Exposure-Efficacy Analysis Supports Proof of Concept for Efzofitimod in Pulmonary Sarcoidosis

Ryan Adams*[1], Gennyne Walker[1], Lauren Guy[1], Abhijeeth Chandrasekaran[2], Nelson Kinnersley[3], Pavithra Ramesh[2], Eileen Sun[1], Lu Zhang[4], Fran Brown[4], Eileen Doyle[4], Elisabeth Brower-Easton[4], Vis Niranjan[2], Sanjay Shukla[1]

[1]aTyr Pharma, San Diego, CA, United States, [2]RxMD, Chennai, India, [3]Octa Consulting Services Ltd, Harpenden, United Kingdom, [4]Certara, Princeton, NJ, United States; *Contact: radams@atyrpharma.com

Introduction

- Efzofitimod is a novel biologic immunomodulator that binds to neuropilin 2 (NRP2) and is in development for treatment of interstitial lung diseases (ILD), including pulmonary sarcoidosis and systemic sclerosis-related-ILD.
- A population pharmacokinetic (PPK) model was developed from 2 double blind, placebo controlled trials, and exposure-efficacy (EE) analyses was performed to assess the relationship between efzofitimod exposure and three prespecified efficacy parameters: mean daily oral corticosteroid (OCS) dose, percent predicted forced vital capacity (ppFVC) and King's Sarcoidosis Questionnaire-Lung (KSQ-Lung) score.
- EE analysis (encompassing PPK analysis) is an accepted approach for providing clinical evidence of effectiveness[1].

Methods

Studies included within the analysis

A Phase 1 study in healthy volunteers and a Phase 1b/2a study in patients with chronic pulmonary sarcoidosis (PS) – both double-blind, controlled, multiple cohort studies - were included in the analysis. Both studies were randomized 1:2 within each cohort to placebo or efzofitimod (**Table 1**).

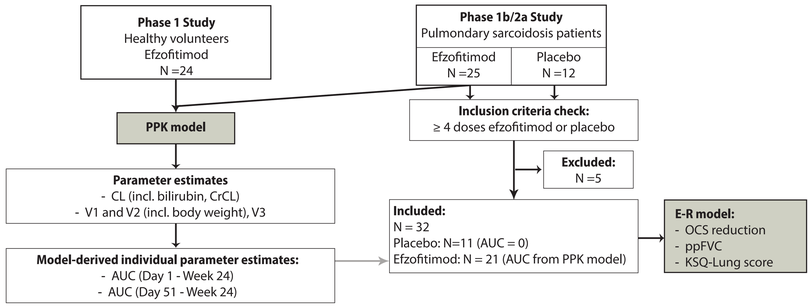
In the 24 week Phase 1b/2a study[2], the investigator initiated a protocol-guided OCS taper. The OCS taper for each participant initiated on Day 15 from a starting dose of 10 to 25 mg/day of prednisone (or equivalent) to a target dose of 5 mg/day to be completed on or before Day 50.

Table 1. Efzofitimod clinical studies included in the PPK and EE analysis.

	Phase 1 Study	Phase 1b/2a study
Number of doses/ intervals	Single/-	Six/monthly
Cohorts	Six	Three
Dose (mg/kg)	0.03, 0.1, 0.3 1.0, 3.0, 5.0	1.0, 3.0, 5.0
Population	Healthy volunteers	Pulmonary sarcoidosis - biopsy confirmed Chronic - duration > 6 mos Baseline OCS - between 10 and 25 mg/day Symptomatic - MRC dyspnea score > 1
Key procedures	-	OCS taper - 5 mg/day every 1 to 2 weeks to Day 50
Assessments	Safety PK	Safety Efficacy - Average daily OCS dose; FVC; PROs PK

Analysis workflow

Figure 1. Workflow for developing the PPK model and performing EE analysis.



Exposure parameter – area under the curve (AUC) for efzofitimod

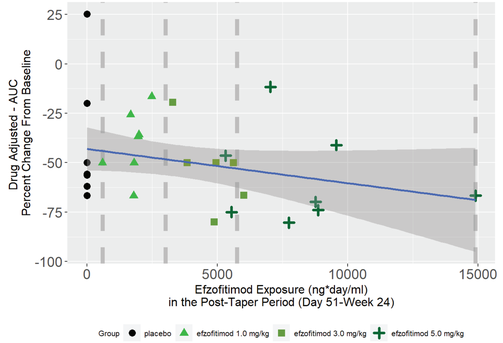
- Day 51 to week 24 (for steroid burden related response, corresponding to post-taper period)
- Day 1 to week 24 for other response parameters

Results

Administration of efzofitimod led to an exposure-dependent decrease in the extent of OCS usage, increase in ppFVC and increase in KSQ-L score

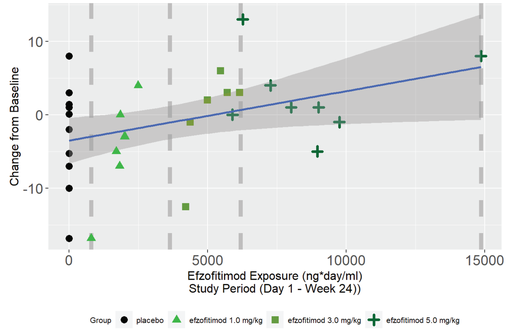
Mean Daily OCS Dose Post-Taper Period - Percent Change from Baseline

Figure 2. Increase in Efzofitimod Treatment Dose Reduces OCS usage.



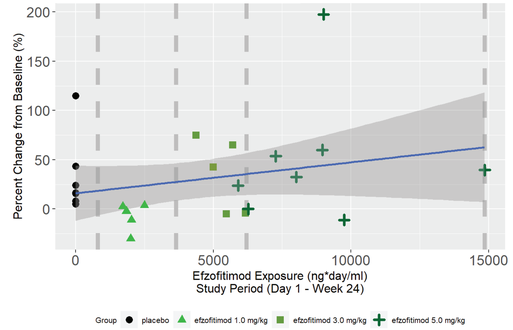
ppFVC at Week 24 - Change From Baseline

Figure 3. Increase in Efzofitimod Treatment Dose Improves ppFVC.



KSQ-Lung Score at Week 24 - Percent Change From Baseline

Figure 4. Increase in Efzofitimod Treatment Dose Improves KSQ-Lung Score.



The gray shaded area is the 90% prediction interval. Vertical lines demarcate the three exposure tertiles.

Administration of efzofitimod increased the proportion of patients with improvements in ppFVC and KSQ-Lung greater than the minimum clinical important difference (MCID)

Figure 5. Increase in Efzofitimod Treatment Dose Increases the Proportion of Participants Achieving MCID Threshold in ppFVC (2.5%).

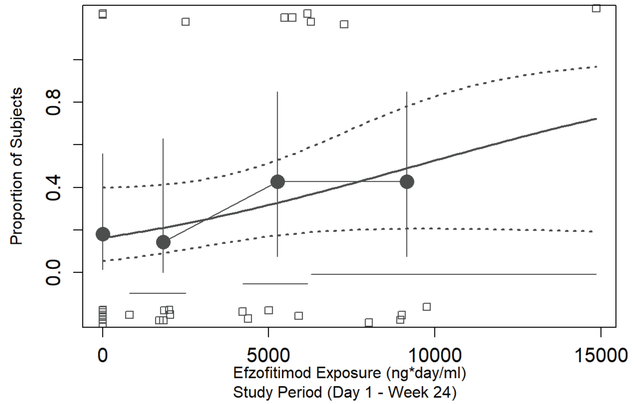
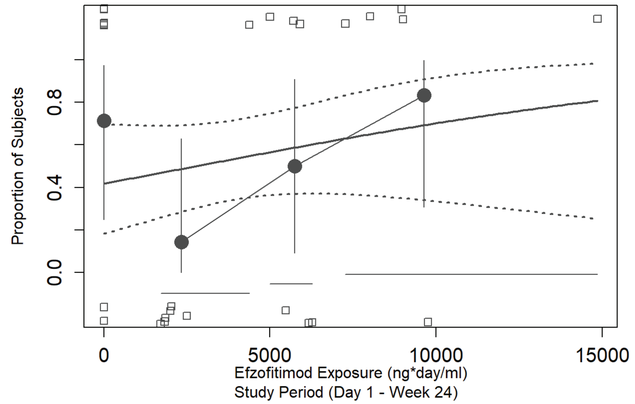


Figure 6. Increase in Efzofitimod Treatment Dose Improves Proportion of Participants Achieving MCID Threshold in KSQ-Lung Score (4 points).



Open squares represent individual values. Solid dots and vertical lines represent the incidence and 95% CI of observation within a quantile. The solid and dashed lines represent the unadjusted logistic regression fit of the data and 95% C I of the regression. Horizontal lines represent the range of the exposure tertiles.

Conclusions

- These preliminary findings of a positive EE response across multiple clinically relevant endpoints support the claim that efzofitimod displays efficacy in pulmonary sarcoidosis.
- Efzofitimod doses of 3.0 and 5.0 mg/kg are being evaluated in a confirmatory Phase 3 study in pulmonary sarcoidosis (NCT05415137).

References

1) US FDA. Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. 2003. Available from: https://www.fda.gov/media/71277/download (accessed 20 Oct 2022).

2) Culver DA, Aryal S, Barney J, 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.

Ph3 Trial: EFZO-FIT

Presented at the ATS 2023 International Conference

Research funded by aTyr Pharma