Zacks Small-Cap Research

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Aevi Genomic Medicine (GNMX-NASDAQ)

GNMX: New ADHD, ASD Studies Kicking Off. Data Mid-2018 Next Value Inflection Point?

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 elongation of the AEVI-001 ADHD program, resulting in a price target of $7/share. This is subject to further updating based in part positive progress in the new mGluR+ADHD (and ASD) study.

Current Price (08/25/17)	$1.29
Valuation	**$7.00**

OUTLOOK

$28M equity raise should provide runway until readout from new ADHD study - which could represent the next potential value-inflection point. Relative to the operational update, study designs and timelines were unveiled for the phase II mGluR/CNTN4+ADHD study and for a proof-of-concept II CNTN4+ASD study. The current game-plan includes somewhat of a parallel approach with the AEVI-001 program (i.e. mGluR+ network) whereby GNMX will forge ahead with trials in both ADHD (looking at all 9 genes of interest, but also parsed for just CNTN4) and ASD (just CNTN4). Management noted that this parallel approach should provide "optionality" in terms of deciding which program to pursue first in pivotal studies and (hopefully) eventual commercialization.

Management also provided an update on the anti-LIGHT phase I study in pediatric Crohn's, which has suffered from ongoing delays due to recruitment headwinds but which could finally start to bring initial patients in. If all goes to plan, initial data from the POC anti-LIGHT study could be available later this year and read-out from AEVI-001 in ADHD could happen by mid-2018.

SUMMARY DATA

52-Week High	**$6.89**
52-Week Low	**$0.98**
One-Year Return (%)	**-78.13**
Beta	**0.54**
Average Daily Volume (sh)	**288,770**
Shares Outstanding (mil)	**37**
Market Capitalization ($mil)	**$48**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**28**
Insider Ownership (%)	**25**
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 A	0 A	0 E	0 E	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	-$0.29 A	-$0.22 A	-$0.29 E	-$0.22 E	-$0.99 E
2018					-$0.85 E
2018					-$0.88 E

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

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Q2 Results / Update: New mGluR+ ADHD, ASD Studies Kick-Off, Data ~Mid-2018

Aevi reported financial results and provided an update on their various clinical programs.

Relative to the financials, operating loss was $8.0M, down considerably from both the year-earlier ($11.7M) and quarter-earlier ($10.9M) comparable periods. EPS was ($0.22), compared to ($0.35) in Q2 2016 and ($0.29) in Q1 of this year.

Cash used in operating activities was $7.9M and $18.5M ($7.2M and $17.1M, ex-changes in working capital) in Q2 and 1H 2017, respectively. Management anticipates that the quarter-end cash balance, of $21.4M, is sufficient to fund operations until ~mid-2018, at which point they also expect to have reported topline data from the recently initiated ADHD/CNTN4+ phase II trial and initial data from a too-be-initiated proof-of-concept study for their anti-LIGHT candidate in pediatric Crohn's.

$28M equity raise should provide runway until readout from new ADHD study - which could represent the next potential value-inflection point.

However, the recently-announced $28M (gross) equity raise, if consummated, **would extend the cash runway into 1H 2019.** Subject to shareholder approval, GNMX will issue 22.2M common shares (via PIPE) at $1.26/share. The deal is expected to close in Q4 of this year. Investors, of which CHOP was the lead, will also receive 18% warrant coverage ($2.84 strike, 5 years). The deal is priced at about a 3% premium to the average prior-10-day trading price. CHOP will commit an additional $5M by 6/30/18 if certain conditions are met.

Relative to the operational update, study designs and timelines were unveiled for the phase II mGluR/CNTN4+ADHD study and for a proof-of-concept II CNTN4+ASD study. The current game-plan includes somewhat of a parallel approach with the AEVI-001 program (i.e. mGluR+ network) whereby GNMX will forge ahead with trials in both ADHD (looking at all 9 genes of interest, but also parsed for just CNTN4) and ASD (just CNTN4). Management noted that this parallel approach should provide "optionality" in terms of deciding which program to pursue first in pivotal studies and (hopefully) eventual commercialization.

Management also provided an update on the anti-LIGHT phase I study in pediatric Crohn's, which has suffered from ongoing delays due to recruitment headwinds but which could finally start to bring initial patients in. If all goes to plan, initial data from the POC anti-LIGHT study could be available later this year and read-out from AEVI-001 in ADHD could happen by mid-2018.

Upcoming Milestones:

Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3
AEVI-001	mGluR+ Genetic Subset ADHD (pediatric, age 6-17)				Top-Line Data Mid-2018
	CNTN4 in Autism Spectrum Disorder				Plan to Initiate Q1 2018
AEVI-002 (anti-LIGHT mAb)	Severe Pediatric Onset Crohn's Disease				Initial Data YE 2017

SOURCE: Aevi Genomic

AEVI-001 (mGluR+) Update and Next Steps

ADHD: As a reminder, in March GNMX announced that while secondary data was positive, SAGA (i.e. the phase II mGluR+ ADHD study) failed to meet the primary endpoint. Then in April the company announced additional data from SAGA which showed that ADHD patients which had mutations to nine of the 273 genes in the mGluR network showed a clinically and statistically significant response to AEVI-001 based on the primary and secondary endpoints. See below for full details.

In May GNMX announced plans for a **new phase II study** (dubbed "ASCEND") which will enrich for this high-responder population – that is, for mutations to CNTN4 and eight specific (still undisclosed) GRMs and neurodevelopmental genes. The study design is very similar to that of SAGA, with certain exceptions in that ASCEND will; include younger subjects and have two distinct treatment cohorts. On the Q2 call (which we missed due to a timing conflict) on August 8th management provided additional details of the study design;

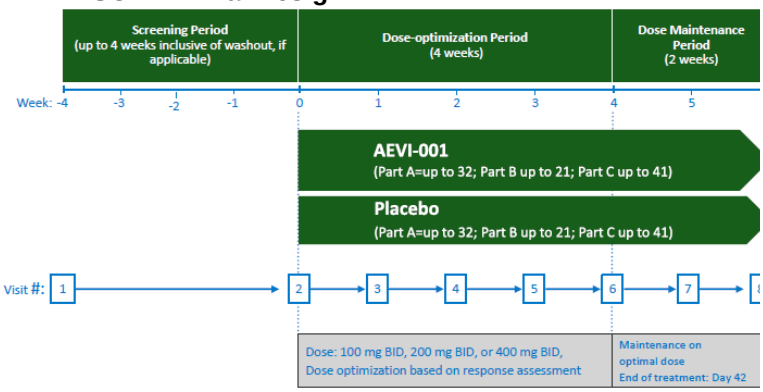
- Multi-center (~20) randomized (1:1), placebo-controlled
- Ages 6 – 17 (i.e. younger population should reduce placebo response) is expected to make up ~75% of total enrollment
- Enrollment will be in sequential stages with CNTN4 patients (N = ~32) enrolling first followed by the 8-gene cohort (N = ~21). A third group (N = ~41), with no genetic mutation, could follow (depending on guidance from FDA)
- Treatment protocol (similar to SAGA): 4-week dose optimization (100-400mg), followed by 2-week dose maintenance
- Endpoints (similar to SAGA); primary: ADHD-RS-5, secondary: CGI-I

The staged adaptive design allows for both super-enrichment (our word) as well as for assessing response on the broader 9-gene population. Given the particularly robust response from CNTN4 patients in SAGA, this could be the low-hanging fruit in terms demonstrating clinically significant response in this follow-on study, although also represents about 50% of the prevalence among the general ADHD population as compared to the full 9-gene subset. Clearly, an important objective is to assess clinically significant response within a broader population (i.e. 9 genes), however, given that it represents a significantly larger potential commercial market as compared to the CNTN4+ population. This follow-on study should provide additional insight in that regard. As a reminder, the 9-gene subset data from SAGA was quite compelling - demonstrating statistical significance on the primary and key secondary endpoints.

In order to facilitate enrollment Aevi is incorporating prescreening methods and utilizing a several-pronged approach to recruit patients. **Patient screening is expected to commence in Q3 (i.e. current quarter) - while this is a slight delay from prior expectations, the company still hopes to have topline data (from at least the CNTN4 cohort) by mid-2018.**

ASCEND Trial Design

- Multi-center (20 US sites)
- Inclusion criteria:
  - 6-17 years of age
  - ADHD-RS-5 ≥ 28
  - Positive for CNTN4 (A), 8 gene subset (B) or non-mutated (C)
- Primary endpoint: ADHD-RS-5
- Key secondary endpoint: CGI-I
- 1:1 randomization
- Placebo-controlled
- Dose optimization: 100-400 mg BID



SOURCE: Aevi Genomic Medicine

We continue to like the chances for success with the study redesign. For one, while SAGA did not meet the primary endpoint, the data was nonetheless reasonably strong. 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 ASCEND effectively begins with a baseline that barely missed statistically significance and enriches for the highest responders.

As a reminder, SAGA showed that among those patients (n=42: 18 AEVI, 24 placebo) which had copy-number variation (i.e. mutations) to one of these nine genes of interest 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. The response appeared to be even more robust among those patients (n=18: 6 AEVI, 12 placebo) with mutations to CNTN4.

We also think the pediatric population should further enhance the chances for success. 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. 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, 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.

Autism Spectrum Disorder: CNTN4 mutations have also been associated with more severe phenotypes and other disorders including Autism Spectrum Disorder. Management referenced study data which has indicated 65% - 85% of individuals with ASD also have ADHD. Using the CHOP database, Aevi found that approximately 6% - 8% of ASD patients have the CNTN4+ mutation. The company is now committed towards moving forward with an ASD program as well. Program specifics are still being worked out but initial thoughts are to start with a an open label dose-ranging (100 - 400mg) study in young (i.e. 6 - 17 years) CNTN4+ patients with randomized-withdrawal-to-placebo design (affording initial comparator data). Proposed endpoints would include clinically relevant ASD measures (specifics still being determined) as well as ADHD scales, such as ADHD-RS and CGI-I (SAGA and ASCEND endpoints). Aevi hopes to have the study protocol finalized for initiation in Q1 2018.

AEVI-001 Subsequent Steps: Aevi hopes to use read-out of ASCEND and the ASD proof-of-concept study to help in determining subsequent steps forward for the AEVI-001 program. While the data may be the most substantive factor, other considerations including financial resources, time-to-market and near-term opportunity may also be significant considerations. The much smaller population of pediatric ASD/CNTN4+ (~75k U.S.) versus that of ADHD/9-gene-mGluR+ (~600k U.S.) or ADHD/CNTN4+ (~300k U.S.) (all our estimates), relative symptom-severity of ASD and lack of alternative therapies, could mean an ASD (orphan) indication may be a particularly attractive pursuit to lead with. But, we should know more about potential subsequent steps forward when both of these studies read out.

Anti-LIGHT Severe Pediatric Crohn's Phase 1/2 Signal Finding Study

While the Anti-LIGHT program in pediatric Crohn's (AEVI-002) has been plagued by persistent delays due to extreme difficulties in recruiting and enrolling patients, screening at the primary site (CHOP IBD center) finally kicked off in late June. Two additional sites have been identified in order to facilitate enrollment. Management also indicated that they are also considering modifying some of the enrollment criteria (in particular, not restricting inclusion only to early-onset), if needed to aid recruitment.

As a reminder, these are patients with severe pediatric onset IBD with DcR3 loss-of-function mutations (10% - 15% of pediatric onset Crohn's patients have this DcR3 mutation) and which have failed anti-TNF alpha therapy. Anticipated to enroll 8 to 12 patients over the age of 18. Clinical endpoints are endoscopic evaluation (i.e. healing) and the Pediatric Crohn's Disease Index. Aevi hopes to have initial data in the Q4 '17 or Q1 '18 (depending on pace of enrollment) timeframe, at which point they will decide whether to continue development (via their license with Kirin).

22q11.2 Deletion Syndrome

Phase I/II study commenced in October 2016 although enrollment was difficult due to the characteristically fragile nature of patients with this disorder. Aevi notes in their Q2 10-Q that only two patients ultimately enrolled. While it is not clear if they will pursue this program in the future, we think it is likely (at least) back-burnered for now.

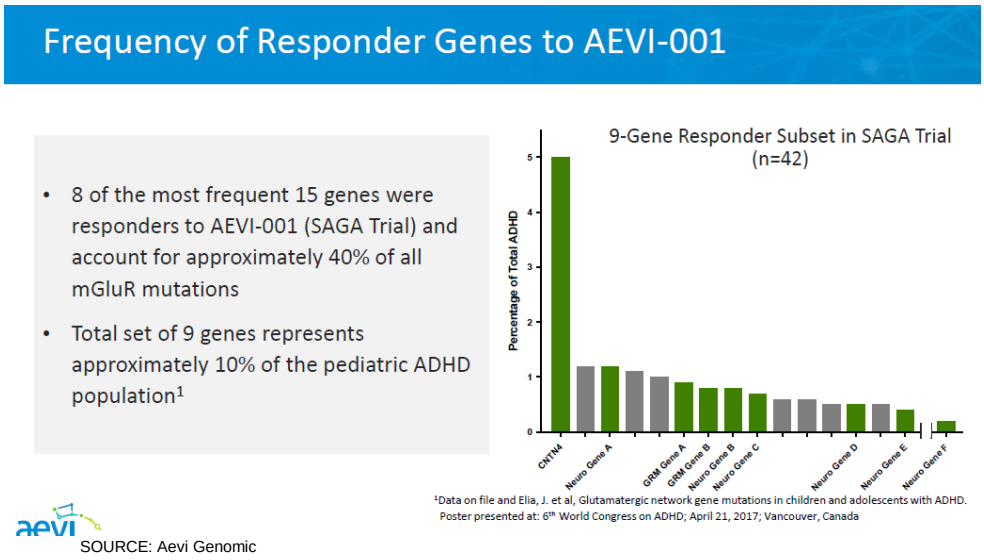
AEVI-001 Refresher

Post-Hoc SAGA Analysis Finds Nine Genes Associated With Potent Response To AEVI-001
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, which is considered a clinical response). 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 meant a study-redesign to better enrich for AEVI-001 responders is necessary.

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.

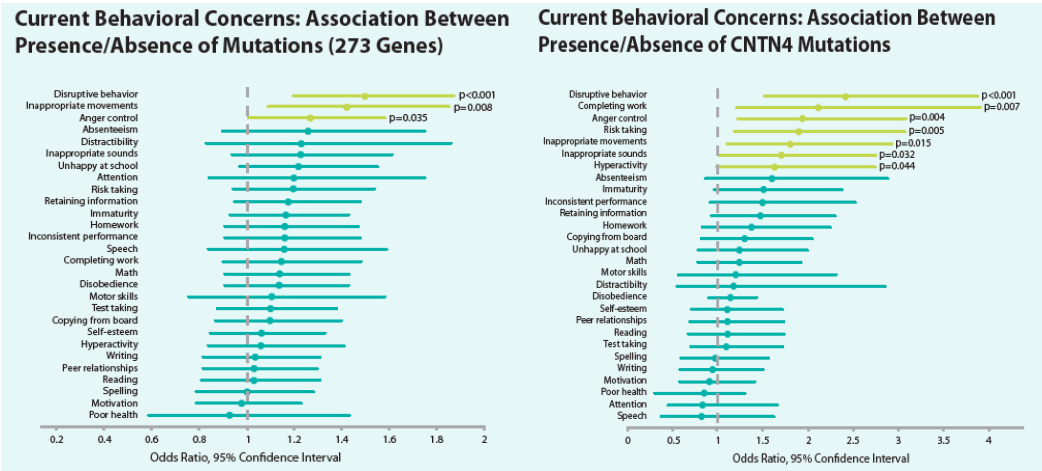
Specifically, patients (n=42: 18 AEVI, 24 placebo) which had copy-number variation (i.e. mutations) to one of nine genes (the identity of only one was revealed as GNMX works on IP) which include "certain glutamate metabotropic receptors (GRM) and neurodevelopmental genes" had a much higher and statistically 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.



SOURCE: Aevi Genomic

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 appear to 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

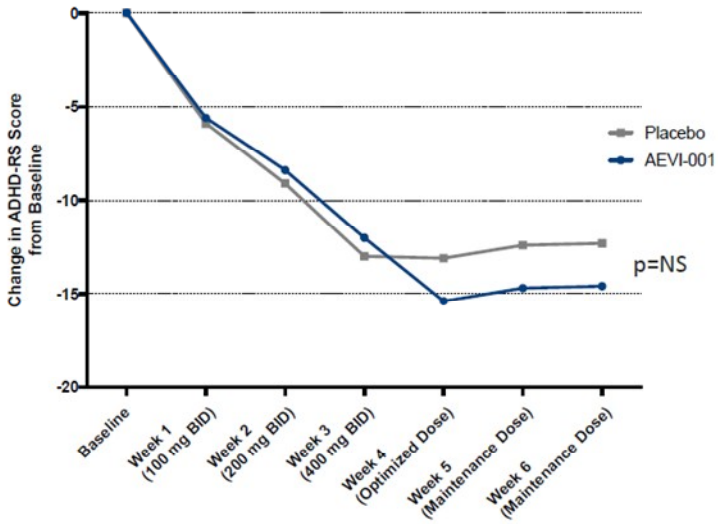
ADHD-RS:

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 and is also the primary endpoint in ASCEND.

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**

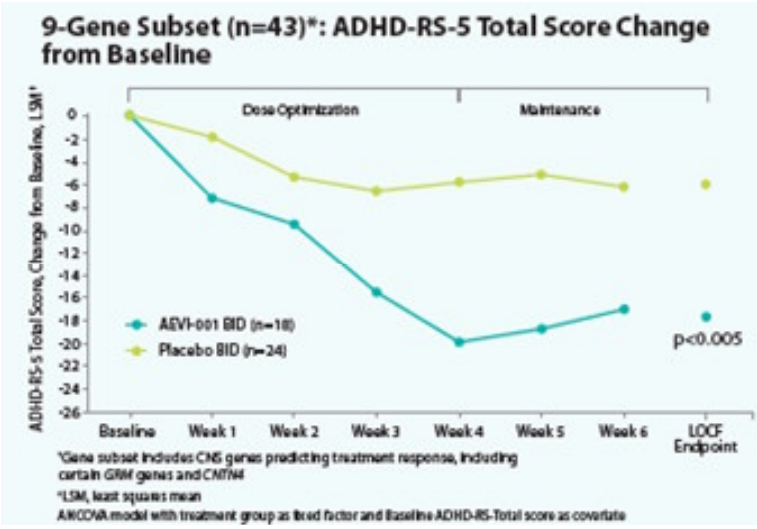
was over 19 points but was "almost nothing" (per management on the April call) among the 30% that did not respond.

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.

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** ($p < 0.005$). Among the patients in this 9-gene subset, 43% had mutation to CNTN4, 14% to one of the GRM's and 42% to neurodevelopment genes.

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 ($p < 0.0001$).

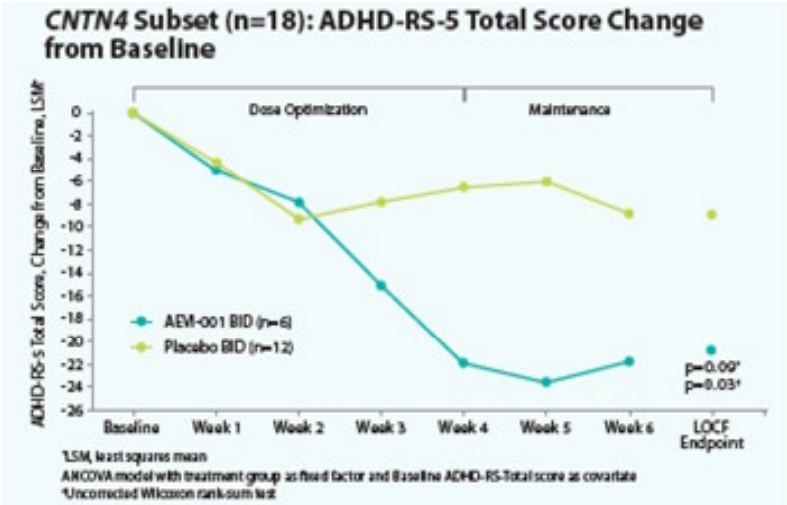


SOURCE Aevi Genomic Medicine. Poster, World Congress on ADHD

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 and will also be a secondary endpoint in ASCEND. 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). Clinical 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. Results of ASCEND, the follow-on phase II study, will hopefully provide much more definitive evidence of this. The design of ASCEND, while similar to SAGA in terms of endpoints and treatment protocol, includes some modifications aimed at improving upon efficacy and meeting the ADHD-RS primary endpoint.

ASCEND: New Phase II mGluR+Genetic Subset ADHD Study

The study design is very similar to that of SAGA, with certain exceptions in that ASCEND will; include younger subjects and have two distinct treatment cohorts. On the Q2 call on August 8th management provided additional details of the study design;

- Multi-center (~20) randomized (1:1), placebo-controlled
- Ages 6 – 17 (i.e. younger population should reduce placebo response) is expected to make up ~75% of total enrollment
- Enrollment will be in sequential stages with CNTN4 patients (N = ~32) enrolling first followed by the 8-gene cohort (N = ~21). A third group (N = ~41), with no genetic mutation, could follow (depending on guidance from FDA)
- Treatment protocol (similar to SAGA): 4-week dose optimization (100-400mg), followed by 2-week dose maintenance
- Endpoints (similar to SAGA); primary: ADHD-RS-5, secondary: CGI-I

The staged adaptive design allows for both super-enrichment (our word) as well as for assessing response on the broader 9-gene population. Given the particularly robust response from CNTN4 patients (again, more detail below) in SAGA, this could be the low-hanging fruit in terms demonstrating clinically significant response in this follow-on study, although also represents about 50% of the prevalence among the general ADHD population as compared to the full 9-gene subset. Clearly, an important objective is to assess clinically significant response within a broader population (i.e. 9 genes), however, given that it represents a significantly larger potential commercial market as compared to the CNTN4+ population. This follow-on study should provide additional insight in that regard. As a reminder, the 9-gene subset data from SAGA was quite compelling - demonstrating statistical significance on the primary and key secondary endpoints.

In order to facilitate enrollment Aevi is incorporating prescreening methods and utilizing a several-pronged approach to recruit patients. Patient screening is expected to commence in Q3 (i.e. current quarter) - while this is a slight delay from prior expectations, the company still hopes to have topline data (from at least the CNTN4

Market Size Reduced (vs. SAGA target population), But Still Substantial

And while enriching for genetic subsets could reduce the potential target ADHD population of AEVI-001 from the initial ~20% (i.e. representative of the initial SAGA population of the entire 273 mGluR gene network) down

to 5% (i.e. CNTN4 only) or 10% (i.e. 9-genes), this still represents a U.S. pediatric/adolescent ADHD population of ~300k – 600k - a potential market opportunity which we calculate to be ~$600M to $1.2B – and with premium pricing it is possible the market could be two to three times this. 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.

And GNMX has potentially additional levers to further improve response to AEVI-001 in future clinical studies including potentially:

- **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**. 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, 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.** The new Phase II 9-gene study will enroll ages 6 – 17 which is expected to reduce placebo response as compared to SAGA.

- **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 further refine their biomarker. This could play a role in future studies.

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. ASCEND, which could have topline data by mid-2018, was designed to improve upon efficacy and increase the chance of meeting the ADHD-RS primary endpoint.

The staged adaptive design allows for both super-enrichment (our word) as well as for assessing response on the broader 9-gene population. Given the particularly robust response from CNTN4 patients in SAGA, this could be the low-hanging fruit in terms demonstrating clinically significant response in this follow-on study, although also represents about 50% of the prevalence among the general ADHD population as compared to the full 9-gene subset. Clearly, an important objective is to assess clinically significant response within a broader population (i.e. 9 genes), however, given that it represents a significantly larger potential commercial market as compared to the CNTN4+ population. This follow-on study should provide additional insight in that regard.

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). We will update our valuation based on development progress - success in ASCEND (and/or AEVI-001 in ASD) would likely increase the probability of eventual approval of AEVI-001 and increase the calculated value of GNMX.

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

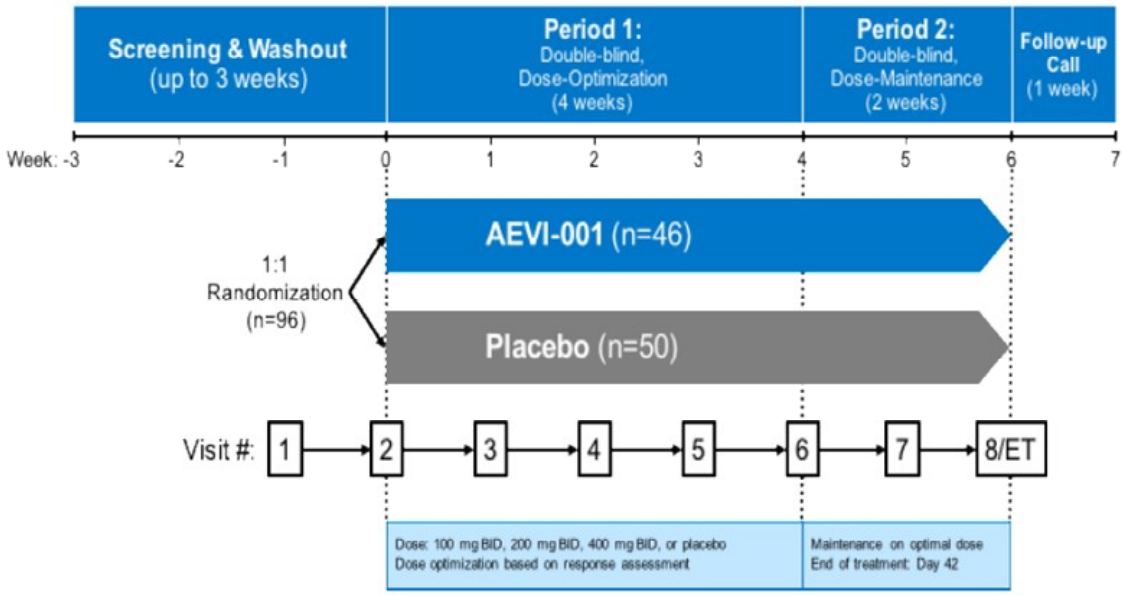
SAGA Results: *Primary Endpoint Missed But Data-Within-The-Data Suggest Reasons To Remain Optimistic*

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).

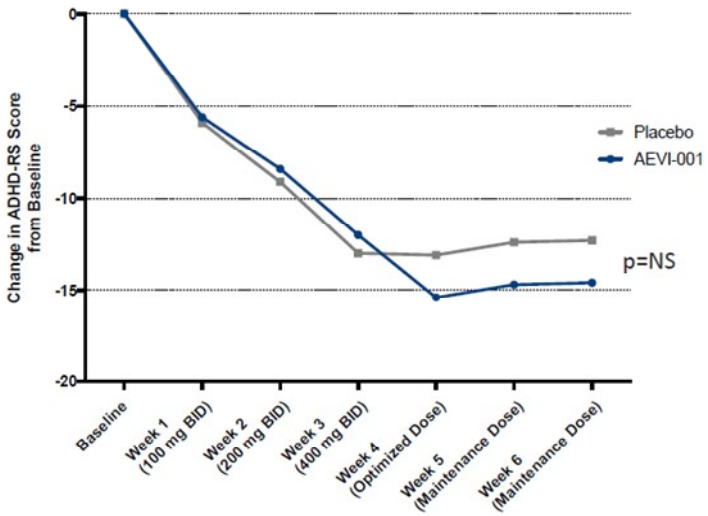
Results showed that the **primary endpoint**, change from baseline in ADHD-RS scores of AEVI-001 patients compared to those receiving placebo, was **not statistically significantly different**. That was the unfortunate news.

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).

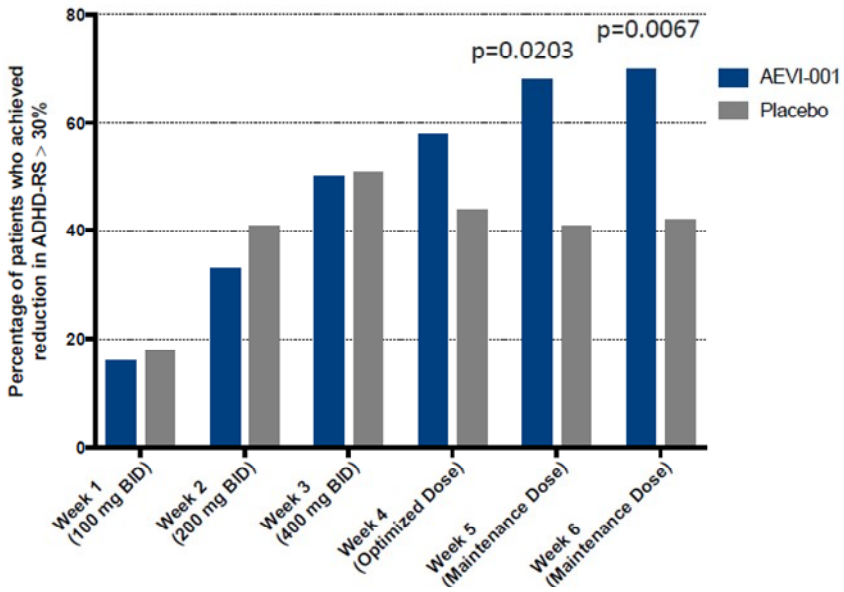


SOURCE: Aevi Genomic Medicine March Presentation

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

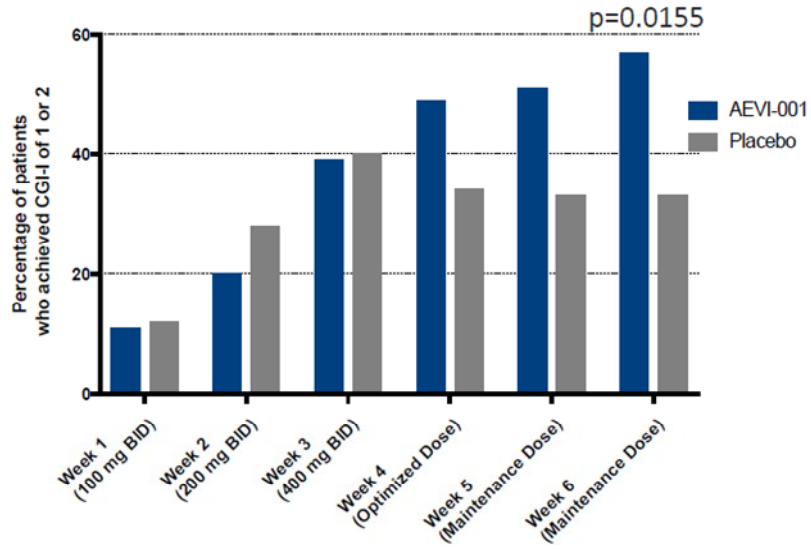
could be an initial sign of the likelihood of a follow-on mGluR+ADHD study's ultimate success. **That (i.e. development of a refined biomarker eliminating non-responders), in our opinion, is a pre-study milestone that investors should be closely following.**

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.



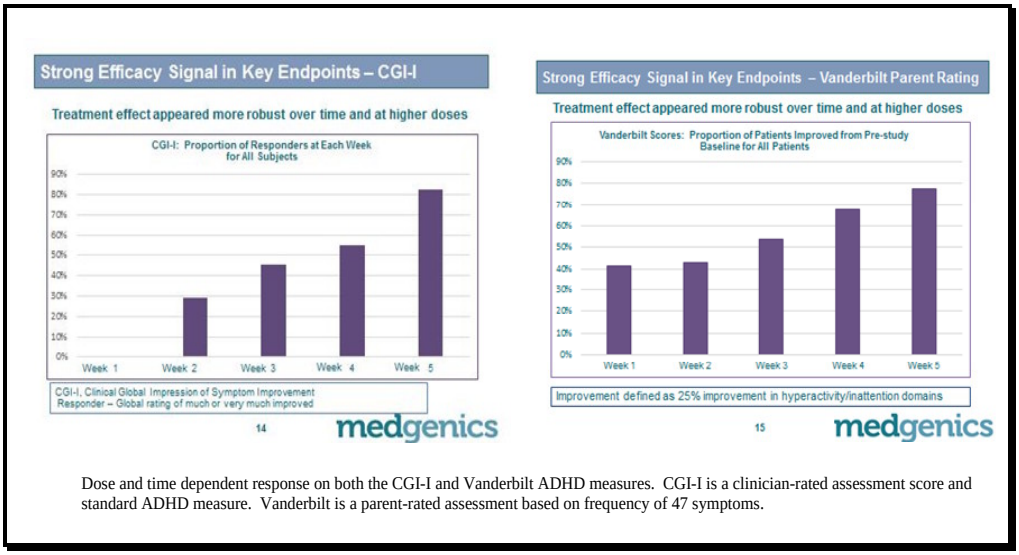
Aevi Genomic Medicine March Presentation

- **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

FINANCIAL MODEL

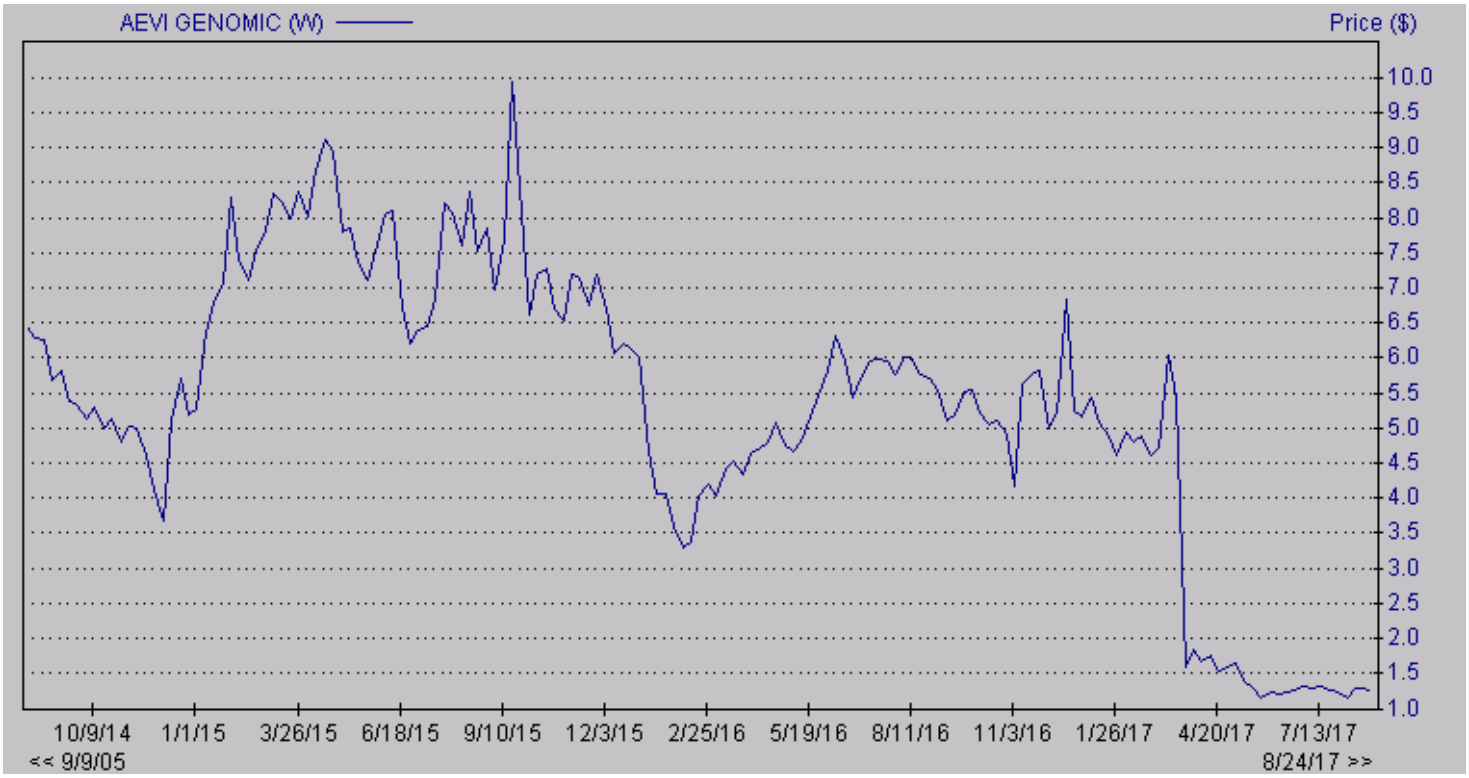
Aevi Genomic Medicine, Inc.

	2016 A	Q1A	Q2A	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	$2,988.0	$2,369.0	$3,174.0	$3,408.0	$11,939.0	$15,444.0	$16,121.0
% SG&A	-	-	-	-	-	-	-	
R&D, net of grants	$28,356.0	$7,947.0	$5,667.0	$7,542.0	$7,440.0	$28,596.0	$35,472.0	$39,556.0
% R&D	-	-	-	-	-	-	-	
Operating Income	($41,879.0)	($10,935.0)	($8,036.0)	($10,716.0)	($10,848.0)	($40,535.0)	($50,916.0)	($55,677.0)
Operating Margin	-	-	-	-	-	-		
Financial expense, net	($9.0)	$18.0	$3.0	$2.0	$10.0	$33.0	$15.0	$4.0
Total Other Income (Expense)	($9.0)	$18.0	$3.0	$2.0	$10.0	$33.0	$15.0	$4.0
Pre-Tax Income	($41,888.0)	($10,917.0)	($8,033.0)	($10,714.0)	($10,838.0)	($40,502.0)	($50,901.0)	($55,673.0)
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)	($10,917.0)	($8,033.0)	($10,714.0)	($10,838.0)	($40,502.0)	($50,901.0)	($55,673.0)
YOY Growth	*10.3%*	*-71.3%*	*-27.9%*	*-8.5%*	*2.5%*	*-3.3%*	*25.7%*	*9.4%*
Net Margin	-	-	-	-	-	-	-	*#DIV/0!*
EPS	($1.19)	($0.29)	($0.22)	($0.29)	($0.22)	($0.99)	($0.85)	($0.88)
YOY Growth	*-21.3%*	*-12.6%*	*-46.8%*	*1.6%*	*-0.3%*	*-17.1%*	*-14.1%*	*4.2%*
Diluted Shares O/S	35,162	37,108	37,110	37,110	48,221	41,000	60,000	63,000

Brian Marckx, CFA

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