Therapeutic doses of efzofitimod significantly improve multiple pulmonary sarcoidosis efficacy measures

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Introduction

- **Efzofitimod is a novel biologic immunomodulator[1].**
- **Phase 1b/2a randomized, double-blind, placebo-controlled, multiple ascending dose study [2] .**
  - Three sequential dose cohorts; 2:1 randomization (efzofitimod to placebo) in each cohort.
  - Treatment period - 6 iv doses 4 weeks apart.
  - Oral corticosteroid (OCS) tapered to 5mg/day by week 8 or <5 mg/day after week 16.
  - Three families of endpoints – steroid taper, lung function and patient reported outcomes (PROs), not powered for efficacy.
  - To increase the power, we pooled placebo and 1 mg/kg (sub-therapeutic group) and compared with pooled 3 mg/kg and 5 mg/kg.

Rationale and Baseline Characteristics

Pooling Justification

- EC50 (half maximal effective concentration) for human NRP2 – 30 nM (1.9 ug/mL)
- In vitro granuloma formation assay – 30 nM (1.9 ug/mL) not clinically significant
- In vitro granuloma formation assay – 300 nM (19 ug/mL) showed clinically significant results[3]

Cavg-based calculation

1. 1 mg/kg Cavg (Cavg = AUC/time = 3,710,315 ng.h/mL ÷ 672 hours) = 5.5 ug/mL
2. 3 mg/kg Cavg = 18.0 ug/mL

Based on the above, it is reasonable to assume that therapeutic efficacy may be expected with 3 mg/kg, and not with 1 mg/kg – and justifies pooling of 3 mg/kg with 5 mg/kg as therapeutic, and placebo with 1 mg/kg as sub-therapeutic groups.

Baseline Characteristics

	Sub-therapeutic (N=20) n (%)	Therapeutic (N=17) n (%)
Patient Demographics		
Age, years (mean; SD), ≥ 65	53.3 (10.4), 1	51.2 (10.0), 2
Sex (Male); n (%)	9 (45)	8 (47)
Race (White/African American)	14/6	9/8
Baseline^ Disease Characteristics, Mean (SD)		
FVCPP (%)	73.7 (11.5)	83.8 (12.7)
FVC (mL)	2816 (739)	3396 (1018)
Duration of Disease (years)	5.5 (4.7)	6.9 (7.9)
Baseline Dyspnea Index Score	4.6 (1.8)	6.9 (2.7)
Background Therapy, n (%)		
Prednisone equivalent dose (mg/day)		
>20	4 (20)	4 (24)
15 to <20	2 (10)	5 (29)
10 to <15	14 (70)	8 (47)
Mean dose	12.5	14.1
Immunomodulator (any)	9 (45)	5 (29)
Methotrexate	6	3
Azathioprine	2	1
Hydroxychloroquine	1	0
Leflunomide	0	1

Baseline characteristics were generally well-balanced albeit with numerical differences that were within the bounds of natural variability. Nevertheless, all efficacy analyses included baseline values as a covariate to ensure appropriate comparison of treatment groups.

^Baseline measures were defined as the last measure assessed on or before the first dose.

References

1) Baughman RP et al. Efzofitimod: A Novel Anti-Inflammatory Agent for Sarcoidosis. Sarcoidosis, Vasculitis and Diffuse Lung Diseases (2023).
2) Culver DA, et al. Efzofitimod for the treatment of pulmonary sarcoidosis. CHEST. 2022 Nov 8; S0012-3692(22)04053-3. doi: 10.1016/j.chest.2022.10.037.
3) Paz S, et al. Immunomodulatory protein ATYR1923 disrupts an in vitro model of sarcoid granuloma formation. Eur Respir J. 2021 58: OA3986; DOI: 10.1183/13993003.congress-2021.OA3986
4) Baughman RP et al. ERS clinical practice guidelines on treatment of sarcoidosis Eur Respir J. 2021 Dec 16;58(6):2004079.

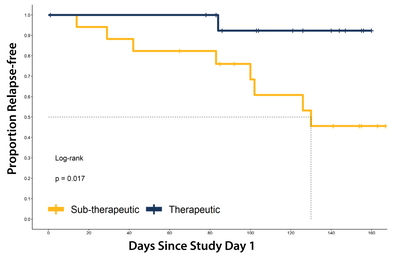
Results

1. Efzofitimod was Safe and Well-Tolerated

Parameter	Sub-therapeutic (N=20) n (%)	Therapeutic (N=17) n (%)
Adverse Events (AEs)	18 (90)	15 (88)
Drug-related AEs	7 (35)	4 (24)
Severe AEs (Gr. 3 or 4)	6 (30)	2 (12)
SAEs	2 (10)	0

2. Efzofitimod Prolonged Time-to-Relapse

Time to First Relapse* (mITT Population)



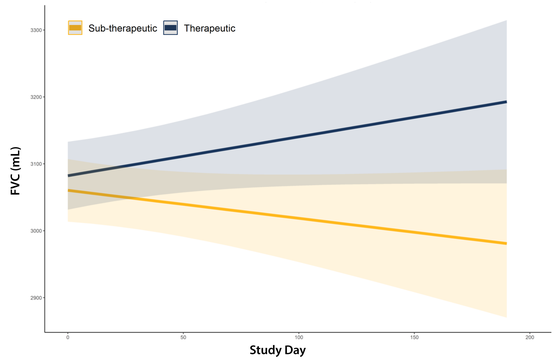
In the subtherapeutic group 54.4% of patients relapsed compared to 7.7% in the therapeutic group (p= 0.017).

*Relapse= Dose of OCS was increased after OCS tapered to 5 mg or less of prednisone or equivalent for at least five consecutive days. Increases in OCS dose due to non-sarcoidosis reasons are not counted towards relapse. (Sensitivity analysis for 1 patient on 3 mg/kg with equivocal disease status on Day 114 support the primary findings.)

Subjects who have never tapered to 5 mg or less are censored at Day 1.

3. Efzofitimod Improved Lung Function

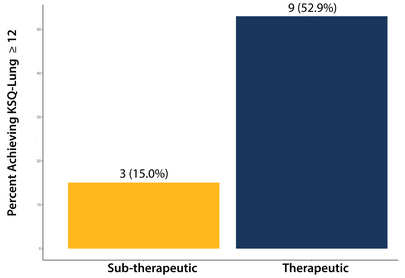
Slopes Analysis for FVC (mL) vs. Study Day



The rate of change for FVC was significantly improved for the therapeutic group (p = 0.035) compared to the subtherapeutic group.

4. Efzofitimod Improved Patient Response

Percent Achieving KSQ-Lung ≥ 12



In the therapeutic group 9 patients (52.9%) showed an increase ≥12 for KSQ-Lung compared with 3 (15.0%) in the subtherapeutic group (p=0.032).

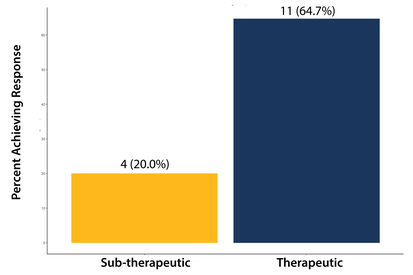
5. Defining Composite/Responder Endpoints in Sarcoidosis

The ERS clinical practice guidelines considers steroid sparing, pulmonary function tests and patient reported outcomes as critical or important outcome measures in pulmonary sarcoidosis[4]. Therefore, we propose steroid reduction, FVC (most representative PFT parameter for sarcoidosis) and KSQ-Lung and FAS (both validated instruments in sarcoidosis) for our responder definition that captures multiple facets of the disease:

1) Reduction in OCS from Baseline
2) Stable lung function as measured by change from Baseline in FVCpp > -2.5% (i.e. improvement or not worsening by more than 2.5%)
3) Stable or improved Patient Reported Outcomes (PROs) as measured by Change from Baseline in KSQ-Lung > -4 and Fatigue Assessment Scale (FAS) < 4

All 3 criteria have to be met to be classified as a response.

Percent Achieving Response



Significantly more patients achieved response on therapeutic doses of efzofitimod compared with sub-therapeutic group (p=0.008).

Conclusions and Future Directions

- **These findings provide further evidence of efficacy for efzofitimod and help inform potential criteria for a responder endpoint in pulmonary sarcoidosis.**
- **EFZO-FIT, a Phase 3 multi-center, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of intraveneous efzofitimod 3 mg/kg and 5 mg/kg versus placebo after 48 weeks of treatment, is actively enrolling.**

e-Poster Website

EFZO-FIT Website

The ERS is not responsible for and does not endorse the data and information presented on external sites.

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