Not So Fast Cowboy A Detailed Analysis of ATYR and lead drug candidate: Efzofitimod Hidden Variables: A Deeper Look into the ATYR Play

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Not So Fast Cowboy

A Detailed Analysis of ATYR and lead drug candidate: Efzofitimod

Hidden Variables: A Deeper Look into the ATYR Play

Matteo, G. E., Doye and Rafael Doye.

contact@doyechalmelfreres.com

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Disclaimer

The authors of this paper have a financial interest in the stock ATYR, a decline in the price of the stock would result in financial gains for the authors. The authors expect the clinical results of the Phase III trial of Efzofitimod to be deceiving, leading to a sharp decline in the stock price of ATYR. This paper is solely based on the authors' readings and analysis of the data that will be presented in this paper. No investment decision should be made solely based on the reading of this paper. This paper does not constitute any type of financial advice and is only there to present the authors' analysis and personal opinions on ATYR. We, the authors, reserve the right to change our position on ATYR in regard to a drastic change in the stock price of ATYR. We make no statement that our positions will remain short for the foreseeable future.

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Executive Summary

This paper presents a critical analysis of aTyr Pharma and the upcoming Phase III study results of efzofitimod for pulmonary sarcoidosis.

Preclinical studies showed no statistically significant impact on granuloma formation, the key marker of disease activity in pulmonary sarcoidosis. Phase I/II clinical data failed to meet their primary endpoint. While the 5 mg/kg cohort showed a modest reduction in steroid use, the effect size is unlikely to meet the statistical threshold required for Phase III success. The Phase III study faces additional challenges when we account for the high spontaneous remission rates in the disease. Despite these concerns, the proximity of the 5

mg/kg group to potential efficacy and the increased trial duration leave open the possibility of a favorable outcome.

We estimate a 65% probability of Phase III failure, projecting a 72% drop in share price upon Phase III trial failure. However, given the trial's design and the narrow margin required for success, this is not a high-conviction short. We push for caution, and a well risk-managed approach to this short.

Overview of aTyr Pharma and Efzofitimod

aTyr Pharma, Inc. is a biotherapeutics company involved in the development and discovery of innovative medicines. Their lead therapeutic candidate efzofitimod is a first-in-class biologic immunomodulator that suppresses the excessive activation of immune cells by binding and agonizing neuropilin-2 (NRP2) receptor (Culver et al., 2022). Efzofitimod is currently being tested in a Phase III study for pulmonary sarcoidosis and in Phase II study for systemic sclerosis-related interstitial lung disease (ILD). In this paper we'll be discussing the Phase III study EFZO-FIT NCT05415137 on pulmonary sarcoidosis as the data will come out in Q3 2025 and is the company's primary focus. aTyr Pharma ended 2024 with $75.1 million in cash and expects its current cash runway to fund operations through 1 year after the EFZO-FIT readout (10-K ATYR Pharma, Inc., 2024). The company has already stopped multiple programs such as ATYR1940 (which was also a human histidyl tRNA synthetase (HARS) molecule), and ATYR2810 development due to insufficient results.

aTyr Pharma has a partnership with Kyorin Pharmaceutical Co. for the development and commercialization of efzofitimod in Japan. aTyr Pharma has received over $20 million under this agreement to date and is eligible to receive up to $155 million in additional milestone payments upon the success of this Phase III and subsequent milestones (10-K ATYR Pharma, Inc., 2024).

The Anti-inflammatory History

Pulmonary sarcoidosis is marked with granuloma formation and high inflammation in the lungs of patients. This disease is complex and is driven by pro-inflammatory cytokines, including TNF-α, IL-1β, IL-12 and IL-18 (Barna et al., 2021). Those inflammatory cytokines have been the main focus of the scientific endeavors centered around finding and developing suitable treatment for pulmonary sarcoidosis.

Corticosteroids (prednisone) have been the standard care for pulmonary sarcoidosis since the mid-20th century (Judson et al., 2015). They're acting via the glucocorticoid receptors and suppress the overall inflammation in the lungs. Thereby, they offer an initial symptomatic relief and radiologic improvements to patients. With no long-term benefits in mortality, lung function, radiologic findings and overall disease progression. Proving that this type of treatment results in short term symptomatic benefits to patients but those results disappear in the long-term. Corticosteroids are also renowned to carry side effects when taken in large quantity and/or for a prolonged period of time (Mayo Clinic, 2022). This issue and unmet need sparked the interest to develop new and better treatment that will have a long-term efficacy and potentially be disease modifying.

Treatments focused on reducing the overall inflammation have mainly resulted in negative results. With a strong rate of failure, demonstrating the inefficacy and non-superiority of new anti-inflammatory treatments in comparison to the current standard of care.

Anti-inflammatory drugs that Failed:

- **Thalidomide**: Targeting CRBN, it failed with a p-value of 1.0.
- **Golimumab**: A TNF-alpha inhibitor, it failed, with placebo outperforming it.
- **Namilumab**: Targeting GM-CSF, it showed no significant benefit (p=NS).
- **Acthar Gel**: Acting on melanocortin receptors, it failed with a p-value of 0.5.
- **Antimicrobial Therapy**: It failed with a p-value of 0.64.
- **CMK389**: An IL-18 inhibitor, it failed with a p-value of 0.18.
- **Nicotine Patches**: Targeting nAChRs, they failed with a p-value of 0.535.
- **Bosentan**: An endothelin-1 inhibitor, it failed with a p-value of 1.0.
- **Canakinumab**: An IL-1Beta inhibitor, it failed, with placebo outperforming it.
- **Atorvastatin**: An HMG-CoA reductase inhibitor, it failed with a p-value of 0.561.
- **Pentoxifylline**: A phosphodiesterase inhibitor, it failed with a p-value of 0.146.
- **Ustekinumab**: An IL-12/IL-23 inhibitor, it failed, with placebo outperforming it.

Anti-inflammatory drugs that Succeeded:

- **Prednisone**: A corticosteroid acting on glucocorticoid receptors (standard frontline therapy). It reduces inflammation and improves short-term symptoms, with no positive effects over the long term.
- **Infliximab**: TNF-alpha inhibitor, with positive results with a p-value of 0.03, showing statistical significance in the primary endpoint in comparison to placebo. Its benefits remained modest.

- **Methotrexate**: Second-line therapy, with positive results in trials as a steroid-sparing agent, showed non-inferiority to prednisone in improving forced vital capacity (FVC) over 24 weeks.

Infliximab vs golimumab both TNF-α inhibitors

Both infliximab and golimumab are TNF-α inhibitors and still, they had different results as infliximab was statistically significant but golimumab wasn't (Moller, 2014). As shown in Figure 1, the results of infliximab were statistically significant at 3 mg/kg and not at 5 mg/kg. The 3 mg/kg was only significant at 2 – 24 – 52 weeks.

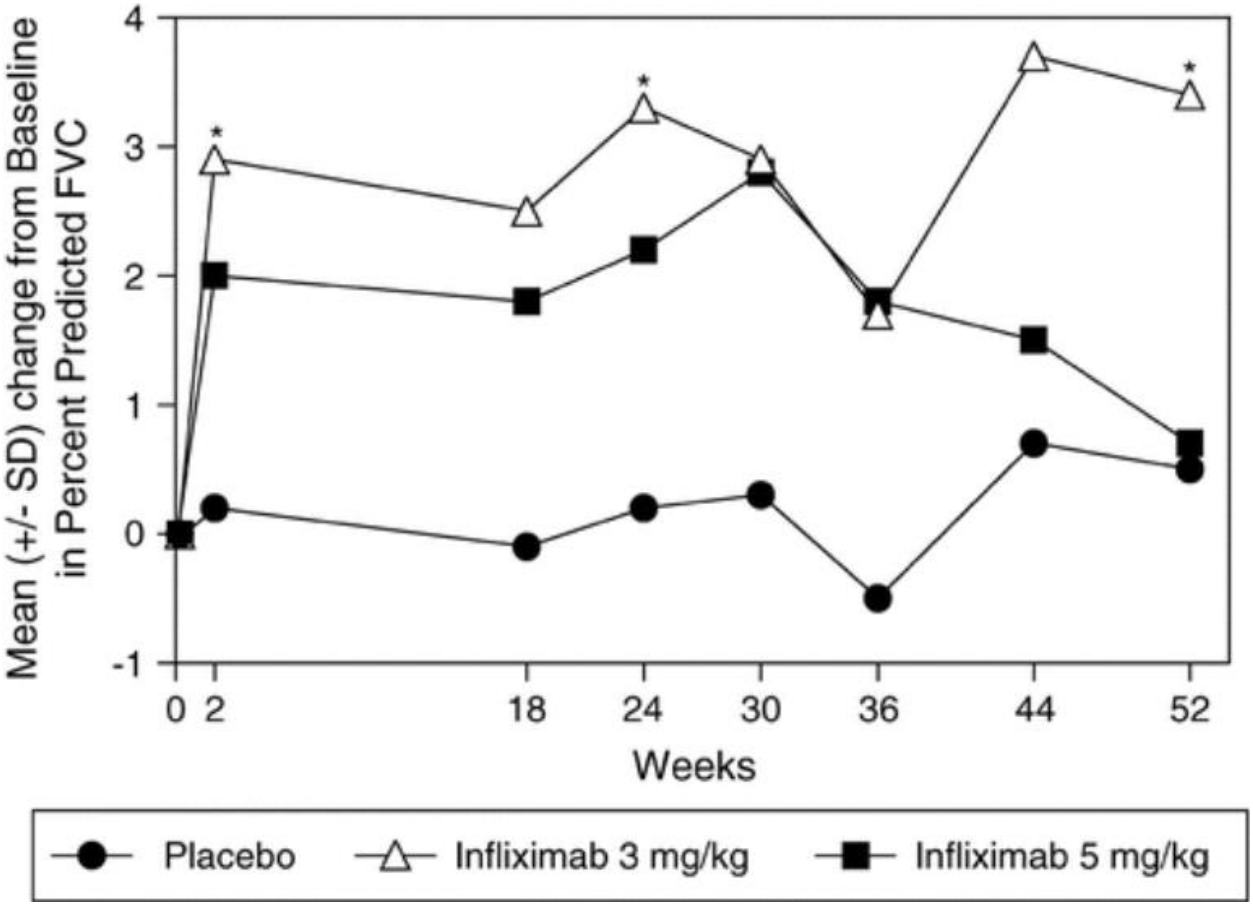

Figure 1: Infliximab data (Baughman et al., 2006).

This difference most likely stems from trial designs, undermining the overall confidence in both drugs. Golimumab's clinical trial used combination therapy, which probably reduced its effect, it also had a reduced dosing regimen which is expected to have weakened golimumab's impact. In addition, the study had an early endpoint which failed to capture any potential benefit on a longer-term period. Infliximab, on his side was administered as a monotherapy, with stable dosing, and had a longer follow-up. The difference in the study results of these two TNF-α inhibitors shows how the statistical significance of a treatment for pulmonary sarcoidosis relies on arbitrary design choice and is highly sensitive to any, and, all factors (Moller, 2014). This high sensitivity only increases the odds of failure for efzofitimod Phase III ongoing study.

The Placebo Powerhouse

Spontaneous remission rates in pulmonary sarcoidosis range broadly but are generally reported for Stage I and II between 30% and 80% (Belperio et al., 2023). These high remission rates occur without any treatment. In Stage I pulmonary sarcoidosis, the spontaneous remission rates are estimated between 55% and 90%. Spontaneous remission often occurs within the first 2 to 5 years after diagnosis for ± 50% of the patients (Bilgin et al., 2023).

These high spontaneous remission rates make it even more difficult to prove a statistical difference between efzofitimod and the placebo cohort. Since many placebo patients can improve on their own without treatment, the placebo group is expected to show some level of improvement throughout the trial. These improvements will increase the effect size that

efzofitimod must exceed in order to show statistical significance. The high spontaneous remission rates in pulmonary sarcoidosis are a factor that must be accounted for when discussing their probability of success in the Phase III study but should be weighted and not overvalued. Furthermore, the Phase I/II trial NCT03824392 with efzofitimod on pulmonary sarcoidosis showed that placebo patients gradually decreased steroids significantly and many showed FVC improvement or stability. This increases credibility by which we must account for the high placebo efficacy and increases difficulty in demonstrating statistical significance.

Negative Preclinical Results

From the start, in preclinical studies, the results weren't great. Specifically, when assessing the model specific to pulmonary sarcoidosis as shown in Figure 2. Those models do not replicate the full spectrum of the disease but provide us with a strong overview of its major characteristics. Furthermore, the P.acnes model is the most important model presented in Figure 2 as it focuses on pulmonary sarcoidosis. This model shows that no statistical significance was found on histopathologic/fibrotic readouts called "Primary Endpoints" for efzofitimod in green in comparison to the vehicle in black. The inflammatory biomarkers were reduced but their relevancy is minimal when we consider the original aim. This original aim was centered around efzofitimod capacity to become and to act as a disease-modifying drug (which it does not). This data adds to the layer discussed in *The Anti-inflammatory Failure History* section of this paper. Indeed, the inflammatory biomarkers were reduced but the disease remained unchanged, as no statistical significance was found to support the idea that efzofitimod could be a disease-modifying drug for pulmonary sarcoidosis.

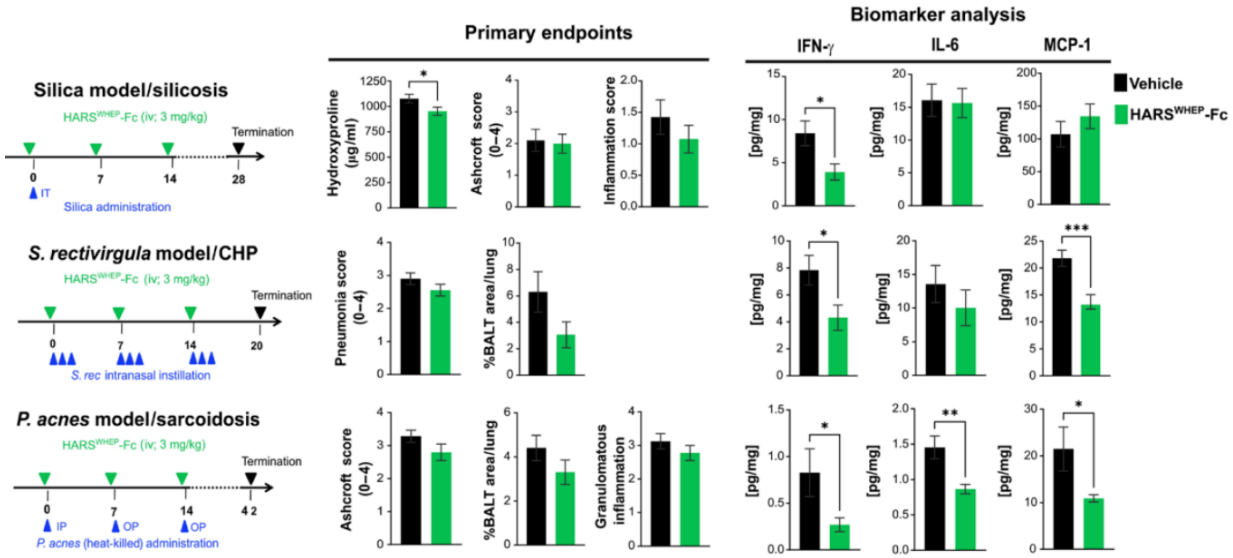

Figure 2: Preclinical models reconstructing pulmonary sarcoidosis (Nangle et al., 2025).

In another preclinical study they also demonstrated that efzofitimod does not reduce granuloma's size or quantity in pulmonary sarcoidosis (Baughman et al., 2023). The granuloma formation and physical burden was not statistically significantly altered in all the tested models. In all preclinical studies efzofitimod demonstrated an ability to reduce some inflammatory biomarkers but failed to show any statistically significant reduction in either the quantity or formation of granuloma. When considering all the above, one must question the efficacy and potential translation of efzofitimod.

Granulomas are a hallmark of pulmonary sarcoidosis and have a major role in the disease, this non-reduction raises critical concerns over the efficacy of efzofitimod (Baughman et al., 2023). Furthermore, these results indicate that efzofitimod is not a disease modifying drugs with no efficacy on the disease and its development. Their original thesis which states that efzofitimod reduces inflammatory biomarkers, and that this reduction will lead to a reduction of granuloma's quantity and size has proven to be a failure, as soon as preclinical (Baughman et al., 2023).

Phase I/II Data Analysis and Evaluation

This Phase I/II NCT03824392 was conducted with 37 patients as a multi-center study exclusively in the USA (ClincalTrials.gov, 2023). It had 4 cohorts: placebo (n = 12), 1 mg/kg of efzofitimod (n = 8), 3 mg/kg of efzofitimod (n = 8), and 5 mg/kg of efzofitimod (n = 9). The primary endpoints were centered around the safety of efzofitimod and successful steroid tapering.

In the ongoing debate, bull vs shorts, on ATYR, one of the most heated subjects is centered around the baseline health difference of patients included in the Phase I/II study. The bears argued that the placebo cohort was sicker than the 3 mg/kg and 5 mg/kg cohorts which were healthier at baseline. However, there is more to that story. The baseline, shown in Figure 3, does have some notable difference in the healthiness of patients but nothing too major to be considered a strong/major factor of the subsequent results in our view.

The lungs' function and dyspnea data show that the 3 mg/kg cohort had the healthiest patients with $FEV_1 \approx 78\%$ predicted, $DLCO \approx 76\%$ predicted, and no patients in the worst dyspnea category (mMRC 3–4). Whereas the 1 mg/kg and 5 mg/kg cohorts had lower lung function and more dyspnea at baseline. In addition, the 3 mg/kg cohort had the highest BDI score at 7.6 indicating less breathlessness related impact on their daily life, as for the placebo and 1 mg/kg cohorts had the lowest levels at ≈ 4–5. As for the disease duration we can see that the 1 mg/kg cohort had a longer median disease duration population with 5.3 years against ~3 years in the placebo and 5 mg/kg cohorts. This could reflect a more chronic population that could be more difficult to treat. The 3 mg/kg and 5 mg/kg cohorts do separate themselves in the FVC data and it does suggest that they had a healthier

population as FVC ≈ 83.8 predicted and placebo was at ≈ 77.3. This could result in skewed results for the Phase I/II data but shouldn't be overestimated. These data do have a strong importance but are not acting as make-or-break factors for this Phase I/II. We must also consider the small dataset which by itself skews the results, a difference in the healthiness of patients is inevitable, especially with such a small n-study.

The 3 mg/kg cohort does seem to have a milder disease profile in comparison to the other cohorts. Thus, the 3 mg/kg cohort appears healthiest at baseline. In our view the only cohort with a bias at baseline is the 3 mg/kg and not the 5 mg/kg as others may have suggested.

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Variable	Placebo (n = 12)	Efzofitimod			All (n = 37)
		1 mg/kg (n = 8)	3 mg/kg (n = 8)	5 mg/kg (n = 9)	
Age, y	52.5 ± 10.2	54.5 ± 11.3	51.8 ± 11.4	50.8 ± 9.8	52.4 ± 10.1
Sex, female	7 (58.3)	4 (50)	4 (50)	5 (55.6)	20 (54.1)
Race					
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, y					
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
Baseline BDI total score	4.8 ± 2	4.3 ± 1.8	7.6 ± 2.9	6.3 ± 2.5	5.65 ± 2.54
Baseline lung function					
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)
FEV_1, % predicted	68.3 ± 20.1	60.4 ± 10.2	77.6 ± 11.1	77.3 ± 19.5	70.8 ± 17.3
FVC, % predicted	77.3 ± 11.5	68.3 ± 9.7	83.8 ± 7.3	83.8 ± 16.6	78.3 ± 12.9
FEV_1 to FVC ratio	0.7 ± 0.15	0.7 ± 0.08	0.73 ± 0.08	0.72 ± 0.1	0.715 ± 0.11
D_{LCO}, % predicted	61.7 ± 19.7	61.9 ± 21.4	75.5 ± 19.9	54.5 ± 14.1	63.8 ± 19.8
Baseline steroid use					
Prednisone equivalent dose, mg/d[b]	13.3 ± 4.4	11.3 ± 3.5	14.4 ± 6.2	13.9 ± 3.3	13.2 ± 4.4
10 to < 15	7 (58.3)	7 (87.5)	5 (62.5)	3 (33.3)	22 (59.5)
15 to < 20	2 (16.7)	0	0	5 (55.6)	7 (18.9)
≥ 20	3 (25)	1 (12.5)	3 (37.5)	1 (11.1)	8 (21.6)
Baseline immunomodulator use					
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)

Figure 3: Baseline characteristics of all the cohorts in Phase I/II (Culver et al., 2022)

aTyr Pharma's partner Kyorin Pharmaceutical, also did a Phase I clinical study in Japan but no data could be found. According to the available information on this Phase I study, which was exclusively conducted on 32 healthy Japanese male volunteers, it reported similar results to the Phase I/II study conducted by aTyr Pharma (aTyr Pharma, 2021). Overall, we can be confident that efzofitimod has a strong safety profile.

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The primary endpoint of the Phase I/II clinical trial was safety and major endpoints included successful steroid tapering, and it did not reach statistical significance in any dose cohort in comparison to placebo in steroid tapering. As shown in Figures 4 and 5 we can see that placebo outperformed all the efzofitimod cohorts. Placebo had the highest ratio and number of patients who successfully achieved and maintained the targeted tapered dose of prednisone from baseline up to week 24.

3. Number of Participants Who Achieved and Maintained The Targeted Tapered Dose of Prednisone 5 mg/Day (or Equivalent)
Type: Secondary | Time Frame: Baseline up to Week 24

Description	[Not Specified]			
Time Frame	Baseline up to Week 24			
Analysis Population Description	The mITT Set included all participants who had received any amount of study drug and were based on the randomized treatment, regardless of which treatment the participant actually received.			
Arm/Group Title	Placebo	Efzofitimod 1.0 mg/kg	Efzofitimod 3.0 mg/kg	Efzofitimod 5.0 mg
Arm/Group Description	eceived placebo fzofitimod via IV y 4 weeks until	Participants received efzofitimod 1.0 mg/kg via IV infusion every 4 weeks until Week 20.	Participants received efzofitimod 3.0 mg/kg via IV infusion every 4 weeks until Week 20.	Participants received ef 5.0 mg/kg via IV infusio weeks until Week 20.
Overall Number of Participants Analyzed	12	8	8	9
Measure Type: Count of Participants | Unit of Measure: Participants	7 58.3%	1 12.5%	4 50.0%	5 55.6%

Figure 4: (ClincalTrials.gov, 2023).

	Placebo	1 mg/kg	3 mg/kg	5 mg/kg
n	12	8	8	9
n patients success	7 (58.3%)	1 (12.5%)	4 (50%)	5 (55.6%)
Placebo-adjusted difference	-	-45.8%	-8.3%	-2.7%

Figure 5: Recapitulative data based on NCT03824392's results (ClincalTrials.gov, 2023).

When assessing the amount of steroid reduction per day over the full course of the study we can see that the 5 mg/kg cohort shows a clear separation from the placebo cohort of **1.8mg/kg** as shown in Figure 6 and 7.

2. Time-adjusted Area Under the Curve (AUC) of Background Oral Corticosteroid (OCS) Usage Over Study Period
Type: Secondary | Time Frame: Baseline up to Week 24 (Day 1 to End of Dosing Period)

Description	Time adjusted AUC is a measure of steroid burden and approximates the average daily OCS dose (mg/day) post-baseline for each participant. Time adjusted AUC was calculated by AUC divided by the number of days between first and last day of time interval of interest.			
Time Frame	Baseline up to Week 24 (Day 1 to End of Dosing Period)			
Analysis Population Description	The modified intent-to-treat (mITT) Set included all participants who had received any amount of study drug and were based on the randomized treatment, regardless of which treatment the participant actually received.			
Arm/Group Title	Placebo	Efzofitimod 1.0 mg/kg	Efzofitimod 3.0 mg/kg	Efzofitimod 5.0 r
Arm/Group Description	s received placebo efzofitimod via IV ery 4 weeks until	Participants received efzofitimod 1.0 mg/kg via IV infusion every 4 weeks until Week 20.	Participants received efzofitimod 3.0 mg/kg via IV infusion every 4 weeks until Week 20.	Participants received 5.0 mg/kg via IV infus weeks until Week 20.
Overall Number of Participants Analyzed	12	8	8	9
Mean (Standard Deviation) | Unit of Measure: mg/day	8.64 (4.20)	6.83 (1.41)	8.36 (3.68)	7.43 (3.30

Figure 6: (ClincalTrials.gov, 2023).

	Placebo	1mg/kg	3mg/kg	5mg/kg
Baseline	13.3	11.3	14.4	13.9
Mean OCS use post-taper	8.64	6.83	8.36	7.43
Delta from baseline	4.66	4.47	6.04	6.47
Placebo-adjusted change from baseline	-	-0.19	**1.38**	**1.81**

Figure 7: Recapitulative data based on NCT03824392's results (ClincalTrials.gov, 2023).

This separation is clear and can be considered as a positive result for efzofitimod 5 mg/kg cohort. The argument that short posits disregard this result considering that the skewed baseline is affecting the results too much for it to be admissible. However, when

considering, as mentioned above that the only cohort, one could consider skewed is 3 mg/kg and not 5 mg/kg. Still, this is not a factor that must be over-interpreted as our personal view on the overall data and information related to efzofitimod remains negative.

The data presented in Figure 8 is from the post-hoc interpretation of the Phase I/II study results. It shows an exclusive benefit for the 5 mg/kg cohort, with 3 patients tapered to 0 mg that maintained it. This positive result for the 5 mg/kg cohort is especially important when considering that this cohort's baseline wasn't "healthier" in contrary to the 3 mg/kg cohort. Moreover, we have to remember Figures 4 and 5 data, as the number of patients who successfully tapered 50% in the cohort 5 mg/kg was lower than the placebo cohort with 58% for placebo and 56% for 5 mg/kg. This doesn't indicate that placebo's efficiency is equal to the 5 mg/kg cohort's efficacy but it does mean that the 5 mg/kg is more effective in the tapered mg as it had 3 patients who reduced it to 0 mg and placebo had no patient who could achieve that 0 mg. Data of Figure 8 shows only 5 mg/kg cohort had patients that tapered to 0 mg and maintained it, not placebo.

TABLE 3] Corticosteroid[a] Burden (Modified Intention-to-Treat Population)

Parameter	Placebo (n = 12)	Efzofitimod		
		1 mg/kg (n = 8)	3 mg/kg (n = 8)	5 mg/kg (n = 9)
Baseline prednisone equivalent dose, mg/d	13.3 ± 4.4	11.3 ± 3.5	14.4 ± 6.2	13.9 ± 3.3
Average daily dose, mg[b]	7.2	6.8	6.5	5.6
Change from baseline, %	−45.7 ± 26.7	−41.4 ± 15.9	−48.9 ± 19.7	−58.1 ± 23.4
Difference in adjusted means, %[c]	—	1.2 (−20.0 to 22.4)	−2.3 (−23.1 to 18.5)	−12.3 (−33.1 to 8.5)
Tapered to 0 mg and maintained taper	0	0	0	3 (33.3)

Data are presented as No. (%), mean ± SD, mean, or time-adjusted area under the curve (95% CI).
[a]Any corticosteroid that was not prednisone was converted to prednisone equivalent dose. All end points use the posttaper period (day 51 to end of dosing).
[b]Adjusted means from analysis of covariance adjusting for baseline steroid use.
[c]Time-adjusted area under the curve of percent change from baseline, $P > .05$.

Figure 8: (Culver et al., 2022).

The patient population of this Phase I/II study remains small, and the Phase III study will be much more rigorous in a number of significant aspects, that will remove any potential

bias effects. We remain confident that efzofitimod will fail its Phase III study. However, we press for caution and wouldn't advocate for an aggressive short, and much rather propose an aggressive hedging strategy.

Overall, we can say that the Phase I/II study data are not clear as they show some positive activity for the 5 mg/kg cohort but do also show, at times, higher activity for placebo. This unclear data should set a clear understanding for all parties that this Phase III study outcome is not a homerun for either bears or bulls, as no clear data sets a principle of whether the drug is or isn't effective. Furthermore, we do want to insist that in our view efzofitimod does provide some type of positive effect at the 5 mg/kg cohort regardless of the potential bias of the baseline healthiness of this cohort's patient population.

Phase III Design and Probability of Success

This Phase III NCT05415137 is multi-national study with 39 sites in the USA, 5 in Brazil, 5 in France, 4 in Germany, 9 in Italy, 16 in Japan, 1 in the Netherlands, 6 in Spain, 6 in the UK (ClinicalTrials.gov, 2025). This trial is a randomized, double-blind and placebo-controlled study. With a positive result in this trial, aTyr Pharma can expect to get an FDA approval for pulmonary sarcoidosis. A failure would result in a strong decline of the price per share by an estimated –72.65%, see *Price Targets* section of this paper.

The design parameters of this trial are set as follows:

- Randomization: 1:1:1 allocation
- Sample Size: 88 patients per cohort (total N = 264)
- Cohorts:

  - Placebo IV monthly
  - Efzofitimod 5 mg/kg IV monthly
  - Efzofitimod 3 mg/kg IV monthly
- Study duration: 48-week treatment period plus 4-week follow-up

aTyr Pharma have set a clear trial design with the primary endpoint being the statistical significance of a change from baseline in mean daily oral corticosteroid (OCS) dose at Week 48 (ClinicalTrials.gov, 2025) shown in Figure 9. Meaning that the in-between period is not accounted for, only baseline and week 48.

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Change from baseline in mean daily oral corticosteroid (OCS) dose at Week 48		Baseline to Week 48

Secondary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Change from baseline in KSQ-Lung score at Week 48		Baseline to Week 48
Steroid withdrawal rate		Baseline to Week 48
Change from baseline in absolute value of FVC at Week 48		Baseline to Week 48

Figure 9: Primary and secondary outcome measures in the Phase III study (ClinicalTrials.gov, 2025).

The baseline patient's characteristics are shown in Figure 10. We can see that overall patient population is healthier than the one in the previous Phase I/II study NCT03824392.

Disease Characteristics	
Baseline OCS dose (prednisone equivalent, mg)	
Mean (SD)	10.55 (4.21)
Range	5–25
MRC dyspnea score (%)	
0	2 (0.7)[4]
1	132 (50)
2	100 (37.9)
3	28 (10.6)
4	2 (0.7)

Figure 10: (aTyr Pharma, 2025).

It's difficult to estimate the effects of efzofitimod and placebo as the Phase I/II primary endpoint and data was focused on a period of 24 weeks and not 48 weeks. This uncertainty has been accounted for in the probability of success we've set in this Phase III study.

A clear prediction of whether the drug will fail or succeed is not possible in this case. However, we can confidently say that the preclinical data is not convincing (failure), and that the Phase I/II data is mitigated. Focusing on the few positive results from the Phase I/II study, a few concerns arise such as a potential healthier patient population at baseline, a bias from the little data set, and not a clear replicability of positive results throughout the entire data set of the study. As written previously, the only cohort that could be effective in this Phase III study would be the 5 mg/kg cohort.

A critical statistical consideration that must be considered is the multiple comparison problem, given the two efzofitimod cohorts. Multiple methods can address this, affecting p-value thresholds and statistical power differently. There is the *Hierarchical Testing Strategy* that prioritizes the 5 mg/kg cohort at $\alpha = 0.05$ and if significant will proceed to the 3 mg/kg cohort at $\alpha = 0.05$ too. There is also the *Bonferroni Correctio*n that splits the error rate by applying a stricter threshold at $\alpha = 0.025$ to both cohorts. This method is conservative, but it provides a straightforward method to control Type I error. Finally, there's the *Holm Step-Down Procedure* that tests the smaller p-value first at $\alpha = 0.025$ and the other at $\alpha = 0.05$ upon first test's significance.

In our view, given the industry standards and dose-response expectations, hierarchical testing appears the most likely. Still, the Bonferroni correction could be adopted as it's a viable method in the presented case.

We'll see how much power the data would need to have in this Phase III study to be statistically significant. *Those are rough estimates as we don't have the full data set, nor the knowledge of what model will be used in the final statistical analysis of the Phase III study.* That said, using 88 patients per cohort and a standard deviation estimate centered around 4.0 mg/day the effect size requirements will vary based on the significance level and the desired power, which we'll put at 90%.

- $\alpha = 0.05$, 90% power: 1.95 mg/day reduction
- $\alpha = 0.025$, 90% power: 2.12 mg/day reduction

In this case, we assume that the SD will be around 3.5 - 5 mg/day and the required reductions will range from **1.71** to **2.65** mg/day.

The most likely scenario would be around hierarchical testing with a SD around 4 mg/day.

- Required effect: 1.7 - 2 mg/day reduction
- p-value threshold: $p < 0.05$ for 5 mg/kg cohort

However, if the SD is higher and aligns around 5 – 6 mg then the required effect size would be around **2.4 - 3.2** mg/day with a higher probability that the study fails to meet its primary endpoint. Our best estimate is that the range of **1.8 - 2.2** mg/day placebo-adjusted OCS reduction is the target for the Phase III results. If the 5 mg/kg cohort can hit that range, the primary endpoint will be met, and the study considered a success.

We wouldn't consider this short an easy short considering the Phase I/II data reported 1.8 mg/d delta to baseline placebo adjusted and that the 5 mg/kg cohort only needs to hit 1.8 - 2.2 mg/day placebo-adjusted OCS reduction to be statistically significant. However, the overall data does strongly support a short position on ATYR, one should understand that our general view of the situation is that the study will fail to demonstrate significance considering the overall low benefits observed and explained throughout this paper. Still, the few positive results shouldn't be dismissed as the range to reach statistical significance is far from unachievable for the 5 mg/kg cohort. If one strongly believes that the 1.8 mg/day data was skewed because of the baseline health difference between 5 mg/kg cohort and placebo's then you shouldn't be too bothered by this closeness as you see that the 1.8 mg/day can't replicate. If you do not believe that this longer study will result in better results as the patients are more exposed to efzofitimod, then you shouldn't worry either. However, if like us you're confident in the overall flaws of efzofitimod but remain vigilant and do not view the baseline difference between cohort 5 mg/kg and placebo as heavily skewed and that you believe that we'll see better results in a longer treatment period then, we would advise caution. ATYR is a short no doubt about it, but the confidence that one should put in this short ought to remain advised. In our view the odds of failure are positive but are not flagrant.

Market Outlook

Pulmonary sarcoidosis affects around 185,000 Americans, however, only ~11,000 – 15,000 are eligible for a high-cost biologic treatment like efzofitimod (Baughman., 2016). This is due to high remission rates, and conservative treatment practices. The current standard of care relies on cheap corticosteroids such as prednisone. Only a minority of patients receive expensive biologic therapies. Efzofitimod faces major commercialization challenges in pulmonary sarcoidosis because of its projected high cost in comparison to available generics (100 - 500 x more expensive), its limited market size, the high payer resistance and overall strict coverage criteria covering biologics. Despite an FDA approval for efzofitimod, its revenues projection remains low, and it's unlikely to achieve commercial success.

Price Targets

With the use of our proprietary valuation model **GRAVITY**, we computed the full pipeline valuation of aTyr Pharma as of today and what impact Phase III readout will have on the company's valuation. The full forecast and valuation are shown in Figure 11. We expect a market cap valuation of $119.6 M upon failure of the Phase III study, bringing the company's price per share to **$1.34** in comparison to the current price of shares of $4.9 (decrease of **–72.65%**).

Disclaimer: This paper discusses our analysis of ATYR. It is important to disclose that we have a financial interest in this matter, as we will profit if the stock price declines.

Name in $, million	Indication	TAM	Peak Sales %	Peak Sales	Phase	Discount	NPV	POS	rNPV	Multiple	Real Value	Weight
Efzofitimod	Pulmonary Sarcoidosis	4,400.0	10.0%	440.0	III	30.0%	308.0	61.66%	189.9	3	569.8	82.6%
Efzofitimod	SSc-ILD	2,024.0	10.0%	202.4	II	45.0%	111.3	13.50%	15.0	2	30.1	4.4%
Efzofitimod	Other ILD (CTD-ILD; CHP)	8,175.0	10.0%	817.5	I	60.0%	327.0	7.55%	24.7	1	24.7	3.6%
ATYR0101	Fibrosis	4,090.0	10.0%	409.0	PC	85.0%	61.4	3.77%	2.3	1	2.3	0.3%
ATYR0750	Liver Disorders	2,150.0	10.0%	215.0	PC	85.0%	32.3	3.77%	1.2	1	1.2	0.2%
Cash											61.3	8.9%

	MC	Per Share
Current Real Value before Catalyst	689.4	*7.75*
After Failure If Market Still Value		
The Rest of Their Pipeline	119.6	*1.34*
Trading at Cash Level	61.35	0.69
If Successful	1,430.2	*16.07*
With Potential Short Squeeze	1,930.7	*21.69*

Figure 11: GRAVITY valuation and forecast upon catalyst for aTyr Pharma.

If we consider a successful data-readout on this Phase III study, then we can expect the market cap to rise to $1, 430.2 M with share prices at $16.07 (considering no dilution). Pushing it further with a potential short squeeze upon Phase III positive data the valuation of aTyr Pharma could rise to $1, 930.7 M with share prices at $21.69 (up 342.65% from today's value).

Overall, we expect a failure of the Phase III study but have pushed for an medium - aggressive hedging strategy. In sum, we've dedicated limited capital to ATYR as we don't see a clear answer on the outcome of the Phase III study (**65% fails** – **35% success**). At DCF we consider a short a no brainer when the probability of success we establish is below 1% (like SAVA with 0.00032% (Doye, 2024)).

Conclusion

Based on our analysis, efzofitimod is unlikely to demonstrate statistically significant efficacy in the ongoing Phase III trial for pulmonary sarcoidosis. Preclinical failures, weak Phase I/II results, and a challenging commercial landscape all point to limited long-term

value for the asset. While some positive signals from the 5 mg/kg cohort suggest limited potential, those are not strong enough to justify optimism.

We maintain a short position on ATYR, with an estimated 65% probability of trial failure and a projected 72% downside in share price. However, due to the small margin needed to meet the trial's primary endpoint and some uncertainty in the data, we do not consider this an aggressive short. Our capital allocation is limited, and risk management essential (strong – medium hedging aggressivity).

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