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Stock Watch: Orphan Drug Profitability Under Threat

High Launch Prices Put Emphasis On Volume For Orphan Drug Sales Growth

by Andy Smith

The difficulty of finding and retaining patients with orphan diseases translates into higher marketing costs and adds to other restrictions that limit the attractiveness of some orphan drugs. Will the IRA exacerbate matters?

Orphan Drug Advantages Under Threat

A recent *publication* in *JAMA* compared the sales of prescription drugs five years after launch and found that those with Orphan Drug Act designation were just as lucrative for their manufacturers as those without. The paper also speculated on whether the incentives for developing orphan drugs – including tax breaks, longer exclusivity and exclusion from Medicare price renegotiation – should continue.

Exclusion from Medicare price renegotiation under the Inflation Reduction Act (IRA) might not appear to be a significant threat to orphan drug makers. This is because orphan drugs administered to small patient populations with limited life spans are unlikely to reach the heady heights of annual sales of the first drugs identified for price renegotiation. (Also see "*First Drugs That Could Be Picked For Price Negotiation Showcase Longevity Of Some Brands*" - Scrip, 30 Mar, 2023.)On the other hand, the study attributed high orphan drug prices as the driver for their profitability. With the propensity for the already controversial annual drug list price increases for non-orphan drugs, could price rises for orphan drugs, despite their initial price renegotiation exclusion, one day come to the attention of the accountants at the Center for Medicare and Medicaid Services? The first-quarter 2023 results of the archetypal orphan drug company *Alnylam Pharmaceuticals Inc.* put it front and center in this debate.

Alnylam's Own Goals

Alnylam's first-quarter total revenues grew by nearly 50% on the same quarter of 2022 and by almost 22% on the fourth quarter of last year. Alnylam's first-quarter loss per share (LPS) also fell by 30% on the same quarter of 2022 while revenue and LPS beat analysts' consensus estimates by 4% and 29%, respectively. Since most of Alnylam's revenues come from its four orphan drugs, first-quarter product revenues were also in the pink, growing by 48% on the corresponding quarter of 2022 and by over 5% on the last quarter of last year. Alnylam's stock price finished the day of its announcement up by 3% against a fall by nearly 1% for the NASDAQ Biotech Index. Alnylam's announcement included its "tracking toward its P5x25 goals," one of which is profitability. This raises a potential chink in the orphan drug armor because nearly five years after its first drug launch Alnylam, according to its full-year 2023 financial guidance, will remain loss-making for at least another year.

Probably for competitive reasons, Alnylam's results do not make it easy to interrogate whether annual price increases, so typical of other pharmaceuticals, are a factor in its growing sales. Alnylam's two largest products – Onpattro (patisiran) and Amvuttra (vutrisiran) – are approved for the same indication of polyneuropathy of hereditary transthyretin-mediated (ATTR) amyloidosis and while Alnylam now reports the number of patients "attained" with its drugs, this definition may be complicated by the cumulative number of patients treated and, as is often referred to on its conference calls, the number of commercial patients.

Static Orphan Drug Pricing

The number of attained or commercial patients may mask the total number treated because some patients qualify for free or discounted drug. Also, since ATTR amyloidosis patients live for seven to 12 years after diagnosis, other patients classed as attained may have sadly expired. But dividing the total net transthyretin (TTR) sales of Onpattro and Amvuttra by the number of commercial patients gave an approximate net price of $222,000 at the end of Onpattro's first year after launch in 2019 and this rose in line with attained patient number to $232,000 by the end of 2021. For reference, the list and net prices for Onpattro at launch were $450,000 and $345,000, respectively. This implies that Alnylam's average net price is a function of the number of patients on free drug and its prowess in recruiting new commercial patients, but probably not list price inflation.

By the end of 2022 – Amvuttra's year of launch – the approximate net price had dropped to just below $220,000. This at least indicates that the more conveniently dosed Amvuttra was probably priced at parity or even at a discount to Onpattro and aligns with what a Medicaid regional director once told me – "payers do not pay for convenience."

At the very least, there does seem to be some elasticity in TTR orphan net drug pricing over time, and the cannibalization of Onpattro by Amvuttra that started in the third quarter of 2022 might also have been associated with a temporary pricing discount to encourage uptake. Alnylam's TTR

franchise illustrates how much more difficult orphan drug marketing is compared to marketing traditional pharmaceuticals because of the demise of a limited patient population for drugs that only slow the time to mortality. Nevertheless, as Alnylam's first-quarter results indicate, it is doing a good (if unprofitable) job of capturing commercial patients.

The IRA And Orphan Drugs

The IRA was not expected to have a significant effect on most orphan drugs, partly because Medicare is for seniors – and patients with inborn errors of metabolism, even after they are corrected by therapy, are unfortunately not associated with normal life spans. By contrast, symptoms in ATTR amyloidosis patients, especially the larger population with cardiomyopathy – for which a supplementary new drug application for Onpattro is currently under review by the FDA and Amvuttra is in Phase III – commonly occur for the first time in people over 50. In addition, orphan drugs are only excluded from Medicare price renegotiation if approved by the FDA for just one indication (by my calculation polyneuropathy ATTR amyloidosis and ATTR amyloidosis with cardiomyopathy make two FDA-approved indications).

Alnylam raised the profile of the impact of the IRA on orphan drugs when it became the first company to blame the Act for its decision to discontinue a Phase III study (of Amvuttra in Stargardt disease). But even without price renegotiation for orphan drugs, Alnylam's continued losses illustrate the pressures on the commercialization of high-priced orphan drugs with small patient populations. (Also see "*IRA Effect: Alnylam Acting 'Rationally' In Halting Second Orphan Indication For Amvuttra – Analysts*" - Pink Sheet, 7 Nov, 2022.) Alnylam may have tacitly hinted at the weaknesses and viability of its orphan drug model with its "expansion beyond rare diseases." Unfortunately, the impact of Alnylam's first foray into common diseases – with *Novartis AG*'s lipid-lowering drug Leqvio (inclisiran) – looks like a rounding error not just in the cardiovascular space (because like all Alnylam's drugs it cannot be self-administered) but also financially, as royalties on Leqvio comprised only 2% of Alnylam's first-quarter revenues.

Orphan Drug Viability

Neurocrine Biosciences, Inc. recently discontinued its approved non-orphan but specialist drug Ongentys (opicapone), an adjunctive treatment for Parkinson's disease, because of "unsustainable" sales. Launched in 2020, Ongentys generated just over $5m in first-quarter revenues. *Clovis Oncology, Inc.* recently filed for bankruptcy after its orphan drug-designated PARP inhibitor Rubraca (rucaparib), approved by the FDA in 2018 for ovarian cancer, only generated $31m in sales in the third quarter of 2022.

Two of Alnylam's products – Givlaari (givosiran) for the treatment of acute hepatic porphyria and Oxlumo (lumasiran) for treating primary hyperoxaluria type 1 – generated first-quarter 2023 sales of $50m and $24m, respectively. Bearing in mind the higher costs and complications in orphan drug marketing, Neurocrine and Clovis may have written the demise of at least one of Alnylam's products on the wall. Meanwhile, the IRA (and superior competition from companies

like *Pfizer Inc.** and *AstraZeneca PLC* in the ATTR amyloidosis with cardiomyopathy indication) may have diminished the attractiveness of its strategy of developing orphan drugs for multiple indications. (Also see "*AstraZeneca/Ionis's Eplontersen Shows Competitive Efficacy In ATTR Polyneuropathy At 66 Weeks*" - Scrip, 24 Apr, 2023.) (Also see "*Stock Watch: Filling In The Blanks In Clinical Trial Result Announcements*" - Scrip, 20 Dec, 2022.)

*Andy's pensions hold Pfizer

Andy Smith gives an analyst and investor's view on life science companies. He joined the independent research house Equity Development in October 2019 having previously been an analyst at Edison group and a Senior Principal in ICON PLC's Commercialization, Pricing and Market Access consulting practice. Smith has been the lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, and was chief investment officer at Mannbio Invest. He was awarded the techMark Technology Fund Manager of the year for 2007 and was a global product manager at SmithKline Beecham Pharmaceuticals until 2000.