BofA SECURITIES

Arrowhead Pharmaceuticals

Previewing RAGE asthma data & ARWR's position in pulmonary RNA-silencing

Maintain Rating: BUY | PO: 51.00 USD | Price: 28.59 USD

FeNO data can unlock de-risking value for RAGE

We see ARWR's 3Q ARO-RAGE Ph1/2 asthma data as a key company catalyst validating the company's pulmonary siRNA efforts. Key to the update is FeNO biomarker data, which is an imperfect measure but has a proven track record with approved biologics that work downstream of RAGE. FeNO is an easier biomarker to interpret at the levels Arrowhead is likely testing and RAGE hitting study bogeys (we think) addresses outstanding questions on RAGE mechanism. We see potential for a good Ph1b update to: 1) potentially improve nominal peak sales outlook – if data hit bull case – more below, 2) if data are base case, it can still improve program POS to 20-25% (from 10%), which could potentially add +$7-10/shr to our risk-adj DCF. We maintain our Buy rating and $51 PO on attractive risk/reward on '24+ derisking catalysts. See details inside.

Study bogey: '30-40%' biologic-like FeNO impact

ARO-RAGE is in Ph1/2 pbo-controlled study evaluating moderate-to-severe t2-inflammatory asthma. The update will include measures of FeNO, other biomarkers and FEV1. We believe 30-40% FeNO decrease (base case) will serve as the best de-risking datapoint for clinical POC. Our bull case scenario is if FeNO > 40% (unlikely). Directional decreases in other biomarkers, lack of FEV1 harm (safety) and clean safety are key to a favorable update; ARO-RAGE has already cleared chronic animal tox and target knockdown. RAGE's full benefit on efficacy might not be captured in FeNO which does not capture all/broader pathways that RAGE modulates.

Severe t2-high asthma could represent an attractive mkt

There is significant evidence that RAGE is involved in disease biology of type-2 high inflammatory asthma, a subsegment of patients currently treated by steroids and biologics, where disease is driven by overactivation of immune cells and cytokines. We estimate ~500k US asthmatics fall in segment where biologic treatments are used vs. ~100k bio-refractory. While ARO-RAGE's profile is not fully characterized, we see potential to be highly safe with efficacy equal or better to biologics.

Arrowhead is leading in pulmonary, 2H24 updates key

Competitor RNA-silencing companies have expressed an interest in moving into pulmonary, but only Arrowhead is in the clinic (3 drugs in Ph1) all leveraging the same platform. So far, RNAi delivery and ability to develop potent therapeutics appear to be a meaningful development hurdle. Arrowhead's earlier stage program could gain traction in 2H24 with target knockdown data but our report is focused on lead ARO-RAGE program. ***See inside for detailed report.***

Estimates (Sep) (US$)	2022A	2023A	2024E	2025E	2026E
EPS	(1.67)	(1.92)	(2.43)	(3.64)	(2.26)
EPS Change (YoY)	-15.2%	-15.0%	-26.6%	-49.8%	37.9%
Consensus EPS (Bloomberg)			(2.71)	(2.59)	(2.15)
DPS	0	0	0	0	0
Valuation (Sep)					
Free Cash Flow Yield*	-5.3%	-5.0%	-6.3%	-8.5%	-4.4%

* For full definitions of *iQmethod℠* measures, see page 16.

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Refer to important disclosures on page 17 to 19. Analyst Certification on page 15. Price Objective Basis/Risk on page 15. 12670313

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Stock Data

Price	28.59 USD
Price Objective	51.00 USD
Date Established	9-Jan-2024
Investment Opinion	C-1-9
52-Week Range	20.67 USD - 42.48 USD
Mrkt Val (mn) / Shares Out (mn)	3,542 USD / 123.9
Free Float	95.5%
Average Daily Value (mn)	44.72 USD
BofA Ticker / Exchange	ARWR / NAS
Bloomberg / Reuters	ARWR US / ARWR.OQ
ROE (2024E)	-32.7%
Net Dbt to Eqty (Sep-2023A)	-36.7%
ESGMeter™	Low

ESGMeter is not indicative of a company's future stock price performance and is not an investment recommendation or rating. ESGMeter is independent of BofA Global Research's equity investment rating, volatility risk rating, income rating, and price objective for that company. For full details, refer to "BofA ESGMeter Methodology".

Acronyms:
Bio: biologic
DCF: discounted cash flow
FeNO: exhaled nitric oxide
FEV1: forced expiratory volume
Mkt: market
Ph: phase
POC: proof of concept
POS: probability of success
RAGE: receptor for advanced glycation end-products
RNA(i): ribonucleic acid (gene) interference
T2: high-type 2 inflammatory
See pages 13-14 for full list of acronyms

*iQ*profile℠ Arrowhead Pharmaceuticals

iQmethod℠ **– Bus Performance***

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Return on Capital Employed	-28.0%	-25.3%	-20.4%	-22.5%	-12.8%
Return on Equity	-42.6%	-47.8%	-32.7%	-32.3%	-17.6%
Operating Margin	-73.4%	-85.2%	-516.2%	NA	-135.9%
Free Cash Flow	(188)	(177)	(224)	(302)	(154)

iQmethod℠ **– Quality of Earnings***

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Cash Realization Ratio	NM	NM	NM	NM	NM
Asset Replacement Ratio	5.1x	4.8x	3.4x	0.6x	0x
Tax Rate	2.2%	1.3%	NM	NM	NM
Net Debt-to-Equity Ratio	-25.8%	-36.7%	-51.4%	-38.8%	-35.9%
Interest Cover	NA	-11.2x	NA	NA	NA

Income Statement Data (Sep)

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Sales	243	241	54	0	195
% Change	89.6%	-1.0%	-77.8%	-100.0%	NA
Gross Profit	243	241	54	0	194
% Change	89.6%	-1.0%	-77.8%	NM	NA
EBITDA	(168)	(195)	(264)	(396)	(252)
% Change	-11.5%	-16.1%	-35.2%	-49.9%	36.2%
Net Interest & Other Income	6	(1)	15	15	15
Net Income (Adjusted)	**(176)**	**(205)**	**(261)**	**(395)**	**(248)**
% Change	**-16.7%**	**-16.6%**	**-27.2%**	**-51.1%**	**37.2%**

Free Cash Flow Data (Sep)

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Net Income from Cont Operations (GAAP)	(169)	(204)	(261)	(395)	(253)
Depreciation & Amortization	10	10	13	14	13
Change in Working Capital	(98)	(37)	(31)	(5)	(7)
Deferred Taxation Charge	NA	NA	NA	NA	NA
Other Adjustments, Net	121	101	97	92	92
Capital Expenditure	(53)	(47)	(42)	(8)	0
Free Cash Flow	**-188**	**-177**	**-224**	**-302**	**-154**
% Change	**NM**	**6.0%**	**-26.8%**	**-34.5%**	**48.9%**
Share / Issue Repurchase	0	0	428	0	0
Cost of Dividends Paid	0	0	0	0	0
Change in Debt	0	0	0	0	0

Balance Sheet Data (Sep)

(US$ Millions)	2022A	2023A	2024E	2025E	2026E
Cash & Equivalents	108	161	594	498	548
Trade Receivables	1	1	1	0	2
Other Current Assets	296	514	734	937	1,144
Property, Plant & Equipment	110	148	178	172	158
Other Non-Current Assets	176	69	62	60	59
Total Assets	**692**	**894**	**1,568**	**1,667**	**1,912**
Short-Term Debt	0	0	0	0	0
Other Current Liabilities	139	98	55	27	31
Long-Term Debt	0	0	0	0	0
Other Non-Current Liabilities	135	356	356	356	356
Total Liabilities	**274**	**454**	**411**	**383**	**387**
Total Equity	**418**	**440**	**1,157**	**1,284**	**1,525**
Total Equity & Liabilities	**692**	**894**	**1,568**	**1,667**	**1,912**

* For full definitions of ***iQ***method℠ measures, see page 16.

Company Sector

Biotechnology

Company Description

Arrowhead Pharmaceuticals is a biotechnology company that develops RNAi-based therapeutics to treat diseases by silencing causative genes. The company's drug platform is called Targeted RNAi Molecule (TRiM) which aims to modify/reduce the production of disease-causing proteins by destroying RNA. ARWR has two (wholly owned) drugs in Ph3 trials and >10 drugs in early to late-stage development with the aim of having 20 drugs in clinical development or on the market in 2025.

Investment Rationale

We rate ARWR a Buy. We expect ARWR to deliver P&L leverage driven by the rollout of new products that are either wholly owned or partnered (future royalty streams). Our thesis is based on favorable risk/reward in front of several key 2024 catalysts including 1) topline data from Ph3 ARO-APOC3 in FCS in 2Q24 - data could facilitate an NDA leading to ARWR's first approved product, 2) Ph1/2 biomarker data from respiratory assets.

Stock Data

Average Daily Volume	1,564,226

Quarterly Earnings Estimates

	2023	2024
Q1	-0.60A	-1.24A
Q2	0.45A	-0.31E
Q3	-0.98A	-0.68E
Q4	-0.80A	-0.32E

Contents

Executive summary

Arrowhead's RNA targeted pulmonary platform is the most advanced in the RNA-silencing field with 3 drugs in the clinic; some programs have cleared chronic tox and established target knockdown. Arrowhead's current clinical-stage pipeline all use ligand-assisted delivery to drive uptake (of siRNAs) into lung epithelial cells, but each candidate differs in siRNA chemistry used to maximize depth/duration of target knockdown (+ dose frequency). The most advanced pulmonary program is ARO-RAGE which may have utility across a breadth of inflammatory lung diseases with an initial focus on severe type 2 asthma. However, Arrowhead will have important target knockdown (KD) data for its ARO-MUC5AC (COPD) and ARO-MMP7 (IPF) programs in 2H24 which are important since KD in those disease settings require evaluation in sick patients. The blue-sky scenario for ARWR is the company having unique access to undruggable targets in epithelial cells that can drive clinically meaningful benefit in diseases limited to symptomatic treatments. We expect Arrowhead to make data-driven decision on which program to advance into Ph2 by late '24/2025E with ARO-RAGE for asthma as the front-runner assuming the drug shows favorable 3Q24 Ph1b biomarker data (more in this report). Key takeaways from our review of ARWR's respiratory programs include:

- **Arrowhead is the most advanced RNA player in pulmonary.** There have been prior efforts by RNA-silencing companies to target lung tissue with little success (Exhibit 6). Recently, competitors (Ionis, Alnylam) have highlighted R&D efforts to develop novel pulmonary assets while other companies have yet to move into the space. All three of Arrowhead's clinical stage pulmonary programs use the same avβ6 ligand-assisted delivery which is specifically designed to improve stability of the RNAi to overcome degradation before target engagement. ARWR is the only company with clinical-stage pulmonary RNA targeting drugs, having cleared chronic animal tox and human target knockdown in healthy volunteers in its lead program (knockdown data summarized in Exhibit 2, Exhibit 3, and Exhibit 4).

- **It is unclear if competitors need to leverage avβ6 ligand-delivery or different approach**. Early attempts at RNA-silencing in the lung failed due to safety signals seen in animals (non-human primates). One hypothesis is that NHPs are sensitive to drug dose levels (see prior Ionis' and ARWR's ENaC programs). While some RNA players have evaluated naked oligonucleotide-based approaches, the field appears to be migrating to ligand or other technology-assisted delivery to improve potency and reduce dose levels. ARWR has secured a patent around certain avβ6 ligands that possess serum stability and can be conjugated to a cargo molecule that comprises an RNAi agent (Exhibit 5). Given limited disclosure, it is unclear if competitors are pursuing avβ6 ligand-delivery or alternative approaches. However, per Ionis, its preclinical experiments indicate no advantage to using avβ6 vs. naked oligonucleotide with pulmonary delivery. In our conversations with ARWR, having a good ligand-assisted delivery is important but the company believes the stability/potency of its molecule sequence is equally important. Arrowhead's prior ARO-ENaC program ran into safety issues with an approach also using avβ6 ligand-delivery but subsequent enhancements to sequence are believed to enable much greater potency and less of a dosing burden with currently clinical stage candidates.

- **ARO-RAGE severe asthma/high FeNO data next key pulmonary catalyst**. In 3Q24, Arrowhead plans to report data in severe asthma patients with high eosinophil/FeNO levels (by default T2 asthma). While ARO-RAGE has demonstrated target KD in healthy pts (all dose levels) and dose-matched knockdown at lowest dose (higher dose data pending) there remain questions around whether RAGE is a driver mechanism of disease or by-product of disease. MOA uncertainties aside, Arrowhead believes its high levels of RAGE KD (to be more fully corroborated with KD data from asthma patients) minimize any concerns around whether its drug candidate achieves the right level of target KD. RAGE works upstream of interleukin-acting biologics that are FDA approved, thus we look to upcoming Ph1b data to see

if ARO-RAGE can have a comparable or better impact on the FeNO biomarker in relevant asthma pts (30-40% reduction) which would provide proof ARO-RAGE is having a similar biologic effect as approved biologics with pharmacodynamic measure linking gene knockdown and a widely utilized clinical marker. For context, FeNO is a gaseous signaling molecule produced by residential and inflammatory cells in large and peripheral airways and it's a validated PD biomarker evaluated in the development of approved biologics for T2 asthma.

- **FeNO is a relevant clinical measure in t2-h, among others –** KOLs we spoke with echo Arrowhead's view that upcoming Ph1b ARO-RAGE data in high FeNo asthma patients is unlikely to yield meaningful data on lung function (FEV1) given the small study size (<70 pts) and short duration follow-up; the focus of KOLs on FEV1 is mainly safety, e.g. "lack of harm". Based on our review of approved asthma biologics, the predictive value of FeNO on improvement in lung function (exacerbations, expired volume) has not been officially established but most biologic data support FeNO as offering evidence of decreasing (overactive) inflammatory pathways (driver t2 asthma). Similar to FeNO, eosinophil (white blood cell) count has been found to correlate with increased exacerbations, but its predictive value is not well defined likely because there are other important drivers contributing to exacerbations. On its recent quarterly call, management did indicate it would also evaluate a number of other cytokines that are elevated during T2 asthma, but we believe these data will likely be 'noisy' as cytokine levels in the blood are low, highly variable, and are not easily measured.

- **Severe asthma is the most characterized market opportunity in ARWR's pulmonary pipeline; other assets/diseases are early days**: As noted, the MUC5AC and MMP7 programs have yet to demonstrate target knockdown and the initial disease areas of focus in COPD and IPF, respectively, involve complex and heterogenous diseases (carry lower POS), thus our focus in this report is on RAGE. Management believes ARO-RAGE, based on where it acts in the inflammatory pathway and preclinical studies demonstrating RAGE upregulation, can address both type-2 and non-type 2 asthma patients though the proof-point for the latter population won't come until future Ph2 data readout. Depending on the ultimate strength of ARO-RAGE's clinical profile, severe asthma could range from a niche to a blockbuster end-market with ~500K US pts with severe-t2 asthma and whether the value-proposition warrants biologic-like pricing ($20k-50k/year). Based on KOL feedback, ARO-RAGE has the potential: 1) to be similar or better than approved biologics, given the drug works upstream of approved biologics, 2) extremely safe – given low bioavailability though biologics appear pretty safe and well tolerated, and 3) preferable route of delivery – inhaled vs. injection. Our report focuses on the upcoming RAGE update in high FeNO but we highlight key upcoming data from pulmonary platform in Exhibit 1.

- **Read-through to other pulmonary assets:** though certain elements of Arrowhead's TriM platform are proprietary, it appears there are key similarities between RAGE, MUC5AC and MMP7 that add weight to the read-through value of RAGE update as it pertains to Arrowhead's broader lung platform. All 3 drugs are dosed at a lower frequency than ENaC, suggesting similar potency, and share characteristics like: small size and net negative charge (avoid macrophage uptake) and targeting ligand (reach the epithelial cells). Further, ARWR's clinical stage candidate possess very small size (conjugates 3-10 nanometers) which is believed to help overcome delivery challenges for muco-obstructive diseases (cystic fibrosis and COPD). Key to replicating success for MUC5AC and MMP7 is maintaining RNAi integrity through inhaled delivery while avoid overloading lung (toxicity), which is ultimately the ability for RNAi to have the right potency in mucosal and inflammatory environments.

Exhibit 1: Current development status of pulmonary assets

The next key updates are from RAGE and include: dose-response biomarker knockdown and improvement in FeNO measures in asthma patients

Program	Stage	Chronic tox status	Knockdown	Human POC	Next update
RAGE	Ph1/2	✓	✓	3Q24	sRAGE knockdown in asthma patients FeNO data in t2-h asthma patients
MUC5AC	Ph1	YE24	2H24	tbd	HV + COPD patient knockdown data
MMP7	Ph1	✓	2H24	tbd	HV + IPF patient knockdown data

Source: Company reports; BofA Global Research

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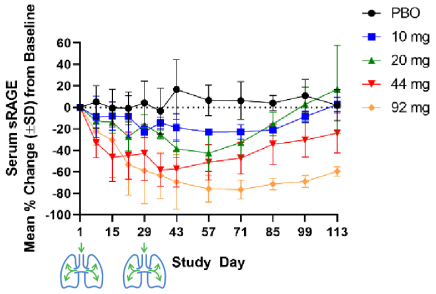
Exhibit 2: MAD of ARO-RAGE in healthy volunteers

MAD of ARO-RAGE achieved mean max serum sRAGE reduction of 80% at 2nd highest dose (92mg)



Source: Company reports; BofA Global Research

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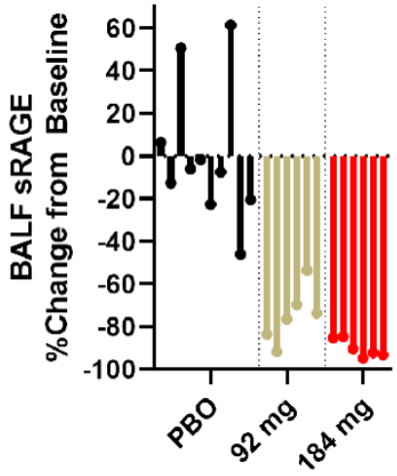
Exhibit 3: SAD of ARO-RAGE in healthy volunteers

SAD of ARO-RAGE achieved mean BALF sRAGE reduction of 90% at highest dose (184mg)



Source: Company reports; BofA Global Research

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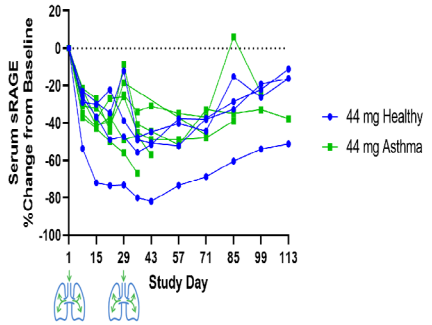
Exhibit 4: MAD of ARO-RAGE in healthy volunteers and asthma patients

MAD of ARO-RAGE achieved mean serum sRAGE knockdown slightly lower in asthma patients than healthy volunteers



Source: Company reports; BofA Global Research

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Exhibit 5: Arrowhead's patents that cover aspects of its pulmonary platform

ARWR has patented the ligand it utilizes for ARO-RAGE, MUC5AC, MMP7, which is key to preventing degradation of the RNAi as it passes through the lung environment

Patent	Type	Publication #	Description	Expiry
Alpha-V Beta-6 Integrin Ligands and Uses Thereof	COM + methods of use	US 11,180,529 B2	Compositions comprising avß6 integrin ligands having improved serum stability to overcome degradation and having affinity for avß6 integrins and methods of using them are described	2037
RNAi Agents for Inhibiting Expression of RAGE	COM + methods of use	WO 2022/216920 A1	Compositions that include RNAi agents and methods for inhibiting of a receptor for advanced glycation end-products gene	Pending
RNAi Agents for Inhibiting Expression of MUC5Ac	COM + methods of use	WO 2022/251394 A1	Compositions that include RNAi agents and methods for inhibition of mucin 5 AC gene.	Pending

Source; Google patents; BofA Global Research

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Exhibit 6: Failed lung targeting nucleic acid approaches
Both ALNY and IONS's prior attempts with naked nucleic acid delivery failed either due to lack of efficacy or tox, respectively

	ALNY		IONS
Failed drugs	ALN-RSV	ALN-COV	ENaC
Chemistry	naked siRNA	· Chemical modification (2'-O-hexadecyl) · Ligand	Naked oligo
Target	RSV	SARS-CoV	epithelial sodium channel
Method of delivery	Inhaled	Inhaled	Inhaled
Discontinuation reason	Lack of stability resulting in low potency and durability of pharmacological effect	Portfolio prioritization	Toxicity due to overloading lung cells with drug
Current pulmonary status	Chemical modification		MsPA backbone to reduce inflammation (cytokine) and complement activation
Utilizing ligand?	No		No
Commentary	Developed after RSV; "utilizing chemical modifications to enhance PD effect of siRNA" Utilization of ligand to facilitate distribution and uptake by lung cells		"Exploring a ligand-assisted delivery to have a more potent compound"

Source: Company reports; PubMed; BofA Global Research

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ARO-RAGE: clear path for T2; upside keyed to future Ph2s

ARO-RAGE is currently in a Ph1/2 trial evaluating safety, efficacy and pharmacodynamic response (on key asthma biomarker). So far, ARO-RAGE has demonstrated dose-dependent target knockdown (sRAGE; a protein biomarker in patients' lung sputum) in healthy volunteers and a handful of asthma patients and cleared chronic tox in animals. Next up, in 3Q24, ARWR plans to present data from three cohorts of asthma patients with high baseline FeNo levels to determine if ARO-RAGE similarly impacts a relevant biomarker in T2 (allergic + eosinophilic) asthma patients that was evaluated in FDA approved biologics (working in the same disease pathway). For ARO-RAGE, Arrowhead plans to prioritize both inflammatory (type-2) and non-inflammatory asthma patients for future Ph2 development, while decisions to pursue COPD and CF are contingent on future data in diseased pts. While the downstream effects of the RAGE pathway have been implicated in multiple inflammatory disease pathophysiology and studies have tied RAGE deficiency to lower FEV1 measures, there remains two key investor debates:

- **Is RAGE a good asthma target**: specifically, is RAGE a driver of disease pathology or a reaction to altered processes in the inflammatory disease state. If RAGE is ancillary to the disease process, then blocking RAGE may not drive clinical benefit and other cytokines elevated in T2 asthma may remain elevated;

- **Is FeNO a good biomarker to study T2 and non-T2 severe asthma**: given its utilization as a diagnostic factor, FeNO was measured in multiple clinical studies of biologics where most studies showed high baseline FeNO correlates to higher efficacy. Few studies measured the correlation of FeNO with reduction of exacerbations, i.e. FeNO as a predictive factor, and data are inconclusive where modest correlation was observed in one study while low correlation was observed in another. Interpatient variability of FeNO was highlighted as a potential factor for the lack of correlation. Importantly, ARO-RAGE's modulation upstream of interleukins/cytokines is shared by recently approved biologic Tezepelumab whose small effect on FeNO but great efficacy can be explained by its broader pathway that impacts other inflammatory drivers.

- **Outside of severe asthma, the hierarchy of pulmonary diseases where RAGE might be viable**: supportive evidence for RAGE's involvement in t2-COPD and neutrophilic asthma is more mixed and pts do not have high FeNO levels. While some clinical studies have linked increased RAGE to disease pathophysiology, others have offered mixed data on the involvement of the soluble version of RAGE (sRAGE) and its importance as a driver of disease. Ultimately, FeNO is not measured as a clinical surrogate in type-2 COPD or asthma so there is no read-through to POS of other diseases other than adding confidence that ARO-RAGE's pharmacodynamic profile has the right balance of potency and safety, in our view.

Exhibit 7: Applicability of ARO-RAGE in inflammatory pulmonary diseases
We summarize supporting evidence for ARO-RAGE in asthma, COPD and CF, and market opportunities for each indication

	Moderate-to-Severe Asthma		COPD	Cystic Fibrosis
Sub-type	Type 2 eosinophilic	Neutrophilic, non-allergic, non-eosinophilic	Type 2-inflammatory	N/A
Prevalence (US)	~1-1.5mill 50% of asthma	~800k-1mill 50% of asthma	~200k <10% of COPD pts	~30k
Treatment options	Steroids Biologics: IgE or T2 cytokines	No approved treatments	Steroids Biologics	CFTR modulators Anti-inflammatory Bronchodilators
Rationale for RAGE	RAGE is necessary for type-2 inflammation and sustained signaling of multiple effector cytokines that drive inflammation in t2-asthma	Mixed data: RAGE is only implicated in t2-low inflammation where ligand-RAGE/sRAGE axis impacts neutrophilic inflammation; however, sRAGE is found to be deficient in neutrophilic asthma	RAGE activated in type-2 COPD patients	RAGE upregulated in CF airway neutrophils and negatively correlated with % predicted FEV1

Source: PubMed, Company reports, BofA Global Research

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The best evidence for RAGE is in severe t2 asthma

ARO-RAGE works by silencing the RAGE receptor to decrease or halt the cascade of complex pro-inflammatory effects that are driven by RAGE activation. Type-2 inflammatory diseases are defined by the over-expression of pro-inflammatory molecules (interleukins) that lead to airway inflammation and obstruction. In type-2 diseases, RAGE is involved in the upstream production of cytokines (pro-inflammatory molecules that include interleukins) that approved biologics work to decrease; however, RAGE also impacts non-interleukin pathways, where their involvement as a driver or reactionary to inflammatory disease is unclear. At the population level we note:

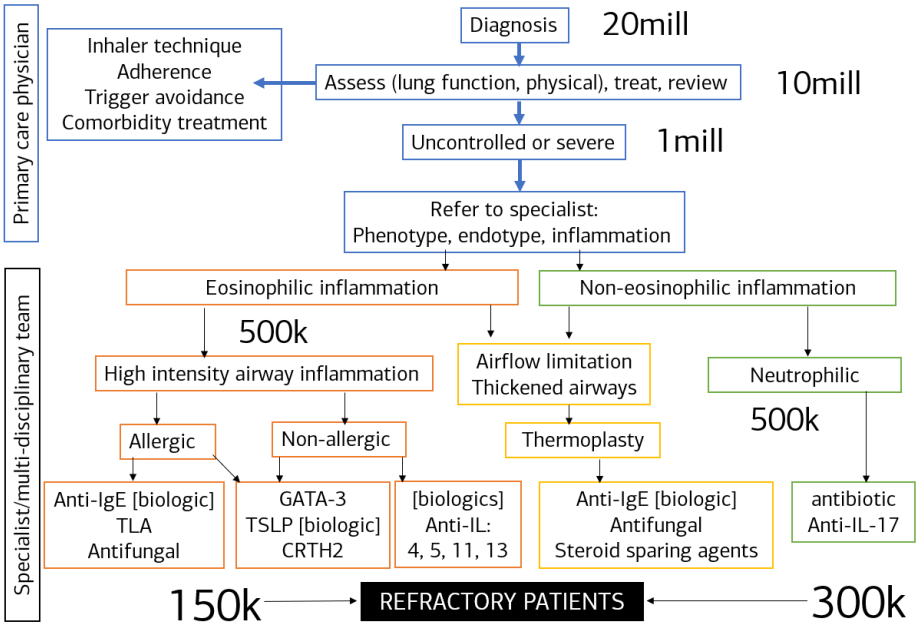
- **Strong evidence for RAGE in type-2-inflammation**: RAGE has been studied as a therapeutic target for decades given its involvement in inflammatory pathways where prior small molecule attempts have failed. Medical literature has flagged failed RAGE-inhibitors that work in ancillary pathways, though none specifically targeted RAGE in epithelial cells and none were advanced into clinical development. RAGE shares an overlapping mechanism with interleukin-targeted biologics and a plethora of studies in the literature support RAGE's role in t2-inflammatory where genomic studies identified RAGE as genetic determinant of airflow obstruction. We look to FeNO data to bridge biomarker knockdown to effect on clinical measures and an indicator that RAGE is reducing key modulators of airway inflammation.

- **Evidence in neutrophilic and non-T2 diseases more nascent and mixed:** there have been fewer studies of RAGE involvement in neutrophilic asthma given less clear involvement of the inflammatory pathways of disease. Our review of the literature found that data are conflicting where some mice studies have supported RAGE activation in a neutrophilic asthma model, but human studies have linked decrease in soluble RAGE as a driver of neutrophilic airway inflammation in asthma.

In asthma, RAGE looks to leverage evidence for biologics in T2 sub-type

Asthma is a highly prevalent (~20mill US patients) heterogenous chronic inflammatory airway disease that is defined by several distinct phenotypes ultimately characterized by variable airflow obstruction. About 10% of total asthma patients present with moderate-to-severe symptoms (exacerbations, difficulty breathing) and are diagnosed with a physical exam to rule out comorbidities, lung function test to assess airway obstruction, and are generally prescribed quick-relief inhalers or steroids. If patients' symptoms do not improve, phenotype testing is performed to segment patients into t2-inflammatory and non-t2 driven asthma (where the neutrophilic phenotype is the largest subgroup) on the basis of involvement of pro-inflammatory drivers of disease. Severe t2 asthma patients are prescribed biologics and respond well to treatment while the majority of severe non-t2 asthma patients usually remain refractory to classical therapies and do not have a specific therapeutic option because exact disease drivers are unclear.

Exhibit 8: Current diagnosis and treatment algorithm for moderate-to-severe asthma patients
Patients with non-eosinophilic asthma have less treatment options than eosinophilic asthma patients and a higher proportion remain refractory to treatment



Source: CDC; PubMed: BofA Research

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RAGE: T2 asthma value prop safety and dosing, assuming biologic-like efficacy

Type-2 inflammatory (T2H) asthma is largely treated with either steroids or biologic drugs, and most pts respond well to treatment. Absent a therapeutic offering a step-change in efficacy vs. biologic therapy, we believe the value-add for ARO-RAGE could be as a highly safe/easy to dose alternative to biologics. So far, KOLs we've spoken with believe ARO-RAGE has the potential to differentiate on efficacy given that RAGE is upstream of approved cytokine-targeting biologics and could benefit in a more heterogenous patient population. Most t2h patients are well controlled on their current regimens, though KOLs pointed to ARO-RAGE's less frequent dosing as an attractive aspect of its drug profile. There are currently ~6 approved biologic therapies that are available for certain types of severe asthma not well controlled with high dose steroid inhalers with varying degrees of efficacy lacking head-to-head trials for national guidelines. While AbbVie's anti-IL-5 biologic Fasenra has the easiest dosing convenience (Q8W), Sanofi/REGN's Dupixent (aniti-IL-13+4) carries a broader and less restrictive label and has had the best launch so far in terms of new-to-brand asthma scripts. There are some estimates by third party pharma data sources that the global asthma biologics market was valued at $6.5bn in 2022, having penetrated ~15-20% of the market, and is

expected to growth low double-digits over the next 10 years (BofA estimates Dupixient asthma achieving ~$3bn global peak sales).

Low-2/neutrophilic asthma: high unmet need but RAGE's role is less clear

Low-t2 (neutrophilic) asthma comprises ~50% of asthma patients and treatment options are limited to steroid and antibiotics that only work in a small % of patients. Neutrophilic asthma is defined as symptomatic asthma lacking eosinophilic airway inflammation, where patients have low FeNO (< 30 ppb) characterized by presence of high levels of neutrophils in the lungs and airways and fixed airflow obstruction. Activated neutrophils release multiple species that cause cell injury, inflammation, hyperresponsiveness, and airway remodeling. While there is some evidence that neutrophilic infiltration can lead to asthma symptomatology, significant heterogeneity in neutrophilic asthma patients with pro-inflammatory and anti-inflammatory subsets and altered neutrophil functions at different ages has led to limited therapeutic options. Neutrophils comprise 70% of total circulatory white cells and play critical defense role during inflammatory and infective challenges, making them a problematic target. Furthermore, neutrophil function changes with age, thus different therapeutic strategies may be required for different patient age groups. RAGE has been implicated as a promotion of neutrophilic airway inflammation in response to an allergen in mice models, but human data is conflicting where some studies support RAGE activation as contributor to allergen driven inflammation and other studies implicate decreased soluble RAGE as a driver of neutrophilic asthma.

FeNO is validated biomarker, offers ARO-RAGE defined Ph1b bogey

Nitric oxide (NO) is a gaseous signaling molecule produced by residential and inflammatory cells in large and peripheral airways. NO plays an important role in regulating airway and vascular function and is generated by 3 NO synthases (enzymes) with different expression and pathophysiologic roles in airways. NO synthases are induced by several stimuli including endogenous mediators (interleukins, cytokines, chemokines), and exogenous factors. FeNO, fractional exhaled nitric oxide, measures % of nitric oxide that is exhaled by a patient and is considered a surrogate marker for eosinophilic airway inflammation. Elevated FeNO levels > 50 ppb can be used to indicate that a patient has eosinophilic-driven asthma (in addition to other clinical surrogate measures tested). Given the link between FeNO and exacerbations, and the ease and speed at which FeNO can be measured, physicians use FeNO to select the right biologic therapy, where reductions in FeNO (in addition with other clinical symptoms) mean that a patient is responding to therapy.

FeNO is performed using a portable device that measures the level of NO in parts per billion (PPB) in the air slowly exhaled out of lungs. An accurate measurement is dependent upon blowing slowly and steadily (not hard and fast). Our KOL checks and biologics studies have found there to be an intra-patient variability for baseline FeNO (mean coefficient of variation ~10-20%) given that FeNO is sensitive to exogenous factors, hence cutoff values as a delineation factor for eosinophilic vs neutrophilic asthma in the clinic (≤ 25 ppb: neutrophilic; ≥ 50 ppb: eosinophilic) are more extreme.

FeNO: reduction could offer directional link to asthma exacerbation

Arrowhead's upcoming Ph1/2 high FeNo data update will include ~68 asthma patients screened for baseline FeNo levels >35 ppb in three dose cohorts (92mg/120mg/184mg) and randomized between drug and placebo. Study subjects will be screened for FeNO level >35 ppb which is characterized as "moderate" severity disease, but Arrowhead believes setting the entry criteria at this level should result in mean levels significantly above 35 ppb. In the high FeNo assessment, Arrowhead plans to treat patients for 2-months and assess FeNO levels every 2 or 4-weeks in the study and more frequently at expected time of maximum PD effect to ensure capturing maximal FeNO reduction (which will be determined by full dose-response curve in asthma patients). The goal of

the high FeNO assessment is to see if ARO-RAGE can reduce FeNO levels by 30-40% which would be comparable to approved biologics and serve as clinical proof of concept.

Biologics that work to reduce cytokines (IL-13, IL-4, IL-5) approved for the treatment of eosinophilic asthma have conducted numerous studies assessing biomarkers at 4-week timepoints, including FeNO, eosinophil count, IgE, and serum periostin, to interrogate the reliability of surrogate biomarkers in predictability of improvement of clinical outcomes (Exhibit 9). Given ARO-RAGE's involvement as an upstream regulator of interleukins, we view a meaningful decrease in FeNO as evidence of clinical improvement and de-risk the drug's ability to demonstrate improvement in airway inflammation and the clinical scales that measure asthma symptoms that relate to lung function (asthma exacerbations, FEV1).

Exhibit 9: Summary of biologics data

While high baseline FeNO stratifies response to biologic treatment, only few studies show modest correlation between FeNO and exacerbation rate reductions

Biologic	Target	Avg Baseline FeNO	Decrease in FeNO	High FeNO as predictor of response?	Correlation to Efficacy	Exacerbation rate reduction	FEV1 change from baseline
Dupilumab	IL-13, IL-4	34 ppb	46%	Yes	High FeNO predicts improvement of exacerbation rate and clinical control	70%	~0.21-0.26
Tezepelumab	TSLP	33 ppb	~25-30%	Higher FeNO (+blood eosinophil) showed best benefit	Unexplored to date	70%	0.13
Omalizumab	IgE	37 ppb	~37% (significant)	Mixed but mostly yes	Modest accuracy of FeNO as prediction factor for significant ACQ change during treatment	25%	
Mepolizumab	IL-5	N/A	Conflicting but sum of evidence generally show significant reduction of FeNO	Yes but baseline eosinophil count more closely associated with response to mepo than baseline FeNO	Exacerbations associated to concomitant increase of FeNO	50%	~61-98 mL
Benralizumab	IL-5-receptor	N/A	Conflicting but sum of evidence generally show significant reduction of FeNO	No; baseline eosinophil best predictor of good response		50%	~0.15
Reslizumab	Il-5	N/A	N/A	N/A	N/A	40%	~93-160mL
Tralokinumab	IL-13	N/A	Significant reduction (in all-comer FeNO)	Baseline FeNO > 37 ppb best biomarker to predict enhanced response	Mixed: two Ph3 trials had conflicting results	Failed to obtain approval	Failed to obtain approval
Lebrikizumab	IL-13	37 ppb	~34%	Yes - high FeNO associated with greater efficacy in improving FEV1 and rate of severe exacerbations	N/A	Failed to obtain approval (prematurely terminated)	Failed to obtain approval (prematurely terminated)

Source: PubMed, BofA Global Research

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Exhibit 10: FeNO measures in Ph3 trial of dupilumab in eosinophilic asthma patients
Average FeNO decrease was 46% observed in the drug arm while placebo averaged a decrease of 10%

	pbo	dupi 200mg	pbo	dupi 300mg
N	313	631	321	632
Baseline	34.5	34.4	38.4	34
change				
wk 12	-2.5	-14.9	-3.6	-15.6
wk 24	-2.8	-16.2	-4.6	-16.2
wk 52	-2.1	-16	-5.5	-16.2
% decrease				
wk 12	-7%	-43%	-10%	-45%
wk 24	-8%	-47%	-13%	-47%
wk 52	-6%	-46%	-16%	-47%
averages	**-7%**	**-46%**	**-13%**	**-46%**

Source: PubMed; BofA Research

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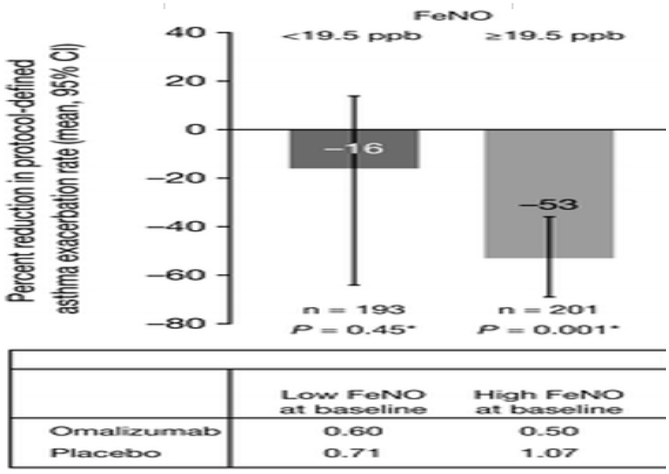
Exhibit 11: Subgroup analysis from omalizumab ph3 trial in asthma
Omalizumab-treated pts with high FeNO (>19.5 ppb) had greater reduction in exacerbations than pts with low FeNO (< 19.5 ppb)



Source: PubMed; BofA Research

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FeNO + other biomarker measures could paint a more complete picture

Only recent studies of biologics (dupilumab, Tezepelumab, omazilumab) have focused on assessing outcome measures that are closely associated with eosinophilic airway inflammation, thus the majority of biomarker data from older biologics (mepolizumab, benralizumab) might not be as robust since studies were performed in populations selected on basis of clinical and physiological characteristics rather than presence of eosinophilic airway inflammation and analysis were performed on a post-hoc basis. Overall, the majority of studies showed higher values of bronchial FeNO may be associated to better outcome in terms of clinical control and reduction of exacerbation rate. Only a few studies demonstrated modest accuracy of FeNO as a predictive factor for significant change in Asthma Control Questionnaire (ACQ) during treatment, while others found weaker correlation, pointing to intra-patient variability in FeNO measures and more close correlation between other biomarkers as limitations. We note that the direct influence of IL-13 on endogenous FeNO production means that FeNO is a more reliable predictor in anti-IL-13 biologics than a therapy that works on a broader pathway, such as ARO-RAGE, given its wider range of activity and target cells. Arrowhead has highlighted other potential biomarkers of anti-inflammatory effect including cytokines, though levels of cytokines in the blood are low and might not be easily measured. We summarize other clinical biomarkers that biologics have assessed as predictors for asthma control in Exhibit 12.

Exhibit 12: Strength of biomarkers as predictive factors of t2 asthma disease
Studies have demonstrated that serum eosinophils and serum periostin appear to have the best predictive value

Biomarker	Definition	Link to clinical outcomes	Bioindicator	Measurability
Serum eosinophils	White blood cell counts where 'eosinophilic': > 300 cells/μL	Moderate	Several studies found serum eosinophils are best bioindicator for response	Blood sample
IgE	High antibodies overactivated in allergic asthma	Not implicated as a major driver of eosinophilic phenotype	Not yet established as biomarker	Blood sample
Serum periostin	Produced from airway epithelial cells and fibroblasts by IL-13	presence associated with greater FEV1 improvement with anti-IL-13 therapy (FEV1)	Some studies support use of serum periostin as predictive marker of t2h	Blood level
Cytokines	pro-inflammatory molecules including interleukin-4, 13, 5, 33, 6, 1B, TSLP	High accumulation cytokines in airways regulate airway inflammation	Susceptibility to pre-analytical behaviors could impact predictability	Circulating levels are low and cannot be measured reliably by commercially available assays

Source: NIH; PubMed; BofA Global Research

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T2-COPD: supportive evidence from biologic

Clarity on COPD Ph2 prioritization is likely a 2025 event, after Arrowhead collects initial de-risking data in diseased patients. COPD is a heterogenous pulmonary disease that is characterized by an exaggerated chronic inflammatory response resulting from unchecked immune response to environmental exposures and can lead to airway remodeling and irreversible loss of lung function. There are an estimated ~200k severe t2 COPD US patients currently treated by symptom management involving bronchodilators or steroids, while first-in-class biologic Dupixent is expecting approval in 2024. Studies have implicated the RAGE receptor plays a central role in the t2-driven subgroup where environmental factors (known to drive COPD) upregulate/activate RAGE, which elicits over-activation of immune system, leading to airway obstruction. Support for RAGE comes from:

- **Clinical studies** that indicate expression of RAGE and accumulation of its ligands are increased in patients with COPD;
- **Mice studies** showing knocking out RAGE ligands or inhibiting the receptor prevents inflammation and reduces changes in respiratory mechanics in response to smoke exposure;
- **Indirect support** comes from clinical success of interleukin-13 targeting Dupixent which significantly reduced exacerbations (34% pbo-adj) in Ph3 trials of t2 COPD patients on triple therapy.

One unknown regarding RAGE in COPD is that studies have found equally strong relationship between decreased sRAGE and disease progression, which calls into question the potential impact of ARO-RAGE's mechanism that leads to reduction of sRAGE in sputum and circulation. Based on addressable ~200k US patients and assuming biologic pricing, we estimate ARO-RAGE's US market opportunity is $6.5-7bn.

Acronyms:
ACQ: asthma control questionnaire
αvβ6: integrin alpha v beta 6 (receptor)
CDC: center for disease control and prevention
CF: cystic fibrosis
COM: composition of matter
COPD: chronic obstructive pulmonary disorder
ENaC: epithelial sodium channel
FeNO: exhaled nitric oxide
FEV1: forced expiratory volume in 1 second
GalNac: n-acetylgalactosamine sugar molecule
HV: healthy volunteers
IgE immunoglobulin E antibodies
IL: interleukin
IPF: idiopathic pulmonary fibrosis
KD: knockdown
KOL: key opinion leader
MAD: multiple ascending dose
MUC5AC: mucin 5ac, oligomeric mucus/gel-forming protein
MMP7: matrix metallopeptidase 7
MOA: mechanism of action
NHP: non-human primates
NIH: national institutes of health
Oligo: oligonucleotide
PK: pharmacokinetic
PD: pharmacodynamic

Ph: phase
POC: proof of concept
POS: probability of success
Ppb: parts per billion
Pt: patient
Q#w: dosing every # week
SAD: single ascending dose
(s)RAGE: soluble receptor for glycated end-products
REGN: Regeneron (covered by BofA Research Analyst Geoff Meacham)
RNAi: ribonucleic acid interference
RSV: respiratory syncytial virus
SARS-CoV: strain of severe-acute-respiratory-syndrome related coronavirus
siRNA: small interfering ribonucleic acid
t2H: high type-2 inflammatory
TLA: temperature-controlled laminar airflow
TriM: targeted RNAi molecule platform
Wk: week

Price objective basis & risk

Arrowhead Pharmaceuticals (ARWR)
Our $51 price objective (PO) is based on a risk-adjusted DCF analysis which assumes 1) risk-adjustment to pipeline programs based on abundance and strength of clinical data with <30% POS assigned to early-stage programs vs >50% POS for mid-to-late stage assets, 2) the biggest value drivers in our DCF valuation are ARO-APOC3 for FCS and sHTG (30%), ARO-AAT (16%), and pipeline programs (60%), 3) we assume 10% discount rate.

Downside risks to our PO: 1) failure of wholly-owned late stage clinical trials, 2) competitor clinical data outperform vs our expectation, 3) failure to partner programs for financing requirements.

Upside potential to our PO: 1) delay to regulatory approval of competitors products, 2) failure of competitors' clinical trials, 3) better-than-expected performance of wholly-owned and/or pipeline assets.

Analyst Certification

I, Jason M. Gerberry, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

US - Specialty Pharma & Biotechnology Coverage Cluster

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	Arrowhead Pharmaceuticals	ARWR	ARWR US	Jason M. Gerberry
	bluebird bio	BLUE	BLUE US	Jason M. Gerberry
	Catalyst Pharma	CPRX	CPRX US	Jason M. Gerberry
	Exelixis	EXEL	EXEL US	Jason M. Gerberry
	Fractyl Health	GUTS	GUTS US	Jason M. Gerberry
	Immunovant, Inc.	IMVT	IMVT US	Jason M. Gerberry
	Intra-Cellular Therapies	ITCI	ITCI US	Jason M. Gerberry
	Ionis	IONS	IONS US	Jason M. Gerberry
	Jazz Pharmaceuticals	JAZZ	JAZZ US	Jason M. Gerberry
	Lyra Therapeutics	LYRA	LYRA US	Jason M. Gerberry
	Oculis Holding AG	OCS	OCS US	Jason M. Gerberry
	Relay Therapeutics	RLAY	RLAY US	Jason M. Gerberry
	Tarsus Pharmaceuticals	TARS	TARS US	Jason M. Gerberry
	Teva Pharmaceuticals	TEVA	TEVA US	Jason M. Gerberry
	Vaxcyte Inc	PCVX	PCVX US	Jason M. Gerberry
	Xenon Pharmaceuticals	XENE	XENE US	Jason M. Gerberry
NEUTRAL				
	Alkermes	ALKS	ALKS US	Jason M. Gerberry
	Amphastar Pharmaceuticals	AMPH	AMPH US	Jason M. Gerberry
	Axsome Therapeutics	AXSM	AXSM US	Jason M. Gerberry
	Galapagos	GLPG	GLPG US	Jason M. Gerberry
	ProKidney Corp	PROK	PROK US	Jason M. Gerberry
	Roivant	ROIV	ROIV US	Chi M. Fong
UNDERPERFORM				
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	Organon	OGN	OGN US	Jason M. Gerberry
	Viatris Inc.	VTRS	VTRS US	Jason M. Gerberry

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Business Performance	Numerator	Denominator
Return On Capital Employed	NOPAT = (EBIT + Interest Income) × (1 − Tax Rate) + Goodwill Amortization	Total Assets − Current Liabilities + ST Debt + Accumulated Goodwill Amortization
Return On Equity	Net Income	Shareholders' Equity
Operating Margin	Operating Profit	Sales
Earnings Growth	Expected 5 Year CAGR From Latest Actual	N/A
Free Cash Flow	Cash Flow From Operations − Total Capex	N/A

Quality of Earnings	Numerator	Denominator
Cash Realization Ratio	Cash Flow From Operations	Net Income
Asset Replacement Ratio	Capex	Depreciation
Tax Rate	Tax Charge	Pre-Tax Income
Net Debt-To-Equity Ratio	Net Debt = Total Debt − Cash & Equivalents	Total Equity
Interest Cover	EBIT	Interest Expense

Valuation Toolkit	Numerator	Denominator
Price / Earnings Ratio	Current Share Price	Diluted Earnings Per Share (Basis As Specified)
Price / Book Value	Current Share Price	Shareholders' Equity / Current Basic Shares
Dividend Yield	Annualised Declared Cash Dividend	Current Share Price
Free Cash Flow Yield	Cash Flow From Operations − Total Capex	Market Cap = Current Share Price × Current Basic Shares
Enterprise Value / Sales	EV = Current Share Price × Current Shares + Minority Equity + Net Debt + Other LT Liabilities	Sales
EV / EBITDA	Enterprise Value	Basic EBIT + Depreciation + Amortization

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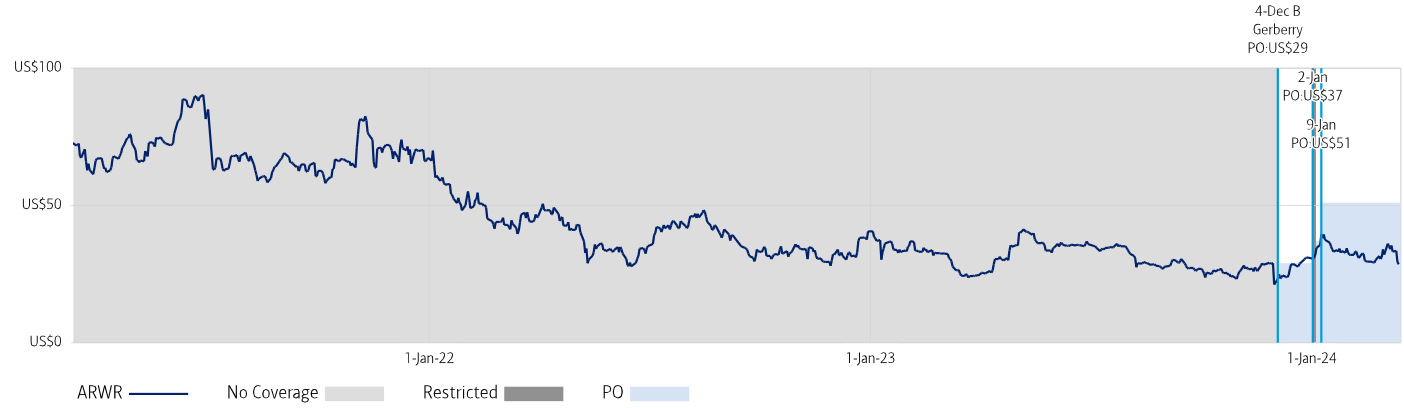
Disclosures

Important Disclosures

Arrowhead (ARWR) Price Chart



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Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

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Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
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Hold	832	23.54%	Hold	454	54.57%
Sell	807	22.84%	Sell	383	47.46%

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