Citron RESEARCH

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AveXis: The Next Biotech Blowup

12-Month Target: $9.00
24-month target $5.00

Rarely in biotech do we see a situation where an investor can simply perform their own due diligence and be on the right side of the trade without needing to be a scientist. In the case of AveXis (NASDAQ:AVXS), all you need is a healthy dose of skepticism, willingness to do the research, and a bit of empathy to reveal that there's nothing here beyond a glorified stock promotion. It will soon trade in the single digits.

The hopeful story of a cure for terminally ill babies is powerful enough to bring forth the worst of Wall Street's greed, which has the power to sell this story to investors despite the absence of real clinical data. If it wasn't for the horrendously warped way the US pharma market prices its drugs, AveXis could not even have completed its IPO.

The background of this story is exposed in an excellent piece published a month ago. Citron unhesitatingly recognizes good quality research and therefore credits Mako Research with a carefully done profile on why AveXis is nothing more but a stock promotion being orchestrated by highly questionable management.

We won't bother repeating all of their points, but for the foundation of the story we suggest readers start here:
http://seekingalpha.com/article/4024171-AveXiss-house-cards-dubious-trials-drug-lawsuit-fraud-allegations-strong-sell-94-percent?page=2

Citron presents the bullet point summary of the Mako Story:

- CEO and company founder both have deeply troubling backgrounds reflecting corporate misdeeds, DOJ indictments, fraud suits, bankruptcy and kickbacks
- Drug's principal investigator's prior company imploded under fraud investigations and SEC-revoked registration, and forced by SEC to retract a recent study for another company, all omitted from his current bio
- Ownership of IP rights to current drug is subject of a lawsuit, with potentially devastating consequences for AveXis; yet, undisclosed in IPO registration docs
- Only efficacy data for its only drug is a highly flawed, non-blinded, subjectively-scored study -- not executed to any reasonable scientific standard of proof
- The single medical institution performing the study has a vested interest in AVXS stock
- AveXis has no other drugs or gene-therapies in pipeline -- if they acquire something else in the marketplace, they have to bid against everyone else
- Tiny addressable market (estimated < 240 births per year) for SMA Type 1 babies

- Superior drug from blue-chip-credentialed competitor is on track for imminent FDA approval and establishing EAP for eligible patients
- Soon-to-be-approved competitor's drug plus existing lawsuit over IP ownership with self-help group insures tremendously narrowed window of opportunity for future trials and ultimately obstructed market penetration for AveXis.

Citron will now add to that story by explaining how this stock will end. Investors won't have long to wait either ... the end will come sooner than later.

AveXis went public in February 2016 at $20. It immediately broke syndicate price as investors reflected obvious concerns about competition in the marketplace for drugs treating Spinal Muscular Atrophy (SMA) and the questionable practices of their study.
https://www.briefing.com/investor/analysis/story-stocks/AveXis-(avxs)--ipo-prices-well-only-to-get-slammed-in-open-market.htm

Yet the stock ran to $36 in May, a price point at which the company was thrilled to execute a fat follow-on offering.

The price run was fueled when AVXS was granted the FDA drug designation of "Breakthrough Therapy", because SMA Type 1 is truly a life-and-death condition. However, this designation **does not grant automatic validation of a drug candidate** (see below)**.** Then, with the market in a frenzy to find Sarepta "me-too" stories, the stock ran over $65, and now hovers around $50.

"How?", you ask? Simple! The market went nuts on the run-up of false-comp Sarepta (SRPT), which is up 500% since January on a surprise, controversial and emotionally-driven FDA approval for a similarly rare indication (Duchenne Muscular Dystrophy), despite questionable efficacy data for Sarepta's drug. Then the market went looking for "me-too" phenomena stocks, and found this one.

Dare we Apply some Logic in an Illogical World?

Since the date of AveXis's IPO at $20 a share in February 2016, they have not enrolled any new patients and have not delivered any clinical data that would compel the FDA to approve this experimental therapy. They continue to analyze data from the same subset of patients. This might be a different landscape if there were no alternative treatments available, but in the intervening months:

Their main competitor (Nusinersen from Biogen and Ionis) is dominating the science behind a real treatment of treating Spinal Muscular Atrophy.

- In April, Ionis and Biogen's Nusinersen met **all primary endpoints** in a Phase 2 study, with **no safety or tolerability concerns identified**.
http://ir.ionispharma.com/phoenix.zhtml?c=222170&p=irol-newsArticle&ID=2158750
- Then just months later, in August, Ionis and Biogen's study **met its primary endpoint** in an interim analysis of its Phase 3 trial for both survival and motor milestone responses:

Ionis and Biogen have plans to obtain FDA approval for Nusinersen in Q1 2017.

"The companies now plan to file for marketing approval with regulatory authorities in the next few months and are working to open an expanded access program (EAP) this Autumn, to patients with infantile onset SMA (consistent with Type 1) prior to potential regulatory approval. "

http://www.smatrust.org/wp-content/uploads/2016/08/EU-Community-Statement_FINALVCB.pdf

Meanwhile, AveXis stock is over **twice the price of its initial offering** despite shareholders biggest risk having become a reality: Nusinersen works, safely and effectively. It will most likely earn FDA and European approval.

This is the worst possible news for AveXis shareholders and was even called out as a risk factor in AveXis's corporate filings:

From the AveXis IPO:

"We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully market or commercialize AVXS-101."

https://www.sec.gov/Archives/edgar/data/1652923/000104746916010121/a2227319z424b4.htm

In fact, AveXis changed this language in their follow-on offering, to address explicitly the looming risk of a Nusinersen approval:

"* availability of competing therapies and clinical trials, including Ionis Pharmaceuticals, Inc. and Biogen's proposed global expanded access program for Nusinersen for eligible patients with SMA Type 1"

https://www.sec.gov/Archives/edgar/data/1652923/000104746916015407/a2229653z424b4.htm

With the news since IPO, it's unimaginable that this stock has run higher than its IPO price. How can it be trading at levels 50% higher than its secondary price of $34?

The writer of this article is a parent. I am sure many of the readers are as well. If you happen to bear the misfortune of a baby born with Type 1 SMA, are you going to treat your child with a drug with FDA approval based on robust multi-site clinical data, or are your going to enroll your child into an experimental gene therapy trial executed at just one clinic? It would be irresponsible, unethical, and should be illegal for anyone to put his or her baby on any alternative treatment. This condition requires early treatment, with good clinical outcomes reflective of early treatment.

In a post-Nusinersen approval world, AveXis faces severe risks of NEVER being able to complete full clinical studies. (**NOTE:** In order to test the efficacy of AVXS-101, babies treated with Nusinersen would obviously never be candidates for enrollment.)

C'mon Citron! AveXis's drug is designated a “Breakthrough”!

Despite the lack of clinical data, part of the enthusiasm for AveXis stock was that it was granted "Breakthrough Therapy Designation" by the FDA in July:

http://investors.AveXis.com/phoenix.zhtml?c=254285&p=irol-newsArticle&ID=2186665

While the word “breakthrough” might seem like the FDA has committed to a fast-track to approval – this is simply not the case. If a drug fits the need of a serious or life threatening disease with the potential of substantial treatment advantages over existing treatments, it can receive “Breakthrough Therapy” status in order to streamline its approval path. Maybe the FDA should rethink that word, as investors are easy confuse its true meaning.

A Bloomberg story that best explains the "Breakthrough Therapy" designation:

"Breakthrough Drugs Don't Always Break Through"

https://www.bloomberg.com/gadfly/articles/2016-08-01/seres-therapeutics-btd-failure-fallout

Even the AMA agrees, deeming the term "aspirational".

http://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2442501

What about the FDA Approving a 20 Patient Phase I Study – Isn’t this a Bullish Sign for Early Approval?

Investors cheered this news, but is it really so bullish? Investors need to take note that the company published only **excerpted segments of the meeting minutes**.

It is Citron's experience that when a company practices **selective disclosure, it is to avoid disclosing what management does not want the investing public to know**.

> **"... with FDA offering a number of constructive suggestions which we believe will better enable implementation of a pivotal study design that is most appropriate for the patients suffering from this devastating disease... "**
>
> *--- Sean Nolan, President and Chief Executive Officer of AveXis*

https://globenewswire.com/news-release/2016/11/01/885355/0/en/AveXis-Announces-Single-Arm-Design-for-U-S-Pivotal-Study-of-AVXS-101-in-SMA-Type-1-Patients.html

The FDA can expedite reviews for drugs when there is **no alternative** for patients with serious and/or life-threatening conditions. Without head-to-head testing against Nusinersen, and its overwhelming approval looming, considering AveXis's clinical trial evidence is so thin, the motivation to expedite AVXS-101's path to approval simply evaporates.

Can't AveXis become the next Sarepta?

Another contributing factor for AveXis to be trading higher than its original IPO price was the FDA approval of Sarepta's treatment for Duchenne Muscular Dystrophy(DMD). The quality of

the clinical data for that drug has long been under scrutiny, and its approval was controversial. FDA approval of Sarepta's eteplirsen left investors in a frenzy chasing “me-too” stories, and AveXis became a beneficiary.

Despite Sarepta's stock price being cut in half from its post-approval highs, Citron notes the key differences between the two companies:

- **There was no alternative therapy even suggested for treating DMD. For SMA, Nusinersen has already filed for multiple approval indications.**
- **Sarepta actually monitors Dystrophin as a biomarker to directly measure efficacy. AveXis has shown no chemical marker of its treatment's method of action, relying only upon a clinician's subjective observations of patients at a single center.**
- **Sarepta had very clear inclusion/exclusion criteria to insure a homogenous patient group. AveXis's study has serious disclosure deficiencies in its tiny patient cohort that could be skewing its results.**

Lastly and most important, the patient advocacy groups for SMA babies are actively trying to advocate for fast approval of Nusinersen, but NOT AveXis-101.

http://thefastmovement.org/wp-content/uploads/Nusinersen-The-Case-for-FDA-Approval-Now1.pdf

Putting the Brakes on the “Citron Bias”

Shareholders of AveXis might be thinking, "of course Citron is going to present a biased presentation!" To that criticism we refer to the informational source to the world – Google.

What looks like Clinical Medicine and what looks like a Stock Promotion:

To illustrate how one-sided this argument really is just go to Google News and search the word “Nusinersen”. **The following 4 articles are from the past week alone on Nusinersen:**

SMA Today: http://smanewstoday.com/2016/12/08/nusinersen-safely-treats-infants-with-type-1-sma-study-reports

Stanford Medical Center: http://med.stanford.edu/news/all-news/2016/12/stanford-patient-is-first-infant-to-receive-lifesaving-drug.html

Science Magazine: http://www.sciencemag.org/news/2016/12/novel-drug-rescues-babies-fatal-neurodegenerative-disease

Neurology Advisor: http://www.neurologyadvisor.com/neuromuscular-disorders/new-drug-for-spinal-muscular-atrophy-shows-promise/article/577967/

YET…when you Google "AveXis" or "AVXS-101", all you can find is a series of articles about the **stock**...

https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#tbm=nws&q=AveXis

https://www.google.com/search?hl=en&gl=us&tbm=nws&authuser=0&q=AVXS-101&oq=AVXS-101&gs_l=news-cc.3..43j0j43i53.1510.4916.0.5589.10.4.1.5.5.0.79.255.4.4.0...0.0...1ac.1.PnIBT8YWXsI

The science behind AveXis's stock has captured the hope of only the investment bankers ... and the hospital who has a vested interest in AveXis's share price...

Conclusion

Given the extremely shady backgrounds of AveXis management and the dubious track records of the lead investigators at the single clinical site at which its drug is trialed, investors need to apply professional skepticism to the much-touted "two babies sitting up" claim in AveXis's trial findings, absent any proof that these babies in fact were symptomatic for SMA Type 1 disease. Bear in mind that this finding is dependent upon only subjective CHOP-INTEND behavioral scoring. There is no biochemical analysis of the subjects' condition in this clinical evaluation. Meanwhile, the anticipated Spring 2017 approval of Biogen/Ionis's competitor drug with overwhelming safety and efficacy data looms over this company.

With only 240 cases of SMA Type 1 in the USA per year, there is not room for another competing drug that does not show SUPERIORTITY over Nusinersen. Synergy is not sufficient, because there is no ethical rationale for a blinded study.

The open label biased testing of AveXis will soon be exposed to the stock market as obviously as it has already been exposed to the scientific community.

Appendix: AVXS-101

For the science types who want to forego logic, and still want to the believe AveXis investment thesis, it is time to demand the company reveals some real science and not just observational CHOP-INTEND scores.

Here is a good start -- and Yes, Citron assembled this with a team of science consultants:

Specific genotypes (genetic testing results) for each child. This should include information about so called 'helper genes' which the literature has suggested result in milder cases. (more detail can be found in the Mako report). Their protocol speaks to a very specific genotype (one of many genotypes that are all considered SMA) that became an exclusion criteria once they had treated 10 kids due to the 'predicted mild phenotype' (aka severity) associated with that genotype. So the company can't claim it doesn't have all this information. Nor can it claim that it isn't aware that specific genotypes matter as far as disease severity. Nor can they claim HIPAA since they put the pictures of the kids in every presentation they can.

Biological proof that the drug is doing what is claimed. Nusinersen shows that treated kids have 2x to 5X increase in mRNA (mRNA leads to protein synthesis) compared with kids that don't. Not only does AVXS not have any of this data, they have no means of collecting it. That would require them to get CSF (cerebrospinal fluid) obtained by a lumbar puncture which their protocol makes no mention of. So they aren't even checking to see if the drug got to its intended target location or if it worked. They just want us to rely on the CHIP-INTEND scores and developmental observations. As Citron mentioned previously, even SRPT had a whiff of dystrophin when they biopsied the muscles. Doing a protocol revision to get some CSF would not be a big deal at all.

The actual complete FDA minutes from their recent meeting. Again, since they are expecting us to believe that they can get approved on a 15 patient study, every tiny bit of data matters. Let us judge for ourselves what the FDA thinks about their trial design. Letting a company move

forward on a trial design does not mean the FDA agrees with it and there might be some telling language in there. But they won't let the public see it, so who knows!?!?

The physician's clinical report for the two walkers at baseline. The protocol requires the kids to have copies of SMN2 and show clinical signs of the disease. The issue with this is that babies known to have two copies of the gene are naturally going to be scrutinized with expectation of seeing any sign of disease whether it exists or not. What appears to be the case is that the two walkers were not showing ANY real signs of the disease (their CHOP-INTEND scores were well in the normal range for children their age — again, the Mako report has the details).

The net result of this is the looming risk of study bias by cherry-picked patients. It is quite clear in the literature that not all kids with two copies develop the severe form of SMA. It's only without the benefit of hindsight, and without the support of approved high-efficacy drugs, that anyone can get away with assuming that two-copies patients will always progress to severe disease. So if they want us to believe these two kids were unalterably headed toward a bad prognosis, they certainly haven't done a good job of documenting it.