treated patients, two events occurred at 1 mg/kg (acute cholecystitis and depression) and two events occurred at 5 mg/kg (toothache and

myalgia). None of the grade 3 events reported with efzofitimod were considered "possibly related" or "related." Serious TEAEs were reported in 1 (8.3%) placebo- and 1 (4%) efzofitimod-treated patients; streptococcal sepsis (placebo) and acute cholecystitis (1 mg/kg efzofitimod).

Two patients discontinued study treatment due to an AE, both of which were assessed as "related" to study drug: one patient in the placebo group due to urticaria and one patient in the 1 mg/kg efzofitimod group due to alopecia. One additional patient in the 1 mg/kg efzofitimod group experienced an acute exacerbation of pulmonary sarcoidosis that was considered "unrelated" to study drug but resulted in treatment discontinuation based on Investigator discretion. Overall, the incidence of patients reporting IRRs was low, with only one patient in the 3 mg/kg efzofitimod group experiencing mild-to-moderate IRRs on three separate occasions which were considered by the Investigator to be "related" to study drug but did not require interruption of the infusion. There were no patients who received efzofitimod that were positive for anti-efzofitimod or anti-HARS antibodies (e.g., Jo-1) and no apparent trends were seen within or across treatment groups for vital signs, ECG, or blood oxygen saturation levels.

CS Use, Lung Function and QoL

The average daily dose of CS at baseline was comparable across treatment arms. All efzofitimod groups had a lower CS use through W24 compared to placebo. These reductions appear to be dose-dependent, with the largest percent reduction observed in the 5 mg/kg treatment group, with a 58% decrease from baseline (Table 3) compared to a 46% decrease in placebo, a difference of 12%. Average daily steroid doses through end of study were 6.8, 6.5 and 5.6 mg for the 1, 3 and 5 mg/kg groups compared to 7.2 mg for placebo, resulting in a baseline-adjusted relative steroid reduction of 5%, 9% and 22%, respectively. A comparison of adjusted means between placebo and efzofitimod revealed that the highest two efzofitimod treatment

groups had a larger, although statistically non-significant, percent decrease from baseline in overall CS use on study (-2% for 3 mg/kg; -12% for 5 mg/kg) compared to placebo. Supporting these dose-related trends in CS reduction, 3 (33%) of patients treated at the highest dose (5 mg/kg) were able to taper off CS completely and maintain this through the EOS.

Overall, the two highest doses of efzofitimod resulted in improvements in key lung function parameters at W24 from baseline compared to placebo, consistent with a dose-dependent effect (online data supplement, Table E2). Relative to placebo, the effects of 5 mg/kg efzofitimod were observed early (e.g., W4 for FVC% and W12 for DL_{CO}%) and were maintained across all evaluated time points through W24. Overall, FVC% declined over the study period with placebo and 1 mg/kg efzofitimod, and increased with the higher doses of efzofitimod (Figure 2). While the improvements in FVC% and DL_{CO}% did not achieve statistical significance at the 5 mg/kg dose level, in part due to the limited sample size, the trend we observed signifies the possibility of biological activity warranting further investigation in a larger population.

Results observed with the PROs evaluated support the hypothesis that the 5 mg/kg dose group may provide a benefit, with trends which were occasionally statistically significant improvements in the mean change from baseline to W24 for SAT-L, KSQ-L, KSQ-GH, and FAS compared to placebo (Table 4); trends in PROs appeared before W24 (online supplement, Figure E1). Following 5 mg/kg efzofitimod, significant improvements were observed prior to W24: SAT-L statistical improvement observed by W12 (online supplement, Table E3); KSQ-L statistical improvement observed by W8 (online supplement, Table E4); KSQ-GH statistical improvement observed by W4 and maintained through W24 (online supplement, Table E5); trends toward improvement in FAS observed at W8 (online supplement, Table E6). The changes in other PROs or PRO domains were variable (online supplement, Table E7).

Discussion

The results from the present study suggest that efzofitimod was safe and well tolerated in patients with pulmonary sarcoidosis, with no clear dose-relationship with regard to the incidence of TEAEs. Specifically, no apparent trends overall, within or across efzofitimod treatment groups, were seen regarding change from baseline in clinical laboratory tests, and no notable differences from placebo were observed. There were no deaths and or discontinuations due to SAEs in efzofitimod-treated patients. Overall, there was a low rate of serious or "related" AEs, with no dose dependent relationship between AE frequency and increased dose. The non-serious Grade 3 AEs reported following efzofitimod (depression, toothache, and myalgia), were deemed by the Investigator as "unlikely" related to study drug and did not result in hospitalization or threat of hospitalization. There was no reported immunogenicity as supported by the low incidence of patients with IRRs (n = 1) and the lack of anti-drug antibody (ADA) induction following repeat infusions.

All efzofitimod treatment groups had a lower CS use at W24 compared to placebo, which appeared to be dose-dependent, with the largest difference observed in the 5 mg/kg treatment group. Four patients were able to taper off prednisone completely (1 on placebo and 3 on 5 mg/kg). However, the placebo patient could not be maintained off prednisone for more than 8 weeks due to worsening sarcoidosis and required resumption of prednisone to 10 mg/daily. Overall, CS tapering was possible in all groups, consistent with prior data showing that sarcoidosis patients in clinical trials can successfully taper CS over a span of several months[25]. However, 20-74% of patients will exhibit relapses, with approximately 50% occurring within six months of stopping therapy[26,27]. Despite the short duration of this trial, we were able to demonstrate numerical differences in tolerance to CS taper among the study groups, which may

suggest biologic activity of the medication. Although the magnitude of steroid reduction might be deemed small, steroid toxicity depends on cumulative exposure (daily dose x duration). A 10% decrease in the daily dose may result in a meaningful decrease in the cumulative exposure over a year. Indeed, the ERS considers steroid reduction a critical outcome measure.[2]

Compared to placebo, the highest doses of efzofitimod resulted in improvements in FVC% and DL_{CO}% through W24, suggesting a dose-dependent effect on lung function. The improvement of FVC% observed in the current study was small, but all patients were on baseline anti-inflammatory therapy for their pulmonary sarcoidosis at time of study entry. Studies of chronic pulmonary sarcoidosis have rarely demonstrated a significant improvement in FVC%[2,28]. The changes in FVC% reported herein were similar to those observed in the treatment arm of a randomized trial of infliximab, where the mean 24-week improvement was 2.5%[29]. In that trial, CS were not tapered. Randomized trials of CS monotherapy as initial therapy for pulmonary sarcoidosis have found similar improvements in FVC%[30,31].

Changes in QOL have been considered a major priority for treatment of sarcoidosis[32]. QoL endpoints were exploratory assessments, which were not corrected for multiple hypothesis testing. We observed significant improvements at W24 in PROs, such as SAT-L, KSQ-L, KSQ-GH, and FAS, in the 5 mg/kg group. Patients who received 5 mg/kg efzofitimod demonstrated significant improvements in KSQ-L at W8, and significant improvements in KSQ-GH as early as W4; both of these PROs maintained significance through W24. The magnitude of change in these PROs at 24 weeks exceeded the minimal clinically important differences (MCID). For example placebo-adjusted KSQ-GH improved by 18.3 points with 5 mg/kg efzofitimod versus the MCID of 8 points; for KSG-L, both the 3 mg/kg (+11.3) and 5 mg/kg (+16.2) efzofitimod groups exceeded the MCID of 4 points, though only the highest dose was statistically significant.

For the SAT-L (MCID estimate -2.7), the change in the 3 mg/kg (-6.5) and 5 mg/kg (-6.4) groups both reflect meaningful improvements[33]. The changes in the FAS also exceeded the MCID of 4 points[34]; however, these patients may still have noted some fatigue. The magnitude of these changes exceeds those seen in prior studies evaluating changes in HR-QOL during treatment of pulmonary sarcoidosis[35,36].

The major limitation of this study was the small sample size and as such the results will need to be confirmed in a larger study. Operational site difficulties imposed by the COVID pandemic accounted for most of the dropouts. Because of the size, there were baseline imbalances for several of the key endpoints and the CIs are fairly wide, which limits our ability to draw firm conclusions. However, statistical analyses when adjusted for baseline value, demonstrated that the major endpoints exhibited directionality in favor of a beneficial effect of efzofitimod, suggesting that a larger sample may solidify the findings. It is also acknowledged that statistical adjustment for multiple hypothesis testing and power analysis have not been performed, due to the exploratory nature of the study. Most patients in this study were receiving >10 mg of prednisone, therefore, further improvement in FVC% was not likely to be demonstrated. However, the current findings suggest a CS sparing effect and improved QOL beyond the MCID. Another limitation is the absence of a rigid CS tapering protocol based on defined thresholds for measurable physiologic indices or PROs. Variability in CS tapering aggressiveness may introduce residual bias in the results, but in general this effect would likely tend to reduce the chance of a positive finding rather than increase it, since the patients were randomized. Allowing some Investigator discretion about CS tapering more accurately mirrors usual practice. It is also not possible to determine whether improvements in QOL scores directly reflect efzofitimod activity or occurred indirectly because efzofitimod allowed a greater

reduction of prednisone, which has been associated with worse QOL as measured by SF-36 and SGRQ[37]. The dose response suggests that the medication itself rather than a CS reduction is more likely to contribute to the observed improvement. Finally, several patients dropped out of the study due to the challenges of clinical trials during the COVID-19 pandemic.

Interpretation

In patients with pulmonary sarcoidosis, efzofitimod was safe and well tolerated. Exploratory analyses suggest clinically meaningful improvements following 5 mg/kg efzofitimod on CS use and improvements in lung function and PROs compared to placebo, without increasing the risk of side effects. However, due to the limited number of patients enrolled in this trial, these findings should be considered only as hypothesis-generating. These results support further evaluation in prospective trials of efzofitimod in patients with pulmonary sarcoidosis.

Take-home points

Study question: What is the tolerability of efzofitimod for pulmonary sarcoidosis, and can we discern any evidence of clinical efficacy to support a larger trial?

Results: There were no differences in adverse effects or tolerability between subjects randomized to efzofitimod or placebo. Patient reported outcomes improved in the higher dose arms, and there were positive trends for other endpoints.

Interpretation: Efzofitimod may be useful for pulmonary sarcoidosis; larger studies are needed to confirm and extend these findings.

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Figure Legends

Figure 1: Patient Disposition (modified Intention-to-Treat Population).

AE = adverse event; COVID-19 related = COVID-related site closures

Figure 2: Change from Baseline Lung Function Efzofitimod vs. Placebo (modified Intention-to-Treat Population). Absolute forced vital capacity (FVC) percent (%) predicted (A) and absolute change from baseline in FVC% predicted (B) from D1 to end of study (EOS).

Table 1: Baseline Demographics, Disease Characteristics, Corticosteroid and Immunomodulator Use (modified Intention-to-Treat Population)

	Placebo	Efzofitimod			
	n = 12	1 mg/kg n = 8	3 mg/kg n = 8	5 mg/kg n = 9	All n= 37
Mean Age (years); SD	52.5 (10.2)	54.5 (11.3)	51.8 (11.4)	50.8 (9.8)	52.4 (10.1)
Sex (female); n (%)	7 (58.3)	4 (50)	4 (50)	5 (55.6)	20 (54.1)
Race, n (%)					
White	9 (75)	5 (62.5)	6 (75)	3 (33.3)	23 (62.2)
Black	3 (25)	3 (37.5)	2 (25)	6 (66.7)	14 (37.8)
Duration of Disease (years), median	2.9	5.3	4.3	2.9	4.2
Range	0.5, 10.2	1.5, 19.6	0.6, 15.0	0.5, 28.0	0.5, 28.0
BDI – Total Score Baseline, mean (SD)	4.8 (2)	4.3 (1.8)	7.6 (2.9)	6.3 (2.5)	5.65 (2.54)
Baseline Lung Function, n (%)					
mMRC Dyspnea Scale Score					
1-2	8 (66.7)	3 (37.5)	8 (100)	5 (55.6)	24 (64.9)
3-4	4 (33.3)	5 (62.5)	0	4 (44.4)	13 (35.1)
FEV1%, mean (SD)	68.3 (20.1)	60.4 (10.2)	77.6 (11.1)	77.3 (19.5)	70.8 (17.3)
FVC%, mean (SD)	77.3 (11.5)	68.3 (9.7)	83.8 (7.3)	83.8 (16.6)	78.3 (12.9)
FEV1/FVC, mean (SD)	0.7 (0.15)	0.7 (0.08)	0.73 (0.08)	0.72 (0.1)	0.715 (0.11)
DLco%, mean (SD)	61.7 (19.7)	61.9 (21.4)	75.5 (19.9)	54.5 (14.1)	63.8 (19.8)
Baseline Steroid Use, mean (SD)					
Prednisone Equivalent Dose (mg/day)†	13.3 (4.4)	11.3 (3.5)	14.4 (6.2)	13.9 (3.3)	13.2 (4.4)
10 to < 15, n (%)	7 (58.3)	7 (87.5)	5 (62.5)	3 (33.3)	22 (59.5)
15 to < 20, n (%)	2 (16.7)	0	0	5 (55.6)	7 (18.9)
≥ 20, n (%)	3 (25)	1 (12.5)	3 (37.5)	1 (11.1)	8 (21.6)
Baseline Immunomodulator Use, n (%)					
Methotrexate	4 (33.3)	2 (25)	0	3 (33.3)	9 (24.3)
Azathioprine	2 (16.7)	0	0	1 (11.1)	3 (8.1)
Hydroxychloroquine	0	1 (12.5)	0	0	1 (2.7)
Leflunomide	0	0	1 (12.5)	0	1 (2.7)
None	6 (50)	5 (62.5)	7 (87.5)	5 (55.6)	23 (62.2)

BDI = Baseline Dyspnea Index; DL_{co}% = precent-predicted diffusing capacity of lung for carbon monoxide; FEV1 = Forced expiratory volume in one second; FVC% = percent-predicted forced vital capacity; mMRC = Modified

Medical Research Council; n = number of patients with an AE; SD = standard deviation; % = percent of patients with AE

* The modified Intention to Treat (mITT) set comprised all randomized patients who had at least 1 administration of study drug.

^ All steroids were converted to prednisone dose equivalent.

Baseline measures were defined as the last measure assessed on or before the first dose date. If multiple measures were taken on D1 (e.g., vital signs, 12-lead ECG), the last measure before the first dose was used as baseline.

Table 2: Treatment-Emergent Adverse Events >15% by Relationship to Treatment (Safety Set)

Preferred Term All Casualty; n(%)	Placebo	Efzofitimod		
	n = 12	1 mg/kg n = 8	3 mg/kg n = 8	5 mg/kg n = 9
Any TEAE	10 (83.3)	8 (100)	7 (87.5)	8 (88.9)
Cough	1 (8.3)	4 (50)	2 (25)	1 (11.1)
Fatigue	0	2 (25)	1 (12.5)	4 (44.4)
Wheezing	0	4 (50)	0	1 (11.1)
AST increased	2 (16.7)	0	0	0
Dizziness	1 (8.3)	1 (12.5)	1 (12.5)	2 (22.2)
Dyspnea	0	0	2 (25)	0
Arthralgia	0	1 (12.5)	2 (25)	0
Headache	1 (8.3)	0	2 (25)	1 (11.1)
Upper respiratory tract infection	1 (8.3)	1 (12.5)	2 (25)	0
Back pain	0	0	2 (25)	0

AE = adverse event; AST = Aspartate aminotransferase; n = number of patients with an AE; TEAE = treatment-emergent adverse events; % = percent of patients with AE

Table 3: Corticosteroid Burden* – (modified Intention-to-Treat Population)

Parameter	Placebo n = 12	Efzofitimod 1 mg/kg n = 8	Efzofitimod 3 mg/kg n = 8	Efzofitimod 5 mg/kg n = 9
Baseline Prednisone Equivalent Dose (mg/day)	13.3 (4.4)	11.3 (3.5)	14.4 (6.2)	13.9 (3.3)
Average daily dose (mg), adjusted mean†	7.2	6.8	6.5	5.6
Change from baseline (%), adjusted mean (SD)	-45.7 (26.7)	-41.4 (15.9)	-48.9 (19.7)	-58.1 (23.4)
Difference in adjusted means (%), (95% CI)§	--	1.2 (-20.0, 22.4)	-2.3 (-23.1, 18.5)	-12.3 (-33.1, 8.5)
Tapered to 0 mg and maintained taper, n (%)	0	0	0	3 (33.3)

CI = confidence interval; SD = standard deviation

*Any corticosteroid that is not prednisone is converted to prednisone equivalent dose. All endpoints use the Post-taper period (Day 51 to End of dosing).

†Adjusted Mean from ANCOVA adjusting for baseline steroid use

§Time adjusted AUC of percent change from baseline, p>0.05

Table 4: Change in Patient Reported Outcomes (PROs) at Week 24 from Baseline Efzofitmod vs. Placebo - (modified Intention-to-Treat Population)

PRO Measurement (Adjusted Mean*)	1 mg/kg n = 8	3 mg/kg n = 8	5 mg/kg n = 9
SAT-L	4.44 (-1.15, 8.19) p = 0.18	-6.49 (-12.22, -0.47) **p = 0.038**	-6.42 (-11.7, -1.13) **p = 0.018**
KSQ-L	-6.41 (-20.47, 7.65) p = 0.35	11.29 (-3.39, 25.96) p = 0.12	16.17 (2.49, 29.85) **p = 0.022**
KSQ-GH	-5.1 (-18.52, 8.32) p = 0.44	2.13 (-12.76, 17.01) p = 0.77	18.33 (5.16, 31.49) **p = 0.008**
FAS-Total	0.76 (-5.09, 6.62) p = 0.79	-4.78 (-11.22, 1.65) p = 0.14	-7.77 (-13.50, - 2.03) **p = 0.010**

FAS = Fatigue Assessment Scale; GH = General Health; KSQ = King's Sarcoidosis Questionnaire; L = Lung ; SAT = Sarcoidosis Assessment Tool

*Adjusted Means taken from MMRM analysis adjusting for corresponding baseline score

Figure 1: Patient disposition (modified intention-to-treat population).

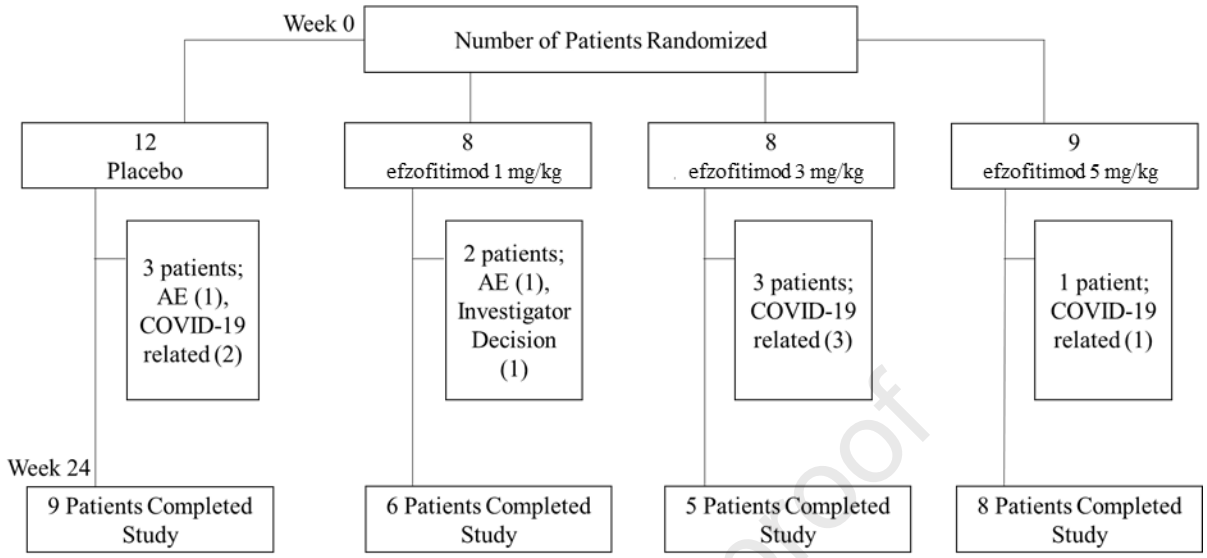
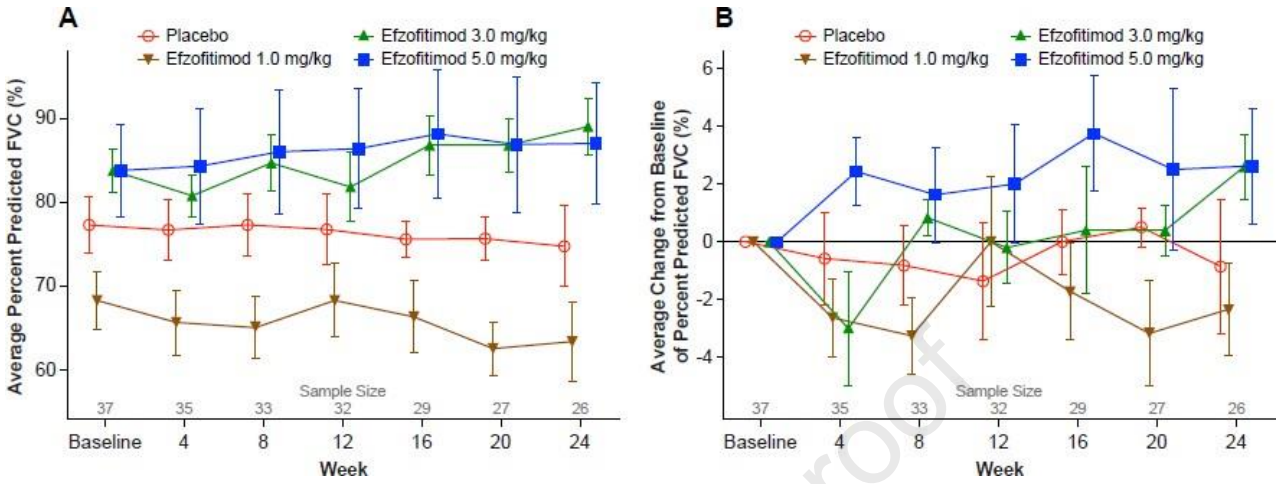


Figure 2: Change from Baseline in Lung Function Efzofitimod vs. Placebo - (modified Intention-to-Treat population)



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Supplement: Efzofitimod for the treatment of pulmonary sarcoidosis

Online Data Supplement

METHODS

Inclusion and Exclusion Criteria

Inclusion Criteria:

The following inclusion criteria must be met for a patient to be eligible for inclusion in the study:

1. Male or female patients aged ≥18 to ≤75 years inclusive at time of informed consent
2. Diagnosis of pulmonary sarcoidosis for ≥6 months (cutaneous and ocular involvement allowed), defined as:
    - Histologically proven diagnosis of sarcoidosis by bronchoscopy, biopsy (any organ) or bronchioalveolar lavage.
    - Evidence of parenchymal lung involvement by historical radiological evidence (eg, computed tomography [CT], magnetic resonance imaging [MRI], 18F-FDG PET/CT or chest X-ray) or on the Screening 18F-FDG PET/CT.
3. Must have symptomatic and/or active pulmonary sarcoidosis as evidence by:
    - Clinical findings of dyspnea, as indicated by a Modified Medical Research Council (MRC) Dyspnea Scale grade of at least 1; and
    - FVC% predicted ≥50%.
4. Must be receiving treatment with 10 to 25 mg/day of oral prednisone (or oral equivalent; eg, methylprednisolone), at a stable dose for ≥4 weeks prior to Day 1, and be determined by the Investigator to be capable of undergoing the protocol-specified steroid taper regimen.
    - Treatment with one oral immunomodulatory therapy (eg, methotrexate, azathioprine, hydroxychloroquine) at a stable dose for ≥1 month prior to Day 1 is allowed but not required. The dose of this therapy should remain constant throughout the study.
5. Body weight ≥45 kg and <160 kg.
6. Female patients may be of childbearing potential or of non-childbearing potential (either surgically sterilized or at least 1 year postmenopausal (confirmed by amenorrhea duration of at least 12 months and serum follicle-stimulating hormone [FSH] ≥30 mIU/mL).
    - Female patients of childbearing potential must be non-pregnant and non-lactating, and have a negative pregnancy test at Screening (serum) and at Day 1 (urine) prior to first study drug infusion.
    - Additionally, female patients of childbearing potential must be willing to use highly-effective contraception (see Section 7.1.6.4) from Screening until 90 days after the last follow-up visit.
7. Male patients, if not infertile or surgically sterilized, must agree to use highly-effective contraception (see Section 7.1.6.4) and not donate sperm from Screening until 90 days after the last follow-up visit.
8. Provision of written informed consent.

9. Be able to communicate well with the Investigator and site personnel, and agree to comply with all study procedures and requirements.

Exclusion Criteria:

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Current disease presentation consistent with Lofgren's syndrome (ie, presence of the triad of erythema nodosum, bilateral hilar lymphadenopathy on chest X-ray, and joint pain).
2. History of severe allergic or anaphylactic reactions to therapeutic proteins, or known sensitivity to ATYR1923 or to its inactive components (L-histidine, sodium chloride, sucrose, L-methionine, and polysorbate-20).
3. Treatment (within 4 months of Day 1) with biological immunomodulators such as tumor necrosis factor-alpha (TNF-α) inhibitors (eg, infliximab, adalimumab).
4. Current evidence of clinically significant cardiovascular, hepatic, renal, hematological, metabolic, or gastrointestinal disease, or has a condition that requires other treatment, may not allow safe participation, or which in the opinion of the Investigator should preclude the patient's participation in the clinical study.
5. Clinically significant pulmonary hypertension requiring vasodilator treatment.
6. Any history of tuberculosis, or evidence of active systemic non-tuberculous fungal or mycobacterial infection within 1 year of Screening.
7. History of clinically significant cardiac, neurological, gastrointestinal, and/or renal manifestations of their sarcoidosis.
8. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma.
9. Major surgery within 3 months prior to Day 1 or anticipated surgery during the study.
10. Any condition that necessitated hospitalization within the 3 months prior to Day 1 or is likely to require so during the study.
11. Participation in another clinical study of an investigational agent or device within 3 months (small molecules) / 6 months (biologics) or 5 half-lives (if known) of the agent, whichever is longer.
12. History of or positive results of screening for hepatitis B (hepatitis B surface antigen [HBsAg]), hepatitis C (anti-hepatitis C virus [HCV] antibodies [Ab]) or human immunodeficiency virus (HIV) (HIV Ab type 1 and 2).
13. Is an active, heavy smoker of tobacco/nicotine-containing products (defined as >20 cigarettes/day or e-cigarette equivalent).
14. Active substance abuse (drugs or alcohol) or history of substance abuse within the 12 months prior to Screening.

15. Clinically significant abnormalities in the Screening physical examination, vital signs, ECG, or clinical laboratory test results that, in the opinion of the Investigator and Medical Monitor should preclude the patient's participation in the clinical study.
16. Patient has received a live vaccination within 8 weeks before Day 1 or inoculation with a live vaccine is planned during study participation.
17. Jo-1 Ab levels >7 U/mL at Screening, or past history of Jo-1 Ab positivity.
18. Any other condition or circumstance that, in the opinion of the investigator, would be likely to prevent adequate compliance with the study protocol.
19. Significant and/or acute illness (eg, change in pulmonary status, infection requiring antibiotics) within 5 days prior to (the first) drug administration that may impact safety assessments, in the opinion of the Investigator.

Grading of Adverse Events

The intensity of each AE was rated by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. AEs not listed on the NCI CTCAE are to be rated by the Investigator as "mild (Grade 1)", "moderate (Grade 2)", "severe" (Grade 3), "life-threatening" (Grade 4), or "fatal" (Grade 5). In addition to patient symptoms, clinically significant new findings on physical exam, 12-lead ECG, vital sign assessment or clinical laboratory reports were to be reported as AEs. The number and percent of patients with any TEAEs as well as number of TEAEs were summarized by system organ class and preferred term by treatment and overall.

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e-Table 1: Schedule of Assessments

Study Period		**Treatment**													
Visit	**Screen**	**1**	**1a**	**2**	**2a**	**3**	**3a, 3b, 3c**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**	**EOS**
Study Day	**-28 to - 1**	**D1**	**W1/ D8**	**W2/ D15**	**W3/ D22**	**W4/ D29**	**W5, 6, 7**	**W8/ D57**	**W10/ D71**	**W12/ D85**	**W14/ D99**	**W16/ D113**	**W18/ D127**	**W20/ D141**	**WK24/ D169**
Visit Window (Days)	-	-	-	**±2**	**±3**	**±3**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Written informed consent	X														
Telephone Contact			X		X		X		X		X		X		
Eligibility check	X	X													
Demographics	X														
Medical history	X														
Height & weight[1]	X	X				X		X		X		X		X	
Modified MRC Dyspnea Scale	X														
Physical examination[2]	X									X					X
Vital signs[3]	X	X		X		X		X		X		X		X	X
Pulse oximetry[4]	X	X				X		X		X		X		X	X
12-lead ECG[5]	X	X[5]				X		X		X[5]		X		X[5]	X
Pulmonary Function Tests[6]	X	X				X		X		X		X		X	X
DL_{CO}[7]		X								X				X	X
Pregnancy test (females only)[8]	X (serum)	X						X				X			X (serum)
Serum FSH[9]	X														
Rheumatoid factor		X													
Jo-1 antibody (serum)	X			X		X		X		X		X		X	X
ADA sampling (serum) for anti-ATYR1923 antibodies[17]	X			X		X		X		X		X		X	X
Safety laboratory testing (hematology, clinical chemistry)	X	X		X		X		X		X		X		X	X
Urinalysis[10]	X	X		X		X		X		X		X		X	X
Coagulation laboratory testing (PT, INR, PTT)	X					X		X		X		X		X	X
Serology (HBsAg, anti-HCV, and anti-HIV 1/2 tests)	X														
Serum complement, serum tryptase, and IgE[11]		X													
Plasma complement[11]		X													
^{18}F-FDG-PET/CT (optional)[12]	X											X			

Supplement: Efzofitimod for the treatment of pulmonary sarcoidosis

Study Period		**Treatment**													
Visit	**Screen**	**1**	**1a**	**2**	**2a**	**3**	**3a, 3b, 3c**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**	**EOS**
Study Day	**-28 to - 1**	**D1**	**W1/ D8**	**W2/ D15**	**W3/ D22**	**W4/ D29**	**W5, 6, 7**	**W8/ D57**	**W10/ D71**	**W12/ D85**	**W14/ D99**	**W16/ D113**	**W18/ D127**	**W20/ D141**	**WK24/ D169**
Visit Window (Days)	**-**	**-**	**-**	**±2**	**±3**	**±3**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Skin lesion visual assessments (if applicable)[13]	X			X		X		X		X		X		X	
Skin lesion biopsy (optional for patients at select sites)[14]	X									X					
AE assessment/Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[15]		X													
King's Sarcoidosis Questionnaire		X				X		X		X		X		X	X
Leicester Cough Questionnaire		X				X		X		X		X		X	X
Baseline/Transitional Dyspnea Indices		X				X		X		X		X		X	X
Fatigue Assessment Scale		X				X		X		X		X		X	X
Sarcoidosis Assessment Tool		X				X		X		X		X		X	X
Blood sampling (serum) for ATYR1923 PK[16]		X[16]		X		X		X		X		X		X[16]	X
PBMC collection[18]		X								X					X
Serum biomarkers[19]		X								X				X	X
Infusion site examination[20]		X				X		X		X		X		X	
Study drug administration		X				X		X		X		X		X	
OCS Taper[21]				X											

ADA = anti-drug antibodies; AE = adverse event; BMI = body mass index; D = Day; ECG = electrocardiogram; EOI = end of infusion; EOS = End-of-Study; ET= Early Termination; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; INR = international normalized ratio; OCS = Oral Corticosteroid; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; SOI=start of infusion; W = week(s).
On dosing days, all assessments will be performed pre-dose unless otherwise specified.

1. **Height** only at Screening.
2. P**hysical examination**. Full physical examinations are to be obtained at Screening, Week 12 and 24, abbreviated symptom-directed physical examination may be completed at other visits if needed.
3. **Vital signs** are to be obtained at every visit. On study drug administration days, vital signs are to be measured pre-infusion and at 15 and 30 minutes (±5 minutes) and at 1, 2, and 4 hours (±15 minutes) after the start of infusion (SOI). Vital signs are to be measured before blood sample collection. Vital signs will include blood pressure (systolic and diastolic, recorded after lying supine for 5 min), heart rate, respiratory rate. Temperature is to be obtained at Screening and on dosing days at pre-dose, 60 minutes (±15 minutes) after the SOI, and again at 4 hours (±15 minutes) after the SOI.
4. **Pulse oximetry:** continuous pulse oximetry is to be measured on dosing days from 5 minutes pre-dose until EOI, and recorded at the same time points as vital signs. On non-dosing days pulse oximetry is to be obtained with vital sign assessments.

5. **12-lead ECG** is to be obtained at Screening, within 1-hour pre-dose on dosing days. At Day 1 and Weeks 12 and 20, an ECG is to be obtained at 4 hours (±30 minutes) after SOI. The ECG is to be obtained after patients have been lying supine for 5 minutes.
6. **Pulmonary Function Testing** is to be performed using the same spirometer throughout the study. Parameters include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio at all specified visits. A minimum of 3 efforts should be obtained that meet the acceptance criteria of the American Thoracic Society or European Respiratory Society.
7. **DL_{CO}** measurements *should* be obtained after patients have been sitting quietly for 5 minutes.
8. **Pregnancy** serum tests are to be performed on all females at Screening and at Week 24/EOS. A urine pregnancy test is to be performed at other time points indicated.
9. **FSH** only required for all female patients.
10. **Urinalysis** (semi-quantitative by dipstick): microscopy is to be performed if indicated by an abnormal and clinically significant result.
11. **Serum Complement, Tryptase/Plasma Complement, and IgE** are to be collected at Day 1 pre-dose and again if an infusion related reaction (IRR) occurs.
12. **^{18}F-FDG-PET/CT scans are optional**; patients who elect to participate agree to have imaging performed within 4 weeks prior to Day 1, and within ±5 days of Week 16 or if early termination prior to Week 16.
13. **Skin lesion evaluation:** To be completed for patients with skin lesions present. Skin lesions will be evaluated by: Skin Physician Global Assessment (SPGA), body surface Area assessment, the Sarcoidosis Activity and Severity Index (SASI).
14. **Skin lesion biopsy:** Optional for patients with skin lesions present. A non-target lesion (ie, a lesion that is not being assessed by SASI over time) is to be selected by the Investigator for biopsy during Screening and confirmed by the patient that it had been identified by his or her private dermatologist as cutaneous sarcoidosis. Skin lesion biopsy may be obtained within 4 weeks prior to Day 1 for patients who are otherwise deemed eligible for the study and within ±5 days of Week 12 or if early termination prior to Week 12.
15. **Randomization** is to be performed within 0-3 days prior to Day 1 or on the day of dosing.
16. **ATYR1923 serum PK** samples are to be collected pre-dose on dosing days. On Day 1 and Week 20 visits, PK samples are also collected post start of infusion at: 1 hr (just prior to [i.e., within 0-10 minutes] EOI), and at any single time point between 4-6 hours.
17. **ADA** samples are to be collected pre-dose when obtained on dosing days.
18. **Blood for PBMC assessments** will be collected pre-dose when obtained on dosing days.
19. **Serum for biomarkers** are to be collected pre-dose when obtained on dosing days.
20. **Infusion site examination:** the IV infusion site should be examined at 0.5 and 1.5 hours (±10 minutes) after the end of infusion.
21. **OCS Taper:** OCS taper to start at Day 15 (Week 2) and continue through Day 50 (Week 7) per the ATYR1923-C-002 OCS Taper Guideline.

e-Table 2: Change from Baseline in Lung Function Efzofitimod vs. Placebo – (modified Intention-to-Treat population)

	efzofitimod		
	1 mg/kg n = 8	**3 mg/kg n = 8**	**5 mg/kg n = 9**
FVC%			
Week 4 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-1.26 (-5.66, 3.15)	-2.98 (-7.35, 1.38)	2.40 (-2.37, 7.18)
p-value	p = 0.58	p = 0.18	p = 0.32
Week 8 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-1.53 (-6.01, 2.95)	0.89 (-3.65, 5.43)	1.88 (-2.56, 6.32)
p-value	p = 0.50	p = 0.70	p = 0.41
Week 12 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	2.23 (-2.34, 6.79)	1.54 (-3.89, 6.97)	2.69 (-2.02, 7.4)
p-value	p = 0.34	p = 0.58	p = 0.26
Week 16 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-1.23 (-5.9, 3.4)	0.06 (-4.9, 5.01)	3.23 (-1.57, 8.03)
p-value	p = 0.61	p = 0.98	p = 0.19
Week 20 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-1.24 (-6.04, 3.6)	1.7 (-3.4, 6.8)	3.46 (-1.59, 8.51)
p-value	p = 0.61	p = 0.51	p = 0.18

Supplement: Efzofitimod for the treatment of pulmonary sarcoidosis

	efzofitimod		
	1 mg/kg n = 8	**3 mg/kg n = 8**	**5 mg/kg n = 9**
Week 24 Active vs. Placebo			
Difference in Adjusted Means	-0.08	2.8	3.3
(95% CI)	(-4.92, 4.76)	(-2.65, 8.26)	(-1.9, 8.51)
p-value	p = 0.97	p = 0.31	p = 0.21
DLco%			
Week 12 Active vs. Placebo			
Difference in Adjusted Means	0.49	6.47	5.64
(95% CI)	(-8.96, 9.94)	(-4.88, 17.82)	(-3.78, 15.06)
p-value	p = 0.92	p = 0.26	p = 0.24
Week 20 Active vs. Placebo			
Difference in Adjusted Means	-0.96	3.37	2.35
(95% CI)	(-11.94, 10.02)	(-8.35, 15.1)	(-8.13, 12.84)
p-value	p = 0.86	p = 0.57	p = 0.65
Week 24 Active vs. Placebo			
Difference in Adjusted Means	-0.04	2.96	7.46
(95% CI)	(-11.27, 11.19)	(-8.87, 14.8)	(-3.08, 18.0)
p-value	p = 0.99	p = 0.62	p = 0.17

CI = confidence interval; DLco% = percent-predicted diffusion capacity of the lungs; FVC% = precent-predicted forced vital capacity

* Adjusted Means taken from MMRM analysis adjusting for baseline value of the corresponding lung function parameter on scheduled visits (FVC%: Baseline, W4, 8, 12, 16, 20, 24; (DLco%: Baseline, W12, 20 and 24)

e-Table 3: Change in SAT-L from Baseline Efzofitimod vs. Placebo - (modified Intention-to-Treat population)

	efzofitimod		
	1 mg/kg n = 8	**3 mg/kg n = 8**	**5 mg/kg n = 9**
SAT-L			
Week 4 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-1.87 (-7.08, 3.34)	-0.87 (-6.5, 4.77)	-3.82 (-8.83, 1.19)
p-value	p = 0.48	p = 0.76	p = 0.13
Week 8 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	0.84 (-4.27, 6.05)	-1.09 (-6.88, 4.69)	-1.55 (-6.56, 3.47)
p-value	p = 0.75	p = 0.71	p = 0.54
Week 12 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-0.18 (-5.39, 5.03)	-5.34 (-11.12, 0.43)	-5.19 (-10.2, -0.17)
p-value	p = 0.94	p = 0.07	**p = 0.043**
Week 16 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	2.84 (-2.6, 8.28)	-4.23 (-10.12, 1.66)	-5.38 (-10.51, -0.25)
p-value	p = 0.30	p = 0.16	**p = 0.040**
Week 20 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	2.69 (-2.82, 8.19)	-6.27 (-12.22, -0.31)	-4.29 (-9.49, 0.9)
p-value	p = 0.33	**p = 0.039**	p = 0.10
Week 24 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	4.44 (-1.15, 10.03)	-6.49 (-12.52, -0.47)	-6.42 (-11.7, -1.13)
p-value	p = 0.12	**p = 0.035**	**p = 0.018**

SAT-L= Sarcoidosis Assessment Tool-Lung
Adjusted Means taken from MMRM analysis adjusting for corresponding baseline score

e-Table 4: Change in KSQ-L from Baseline Efzofitimod vs. Placebo - (modified Intention-to-Treat population)

	efzofitimod		
	1 mg/kg n = 8	**3 mg/kg n = 8**	**5 mg/kg n = 9**
KSQ-L			
Week 4 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-2.68 (-8.97, 3.61)	1.04 (-5.73, 7.82)	5.06 (-1.19, 11.3)
p-value	p = 0.39	p = 0.76	p = 0.11
Week 8 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-2.34 (-10.13, 5.46)	0.81 (-7.93, 9.55)	11.46 (3.7, 19.22)
p-value	p = 0.55	p = 0.85	**p = 0.005**
Week 12 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-4.47 (-15.55, 6.62)	4.26 (-7.47, 15.99)	17.02 (5.95, 28.09)
p-value	p = 0.42	p = 0.47	**p = 0.004**
Week 16 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-5.47 (-16.76, 5.81)	8.01 (-4.08, 20.09)	14.72 (3.56, 25.88)
p-value	p = 0.33	p = 0.19	**p = 0.012**
Week 20 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-2.02 (-17.36, 13.33)	9.75 (-5.28, 24.79)	15.93 (1.09, 30.78)
p-value	p = 0.79	p = 0.19	**p = 0.036**
Week 24 Active vs. Placebo			
Difference in Adjusted Means (95% CI)	-6.41 (-20.47, 7.65)	11.29 (-3.39, 25.96)	16.17 (2.49, 29.85)
p-value	p = 0.35	p = 0.12	**p = 0.022**

KSQ-L = King's Sarcoidosis Questionnaire – Lung Subscore
Adjusted Means taken from MMRM analysis adjusting for corresponding baseline score

e-Table 5: Change in KSQ-GH from Baseline Efzofitimod vs. Placebo - (modified Intention-to-Treat population)

	efzofitimod		
	1 mg/kg n = 8	**3 mg/kg n = 8**	**5 mg/kg n = 9**
KSQ-GH			
Week 4 Active vs. Placebo			
Difference in Adjusted Means	-1.45	1.47	10.78
(95% CI)	(-9.64, 6.74)	(-7.26, 10.21)	(2.4, 19.17)
p-value	p = 0.72	p = 0.73	**p = 0.0133**
Week 8 Active vs. Placebo			
Difference in Adjusted Means	-0.41	0.45	12.7
(95% CI)	(-8.14, 7.32)	(-8.3, 9.3)	(4.74, 20.65)
p-value	p = 0.91	p = 0.92	**p = 0.003**
Week 12 Active vs. Placebo			
Difference in Adjusted Means	-1.9	1.66	17.85
(95% CI)	(-12.73, 8.93)	(-9.98, 13.31)	(6.86, 28.83)
p-value	p = 0.72	p = 0.77	**p = 0.002**
Week 16 Active vs. Placebo			
Difference in Adjusted Means	-3.99	7.85	18.5
(95% CI)	(16.45, 8.46)	(-5.63, 21.33)	(6.15, 30.84)
p-value	p = 0.52	p = 0.25	**p = 0.005**
Week 20 Active vs. Placebo			
Difference in Adjusted Means	-2.01	0.89	19.9
(95% CI)	(-17.44, 13.42)	(-14.69, 16.46)	(4.88, 34.92)
p-value	p = 0.79	p = 0.91	**p = 0.011**
Week 24 Active vs. Placebo			
Difference in Adjusted Means	-5.1	2.13	18.33
(95% CI)	(-18.52, 8.32)	(-12.76, 17.01)	(5.16, 31.49)
p-value	p = 0.44	p = 0.77	**p = 0.008**

KSQ-GH = King's Sarcoidosis Questionnaire – General Health (GH) Status Subscore
Adjusted Means taken from MMRM analysis adjusting for corresponding baseline score

e-Table 6: Change in FAS-total from Baseline Efzofitimod vs. Placebo - (modified Intention-to-Treat population)

	efzofitimod		
	1 mg/kg n = 8	**3 mg/kg n = 8**	**5 mg/kg n = 9**
FAS - Total			
Week 4 Active vs. Placebo			
Difference in Adjusted Means	1.04	0.36	-2.08
(95% CI)	(-2.53, 4.6)	(-3.47, 4.18)	(-5.75, 1.58)
p-value	p = 0.56	p = 0.85	p = 0.26
Week 8 Active vs. Placebo			
Difference in Adjusted Means	0.64	-0.60	-5.23
(95% CI)	(-3.53, 4.81)	(-5.08, 3.87)	(-9.49, -0.97)
p-value	p = 0.76	p = 0.79	**p = 0.018**
Week 12 Active vs. Placebo			
Difference in Adjusted Means	5.33	0.71	-3.91
(95% CI)	(0.86, 9.8)	(-4.26, 5.69)	(-8.46, 0.64)
p-value	p = 0.021	p = 0.77	p = 0.09
Week 16 Active vs. Placebo			
Difference in Adjusted Means	4.45	-1.19	-4.31
(95% CI)	(-1.2, 10.1)	(-6.98, 4.59)	(-9.89, 1.27)
p-value	p = 0.12	p = 0.68	p = 0.13
Week 20 Active vs. Placebo			
Difference in Adjusted Means	2.12	-1.81	-4.47
(95% CI)	(-4.24, 8.48)	(-8.22, 4.6)	(-10.63, 1.7)
p-value	p = 0.51	p = 0.57	p = 0.15
Week 24 Active vs. Placebo			
Difference in Adjusted Means	0.76	-4.78	-7.77
(95% CI)	(-5.09, 6.62)	(-11.22, 1.65)	(-13.5, -2.03)
p-value	p = 0.79	p = 0.14	**p = 0.010**

FAS = Fatigue Assessment Scale – Total Score
Adjusted Means taken from MMRM analysis adjusting for corresponding baseline score

e-Table 7: Change in Patient Reports Outcomes (PROs) at Week 24 from Baseline Efzofitimod Treatment vs. Placebo – (modified Intention-to-Treat population)

PRO Measurement (Adjusted Mean*)	1 mg/kg (N = 8)	3 mg/kg (N = 8)	5 mg/kg (N = 9)
LCQ-Total	-3.49 (-6.18, -0.79) **p = 0.01**	2.98 (0.13, 5.83) **p = 0.04**	2.05 (-0.58, 4.69) p = 0.12
LCQ-Psychological	-1.04 (-2.22, 0.13) p = 0.08	0.98 (-0.26, 2.23) p = 0.12	1.15 (0.01, 2.30) **p = 0.05**
SAT-Satisfaction with Roles and Activities	-1.41 (-9.0, 6.17) p = 0.71	6.50 (-1.79, 14.78) p = 0.12	7.6 (-0.02, 15.2) **p = 0.05**
SAT-Fatigue	2.52 (-4.18, 9.23) p = 0.46	-5.96 (-13.14, 1.22) p = 0.10	-10.76 (-17.76, -3.95) **p = 0.002**
SAT-Physical Functioning	0.44 (-4.47, 5.34) p = 0.86	6.21 (0.78, 11.63) **p = 0.03**	3.93 (-0.87, 8.73) p = 0.11
TDI-Change in Functional Impairment	-0.8 (-4.55, 2.95) p = 0.66	1.87 (-1.93, 5.67) p = 0.32	2.34 (-1.20, 5.88) p = 0.19
FAS-Physical Fatigue	-0.09 (-3.83, 3.64) p = 0.96	-3.13 (-7.24, 0.97) p = 0.13	-4.19 (-7.92, -0.46) **p = 0.03**

FAS = Fatigue Assessment Scale; LCQ = Leicester Cough Questionnaire; SAT = Sarcoidosis Assessment Tool; TDI = Transition Dyspnea Index

Adjusted Means taken from MMRM analysis adjusting for corresponding baseline score

e-Figure 1: Change in Patient Reports Outcomes (PROs) at Week 24 from Baseline Active Treatment vs. Placebo – (modified Intention-to-Treat population)

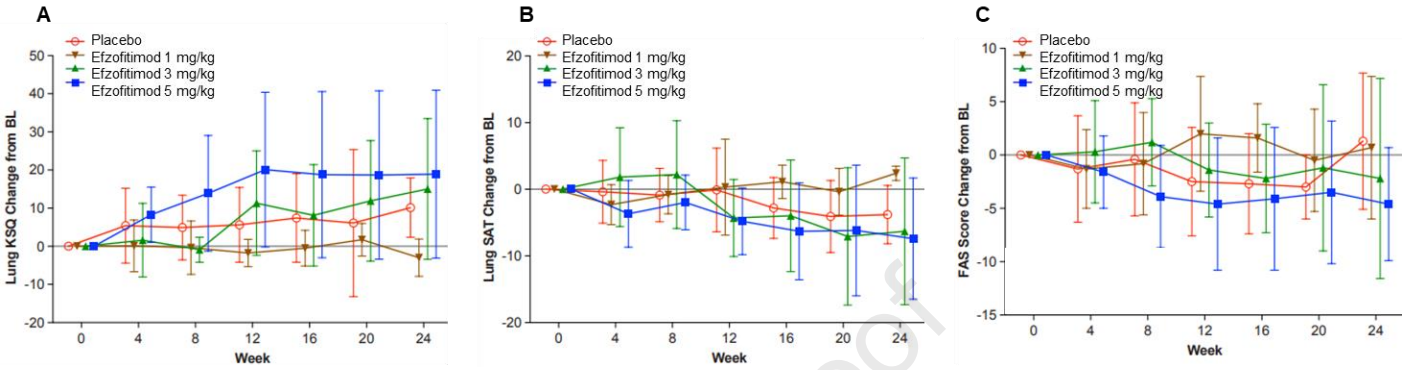

Figure E1: Change in patient reported outcomes (PROs) presented as change from baseline x treatment week for Lung KSQ (A), Lung-SAT (B), and FAS-Total. All data is represented as mean(SD).