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Safety and Efficacy of Efzofitimod (ATYR1923), a Novel Immunomodulator for Pulmonary Sarcoidosis: Results of a Phase 1b/2a Randomized Placebo-Controlled Trial

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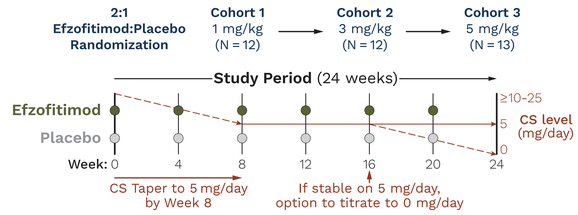
Introduction

For patients with pulmonary sarcoidosis, the goals of treatment are to reduce inflammation, prevent fibrosis and loss of lung function, and improve quality of life (QOL). The consensus standard of care includes oral corticosteroids (CS). While these have been shown to stabilize or improve disease, long-term CS use is associated with significant side effects and impaired QOL.[1,2] Efzofitimod is a novel immunomodulator that selectively binds neuropilin-2 (NRP2), which is upregulated on key immune cells within sarcoid granulomas.[3] In preclinical studies, efzofitimod has been shown to downregulate inflammatory cytokine/chemokine signaling and reduce lung inflammation and fibrosis.[4–6] The potential of efzofitimod as a novel anti-inflammatory therapy for pulmonary sarcoidosis that might reduce CS burden while stabilizing or improving lung function and symptoms was investigated.

Methods

Trial Design and Procedures

This trial (NCT03824392) 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. Placebo patients from each of the 3 cohorts were pooled when comparing safety and efficacy between efzofitimod and placebo.



Outcomes and Statistical Analyses

All data presented represent the modified intent-to-treat (mITT) set, defined as all randomized patients who received at least 1 dose of study drug.

- **Primary Endpoint:** Safety and tolerability
- **Secondary Endpoints:** CS sparing effect of efzofitimod over the study duration (D1 to W24) and number of patients who achieved and maintained the targeted taper dose of prednisone 5 mg/day (or equivalent) during the post-taper period (D51 to W24)
- **Exploratory (Baseline to W24):**
  - » Pulmonary function tests, such as percent-predicted forced vital capacity (FVCPP) and percent-predicted diffusing capacity of the lungs for carbon monoxide ($DL_{co}PP$)
  - » Change in patient reported outcomes (PROs): King's Sarcoidosis Questionnaire (KSQ), sarcoidosis assessment tool (SAT), and fatigue assessment scale (FAS)

Key Inclusion Criteria

- 18–75 years of age
- Pulmonary sarcoidosis for ≥ 6 months according to the 1999 ATS standards + histologic confirmation
- Parenchymal involvement
- FVCPP > 50%
- Receiving stable treatment with 10-25 mg/day of CS (prednisone or equivalent)
  - » Stable treatment with 1 oral immunomodulator was allowed but not required

Key Exclusion Criteria

- Disease presentation consistent with Lofgren's syndrome
- Biological immunomodulator use
- Clinically significant cardiac, neurological, gastrointestinal, and/or renal manifestations of sarcoidosis, and pulmonary hypertension requiring vasodilator treatment

Baseline Characteristics

Baseline demographics, disease characteristics, and CS use were generally well-balanced across the treatment groups.

Patient Demographics	Placebo (N = 12)	Efzofitimod 1 mg/kg (N = 8)	Efzofitimod 3 mg/kg (N = 8)	Efzofitimod 5 mg/kg (N = 9)
Age, years (mean), ≥ 65	52.5 (10.2), 0	54.5 (11.3), 1	51.8 (11.4), 2	50.8 (9.2), 0
Sex (Male); N (%)	5 (42)	4 (50)	4 (50)	4 (44)
Race (White/African American)	9 / 3	5 / 3	6 / 2	3 / 6
Baseline[a] Disease Characteristics, Mean (SD)				
FVCPP	77.3 (11.5)	68.3 (9.7)	83.8 (7.3)	83.8 (16.6)
Duration of disease (years)	4.2 (3.3)	7.4 (6.1)	5.9 (5.1)	7.7 (9.9)
Baseline Dyspnea Index Score	4.8 (2.0)	4.3 (1.8)	7.6 (2.9)	6.3 (2.4)
Background Therapy, n (%)				
Prednisone equivalent dose (mg/day), mean	13.3	11.3	14.4	13.9
10 to < 15	7 (58)	7 (88)	5 (63)	3 (33)
15 to < 20	2 (17)	0	0	5 (56)
> 20	3 (25)	1 (13)	3 (38)	1 (11)
Immunomodulator (any)	6 (50)	3 (38)	1 (13)	4 (44)
methotrexate	4	2	0	3
azathioprine	2	0	0	1
hydroxychloroquine	0	1	0	0
leflunomide	0	0	1	0

[a] Baseline measures were defined as the last measure assessed on or before the first dose date.

Efzofitimod was Safe and Well-Tolerated

- No new or unexpected findings with repeat dosing
- No signal of immunogenicity or induction of anti-drug antibodies
- No drug-related serious adverse events (SAEs)
- No deaths

Parameter, n (%)	Placebo (N = 12)	Efzofitimod 1 mg/kg (N = 8)	Efzofitimod 3 mg/kg (N = 8)	Efzofitimod 5 mg/kg (N = 9)
Adverse Events (AEs)	10 (83)	8 (100)	7 (88)	8 (89)
Drug-related AEs	4 (33)	3 (38)	1 (13)	3 (33)
Severe AEs (Gr. 3 or 4)	4 (33)	2 (25)	0	2 (22)
SAEs	1 (8)	1 (13)	0	0
Infusion-Related Reactions (IRRs)	0	0	1 (13)	0

Most Common TEAEs Consistent with Underlying Disease

Preferred Term All Causality, n (%)	Placebo (N = 12)	Efzofitimod 1 mg/kg (N = 8)	Efzofitimod 3 mg/kg (N = 8)	Efzofitimod 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	(8.3)	1 (12.5)	1 (12.5)	2 (22.2)
Dyspnea	0	0	2 (25)	0
Arthralgia	0	(12.5)	2 (25)	0
Headache	1 (8.3)	0	2 (25)	1 (11.1)
Upper respiratory tract	1 (8.3)	1 (12.5)	2 (25)	0
Back pain	0	0	2 (25)	0

Dose-Dependent Reduction in Corticosteroid Use

- Compared to placebo, all efzofitimod groups had a lower CS use through W24, with 3 and 5 mg/kg efzofitimod having the greatest reduction.
- 3 patients in the 5 mg/kg group were able to taper completely off CS and maintain that taper through W24.

CS Use	Placebo (N = 12)	Efzofitimod 1 mg/kg (N = 8)	Efzofitimod 3 mg/kg (N = 8)	Efzofitimod 5 mg/kg (N = 9)
Ability to taper to 5 mg, n (%)	9 (75)	8 (100)	7 (88)	8 (89)
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)

*Any non-prednisone CS is converted to prednisone equivalent dose. All endpoints use post-taper period (D51 to W24).
^Adjusted mean from ANCOVA adjusting for Baseline CS use.
§Time-adjusted AUC of percent change from Baseline, p > 0.05.

Dose-Dependent Improvement in Patient-Reported Outcomes

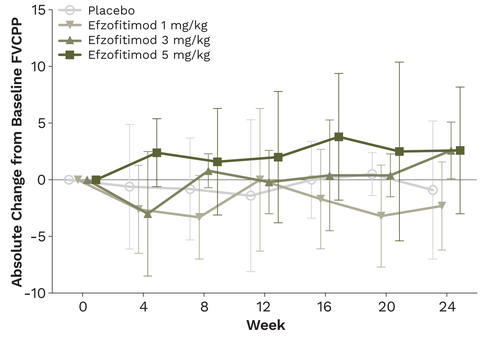
- Significant improvements at W24 in PROs in the 5 mg/kg group.
- The magnitude of change in KSQ-GH and KSQ-L at W24 exceeded the minimal clinically important differences (MCID).
- The changes in the FAS also exceeded the MCID of 4 points.[7]

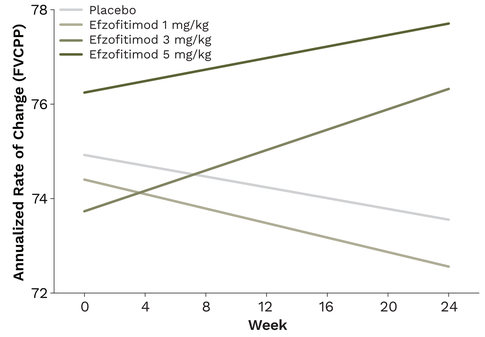
PRO Measurement, Adjusted Mean* (95% CI)	Efzofitimod 1 mg/kg (N = 8)	Efzofitimod 3 mg/kg (N = 8)	Efzofitimod 5 mg/kg (N = 9)
KSQ-General Health[a]	-5.1 (-18.52, 8.32) p = 0.18	2.13 (-12.76, 17.01) p = 0.77	18.33 (5.16, 31.49) **p = 0.008**
KSQ-Lung[a]	-6.41 (-20.47, 7.65) p = 0.35	11.29 (-3.39, 25.96) p = 0.12	16.17 (2.49, 29.85) **p = 0.022**
SAT-Lung[b]	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**
FAS-Total[c]	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**

*Difference in adjusted means vs placebo at W24 taken from MMRM analysis adjusting for corresponding baseline score. [a]Higher scores indicate better health. [b]Negative scores indicate better health. [c]<22 indicates no fatigue (normal), >22 indicates substantial fatigue.

Dose-Dependent Improvement in Lung Function

- Dose-dependent improvements in lung function were observed for 3 and 5 mg/kg efzofitimod.





Pulmonary Function Test Result, Adjusted Mean* (95% CI)	Efzofitimod 1 mg/kg (N = 8)	Efzofitimod 3 mg/kg (N = 8)	Efzofitimod 5 mg/kg (N = 9)
FVCPP	-0.08 (-4.92, 4.76)	2.81 (-2.65, 8.26)	3.30 (-1.90, 8.51)
FEV$_1$PP	0.93 (-4.37, 6.22)	3.86 (-1.73, 9.46)	2.68 (-2.62, 7.98)
$DL_{CO}PP$	-0.04 (-11.27, 11.19)	2.96 (-8.87, 14.79)	7.46 (-3.08, 18.00)

*Difference in adjusted means vs placebo at W24 taken from MMRM analysis adjusting for corresponding baseline score. A positive difference in LS means indicates higher average values in active treatment arm.

Abbreviations: AE=adverse event; AST=aspartate aminotransferase; AUC=area under curve; CI=confidence interval; D=day; FEV$_1$PP=forced expiratory volume in 1 second percent predicted; KSQ-L=King's Sarcoidosis Questionnaire (Lung); KSQ-GH=King's Sarcoidosis Questionnaire (General Health); MMRM=mixed model repeated measures; SD=standard deviation; TEAE=treatment-emergent adverse event; W=week.

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Disclosures: PHSS has received grants from the National Institutes of Health (R13HL142300 and R01HL131745), the American Thoracic Society Foundation, the FSR, aTyr Pharma, Inc., and Novartis. **RB** has received grants from Bayer, Genentech, Mallinckrodt Pharmaceuticals, the FSR, and Actelion; consulting fees from Mallinckrodt Pharmaceuticals, Meitheal Pharmaceuticals, Actelion, and Kineant; and received payment for speaker bureaus from Mallinckrodt Pharmaceuticals, United Therapeutics, and Boehringer Ingelheim. **SS, GW,** and **LC** are employed by and own stock in aTyr Pharma, Inc.

Acknowledgments: Supported by aTyr Pharma, Inc. aTyr thanks Nelson Kinnersley of Octa Consulting for his biostatistics support.

Conclusions

- Efzofitimod was safe and well-tolerated in patients with pulmonary sarcoidosis.
- There was a dose-dependent improvement in efficacy parameters (CS taper, FVCPP, and PROs):
  - » All efzofitimod treatment groups had lower CS use at W24 vs placebo, with the largest difference observed at the 5 mg/kg dose group. 3 patients were able to taper off prednisone completely and maintain that taper through completion of the study, all in the 5 mg/kg group.
  - » Compared to placebo, the two higher doses of efzofitimod resulted in improvements in FVCPP and $DL_{CO}PP$ through W24.
  - » Clinically meaningful and statistically significant improvements at W24 were observed for key symptom measures in the 5 mg/kg group.
- In small studies (not powered for statistical testing), dose-dependent improvements are strong evidence for efficacy.

Presented at ATS2022