June 19, 2018

Zacks Small-Cap Research

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Aevi Genomic Medicine (GNMX-NASDAQ)

GNMX: ASCEND Enrolling to 64 In Order To "Ensure…Robust Treatment Effect"

Given the early stage of GNMX we continue to value the company using DCF model based on annual revenue of an "average" orphan drug. Our valuation will continue to be highly influenced by development progress as well as value of the pipeline as a whole.

Current Price (06/19/18)	$1.20
Valuation	**$6.00**

OUTLOOK

Indicating that after an interim look at the placebo arm, the decision was made to continue to enroll to n=64 in order to "ensure sufficient power to detect a robust treatment effect". In other words, in order to further reduce the risk of placebo effect. Importantly, this decision was based solely on a statistically-derived estimate of placebo response based solely on the placebo arm (i.e. no inferences relative to effectiveness, or lack thereof, of AEVI-001 should be drawn by the decision to increase enrollment). As a reminder, greater than expected placebo effect in SAGA diluted treatment delta in that study. ASCEND was designed to reduce placebo noise – specifically, it includes only high-responders (i.e. those with mutations to nine specific genes in the mGluR network that showed a clinically and statistically significant response to AEVI-001 in SAGA). In addition, ~75% of ASCEND participants are expected to be ages 6 – 12 - this younger population should further enhance separation as compared to SAGA (ages 12 – 17). We continue to like the chances for success of ASCEND.

SUMMARY DATA

52-Week High	**$2.65**
52-Week Low	**$1.01**
One-Year Return (%)	**-12.50**
Beta	**1.12**
Average Daily Volume (sh)	**104,258**
Shares Outstanding (mil)	**59**
Market Capitalization ($mil)	**$71**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**23**
Insider Ownership (%)	**12**
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 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in '000s of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	0 A	0 A	0 A	0 A	0 A
2018	0 A	0 E	0 E	0 E	0 E
2019					0 E
2020					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.29 A	-$0.22 A	-$0.23 A	-$0.13 A	-$0.83 A
2018	-$0.15 A	-$0.15 E	-$0.15 E	-$0.14 E	-$0.59 E
2019					-$0.57 E
2020					-$0.51 E

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

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ASCEND Will Enroll To N=64, (consistent with initial trial design):

Last week Aevi announced that they will go ahead and continue to enroll ASCEND to 64 patients, which was an option within the initial trial design. ASCEND was designed to enroll in sequential stages with the 9-gene cohort (subsequently modified to 8 genes) enrolling first ("part A") followed by those with no genetic mutation ("part B"). Both parts are randomized 1:1 versus control. The study was designed with anticipated enrollment of up to n=64 in part A and n=42 in part B.

Indicating that after an interim look at the placebo arm, the decision was made to continue to enroll to n=64 in order to "ensure sufficient power to detect a robust treatment effect". In other words, in order to further reduce the risk of placebo effect. Importantly, this decision was based solely on a statistically-derived estimate of placebo response based solely on the placebo arm (i.e. no inferences relative to effectiveness, or lack thereof, of AEVI-001 should be drawn by the decision to increase enrollment). As a reminder, greater than expected placebo effect in SAGA diluted treatment delta in that study. ASCEND was designed to reduce placebo noise – specifically, it includes only high-responders (i.e. those with mutations to nine specific genes in the mGluR network that showed a clinically and statistically significant response to AEVI-001 in SAGA). In addition, ~75% of ASCEND participants are expected to be ages 6 – 12 - this younger population should further enhance separation as compared to SAGA (ages 12 – 17). We continue to like the chances for success of ASCEND (more commentary on this topic below, which is unchanged from our most recent update).

While GNMX's press release notes that ASCEND has already enrolled more than 42 patients, their timelines have slipped a bit. Previously they had guided for Part A data in mid-2018, which is now updated to topline data in Q4 2018. While the delays have been unfortunate, given the potential opportunity of AEVI-001 in the treatment of a (significant) subset of the ADHD population and depending on the ultimate success of ASCEND, they could prove to be largely meaningless. And if the trial would have otherwise failed but will now succeed with the increase in enrollment, the additional ~4 - 6 month delay is completely immaterial.

AEVI-001 (mGluR+) Refresher

ADHD: As a reminder, in March 2017 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 of that same year additional data from SAGA was released which demonstrated 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.

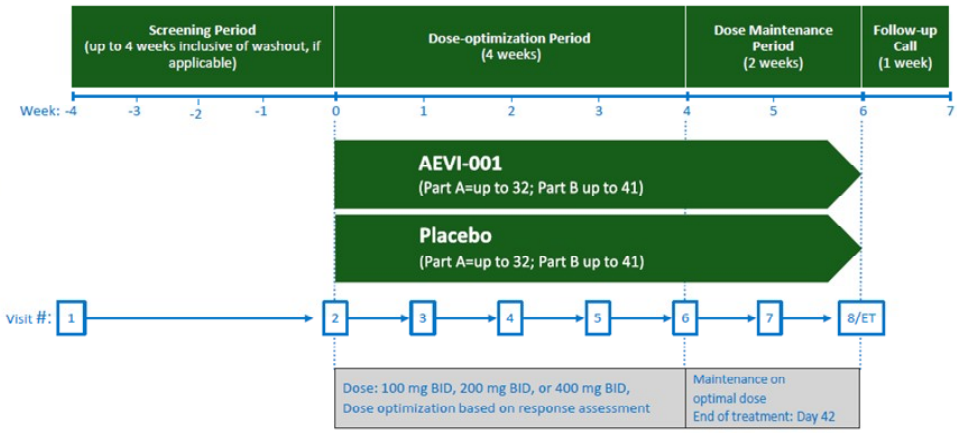
In May 2017 GNMX announced plans for a **new phase II study** (dubbed "ASCEND") which will enrich for this high-responder population – that is, a population with mutations to eight specific genes in the mGluR network (CNTN4 and seven undisclosed GRMs and neurodevelopmental genes). The study design is very similar to that of SAGA, with certain exceptions in that ASCEND will; include younger subjects (6-17 vs 12-17 in SAGA) and incorporates two patient cohorts which will run through sequentially in each arm. Additional details;

- Multi-center (~20-25 sites) randomized (1:1), placebo-controlled
- Ages 6 – 17, ~75% of which are expected to be ages 6 – 12. This younger population should reduce placebo response as compared to SAGA
- Enrollment will be in sequential stages with the 8-gene cohort (N = 32 per arm) enrolling first ("part A") followed by those with no genetic mutation (N = 41 per arm). This current design is slightly modified from the initial 'draft' which included two distinct groups; 1) CNTN4+ patients and 2) the other 7 genes, whereas the current design, similar to SAGA, includes all 8 genes in one group
- Treatment protocol (similar to SAGA): 4-week dose optimization (100mg, 200mg or 400mg, bid), followed by 2-week dose maintenance
- Endpoints (similar to SAGA); primary: ADHD-RS-5, secondary: CGI-I

While the initial drafted design of ASCEND may have provided greater enrichment, CNTN4+-only prevalence among the general ADHD population is only about 50% of that of those with mutations to the full 9-gene subset. As we have noted in prior updates, clearly an important objective is to assess clinically significant response within a broader population (i.e. 9 genes) given that it represents a substantially 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.

ASCEND Trial Design

- Multi-center (20-25 US sites)
- Inclusion criteria:
  - 6-17 years of age
  - ADHD-RS-5 ≥ 28
  - Positive for 9 gene subset, including CNTN4 (Part A) - or - non-mutated (Part B)
- 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 (as compared to SAGA). 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.

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 including (and weighting towards) pediatric subjects (6 – 12 years) including that mGluR network mutations are more prevalent in the 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 pediatrics 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-only clinical trials given the typical greater oversight by parents of younger children – this can result in a greater placebo response in adolescent, as compared to pediatric, studies.

FINANCIAL MODEL

Aevi Genomic Medicine, Inc.

	2017 A	Q1A	Q2E	Q3E	Q4E	2018 E	2019 E	2020 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	-	-	-	-	-	-	-	*75.0%*
SG&A	$9,524.0	$2,174.0	$2,477.0	$2,680.0	$2,641.0	$9,972.0	$13,226.0	$13,557.0
% SG&A	-	-	-	-	-	-		
R&D, net of grants	$25,176.0	$6,561.0	$6,422.0	$6,749.0	$7,042.0	$26,774.0	$32,598.0	$32,664.0
% R&D	-	-	-	-	-	-		
Operating Income	($34,700.0)	($8,735.0)	($8,899.0)	($9,429.0)	($9,683.0)	($36,746.0)	($45,824.0)	($46,221.0)
Operating Margin	-	-	-	-	-			
Financial income, net	($14.0)	$26.0	$11.5	$7.0	$2.0	$46.5	$4.0	$0.0
Total Other Income (Expense)	($14.0)	$26.0	$11.5	$7.0	$2.0	$46.5	$4.0	$0.0
Pre-Tax Income	($34,714.0)	($8,709.0)	($8,887.5)	($9,422.0)	($9,681.0)	($36,699.5)	($45,820.0)	($46,221.0)
Tax expense (benefit)	$0.0	$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	($34,714.0)	($8,709.0)	($8,887.5)	($9,422.0)	($9,681.0)	($36,699.5)	($45,820.0)	($46,221.0)
YOY Growth	*-17.2%*	*-79.2%*	*-18.6%*	*17.3%*	*12.5%*	*5.7%*	*24.9%*	*0.9%*
Net Margin	-	-	-	-	-	-	*#DIV/0!*	*#DIV/0!*
EPS	($0.83)	($0.15)	($0.15)	($0.15)	($0.14)	($0.59)	($0.57)	($0.51)
YOY Growth	*-30.1%*	*-68.1%*	*-28.8%*	*-64.3%*	*1.5%*	*-29.6%*	*-2.4%*	*-10.3%*
Diluted Shares O/S	41,675	59,335	59,338	63,350	68,200	62,556	80,000	90,000

Brian Marckx, CFA

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APPENDIX

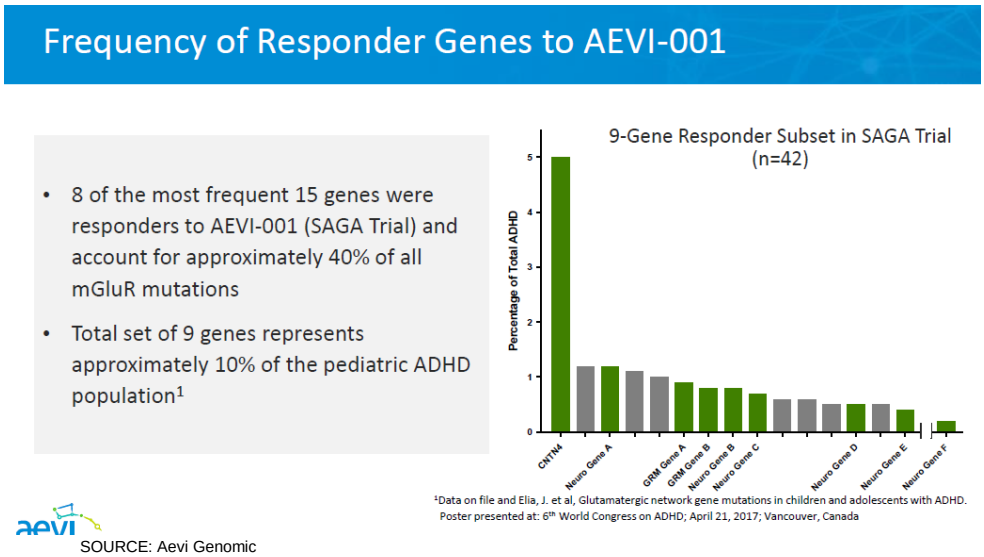
AEVI-001 Refresher

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 in April 2017, 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.

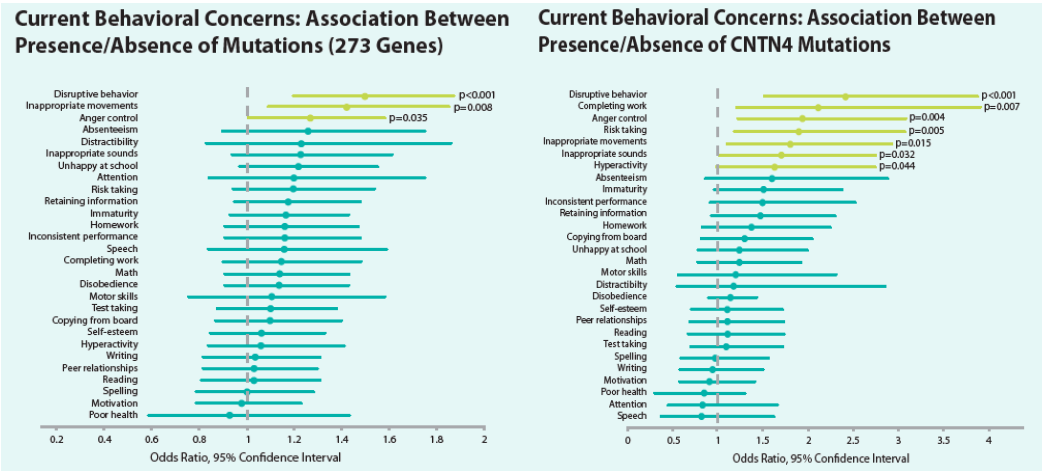


SOURCE: Aevi Genomic

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.

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Top-line data (273 genes) **CNTN4**



SOURCE AEVI Genomic Medicine. Poster, World Congress on ADHD

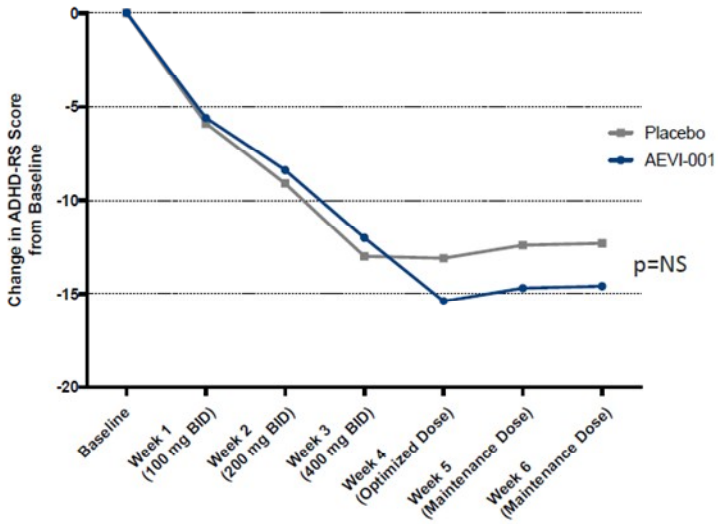
ADHD-RS:

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 2017):

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

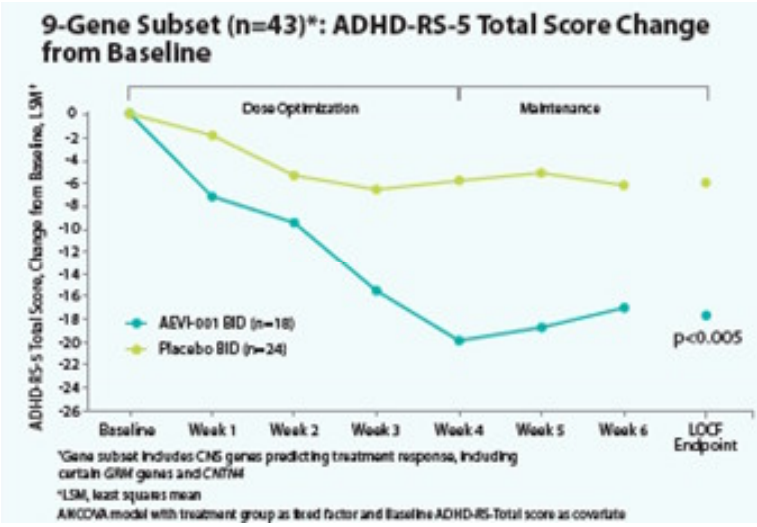
In terms of **ADHD-RS response** (a key secondary endpoint used in SAGA), 70% of AEVI-001 subjects showed ADHD-RS decrease of 30% or more, compared to 42% of placebo subjects. The difference **was highly statistically significant** (p=0.0067) at week-6 and also statistically significant at week-5 (p=0.0203). 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.

9 Genes of Interest:

Mutations in one of nine genes, per the updated data presented at the World Congress on ADHD in April 2017, 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 ($p < 0.0001$).

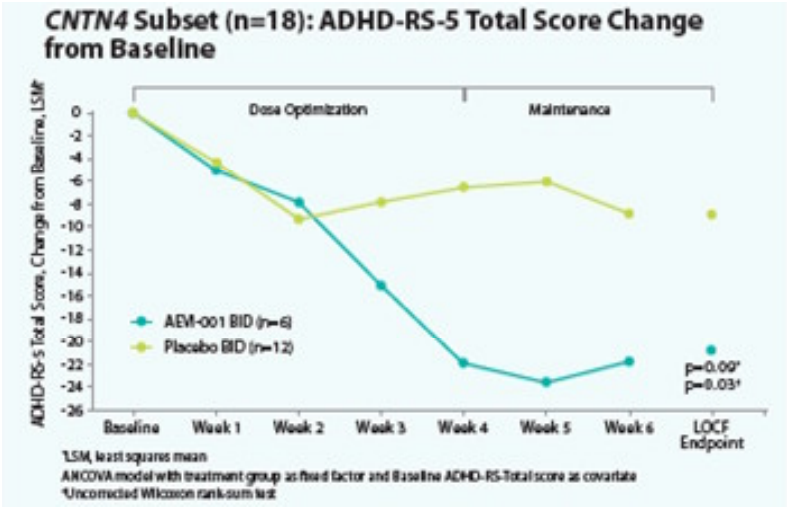


SOURCE Aevi Genomic Medicine. Poster, World Congress on ADHD

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, 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.

HISTORICAL STOCK PRICE



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