EQUITY RESEARCH

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November 11, 2020

US Biotech: AHA Abstracts, Takeaways On ARWR/ IONS/ALNY

ARWR CV franchise is full steam ahead and we: 1) are very impressed by APOC3 triglyceride (TG) lowering when benchmarked to Vascepa and 2) think ANG3 data for cholesterol is exciting and eager to see mix of PCSK9 experienced/naïve to get full picture. We think APOC3 can be pursued without a partner while we expect ANG3 to be partnered later. IONS/AZN oral PCSK9 was encouraging, but sparks more questions than answers. ALNY hypertension asset shows a signal, but dose-response a bit puzzling and washout period confounding.

ARWR: APOC3 Data Very Impressive - This is the first time we are seeing full-data in patients (link - prior data in NHV here). Overall, we are very impressed given TG reductions of 78-92% after single injection vs 27% for Vascepa (~$650m/year drug). The n is small but average was within normal range after dosing (from 587 mg/dl to 109 mg/dl) while levels remain high on Vascepa (from 680 mg/dl to 496 mg/dl). Other biomarkers checked the box (96% KD in APOC3) and the HDL boosting (71-136%) may possibly be icing on the cake. 2/6 MCM patients experiencing ALT elevations will raise some eyebrows but they were transient and unlikely drug-related given GalNAc's profile. IONS also has an APOC3 but: 1) has a more modest impact on APOC3/TG (70% vs 96%/23-60% vs 78-92%), 2) ARWR offers less frequent dosing and 3) wonder if lack of potency is the reason why NVS passed on the IONS asset. ARWR to start a pivotal in H1:21 for MCM patients first (30k in US) followed by patients TG>500 mg/dl (10s of millions in US). We believe both indications can be pursued without a partner as CVOT likely not needed.

ARWR: ANG3 Data Solid, Look Forward To Full Picture At AHA - On ANG3, this is first look at high cholesterol patients (link - prior data in NHV here). We think data is superior to IONS/PFE given LDL reductions of 23-37% vs 5-10%, possibly driven by higher potency (ANG3 KD of 62-85% vs 40-60%). Importantly, all patients were on statins but we look forward to full data at the conference as it is unclear if they are PCSK9 experienced or naïve (former would be more impressive than latter). The good news is ANG3 may address a very large population, the bad news is an expensive CVOT trial is likely needed. We think ARWR will ultimately partner the asset and IONS/PFE deal is the obvious comp ($250m upfront, $1.3b in bio-bucks, double-digit royalties).

IONS: First Look at Oral PCSK9 Encouraging But Still Early Days - IONS/AZN are exploring oral ASO as they have a next-gen chemistry with ~100x higher potency (link). IONS has been vocal about the program as competitors (ALNY/ARWR/DRNA) may not be able to follow given higher MW for siRNA vs ASO. In humans, 90 mg single subQ dose drove a 90%+ reduction of PCSK9 (on par with inclisiran). In rats, a formulation with similar chemistry and delivered intestinally (intrajejunally) drove a 78% KD and biodistribution data in NHP/dogs was also corroborating. We are encouraged by the data but we wonder if the need to bypass the stomach with an intrajejunal approach speaks for the challenges of withstanding stomach acidity. We need to see more data before becoming believers.

ALNY: AGT Shows Signal But Washout Confounding - ALN-AGT drove a >10 mmHg reduction in systolic blood pressure at high doses (link). The signal is intriguing but we note: 1) dose dependence was a bit puzzling (25/50 mg KD curves are superimposable), 2) data is single arm so lifestyle modifications may factor in (diet alone can drive 8-14 mmHg reduction) and 3) patients were washed out before enrollment so wondering how the blood pressure at the end of the study compares to values pre-washout.

Disseminated: Nov 11, 2020 14:27ET; Produced: Nov 11, 2020 14:27ET

Priced as of prior trading day's market close, EST (unless otherwise noted).
All values in USD unless otherwise noted.
For Required Conflicts Disclosures, see Page 2.

Companies mentioned

Alnylam Pharmaceuticals, Inc. (NASDAQ: ALNY US; $125.05; Sector Perform)
Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR US; $68.68; Outperform; Speculative Risk)
Ionis Pharmaceuticals, Inc. (NASDAQ: IONS US; $50.18; Outperform)

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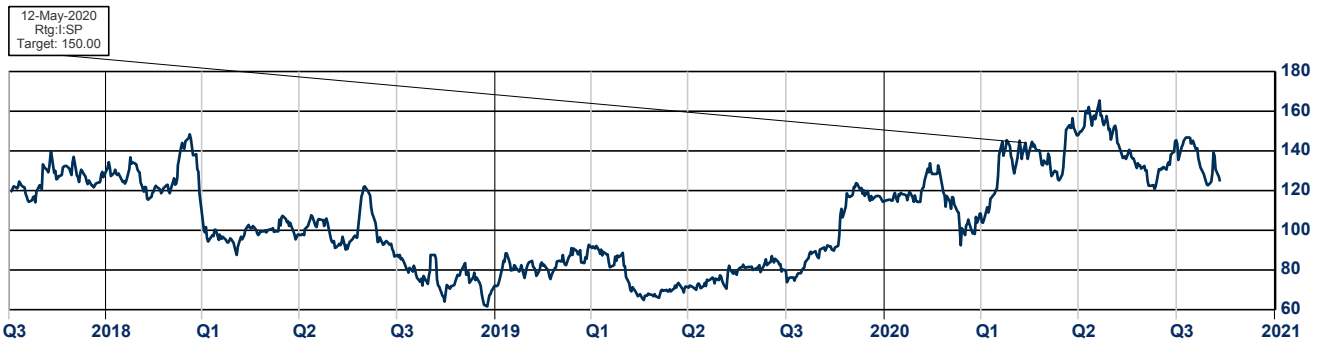
Rating and price target history for: Alnylam Pharmaceuticals, Inc., ALNY US as of 10-Nov-2020 (in USD)



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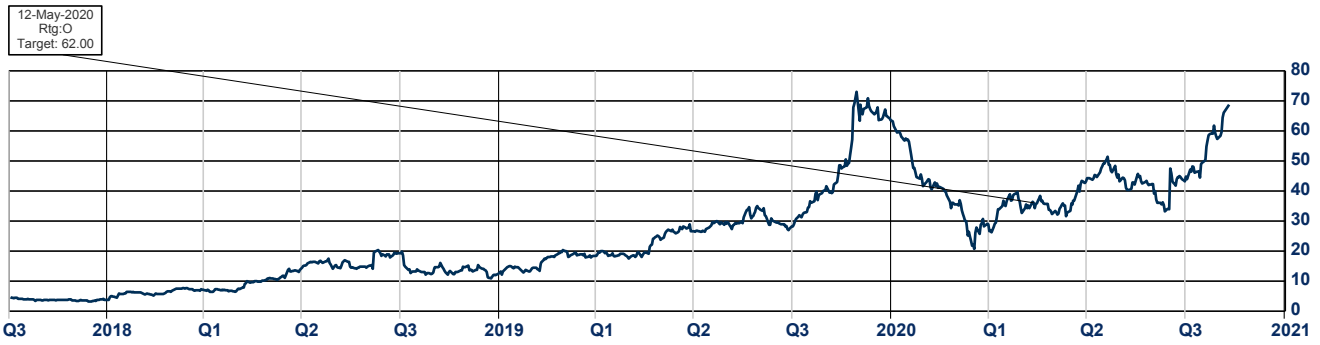
Rating and price target history for: Arrowhead Pharmaceuticals, Inc., ARWR US as of 10-Nov-2020 (in USD)



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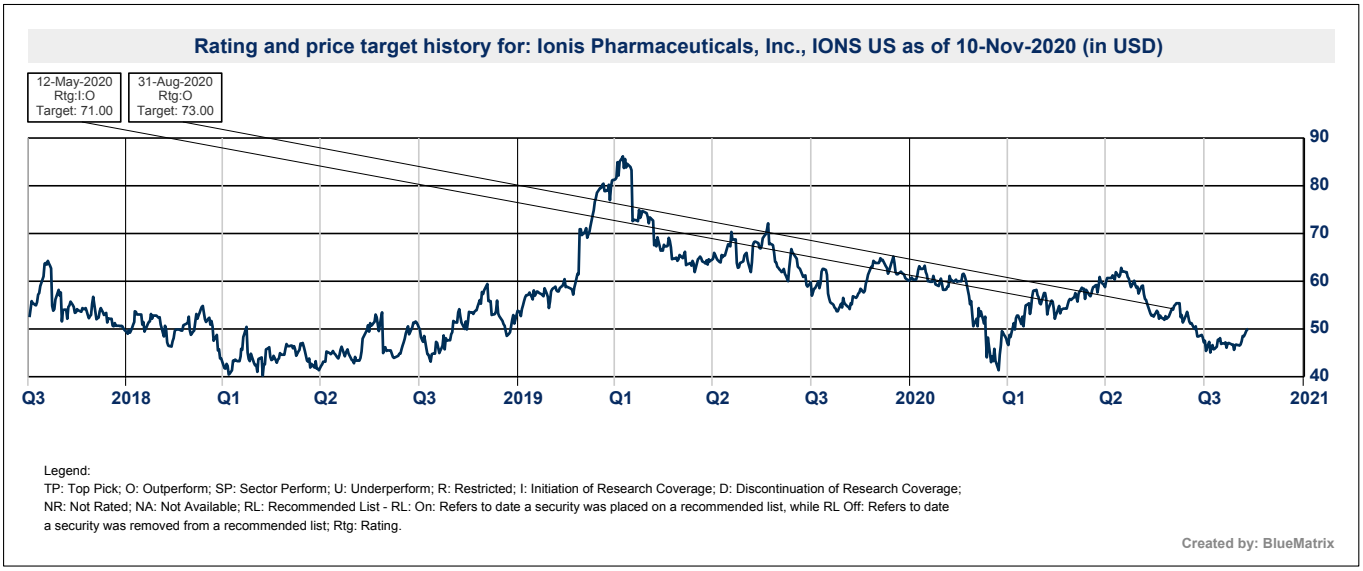

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Alnylam Pharmaceuticals, Inc.

Valuation

Our base case assumes 90% PoS for lumasiran, 85% for inclisiran, 70% for vutrisiran and 65% for fitusiran. Our $150 price target is based on a DCF that assumes a 10% WACC (same for all stocks in our coverage) and a 1% terminal growth rate (with a 0–2% range applied to our coverage depending on the relative maturity of the platforms). Our target price supports our Sector Perform rating.

Risks to rating and price target

Upside risk to our thesis include: 1) vutrisiran becomes the drug of choice for TTR-CM as ALNY shows materially better results vs. Vyndaqel; 2) docs use vutrisiran and Vyndaqel in combination given complementary MOA/non overlapping tox/no payor pushbacks; 3) current epidemiology for AHP and PH substantially underestimates opportunity; 4) inclisiran quickly gains market share given convenient dosing and no payor pushback; and 5) siRNA approach for hemophilia is more complementary than competitive to gene therapy. Downside risk to our thesis include clinical program execution (vutrisiran, lumasiran), regulatory uncertainties, intellectual property risk, failure to demonstrate sustained efficacy in trials, potential emergence of a safety signal, competition (Vyndaqel, nedosiran), and long-term pricing pressure in the space. COVID-19 may also disrupt/delay clinical programs.

Arrowhead Pharmaceuticals, Inc.

Valuation

Our $62 price target is based on a DCF analysis that assumes a 10% WACC (same for all stocks in our coverage), 1% terminal growth rate (with a 0-2% range applied to our coverage depending on the relative maturity of platforms), 65% PoS for A1AT, 45% PoS for

HBV, 30% for Lpa and 35% for the platform. Non-PoS adjusted platform value is determined by the sum of the terminal value of each program. Our price target supports our Outperform, Speculative Risk rating. We assign a Speculative Risk qualifier given the unpredictability of future revenues and expenses, non-revenue generating status, and stock price volatility that could result in substantial upside/downside swings not anticipated in our valuation.

Risks to rating and price target

Risks include clinical program execution, regulatory uncertainties, intellectual property risk, failure to demonstrate sustained efficacy in trials, potential emergence of a safety signal, competition, and long-term pricing pressure in the space. Specifically:

- **COVID-19:** The ongoing COVID-19 pandemic may disrupt, delay enrollment or completion for some of ARWR's clinical programs (AROA1AT).
- **Clinical:** ARWR's candidates are early stage and it is possible that a safety signal may emerge with ARO-A1AT, ARO-HBV, ARO-ANG3, AROLpa or ARO-APOC3. Alternatively, these agents may not demonstrate statistically significant efficacy in larger and late stage clinical studies. Any of these situations could potentially limit the likelihood of marketing approval and overall commercial success of the company.
- **Regulatory:** Failure to garner regulatory approval for ARO-A1AT, ARO-HBV, ARO-ANG3, ARO-Lpa or ARO-APOC3, in the U.S. or key ex-U.S. regions, such as the EU, could significantly limit ARWR's ability to generate revenues and lead to downside to our estimates.
- **Commercial:** Inability to hire and/or retain required personnel to conduct critical research and development; poor market penetration due to competition, lack of demand, or perception of insignificant clinical activity; interruptions in the availability of commercial supply from third-party manufacturers and/or setbacks in establishing in-house manufacturing capabilities; inability to obtain or maintain intellectual property protection of their product candidates.
- **Financial:** Inability to fund operations as a small-cap company with no marketed commercial product; high probability that ARWR will need additional capital to support the ongoing development of their clinical and preclinical assets prior to becoming revenue-generating and cash flow positive.

Ionis Pharmaceuticals, Inc.

Valuation

Our base case assumes 100% PoS for Spinraza, Tegsedi and Waylivra (already approved), 35% for Huntington disease, 30% for Lp(a) and 75% for revenue from future collaboration. Our $73 price target is based on a DCF analysis using a 10% discount rate (same for all stocks in our coverage) and a 2% terminal growth rate (with a 0-2% range applied to our coverage depending on the relative maturity of the platforms). Our target price supports our Outperform rating.

Risks to rating and price target

Risks include clinical program execution (tominersen, TQJ230, AKCEA-TTR-LRx), regulatory uncertainties, intellectual property risk, failure to demonstrate sustained efficacy in trials, potential emergence of a safety signal, competition (Zolgensma, Onpattro, Vyndaqel), and long-term pricing pressure in the space. The ongoing COVID-19 pandemic may disrupt, delay enrollment or completion for some clinical programs.

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