Zacks Small-Cap Research

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Aevi Genomic Medicine (GNMX-NASDAQ)

GNMX: 9 Genes Associated With Particularly Potent Response to AEVI-001

Given the early stage of GNMX we continue to value the company using DCF model based on annual revenue of an "average" orphan drug. See the end of this report for a detailed explanation of our model inputs. We have discounted our fair value based on delays to AEVI-001 in ADHD, resulting in our price target moving from $10/share to $7/share. This is subject to further updating based in part on developments towards commencing new mGluR+ADHD study.

Current Price (04/26/17)	$1.52
Valuation	**$7.00**

OUTLOOK

Post-hoc analysis showed that 9 specific genes are predictive of a clinically meaningful and statistically significant response to AEVI-001. Response appears to be even more robust among those patients with mutations to CNTN4, which has been associated with more severe ADHD. Given that CNTN4 mutations/deletions, which may also play a role in ASD, relate to such problematic phenotypes, we think that effectively addressing and treating these patients could be a major breakthrough. Part of the expected clinical trial redesign includes refining the biomarker to improve response to AEVI-001. This more recent updated data that have been identified as particularly sensitive responders, clearly represent at least one major step towards further refining and enriching the next mGluR+ADHD trial for improved response to AEVI-001. And while such a redesign could reduce the potential target ADHD population of AEVI-001 from the initial ~20% down to 5% or 10%, this still represents a U.S. pediatric/adolescent ADHD population of ~300k – 600k - a potential market opportunity which we calculate to be ~$600M - $1.2B. And critically, the CNTN4-mutation positive ADHD population are generally associated with the most severe disruptive behaviors and may be among the most challenging to effectively treat with traditional ADHD drugs such as stimulants.

SUMMARY DATA

52-Week High	**$6.89**
52-Week Low	**$1.30**
One-Year Return (%)	**-68.75**
Beta	**0.81**
Average Daily Volume (sh)	**825,796**
Shares Outstanding (mil)	**37**
Market Capitalization ($mil)	**$56**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**46**
Insider Ownership (%)	**23**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Value**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in '000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	0 A	0 A	0 A	0 A	0 A
2017					0 E
2018					0 E
2019					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.34 A	-$0.35 A	-$0.29 A	-$0.23 A	-$1.19 A
2017	-$0.28 E	-$0.30 E	-$0.29 E	-$0.29 E	-$1.10 E
2018					-$1.04 E
2018					-$0.96 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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Post-Hoc SAGA Analysis Finds Nine Genes Associated With Potent Response To AEVI-001
Management indicated during the March 20th reveal of topline SAGA data, which showed the studies' primary endpoint (i.e. change from baseline in ADHD-RS-5 score) was not met, that they believed further parsing of the results may offer opportunities to further refine design of the next study in order to improve on efficacy.

As a reminder (and which is explained in further detail below), while SAGA data showed that the primary endpoint was not met, secondary analyses were quite positive. This includes meeting statistical significance on the CGI-I secondary endpoint as well as on the ADHD-RS responder measure (prespecified as decrease of ADHD-RS score of 30% or more). Additionally, the ADHD-RS inattention subscale (i.e. the 9 questions related to inattention), just barely missed statistical significance (p=0.0515). And, importantly, AEVI-001 was deemed to be well tolerated with no associated serious adverse events.

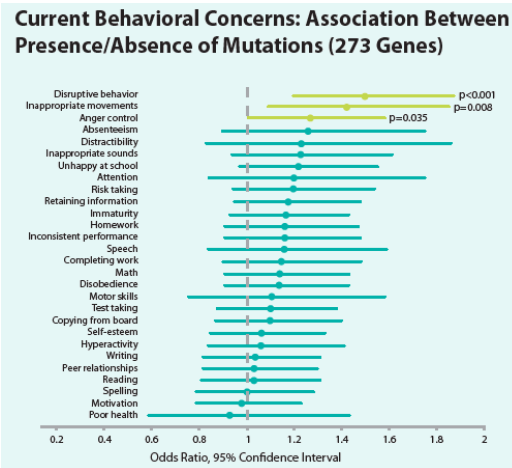
But, given that change from baseline in ADHD-RS score has been FDA's preferred measuring stick in assessing pivotal ADHD drug studies, SAGA's failure on the primary endpoint means a study-redesign to better enrich for AEVI-001 responders is necessary. It didn't take long for GNMX to parse out what appears may be the low-hanging-fruit in that regard.

Post-hoc analysis, presented at the World Congress on ADHD on April 21st, showed that among the 273 genes encompassing the 'Tier 1' (76 genes in the mGluR receptors) and 'Tier 2' (197 genes that encode proteins that influence mGluR) mGluR network, mutations of which have been found in approximately 22% of children with ADHD, GNMX found nine that were predictive of a clinically meaningful and statistically significant response to AEVI-001.

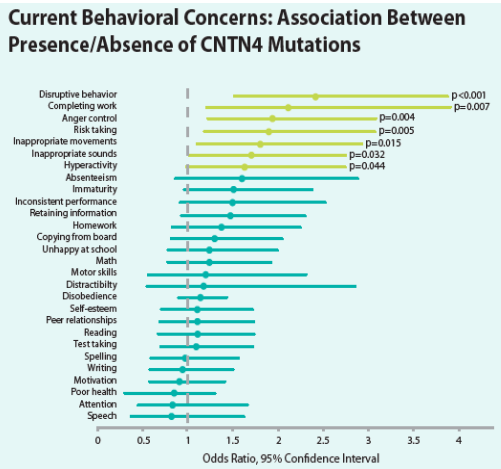
Specifically, patients (n=42: 18 AEVI, 24 placebo) which had copy-number variation (i.e. mutations) to one of nine genes (the identity of only one was revealed) which include "certain glutamate metabotropic receptors (GRM) and neurodevelopmental genes" had a much higher and statistically significant response to AEVI-001 – which included the primary endpoint as well as CGI-I and 'responder' secondary measures. These nine genes are believed to be prevalent in approximately 10% of all pediatric ADHD subjects – or about one-half the prevalence with mutations in the entire Tier 2 network.

The response appears to be even more robust among those patients (n=18: 6 AEVI, 12 placebo) with mutations to contactin-4 (CNTN4), which has been associated with more severe ADHD due to a higher prevalence of disruptive behavior including inability to control anger as well as inappropriate movements and sounds (graphics below). Given that CNTN4 mutations/deletions, which may also play a role in Autism Spectrum Disorder (ASD), relate to such problematic phenotypes, we think that effectively addressing and treating these patients could be a major breakthrough. Approximately 5% of people with ADHD are believed to carry a CNTN4 mutation.

Top-line data (273 genes)



CNTN4



SOURCE AEVI Genomic Medicine. Poster, World Congress on ADHD

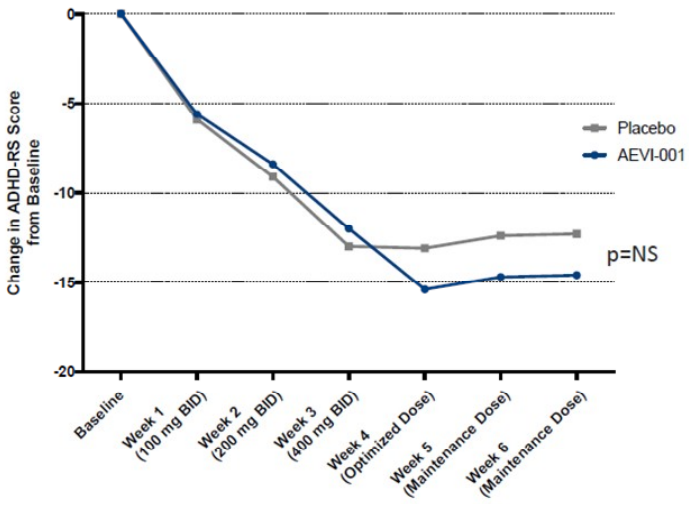
ADHD-RS:

As a reminder, **ADHD-RS (rating scale)** is a parent-reported measure consisting 18 questions across two 9-question subscales; inattention and hyperactivity. Each question is scored on a 4-point scale (0=never, 1=rarely, 2=sometimes, 3=often, 4=very often) relative to observance of behaviors. ADHD-RS is a well-established primary endpoint in ADHD clinical trials.

Topline (announced March 20th):

While GNMX did not disclose the specific ADHD-RS data (i.e. % change in each arm or p-value), they did note that absolute change was approximately 15 in the AEVI-001 arm and ~12 in the placebo group, with separation (although not statistically different) between the two exhibited at the highest (i.e. 400mg) dose (graphic below). Also noteworthy, was that 20% of AEVI-001 subjects had no appreciable reduction (i.e. ≤ 3) in ADHD-RS score.

Topline Data (March 2017)



SOURCE: Aevi Genomic Medicine March Presentation

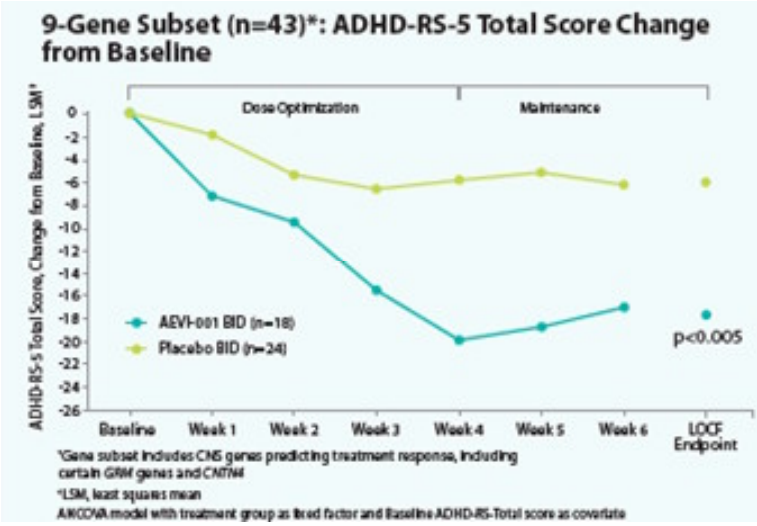
In terms of **ADHD-RS response** (a key secondary endpoint used in SAGA), 70% of AEVI-001 subjects showed ADHD-RS decrease of 30% or more, compared to 42% of placebo subjects. The difference **was highly statistically significant** (p=0.0067) at week-6 and also statistically significant at week-5 (p=0.0203). Interestingly, the **absolute reduction in ADHD-RS among the 70% of AVEI-001 subjects that responded was over 19 points but was "almost nothing" (per management on the call) among the 30% that did not respond**.

GNMX noted on the topline data conference call that their game plan would be to (genetically) identify and weed-out this 30% in a planned pediatric study through further refinement of a biomarker. As we noted at the time, given the huge discrepancy in reduction of ADHD-RS between responders and non-responders, if a biomarker can indeed 'identify' and eliminate non-responders, we think successful development of it could be a significant near-term win for GNMX as it could be an initial sign of the likelihood of a follow-on mGluR+ADHD study's ultimate success. That (i.e. development of a refined biomarker eliminating non-responders), in our opinion, is a pre-study milestone that investors should be closely following.

9 Genes of Interest:

Mutations in one of nine genes, per the updated data presented at the World Congress on ADHD on April 21st , were associated with a relatively much more robust and clinically meaningful and statistically significant response. Specifically, reduction of ADHD-RS (i.e. **primary endpoint**) among the 18 patients in this cohort (i.e. with a mutation in one of these nine genes) treated with AEVI-001 was 17.6 – compared to just 5.9 among the 24 subjects in this cohort receiving placebo. The difference was **highly statistically significant** ($p < 0.005$).

The percentage of responders (i.e. **one of two key secondary measures),** as measured by the number of patients in each arm that achieved 30% or more reduction in ADHD-RS score from baseline, was **also highly statistically significant** among the 9-genes subset and also improved as compared to the unparsed data (i.e. topline results incorporating data from all study participants). 16 of 18 patients, or 89%, treated with AEVI-001 among this 9-gene subset met the 30%+ responder endpoint – compared to just 5 of the 24, or 21%, of those patients receiving placebo ($p < 0.0001$).

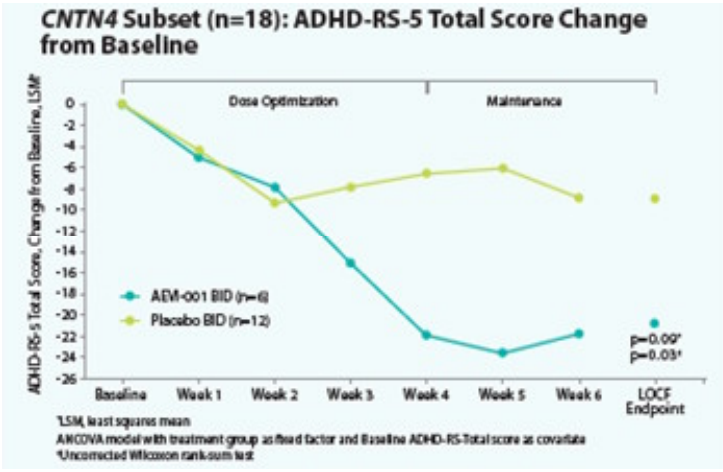


SOURCE Aevi Genomic Medicine. Poster, World Congress on ADHD

CNTN4:

The data at the World Congress on ADHD was even more compelling when looking at just the CNTN4 gene. CNTN4 encodes a member of the immunoglobin family. It is a glycosylphosphatidylinositol-anchored neuronal membrane protein that is believed to play a role in the formation of axon connections in the developing nervous system. As noted, it has also been implicated in playing a role in ASD.

Reduction of ADHD-RS (i.e. **primary endpoint**) among the 6 patients in this subset (i.e. CNTN4 CNV) treated with AEVI-001 was 20.8 – compared to 8.9 among the 12 patients receiving placebo. Despite the relatively small sample size, the difference was statistically significant ($p = 0.03$).



SOURCE Aevi Genomic Medicine. Poster, World Congress on ADHD

The percentage of responders (i.e. **one of two key secondary measures),** as measured by the number of patients in each arm that achieved 30% or more reduction in ADHD-RS score from baseline, was **also highly statistically significant** among this CNTN4 gene subset and also improved as compared to the unparsed data

(i.e. topline results incorporating data from all study participants). 6 of 6 patients, or 100%, treated with AEVI-001 among this CNTN4 subset met the 30%+ responder endpoint – compared to just 3 of the 12 patients, or 25%, receiving placebo (p = 0.0027).

ADHD-RS												
	Initial Data (unparsed)				9 Genes of interest				CNTN4 Mutation			
	Evaluable	No. of rspnders	% rspnders	ADHD-RS redction	N =	No. of respndrs	% rspnders	ADHD-RS redction	N =	No. of rspndrs	% rspndgrs	ADHD-RS redction
AEVI-001	46	32	69.6%	~15	18	16	88.9%	17.6	6	6	100.0%	20.8
P-value			0.0067	not meaningful			< 0.0001	< 0.005			0.0027	0.03
Placebo	50	21	42.0%	~12	24	5	20.8%	5.9	12	3	25.0%	8.9
Total	**96**	**53**			**42**	**21**			**18**	**9**		

CGI-I:

As a reminder, **CGI-I (Clinical Global Impressions)** was another key secondary measure used in SAGA. It is a clinician-scored measure which uses a 7-point scale (1=very much improved…, 7=very much worse) to assess how much a patient's condition improved or worsened (or stayed the same). Treatment response in SAGA was prespecified as CGI-I of 1 (very much improved) or 2 (much improved).

The updated data (i.e. 9-genes including CNTN4) on the CGI-I measure were similar to that for both the ADHD-RS measures – that is, reaching statistical significance and improving relative to the unparsed topline data announced in March. Additionally, response was further improved when parsed to only those patients with CNTN4 mutations.

9 Genes of Interest:

13 of 18 patients, or 72%, treated with AEVI-001 among the 9-gene subset achieved a CGI-I score of 1 or 2, compared to 3 of 24 patients, or 13%, receiving placebo (p < 0.001).

CNTN4:

5 of 6 patients, or 83%, treated with AEVI-001 among the CNTN4 subset achieved a CGI-I score of 1 or 2, compared to 2 of 12 patients, or 17%, receiving placebo (p < 0.01).

CGI-I Score of 1 or 2									
	Initial Data (unparsed)			9 Genes of interest			CNTN4 Mutation		
	Evaluable	No. of rspnders	% rspnders	N =	No. of respndrs	% rspnders	N =	No. of rspndrs	% rspndgrs
AEVI-001	46	26	56.5%	18	13	72.2%	6	5	83.3%
P-value			<0.05			<0.001			<0.01
Placebo	50	16	32.0%	24	3	12.5%	12	2	16.7%
Total	**96**	**42**		**42**	**16**		**18**	**7**	

Our Comments:

As we noted following release of the SAGA topline data in March, while it was disappointing that the primary endpoint was not met, there were reasons to remain optimistic. This includes meeting statistical significance on the CGI-I secondary endpoint as well as on the ADHD-RS responder measure. Additionally, the ADHD-RS inattention subscale, just barely missed statistical significance (p=0.0515). And, importantly, AEVI-001 was deemed to be well tolerated with no associated serious adverse events.

So while the primary endpoint was not met, we think there was a clear signal of efficacy of AEVI-001 based on the supplementary measures. This combined with a lack of serious safety issues is expected to bolster

GNMX's anticipated petition to FDA to conduct another mGluR+AHDH study – management outlined their plans on the SAGA call which includes several updates to the trial design, all of which are aimed at improving upon efficacy and meeting the ADHD-RS primary endpoint.

Part of the redesign includes refining the biomarker to improve response to AEVI-001. This more recent updated data related to nine specific genes, including CNTN4, that have been subsequently identified as particularly sensitive responders, clearly represent at least one major step towards further refining and enriching the next mGluR+ADHD trial for improved response to AEVI-001.

And while such a redesign could reduce the potential target ADHD population of AEVI-001 from the initial ~20% down to 5% or 10%, this still represents a U.S. pediatric/adolescent ADHD population of ~300k – 600k - a potential market opportunity which we calculate to be ~$600M - $1.2B. And critically, the CNTN4-mutation positive ADHD population are generally associated with the most severe disruptive behaviors and may be among the most challenging to effectively treat with traditional ADHD drugs such as stimulants.

As such, further validation of AEVI-001 in this subset of ADHD patients could eventually provide it with a very receptive market and one with little direct competition – the benefits of which would mean not having to fight for 'space' among the traditional ADHD drugs (backed by substantial marketing resources) nor worry about pricing pressure from related off-patent generics. Additionally, targeting (genetically identified) subset patient populations affords the benefit of lean marketing budgets. And, finally, it is important to note that severity of disease among the general pediatric/adolescent ADHD population ranges from relatively mild (including those exhibiting more attention-deficit than hyperactivity) to quite severe (marked by greater hyperactivity) – (parents of) the more extreme cases are likely to be particularly receptive to trying novel therapies, such as AEVI-001 – which, these nine-gene and CNTN4 subsets, suggest may be effective for these particularly severe cases.

Based on management's comments on the March topline data call (while GNMX still needs to meet with FDA to discuss specifics of another study), the following are currently being considered by management:

- **Increase dose and/or treatment duration:** given the safety profile of AEVI-001, the fact that is has been safely used in over 1,000 patients (for as long as 12 months) and that 88% of AEVI patients titrated up to the highest dose in SAGA, could provide a compelling case to increase dose beyond 400mg BID. Important to understand is that the relatively short treatment period (i.e. four weeks) of ADHD studies largely **reflects concerns of side effects of stimulant drugs** (such as cardiovascular risks, sleeplessness and anxiety) - despite **AEVI-001 not being associated with these potentially serious side effects**, SAGA's design was nonetheless similar to that of previous stimulant studies. AEVI-001's evidentiary safety profile may pave the way for FDA to accept a longer treatment duration and/or higher dose. Higher dose or longer duration could further improve upon the dose response witnessed in both ADHD-RS and CGI-I.

- **Pediatric, as opposed to adolescent, study**: SAGA was an adolescent study (12 – 17 years). There could be several advantages relative to improving upon efficacy by going to a pediatric study (6 – 12 years) including that **mGluR network mutations are more prevalent in pediatric population** (~26%) as compared to adolescents (~20%) and **inattentiveness is more pronounced in younger ADHD subjects**. As noted earlier, the ADHD-RS inattention subscale just barely missed statistical significance in SAGA – since a pediatric study should further enrich for inattention, presumably it would improve upon the chances of AEVI-001 showing statistical significance on total ADHD-RS score. And, finally, as management indicated on the call, protocol compliance (including dosing, particularly BID dosing) is more likely to suffer among adolescent clinical trials as compared to pediatric trials given the typical greater of oversight by parents of younger children – this can result in a **greater placebo response in adolescent, as compared to pediatric, studies.**

- **Refined biomarker**: approximately 30% of patients in the treatment group showed no meaningful response to AEVI-001 therapy. GNMX hopes to genetically identify what caused the non-response in these patients and refine their biomarker in order to be able to more effectively enroll patients most likely to benefit from AEVI-001 therapy. If and when they **successfully refine the biomarker** to weed out these patients, it would likely be a major milestones in our opinion as it could **add significant confidence to the likelihood of a follow-on phase II study demonstrating statistical significance** on the ADHD-RS endpoint. As such, biomarker development is on our list of items that we will be eagerly awaiting to updates about. Clearly, identifying the nine genes, including CNTN4, figures into this gameplan.

FDA Meeting: Increasing the dose and/or treatment duration will mostly hinge on an acceptable safety profile. Per the March call, GNMX recently submitted the toxicology data to FDA, expects to submit the

pharmacokinetic data in Q2 and hopes to meet with the agency by mid-2017 to discuss design (including higher dose, longer treatment duration, refined biomarker) of a follow-on study. **Results of that meeting will obviously also be highly anticipated.**

In parallel GNMX expects;

- AEVI-001: to initiate signal finding studies in autism spectrum disorder (ASD) and pediatric anxiety disorder, both of which have also been associated with mutations in the mGluR network

- Anti-LIGHT (AEVI-002): to announce data from the ongoing phase I/II signal finding study in Severe Pediatric Onset IBD in 2H 2017

VALUATION: Value GNMX at $7/share

As we noted following release of the SAGA topline data in March, while it was disappointing that the primary endpoint was not met, there were reasons to remain optimistic. This includes meeting statistical significance on the CGI-I secondary endpoint as well as on the ADHD-RS responder measure. Additionally, the ADHD-RS inattention subscale, just barely missed statistical significance (p=0.0515). And, importantly, AEVI-001 was deemed to be well tolerated with no associated serious adverse events.

So while the primary endpoint was not met, we think there was a clear signal of efficacy of AEVI-001 based on the supplementary measures. This combined with a lack of serious safety issues is expected to bolster GNMX's anticipated petition to FDA to conduct another mGluR+AHDH study – management outlined their plans on the SAGA call which includes several updates to the trial design, all of which are aimed at improving upon efficacy and meeting the ADHD-RS primary endpoint.

Part of the redesign includes refining the biomarker to improve response to AEVI-001. This more recent updated data related to nine specific genes, including CNTN4, that have been subsequently identified as particularly sensitive responders, clearly represent at least one major step towards further refining and enriching the next mGluR+ADHD trial for improved response to AEVI-001.

Prior to SAGA topline results we used an "average" orphan company valuation methodology based on statistics from the study done by Thomson Reuters Life Sciences Professional Services and Pfizer (which we detailed in our June 2014 initiation report) to value GNMX.

According to that study, the average per-year revenue of orphan drugs is approximately $600M. We have built a DCF model that more conservatively assumes $550M of revenue is generated over the remaining patent life of one orphan designated product. Other assumptions had been that this product launches within three years (given the delay due to SAGA missing primary endpoint we pushed initial launch back), has 14 - 15 years of patent life remaining, revenue falls 50% per year each year after patent expiration and, given the high selling prices of orphan drugs, commands gross margins of 80% - 85%. We estimate operating expenses at just 20% of revenue given that orphan drugs can typically be detailed with a small sales force and relatively little overall marketing support.

Using these inputs and a 10% discount rate would value the company at approximately $1.5B. Discounting this by the ~22% probability (per Thomson study) that an orphan drug in phase I eventually is approved, values GNMX at $250M (~$7/share).

Our calculated value is subject to updating and considers the likelihood of eventual FDA approval of a proposed pediatric AEVI-001 ADHD study (designed in a way to increase chances of success) as well as eventual success of such a study.

APPENDIX

NOTE – what follows is discussion of the top-line SAGA data announced March 20th and does not include updates including results presented in April related to mutations in 9 genes that suggest a much more robust response to AEVI-001

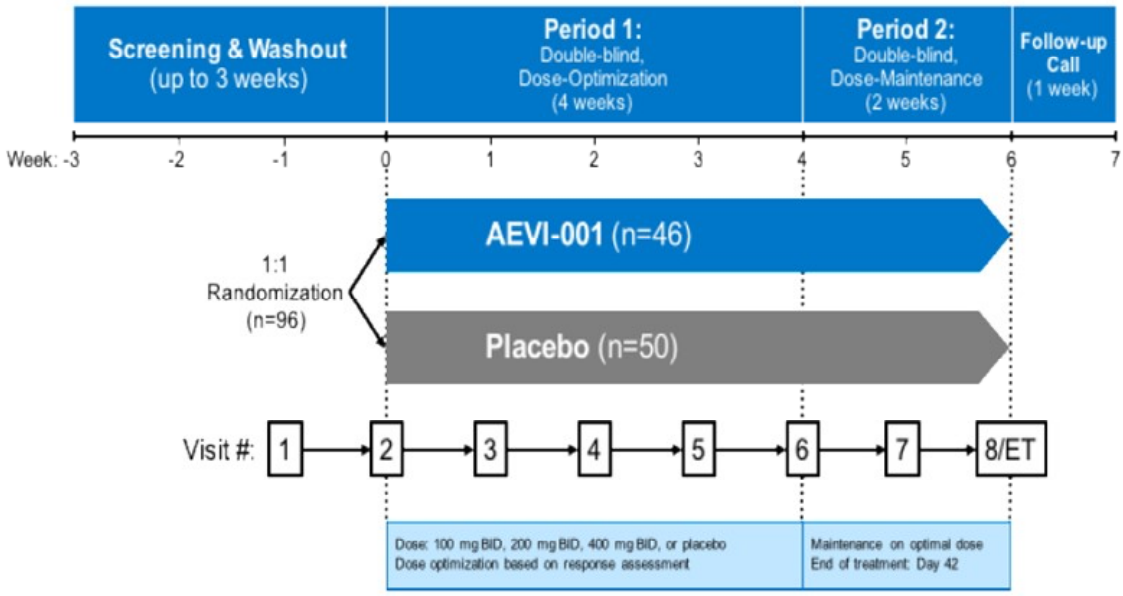
SAGA Results: *Primary Endpoint Missed But Data-Within-The-Data Suggest Reasons To Remain Optimistic*

Aevi Genomic Medicine announced topline results of SAGA (Study of Adolescent Glutamate Receptor Network Copy Number Variant ADHD), its phase II/III randomized, placebo-controlled study assessing safety and efficacy of AEVI-001 (formerly known as NFC-1) in adolescents (n=90, ages 12 – 17). Full results will be presented at the World Congress on ADHD (April 20 – 23).

As a reminder of SAGA's design:

- enrolled 101 (96 evaluable)
- double-blinded, randomized 1:1; NFC-1/placebo
- following (up to 3-week) wash-out period patients received
    - placebo or
    - AEVI-001
        - in weekly escalating doses from 100mg BID (i.e. twice/day) to 400mg BID based on tolerability to establish optimized dose
        - after the 4th week patients remain on the optimized dose for 2-week maintenance phase
        - followed by 1 week off-drug for safety observation
- **Endpoints**
    - Primary endpoint is change in ADHD-RS (parent assessment) from baseline of AEVI-001 treated patients versus those receiving placebo
    - Key secondary endpoint is change in Clinical Global Impressions (CGI-I) Scale from baseline
    - Additional measures were also assessed including an ADHD-RS responder analysis (pre-specified improvement of ≥ 30%)

SAGA Design



SOURCE: Aevi Genomic Medicine March Presentation

Results:

ADHD-RS (rating scale) is a parent-reported measure consisting 18 questions across two 9-question subscales; inattention and hyperactivity. Each question is scored on a 4-point scale (0=never, 1=rarely, 2=sometimes, 3=often, 4=very often) relative to observance of behaviors. ADHD-RS is a well-established primary endpoint in ADHD clinical trials.

CGI-I (Clinical Global Impressions) is a clinician-scored measure which uses a 7-point scale (1=very much improved…, 7=very much worse) to assess how much a patient's condition improved or worsened (or stayed the same). Treatment response in SAGA was prespecified as CGI-I of 1 (very much improved) or 2 (much improved).

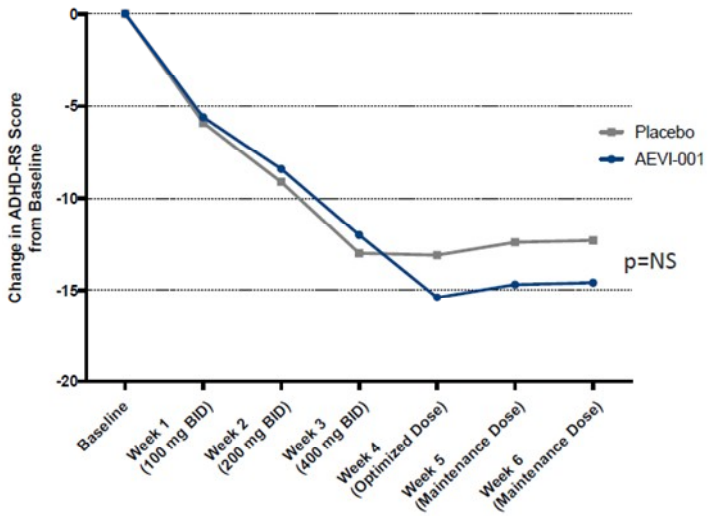
Results showed that the **primary endpoint**, change from baseline in ADHD-RS scores of AEVI-001 patients compared to those receiving placebo, was **not statistically significantly different**. That was the unfortunate news.

On the brighter side, however, is that data-within-the-data **suggests that there was indeed a treatment response.** This includes meeting statistical significance on the CGI-I secondary endpoint as well as on the ADHD-RS responder measure (prespecified as decrease of ADHD-RS score of 30% or more). Additionally, the ADHD-RS inattention subscale (i.e. the 9 questions related to inattention), just barely missed statistical significance (p=0.0515). And, importantly, AEVI-001 was deemed to be well tolerated with no associated serious adverse events.

So while the primary endpoint was not met, we think there was a clear signal of efficacy of AEVI-001 based on the supplementary measures. This combined with a lack of serious safety issues is expected to form the basis of management's anticipated petition to FDA to conduct another mGluR+AHDH study – management outlined their plans on the SAGA call which includes several updates to the trial design, all of which are aimed at improving upon efficacy and meeting the ADHD-RS primary endpoint (which we discuss in detail later).

Additional SAGA results details:

- **ADHD-RS**: While GNMX did not disclose (full data will be at World Congress in late April) the specific ADHD-RS data (i.e. % change in each arm or p-value), they did note that absolute change was approximately 15 in the AEVI-001 arm and ~12 in the placebo group, with separation (although not statistically different) between the two exhibited at the highest (i.e. 400mg) dose (graphic below). Also noteworthy, was that 20% of AEVI-001 subjects had no appreciable reduction (i.e. ≤ 3) in ADHD-RS score (more on this later).

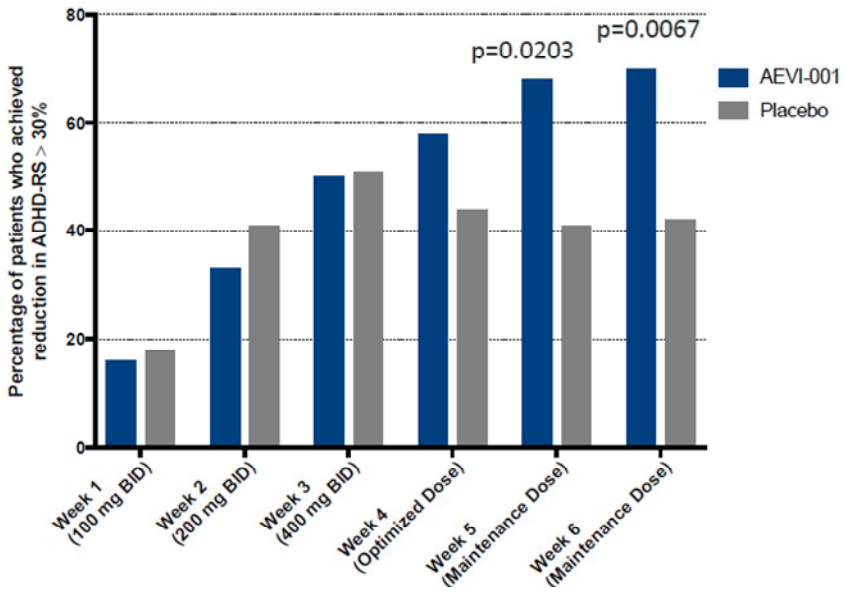


SOURCE: Aevi Genomic Medicine March Presentation

In terms of **ADHD-RS response** (also an oft-utilized measure in ADHD trials), 70% of AEVI-001 subjects showed ADHD-RS decrease of 30% or more, compared to 42% of placebo subjects. The difference **was highly statistically significant** (p=0.0067) at week-6 and also statistically significant at week-5 (p=0.0203). Interestingly, the **absolute reduction in ADHD-RS among the 70% of AVEI-001 subjects that responded was over 19 points but was "almost nothing" (per management on the call) among the 30% that did not respond**. GNMX's game plan is to (genetically) identify and weed-out this 30% in a planned pediatric study through further refinement of a biomarker. Given the huge discrepancy in reduction of ADHD-RS between responders and non-responders, if a biomarker can indeed 'identify' and eliminate non-responders, we think successful development of it could be a significant near-term win for GNMX as it

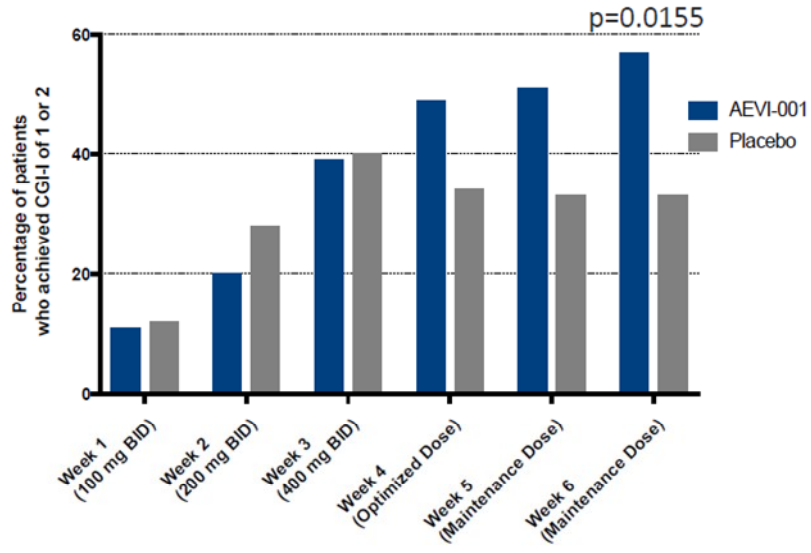
could be an initial sign of the likelihood of a follow-on mGluR+ADHD study's ultimate success. **That (i.e. development of a refined biomarker eliminating non-responders), in our opinion, is a pre-study milestone that investors should be closely following.**

Additionally, as the graphic bellow illustrates, there appears to be an **obvious dose response with a consistent increase in ADHD-RS response as the dose is titrated higher over the course of the four-week treatment period** and then appears to (roughly) stabilize during the two week maintenance phase. And while the treatment arm exhibited consistently greater response as the dose was increased, there was not a similar trend among the placebo arm – in fact placebo trended lower after week 3 of treatment through the end of the study.



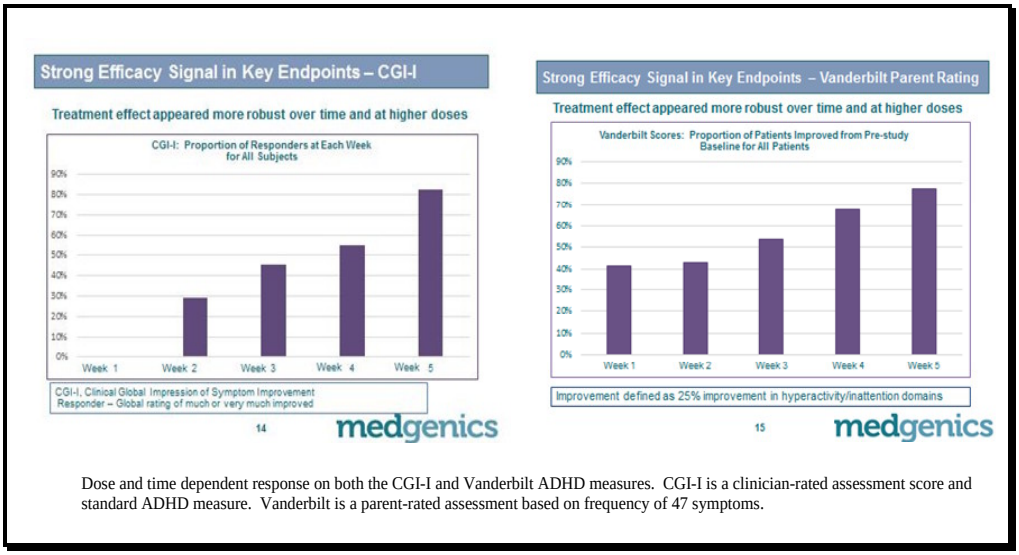
Aevi Genomic Medicine March Presentation

- **CGI-I:** Relative to CGI, also a well-established ADHD-related measure, 57% of AEVI-001 subjects and 33% of those on placebo achieved CGI-I scores or 1 or 2 – the difference **was statistically significant** (p=0.0155). The CGI-I response chart (below) is very similar to that of the ADHD-RS response with consistent improvement in CGI-I response as the dose is increased while the placebo arm falls off after week 3 of treatment.



SOURCE: Aevi Genomic Medicine March Presentation

We also remind investors that a similar response was seen in the GREAT study. In GREAT, treatment was dose-escalating from 50mg (BID) to a maximum of 400mg (BID). Dose was escalated weekly. Results showed a **statistically significant dose and time-dependent response** on CGI-I (as well as on Vanderbilt, the other efficacy-related endpoint) and approximately 80% of AEVI-001 patients responded based on both CGI-I and Vanderbilt. See chart below.



Dose and time dependent response on both the CGI-I and Vanderbilt ADHD measures. CGI-I is a clinician-rated assessment score and standard ADHD measure. Vanderbilt is a parent-rated assessment based on frequency of 47 symptoms.

- **Safety**: **no meaningful safety issues** including no serious adverse events in either the treatment or placebo arm. Noteworthy is that **88% of AEVI-001 patients were able to titrate up to the highest dose** (i.e. 400mg BID). The **lack of significant safety concerns of AEVI-001** in this, as well as prior, studies (including dose as high as 800mg once/day), should lend itself to potentially increasing the dose above 400mg BID and/or extending the duration of the treatment period beyond four weeks in order to improve upon the efficacy seen in SAGA.

	AEVI-001	Placebo
Number of subjects with ≥1 AE	33/47 (70.2%)	28/50 (56%)
AEs > 5%		
Weight gain	7 (14.9%)	2 (4%)
Fatigue	7 (14.9%)	3 (6%)
Headache	4 (8.5%)	5 (10%)
Nausea	3 (6.4%)	4 (8%)

SOURCE Aevi Genomic Medicine March Presentation

Down But Not Out: GNMX Hopes To Improve Efficacy w/ Refined Design Pediatric Study

Despite not meeting the primary endpoint, statistical significance on CGI-I and ADHD-RS response as well as what appears to be a clear dose response on both of these measures (and lack of similar placebo response over time) **suggests a clear efficacy signal** of AEVI-001 in mGluR+ ADHD subjects. Management expects to forge ahead and will present to FDA a modified trial design and updated biomarker aimed at improving upon efficacy and the chances of meeting the ADHD-RS primary endpoint.

While GNMX still needs to meet with FDA to discuss specifics of another study, the following are currently being considered by management:

- **Increase dose and/or treatment duration:** given the safety profile of AEVI-001, the fact that is has been safely used in over 1,000 patients (for as long as 12 months) and that 88% of AEVI patients titrated up to the highest dose in SAGA, could provide a compelling case to increase dose beyond 400mg BID.

Important to understand is that the relatively short treatment period (i.e. four weeks) of ADHD studies largely **reflects concerns of side effects of stimulant drugs** (such as cardiovascular risks, sleeplessness and anxiety) - despite **AEVI-001 not being associated with these potentially serious side effects**, SAGA's design was nonetheless similar to that of previous stimulant studies. AEVI-001's evidentiary safety profile may pave the way for FDA to accept a longer treatment duration and/or higher dose. Higher dose or longer duration could further improve upon the dose response witnessed in both ADHD-RS and CGI-I.

- **Pediatric, as opposed to adolescent, study**: SAGA was an adolescent study (12 – 17 years). There could be several advantages relative to improving upon efficacy by going to a pediatric study (6 – 12 years) including that **mGluR network mutations are more prevalent in pediatric population** (~26%) as compared to adolescents (~20%) and **inattentiveness is more pronounced in younger ADHD subjects**. As noted earlier, the ADHD-RS inattention subscale just barely missed statistical significance in SAGA – since a pediatric study should further enrich for inattention, presumably it would improve upon the chances of AEVI-001 showing statistical significance on total ADHD-RS score. And, finally, as management indicated on the call, protocol compliance (including dosing, particularly BID dosing) is more likely to suffer among adolescent clinical trials as compared to pediatric trials given the typical greater of oversight by parents of younger children – this can result in a **greater placebo response in adolescent, as compared to pediatric, studies.**

- **Refined biomarker**: approximately 30% of patients in the treatment group showed no meaningful response to AEVI-001 therapy. GNMX hopes to genetically identify what caused the non-response in these patients and refine their biomarker in order to be able to more effectively enroll patients most likely to benefit from AEVI-001 therapy. If and when they **successfully refine the biomarker** to weed out these patients, it would likely be a major milestones in our opinion as it could **add significant confidence to the likelihood of a follow-on phase II study demonstrating statistical significance** on the ADHD-RS endpoint. As such, biomarker development is on our list of items that we will be eagerly awaiting to updates about.

FDA Meeting: Increasing the dose and/or treatment duration will mostly hinge on an acceptable safety profile. GNMX recently submitted the toxicology data to FDA, expects to submit the pharmacokinetic data in Q2 and hopes to meet with the agency by mid-2017 to discuss design (including higher dose, longer treatment duration, refined biomarker) of a follow-on study. **Results of that meeting will obviously also be highly anticipated.**

In parallel GNMX expects;

- AEVI-001: to initiate signal finding studies in autism spectrum disorder (ASD) and pediatric anxiety disorder, both of which have also been associated with mutations in the mGluR network

- Anti-LIGHT (AEVI-002): to announce data from the ongoing phase I/II signal finding study in Severe Pediatric Onset IBD in 2H 2017

FINANCIAL MODEL

Aevi Genomic Medicine, Inc.

	2016 A	Q1E	Q2E	Q3E	Q4E	2017 E	2018 E	2019 E
Total Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Margin	-	-	-	-	-	-	-	-
SG&A	$13,523.0	$3,841.0	$3,754.0	$3,668.0	$3,895.0	$15,158.0	$15,925.0	$16,324.0
% SG&A	-	-	-	-	-	-	-	
R&D, net of grants	$28,356.0	$6,684.0	$7,645.0	$7,808.0	$7,827.0	$29,964.0	$28,674.0	$27,795.0
% R&D	-	-	-	-	-	-	-	
Operating Income	($41,879.0)	($10,525.0)	($11,399.0)	($11,476.0)	($11,722.0)	($45,122.0)	($44,599.0)	($44,119.0)
Operating Margin	-	-	-	-	-	-		
Financial expense, net	($9.0)	$2.0	($4.0)	$7.0	$4.0	$9.0	$0.0	$0.0
Total Other Income (Expense)	($9.0)	$2.0	($4.0)	$7.0	$4.0	$9.0	$0.0	$0.0
Pre-Tax Income	($41,888.0)	($10,523.0)	($11,403.0)	($11,469.0)	($11,718.0)	($45,113.0)	($44,599.0)	($44,119.0)
Tax expense (benefit)	$16.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($41,904.0)	($10,523.0)	($11,403.0)	($11,469.0)	($11,718.0)	($45,113.0)	($44,599.0)	($44,119.0)
YOY Growth	*10.3%*	*-72.3%*	*2.3%*	*-2.0%*	*10.9%*	*7.7%*	*-1.1%*	*-1.1%*
Net Margin	-	-	-	-	-	-	-	*#DIV/0!*
EPS	($1.19)	($0.28)	($0.30)	($0.29)	($0.29)	($1.10)	($1.04)	($0.96)
YOY Growth	*-21.3%*	*-15.6%*	*-15.7%*	*2.2%*	*5.4%*	*-7.7%*	*-5.7%*	*-7.5%*
Diluted Shares O/S	35,162	37,120	37,400	39,540	40,000	41,000	43,000	46,000

Brian Marckx, CFA

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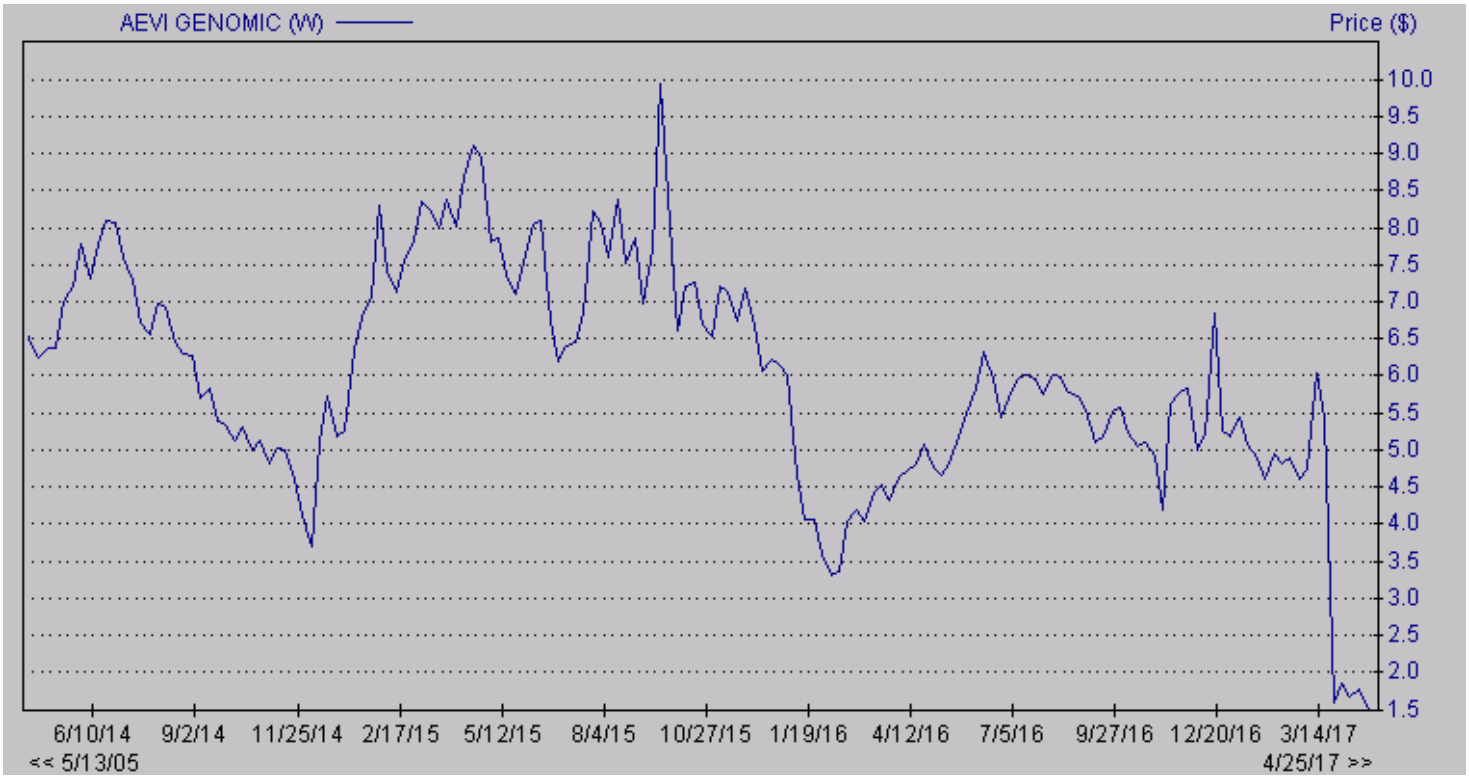

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