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aTyr Pharma

Equity Research
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Our Thoughts on Short Theses and Continued View of Efzo Ph3 Good Chance to Win

With a few short reports mostly focused on efzo's MOA and Ph1/2 translatability to Ph3, we provide our thoughts and continue to believe efzo has scientific rationales to be developed in treating pulmonary sarcoidosis (PS), and Ph1/2 has encouraging evidence to support a Ph3, which is enhanced to further increase POS. With very detailed discussions in our PREVIEW, we continue to see ~60% probability for Ph3 to hit stat sig and ~40%+ prob as practice changing.

Bottom line. The stock has had a good run-up into the transformational Ph3 efzofitimod PS readout in mid-Sept (YTD +~37% vs. XBI -~0.2%), in line with our expectations given the high interest from investors, Ph3 definitive nature to support near-term approval if successful, sig blockbuster market opportunity with limited comp pipeline on the horizon, and inexpensive valuation (<~$400M EV with ~$100M+ cash). However, a few short reports came out following the recent high point at $6.6/ share in late July (~83%+ up from the year beginning), the stock has been pulled back/ choppy, now at ~$5/share. We took a close exam to those short theses, which were mostly focused on efzo's MOA and Ph1/2 translatability to Ph3; we provide our thoughts below and continue to believe that *efzo had decent scientific rationale to treat inflammatory disease, including PS, and Ph3 has many enhanced elements to support a good chance to win while acknowledging limited clinical data from a small Ph1/2.*

As a novel MOA of NRP2/ HARS, efzo has decent scientific ground to address inflammation in sarcoidosis. Despite an old *Howard 2002* suggesting that HARS might be pro-inflammatory via CCR5 pathway, which might be a driver for sarcoidosis inflammation, we have a few counterarguments: **1)** in *STM 2025*, efzo only binds NRP2 with no off-targets including CCR5; **2)** *Adams 2021* showed HARS down-regulates immune activation in *in vivo* models and neutralization of HARS increases susceptibility to immune attack, and stated that they "*could not verify the (Howard 2002) results, in spite of several attempts*"; **3)** no other publications explicitly repeated *Howard 2002 in vitro* chemotaxis effect of HARS; **4)** extracellular HRAS fragment could be a multifunctional ligand to multiple receptors, but some could be dominant, and Fc modified efzo could specifically bind to NRP2, different from endogenous HARS splice fragment.

Despite the limitations of a small Ph1/2 study, we see Ph3 efzo was well-designed to enhance POS. As we highlighted in our PREVIEW NOTE, there are quite a few Ph3 differences vs. Ph1/2, most of which favor Ph3 results, including baseline OSC use, background Tx, tapering/ rescue protocol, study Tx duration, endpoint measures. Based on FDA's feedback, ERS guideline, and regulatory precedents, we believe that steroid sparing is clinically meaningful to PS pts and supportive of approval, if successful. While PS is tough to develop drug, we note a few positive small/ open-label steroid reduction trials.

See Content for detailed discussions.

FY (Dec)	2023A	2024A	2025E	2026E
Adj EPS	(0.94)	(0.86)	(0.82)	(0.88)
Rev. (MM)	0.4	0.2	0.0	0.0

COMPANY UPDATE

RATING	**BUY**
PRICE	**$4.92^**
PRICE TARGET | % TO PT	**$17.00 | +246%**
52W HIGH-LOW	**$7.29 - $1.67**
FLOAT (%) | ADV MM (USD)	**83.9% | 25.92**
MARKET CAP	**$482.1M**
TICKER	**ATYR**

^Prior trading day's closing price unless otherwise noted.

FY (Dec)	CHANGE TO JEFe		JEF vs CONS	
	2025	2026	2025	2026
REV	NA	NA	NA	NA
EPS	NA	NA	NA	NA

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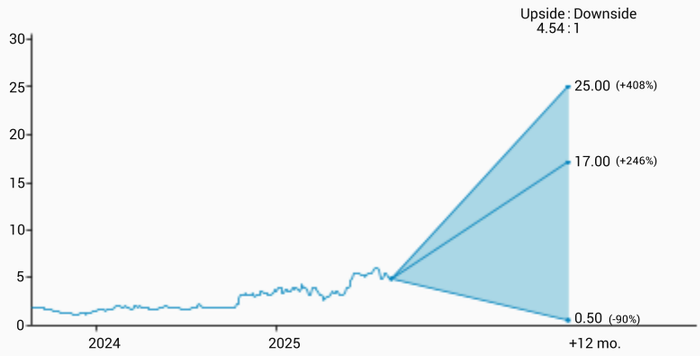
The Long View: aTyr Pharma

Investment Thesis / Where We Differ

Efzofitimod has established clinical POC in pulmonary sarcoidosis, which is a sizable market with no approved drugs and limited competitors. Efzofitimod could be the first approved drug in PS, with additional opportunities in SSc-ILD and other ILDs.

With its unique discovery platform leveraging extracellular tRNA synthetase, ATYR has a growing pipeline of tRNA synthetase-derived candidates targeting inflammation and fibrosis.

Risk/Reward - 12 Month View



Base Case,
$17, +246%

- Efzofitimod US adjusted peak sale in pulmonary sarcoidosis: ~$824M (POS 55%)
- Efzofitimod US adjusted peak sale in SSc-ILD: ~ $74M (POS 10%)
- Platform and pipeline value: $100M
- **Price target: $17 (DCF-based)**

Upside Scenario,
$25, +408%

- Efzofitimod US adjusted peak sale in pulmonary sarcoidosis: ~$1.1B (POS 75%)
- Efzofitimod US adjusted peak sale in SSc-ILD: ~ $184M (POS 25%)
- Platform and pipeline value: $100M
- **Price target: $25 (DCF-based)**

Downside Scenario,
$0.5, -90%

- Failed Efzofitimod
- No platform value
- **Price target: $0.50 (YE25 cash)**

Sustainability Matters

Top Material Issues: 1) Supply Chain Management. Currently, all supply of drug candidates comes from contract manufacturing organizations (CMOs). There are no assurances that the manufacturing and supply chain infrastructure will remain uninterrupted and reliable. **2) Product Quality and Safety.** CMOs must comply with cGMP regulations, which include requirements related to quality control and quality assurance, as well as the corresponding maintenance of records and documentation. **3) Employee Engagement.** Many of the company's employees/consultants/outside scientific collaborators may have executed proprietary rights, nondisclosure, and/or noncompetition agreements in connection with such previous employment or engagement.

Company Targets: NA

Qs to mgmt.: 1) How are you promoting patient diversity when enrolling your pivotal trials? **2)** What efforts have you made to hire diverse candidates into your workforce?

Catalysts

Mid-Sept '25: Efzofitimod Ph3 pulmonary sarcoidosis topline

Efzofitimod

Efzofitimod (ATYR1923) is a slightly modified piece of the HARS fragment. It consists of the N-terminal domain of human HARS (amino acids 2–60) fused to the Fc region of an IgG1 antibody. The HARS fragment is the active moiety, and the Fc portion serves to stabilize the molecule and extend its half-life. ATYR found/ discovered that the human body produces a HARS splice (roughly the same 58-amino-acid N-terminal piece) in lung tissue during inflammation. The splice is upregulated by inflammatory signals (e.g.interferon-γ and TNF-α) and is secreted by cells in the lung.

Efzo was found to bind neuropilin-2 (NRP2), which is found on inflammatory myeloid cells (e.g., macrophages and dendritic cells). In sarcoidosis patients, NRP2 is enriched in the granulomas within the lungs. ATYR believes that NRP2 is a novel immune checkpoint in interstitial lung disease, acting upstream of multiple inflammatory pathways. When efzofitimod engages NRP2, it sends a signal to those myeloid cells to reduce their production of pro-inflammatory mediators. In preclinical studies, efzofitimod binding to NRP2 caused macrophages to adopt an anti-inflammatory profile lowering key cytokines like TNFα, IL-6, and MCP-1, and reducing surface receptors that drive inflammation.

What's the role of extracellular HARS fragment - can it be repurposed to calm the immune system, or does it work the opposite to activate immune cells?

This bear thesis focuses on efzofitimod's MOA: the same HARS fragment used by efzo has known immune-recruiting effects via CCR5 (pro-inflammatory), seemingly at odds with the drug's anti-inflammatory goal. Skeptics question if efzofitimod can truly suppress inflammation or if its MOA lacks scientific rationale.

The Bear Thesis

In 2002, *Howard et al.* reported that HARS (also called Jo-1 antigen in autoimmune myositis) can act outside cells to attract immune cells:

- **HARS causes immune cell migration.** HARS induced CD4(+) and CD8(+) lymphocytes, IL-2-activated monocytes, and immature dendritic cells (iDCs) to migrate, but not neutrophils, mature DCs, or unstimulated monocytes. HARS selectively activated cells expressing the chemokine receptor CCR5. When CCR5 was blocked by an antibody, HARS-induced cell migration stopped, indicating HARS was working through that pathway.
- **The active region is the N-terminus.** An N-terminal domain, 1-48 HARS, was chemotactic for lymphocytes and activated monocytes, whereas a deletion mutant, HARS-M, was inactive. This N-terminal region is exactly the part of HARS that the immune system often targets with autoantibodies in myositis patients, hinting that its pro-inflammatory nature might be why the immune system reacts to it.
- **NARS has a similar effect.** NARS (another tRNA synthetase) likewise induced migration of lymphocytes and monocyte-derived cells, but via CCR3 (a different chemokine receptor). In contrast, tRNA synthetases that are not autoantigens (e.g. aspartyl- and lysyl-tRNA synthetase) did not attract cells. This suggests a unique property of the synthetases that are targets in autoimmune disease: they have pro-inflammatory chemokine-like activity when extracellular.

Although the underlying cause of pulmonary sarcoidosis is unknown, it is believed to be related with an exaggerated immune response, which extracellular HARS and the associated chemokine pathway were suspected to play a role:

- **The CCR5 pathway might be a driver of inflammation in sarcoidosis.** Granulomas form when immune cells continuously recruit each other to a local site. Chemokine signaling (like CCR5 and CCR3 pathways) plays a role in gathering T-cells and monocytes in the lungs. Studies have

found CCR5 is upregulated on immune cells in sarcoidosis lungs, and high levels of CCR5-binding chemokines (such as CCL5/RANTES and CCL3) correlate with more severe, chronic lung involvement.

- **HARS is the target of anti-Jo-1 autoantibodies in antisynthetase syndrome.** Patients with anti-Jo-1 syndrome develop ILD, myositis, and arthritis as a triad. The presence of autoantibodies against HARS in a lung-involving autoimmune disease suggests that HARS's extracellular role might be relevant in lung inflammation. In anti-Jo-1 syndrome, HARS's N-terminal domain is essentially under immune attack.

Our Counterargument

First, ATYR published in *Science Translational Medicine* (2025) on efzo's proposed MOA, showing that the screening against ~4,550 receptors (Retrogenix receptor screening, which includes virtually all chemokine receptors, cytokine receptors, etc.) finds NRP2 as the sole binder with no off-targets including CCR5.

The steroid tapering and antiinflammatory effects in the reported Ph1/2 study do not support the pro-inflammatory effects of CCR5 binding. If efzo indeed agonizes CCR5, it might recruit some T cells to the lung. As a fact, we haven't seen evidence of disease worsening but seen patients improved.

Furthermore, after the *Howard et al.* (2002) paper, no other published study explicitly repeated an *in vitro* chemotaxis experiment (how cells move in response to chemical signals) with the HARS fragment. Although HARS's role in inflammation was examined through *in vivo* models of antisynthetase syndrome (ASS, autoimmune myositis). For example:

- *Adams et al.* (2021) showed that in mouse and rodent models of acute inflammatory diseases (bleomycin-induced lung injury and the statin-induced myopathy models), HARS administration down regulates immune activation. In contrast, neutralization of extracellular HARS by high-titer antibody responses during tissue injury increases susceptibility to immune attack, similar to what is seen in humans with anti-Jo-1-positive disease. Notably, the authors stated that "Given that more than 15 years have passed since these studies (e.g., *Howard et al.* 2002*)* were published and the lack of subsequent investigations, we attempted to repeat the work with HARS. **In spite of several attempts, we could not verify the results**."

Considering there are circulating HARS splice detected in healthy individuals, and absence of HARS in ASS, which has chronically activated immune cells and tissue infiltrating T cells, it's hard to draw the conclusion that HARS splice is pro-inflammatory. We are leaning toward that extracellular HARS splice may play a complex immunomodulatory role in maintaining tissue-specific homeostasis, rather than simply being pro-inflammatory or antiinflammatory, although the exact mechanism needs to be investigated. Regardless, even the *Howard et al.* (2002) paper can be replicated, and to demonstrate what truly happens in human body, we may suspect:

- **The extracellular HARS fragment could be a multifunctional ligand.** While the *Howard et al.* (2002) paper showed that the HARS fragment bound CCR5 on immune cells in the lab, ATYR's 2025 paper in *Science Translational Medicine* showed it has high affinity for NRP2. We note some chemokines can bind multiple receptors (e.g. CCL5 can signal through CCR1/3/5, CXCL8 binds to CXCR1 or CXCR2), and the dominant effect might depend on which receptors are available or prevalent in a given context. In pulmonary sarcoidosis granulomas, NRP2 is highly expressed on macrophages, whereas CCR5 is expressed on T-cells and some monocytes. Efzo could potentially engage both receptors, while NRP2 can be the functionally dominant pathway in the disease microenvironment.

- **The Fc modified Efzo could have a different binding pattern vs. the endogenously released HARS splice fragment.** The Fc portion might sterically hinder or alter the way the HARS domain interacts with certain receptors.

Is the Ph1/2 clinical result sound and translatable to the upcoming Ph3?

The Bear Thesis

This bear thesis scrutinizes the Ph1b/2a trial results with skepticism on several fronts:

- **Sample size was small.** There were only 6-10 patients per dosing arm, which means any results could be heavily influenced by a few patients. For example, if one or two patients in the placebo group happened to flare badly (making outcomes look worse) or if one patient on drug had an unusually excellent response, that could skew such a tiny study.
- **FVC improvement was not as significant.** The bears argue that regulatory or physician uptake might be cautious if benefits are marginal.
- **Past failures and complexity of Sarcoidosis.** Sarcoidosis is heterogeneous. Some patients spontaneously improve, others have chronic disease. Bears might point out that in any given six-month period, some sarcoid patients won't flare even without effective therapy (which might have happened in the efzo group). Bears think that sarcoidosis is a "tough disease" to show a drug effect. There have been other attempts in the past to find steroid-sparing agents (e.g., methotrexate, TNF inhibitors) with mixed success. No one has yet run a successful Ph3.

Our Counterargument

As we detailed in our PREVIEW NOTE, we see Ph1/2 results as encouraging and supportive of a potentially successful Ph3, while acknowledging the limitations of a small trial and the difficulty of developing drugs for PS.

While Ph1/2 results does have inherent uncertainty given the small N, we cautiously interpret the results and give conservative readthrough to Ph3 with discount to the potential treatment effect based on baseline OSC use and real-world practice. Importantly, we note quite a few Ph3 design parameters, most of which could favor the Ph3 results vs. Ph1/2:

- **Baseline**
  - OCS - neutral or unfavorable to Ph3
    - The starting steroid dose could create a ceiling for possible reduction. Therefore, Ph1/2 pts (13.9mg/d by 5mg/kg group, vs. 10.55mg/d in Ph3) had more room for steroid reduction. However, we applied the same % reduction to mitigate the impact.
  - Disease severity – neutral to Ph3
    - Extremely severe cases were excluded (e.g., those with very low lung function or sig organ involvement requiring high-dose OCS). Ph1/2 baseline lung function was "mild-to-moderately" reduced (~74–84% ppFVC) vs. Ph3 excluded ppFVC<50% (baseline not reported)
  - Background immunomodulators – favoring Ph3
    - Background therapy (e.g., MTX) could help all patients maintain disease control during taper. Ph1/2 (pbo and 5mg/kg group) had ~45-50% pts on background immunomodulators vs. lower in Ph3 (~38% concomitant immunosuppressant). Thus, *Ph3 could have more room for tapering delta between Tx and pbo*.
- **Tapering protocol**
  - Aggressiveness of taper – favoring Ph3

    - Ph3 taper is relatively rapid and uniform to get pts from ~10.55mg baseline to target of 0mg in 10W. This stresses the patient's disease control: if the underlying sarcoidosis is not well-controlled by the study drug, we expect to see disease flare-ups during or shortly after this taper, *more likely occurring to pbo arm*.
  - Uniform taper vs. individualized taper – favoring Ph3
    - Ph3 uses a uniform taper schedule (PGA every two weeks, as opposed to letting physicians taper based on clinical judgment) reduces variability and accentuates drug-placebo differences. Random "easy tapers" (due to on and off periods of pulmonary sarcoidosis pts) in pbo arm are less likely.
- **Steroid rescue use criteria** favoring Ph3
  - Similar to the uniformed tapering protocol, the steroid rescue use criteria (*guided by PGA/ FVC vs. Physicians' discretion*) in the trial reinforce the effect size.
- **Study/ Tx duration** favoring Ph3
  - The one-year duration of the Ph3 study (double the length of the Ph1/2) can further enlarge the observed treatment effect size. A longer study allows us to see how outcomes diverge over an extended period and ensures transient effects are distinguished from durable benefits. For example, *a pbo patient who might have briefly tapered to low dose could relapse later in the year, supported by Ph1/2 KM curve*. Longer treatment (with more doses) potentially allows for accumulation of clinical benefits.
- **Endpoint measures** – positive effect on Ph3 pbo arm, given pts likely rebound post tapering, thus making last 4W higher OSC use; mixed effect on Ph3 efzo arm, depending on the balance between OSC rebound post tapering and OSC re-reduction with Tx.
  - Ph3 utilizes absolute change in OCS dose, and importantly, the absolute change is calculated as a 4W avg of W45-W48 from baseline, vs. Ph1/2 applied an AUC-based measurement of post tapering period (W12-W24). By only including the later period during the treatment, assuming a deepening response, the treatment effect could be more substantial.

The FDA's recent agreement via the Type C meeting on confirming measuring absolute change in steroid dose (vs. FVC) as the primary endpoint in Ph3 further supports that meeting this endpoint would be viewed favorably in an approval decision.

- Note, current ERS treatment guideline considers steroid sparing as a critical outcome,
  - We acknowledge that steroid use is not a direct measure of disease control but more of a patient-centric outcome.
- Ph3 study includes lung function (FVC) and symptom (KSQ-Lung) endpoints to ensure that reducing steroids does not compromise disease control.
  - If efzofitimod group shows stable (base)/ improved (upside) FVC and symptoms while steroids are tapered, whereas pbo pts might experience symptom worsening or lung function decline when steroids are tapered, it would show efzofitimod can replace the chronic steroid's role in controlling the disease.
  - *Co expects FVC maintenance as the protocol is designed to induce flares and force pts to get rescued (assuming pbo will require more rescue than efzo), and prednisone improves FVC*.
- In Ph1/2, efzo showed lung function stabilization/ slight improvement over 26w, with variability likely due to small N, the nature of steroid tapering and efzo use time-course.

While we agreed that PS is a tough indication to develop drug (thus limited comp pipeline, a positive if efzo could pull this off), we note two past trials achieved steroid reduction, despite small/ open-label studies.

- In a small Ph2 RCT N=27 (mild to moderate PS disease) on stable dose of prednisone with attempts to taper, pentoxifylline achieved lower daily OCS dose vs. pbo at 6 months/ 8 months/ 10 months.
- In an open-label study N=56 sarcoidosis pts (N=34 PS) unresponsive to 1L/ 2L Tx or who had severe AEs, infliximab reduced mean daily dose of prednisone by 8.8mg at 26W in 19 pts taking prednisone at the start of study.

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