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Aevi Genomic Medicine (GNMX-NASDAQ)

GNMX: ASCEND Data By Year-End, Enhanced 001 Co-Crystal

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 (08/13/18)	$1.00
Valuation	**$6.00**

OUTLOOK

While Q2 financials were largely in-line with our estimates, there were a couple of noteworthy updates on the operational front. That includes the announcement around mid-June that ASCEND will enroll to 64 patients - which was an option within the initial design, introduction of an enhanced AEVI-001 (i.e. AEVI-004) and commencement of preclinical work on AEVI-005 (i.e. the second monoclonal antibody w/ Kirin). Despite the slight additional delay to ASCEND (as a result of the optioned increased enrollment), we continue to think there may be several pipeline-related events over the very near term that could potentially favorably influence equity valuation and related pricing of any near-term financings. This could include ASCEND topline data (now expected Q4 '18, delayed from ~mid-2018), initiation of AEVI-001 in ASD/ADHD (possibly early '19) and topline results of 002 in severe pediatric onset Crohn's (still, possibly happening in late-2018). We also think there is high potential for additional pipeline-stocking over the next six to twelve months, particularly given the recent burgeoning discussions with, and interest from, outside parties which could also benefit GNMX's share price.

SUMMARY DATA

52-Week High	**$2.65**
52-Week Low	**$0.83**
One-Year Return (%)	**-25.48**
Beta	**0.90**
Average Daily Volume (sh)	**119,517**
Shares Outstanding (mil)	**59**
Market Capitalization ($mil)	**$59**
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 A	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	-$0.14 A	-$0.15 E	-$0.14 E	-$0.57 E
2019					-$0.56 E
2020					-$0.51 E

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

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Q2 2018 Results / Business Update: *ASCEND Data By Year-End, Enhanced 001 Co-Crystal*

Aevi reported Q2 financial results and provided a business update. While the financials were largely in-line with our estimates, there were a couple of noteworthy updates on the operational front. That includes the announcement around mid-June that ASCEND will enroll to 64 patients - which was an option within the initial design, introduction of an enhanced AEVI-001 (i.e. AEVI-004) and commencement of preclinical work on AEVI-005 (i.e. the second monoclonal antibody w/ Kirin). We provide additional discussion below.

Despite the slight additional delay to ASCEND (as a result of the optioned increased enrollment), we continue to think there may be several pipeline-related events over the very near term that could potentially favorably influence equity valuation and related pricing of any near-term financings. This could include ASCEND topline data (now expected Q4 '18, delayed from ~mid-2018), initiation of AEVI-001 in ASD/ADHD (possibly early '19) and topline results of 002 in severe pediatric onset Crohn's (still, possibly happening in late-2018). We also think there is high potential for additional pipeline-stocking over the next six to twelve months, particularly given the recent burgeoning discussions with, and interest from, outside parties which could also benefit GNMX's share price.

AEVI-004 = AEVI-001+ IP + enhanced manufacturability…
GNMX hopes to swap out AEVI-001 (which is in phase 2 mGlur+ ADHD ASCEND study) with an improved version. In July the company announced that they expect to replace the current version of AEVI-001 with that of an enhanced version of the compound, dubbed AEVI-004. AEVI-004 provides the benefits of intellectual property protection (out to 2039) and is designed to maintain substantially similar solubility, dissolution and pharmakokinetics of AEVI-001 but with (per GNMX's press release) "greater stability and a higher melting point".

Our interpretation is that AEVI-004 is expected to retain the drug-delivery characteristics of AEVI-001 but enhance it with much more substantial IP (than fasoracetam) and better manufacturability - all of which are key to an eventual commercialized product.

For FDA purposes, AEVI-004 is considered a pharmaceutical 'co-crystal', which the agency (per FDA Guidance doc) describes as "crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers"), in the same crystal lattice. Pharmaceutical co-crystals have provided opportunities for engineering solid-state forms beyond conventional solid-state forms of an API, such as salts and polymorphs. Co-crystals can be tailored to enhance drug product bioavailability and stability and to enhance the processability of APIs during drug product manufacture (Schultheiss, N et al.)."

GNMX has already received initial classification-related feedback from FDA on AEVI-004, noting in their July PR that the agency provisionally agreed that AEVI-004 is considered a co-crystal and is eligible as a new chemical entity (NCE). Additionally, GNMX notes that FDA provisionally agreed that existing toxicology and pathology are sufficient to evidence of safety for use in human studies and that, with minimal bridging studies (preclinical and clinical), that AEVI-004 can be used in place of AEVI-001 in eventual phase 3 studies (assuming positive results of AEVI-001 phase 2 mGluR+ ADHD).

ASCEND Will Enroll To N=64, (consistent with initial trial design):
In June 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 June press release noted that ASCEND had already enrolled more than 42 patients (to-date enrollment was not provided in the Aug 2nd Q2 earnings release or 10-Q), 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.

Relative to the Q2 financials; operating loss was $8.3M, meaningfully lower than our $8.9M estimate with almost all of the difference related to less than anticipated R&D spend. We continue to expect R&D expense to trend higher with further development progress, particularly as it relates to the AEVI-001/AEVI-004 programs.

Cash used in operating activities was $7.2M and $14.5M ($7.4M and $15.3M, ex-changes in working capital) in the three and six months ending 6/30/18, compared to $7.9M and $18.5M ($7.2M and $17.1M, ex-changes in working capital) in the comparable prior-year periods. Cash balance at the close of the most recent quarter was $19.2M, which GNMX anticipates being sufficient to fund operations into Q1 '19. Additional near-term capital is available via an ATM program through JMP securities, which was set up in May (no ATM-related sales were made in Q2). The agreement covers the sale of up to $20M worth of common shares - which, given the potential for near-term valuation triggers, we think could prove to be an efficient financing tool.

Pipeline Status:

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.

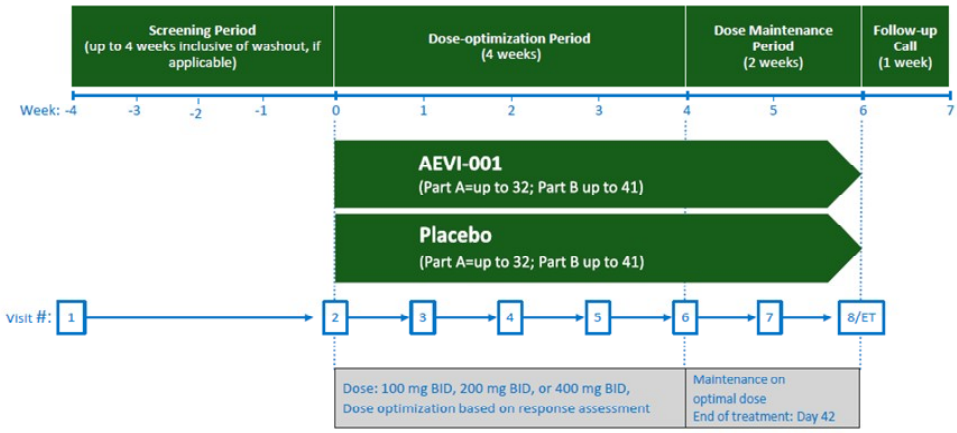
In May 2017 GNMX announced plans for a **new phase II study** (dubbed "ASCEND") which will enrich for this high-responder population – that is, a population with mutations to one of eight specific genes in the mGluR network (CNTN4 and seven undisclosed GRMs and neurodevelopmental genes). The study design 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)
- 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

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.

Autism Spectrum Disorder: CNTN4 mutations have also been associated with more severe phenotypes and other disorders including Autism Spectrum Disorder. Management has referenced study data that indicated 65% - 85% of individuals with ASD also have ADHD. Using the CHOP database, Aevi found that approximately 6% - 10% of ASD patients have the CNTN4+ mutation. While GNMX had previously talked about potentially pursuing an ASD-primary endpoint study, that has since evolved to one that potentially could have an ADHD-related primary endpoint given that the latter may offer a potentially more straightforward regulatory pathway. And, importantly, (current) DSM-5 defines a combined diagnosis of ADHD and ASD. The current thinking is that if 001/004 can show improvement on ADHD symptoms, that that may be enough to demonstrate overall improvement. While there could be further tweaks to the proposed design, recent thoughts have been:

- open label dose-ranging (100 - 400mg bid), multi-center
- n = 15 - 20
- 6 - 17 years, 9-gene+ patients that are ADHD/ASD comorbid and with IQ of $\geq$ 70 (rationale being that higher functioning = better chance of demonstrating treatment effect)
- ADHD-RS primary endpoint (also primary in SAGA and ASCEND). Secondary endpoints reflect established ASD measures.

- timeline: specifics TBD with decisions post-ASCEND topline. Could initiate following ASCEND data

AEVI-001/004 Subsequent Steps: We do not think there will be any major decisions relative to next steps for AEVI-001 until at least read-out of ASCEND top-line data. 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. In terms of market considerations, the relatively very high unmet need in addressing the core symptoms of ASD may mean a particularly receptive market for a related indication. We estimate that U.S. prevalence of ASD comorbid with ADHD and mGluR+ is approximately 75k – 125k children (slightly less if parsed for only IQ $\geq$ 70) – which could represent an attractive orphan-opportunity – so that may also play into management's decision-making.

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

The Anti-LIGHT program in pediatric onset Crohn's (AEVI-002) has been plagued by persistent delays due to extreme difficulties in recruiting and enrolling patients. While GNMX previously noted that screening at the primary site (CHOP IBD center) commenced last June, no patients have yet to actually enroll. But, with three additional sites having now been activated (Salt Lake City, Emory and Vanderbilt), management hopes enrollment will begin. They are now considering adding one or more study sites outside of the U.S. in another effort to enhance patient recruitment. As it stands now, GNMX believes that if enrollment commences by Q3, that initial data from a small number of patients may still be available before current year-end. Importantly, no modifications to enrollment criteria appear to have been necessary - as a reminder, GNMX had previously indicated that they were 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 or without 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, AEVI-002 will be administered in one of two doses (1.0mg/kg or 3.0 mg/kg) via subcutaneous injection for 14 days. Clinical endpoints are endoscopic evaluation (i.e. healing) and the Crohn's Disease Activity Index. Aevi will use the topline data to decide whether to continue development (via their license with Kirin).

'AEVI-005' and further pipeline expansion

GNMX exercised their option under their existing agreement with Kyowa Hakko Kirin (i.e. related to their anti-LIGHT candidate), licensing rights to 'AEVI-005. Citing competitive reasons, specifics regarding the compound ('first in-class monoclonal antibody'), target ('specific cell-surface marker) and disease/condition ('autoimmune ultra-orphan pediatric disease as well as larger adult orphan diseases') have yet to be disclosed. Currently in preclinical development stage. Preclinical research commenced in Q2 '18.

Pipeline expansion is likely to continue. GNMX indicated lots of recent external interest from potential partners/collaborators. Access to CHOP biobank appears to provide GNMX somewhat of gatekeeper positioning, attracting interest from external early-stage, orphan-oriented programs. Indications from the Q4 call was that this has afforded GNMX greater selectivity and growing lists of potential options in the context of pipeline expansion.

VALUATION: Value GNMX at $6/share

As we noted following release of the SAGA topline data back in March 2017, 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-001/004 based on the supplementary measures. Design of ASCEND, which could have topline data by late-2018, includes some modifications aimed at improving upon efficacy and meeting the ADHD-RS primary endpoint. Topline read-out of ASCEND is also expected to provide direction to the AEVI-001 program – a possible significant event in terms of defining the commercial market opportunity for the compound. Depending on the strength of the data, this could also be a value-inflection event.

We use 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. We have updated our inputs since our last report to reflect the development progress of the lead compound (001) as well as complementary progress towards expanding the pipeline as a whole. The former includes final modifications to ASCEND trial design as well as enrollment progress (42+ enrolled as of mid-June 2018). The latter reflects acquiring rights to AEVI-005 as well as burgeoning outside interest from potential external collaborators, partners and licensors – and while we currently 'assign' relatively minimal tangible value to both, we think consideration is warranted given that they represent ever-increasing ability of GNMX to be more selective in pipeline expansion-related decision-making.

According to the Thomson 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, 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. While we had previously discounted this at 22% (i.e. probability (per Thomson study) that an orphan drug in phase I eventually is approved), the decreased risk of failure as a result of the pipeline progress warrants a discount closer to 15%, which values GNMX at $350M (~$6/share). Our valuation will continue to be highly influenced by development progress as well as value of the pipeline as a whole.

FINANCIAL MODEL

Aevi Genomic Medicine, Inc.

	2017 A	Q1A	Q2A	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	$2,504.0	$2,680.0	$2,641.0	$9,999.0	$13,226.0	$13,557.0
% SG&A	-	-	-	-	-	-		
R&D, net of grants	$25,176.0	$6,561.0	$5,747.0	$6,337.0	$6,785.0	$25,430.0	$31,889.0	$32,418.0
% R&D	-	-	-	-	-	-		
Operating Income	($34,700.0)	($8,735.0)	($8,251.0)	($9,017.0)	($9,426.0)	($35,429.0)	($45,115.0)	($45,975.0)
Operating Margin	-	-	-	-	-			
Financial income, net	($14.0)	$26.0	$60.0	$15.5	$7.2	$108.7	$4.0	$0.0
Total Other Income (Expense)	($14.0)	$26.0	$60.0	$15.5	$7.2	$108.7	$4.0	$0.0
Pre-Tax Income	($34,714.0)	($8,709.0)	($8,191.0)	($9,001.5)	($9,418.8)	($35,320.3)	($45,111.0)	($45,975.0)
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)	($8,191.0)	($9,001.5)	($9,418.8)	($35,320.3)	($45,111.0)	($45,975.0)
YOY Growth	*-17.2%*	*-79.2%*	*-25.0%*	*12.1%*	*9.5%*	*1.7%*	*27.7%*	*1.9%*
Net Margin	-	-	-	-	-	-	*#DIV/0!*	*#DIV/0!*
EPS	($0.83)	($0.15)	($0.14)	($0.15)	($0.14)	($0.57)	($0.56)	($0.51)
YOY Growth	*-30.1%*	*-68.1%*	*-33.8%*	*-63.5%*	*1.1%*	*-31.3%*	*-1.4%*	*-9.4%*
Diluted Shares O/S	41,675	59,335	59,338	60,100	68,200	61,743	80,000	90,000

Brian Marckx, CFA

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APPENDIX

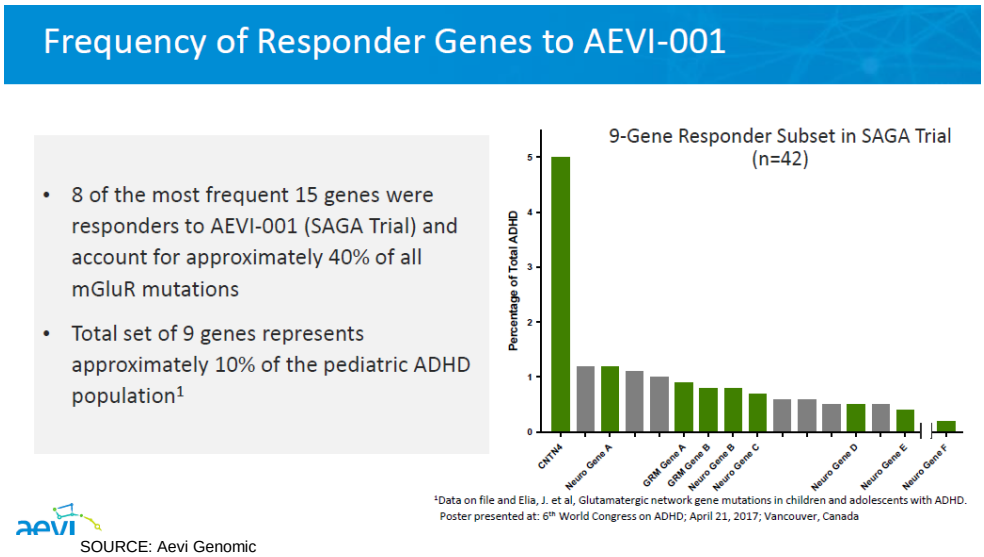
AEVI-001 Refresher

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.

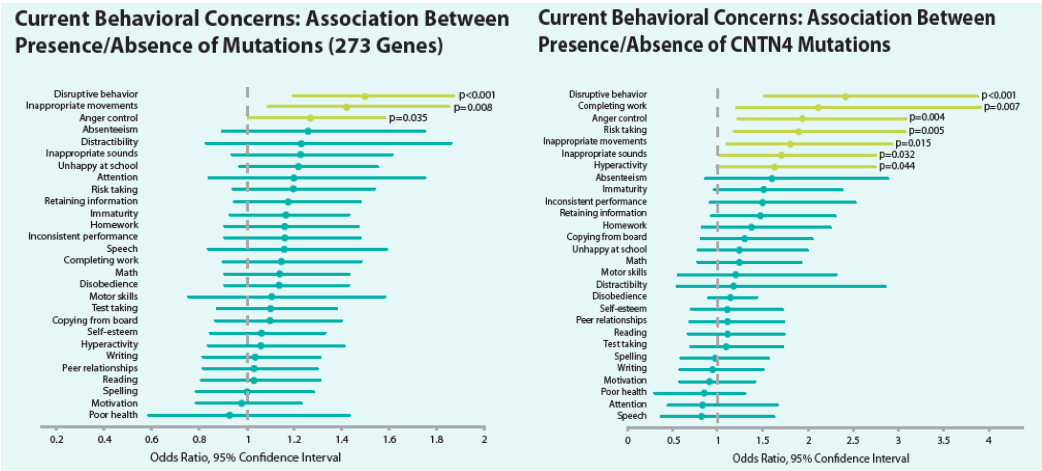


SOURCE: Aevi Genomic

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

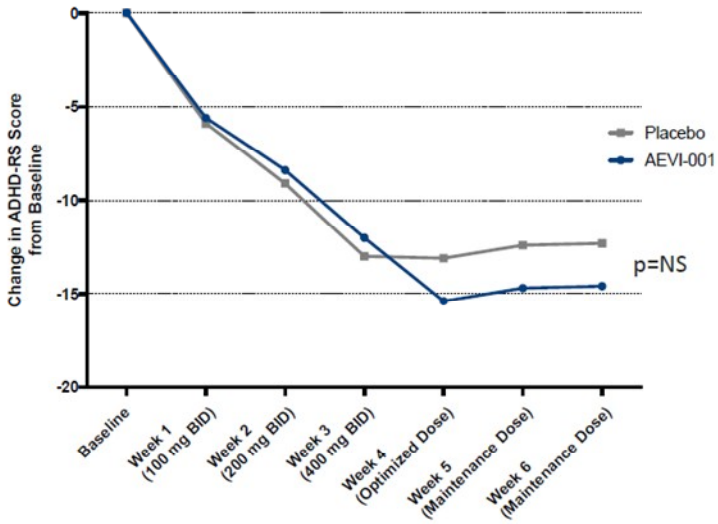
ADHD-RS:

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

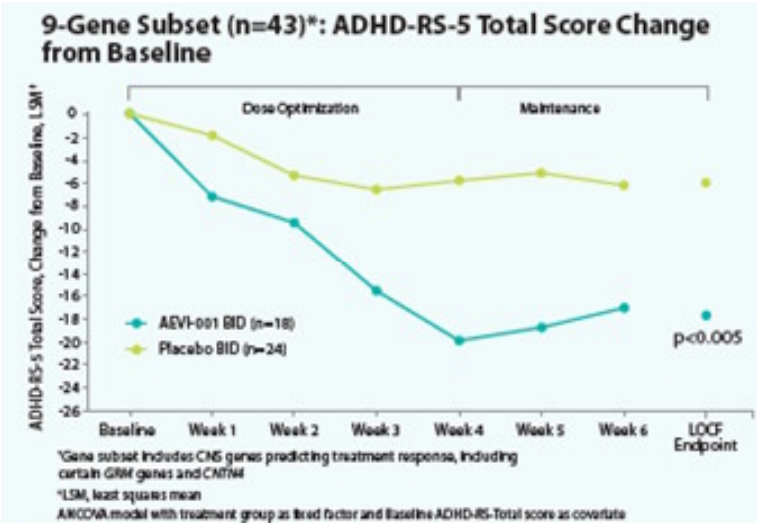
In terms of **ADHD-RS response** (a key secondary endpoint used in SAGA), 70% of AEVI-001 subjects showed ADHD-RS decrease of 30% or more, compared to 42% of placebo subjects. The difference **was highly statistically significant** (p=0.0067) at week-6 and also statistically significant at week-5 (p=0.0203). 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 ($p < 0.0001$).

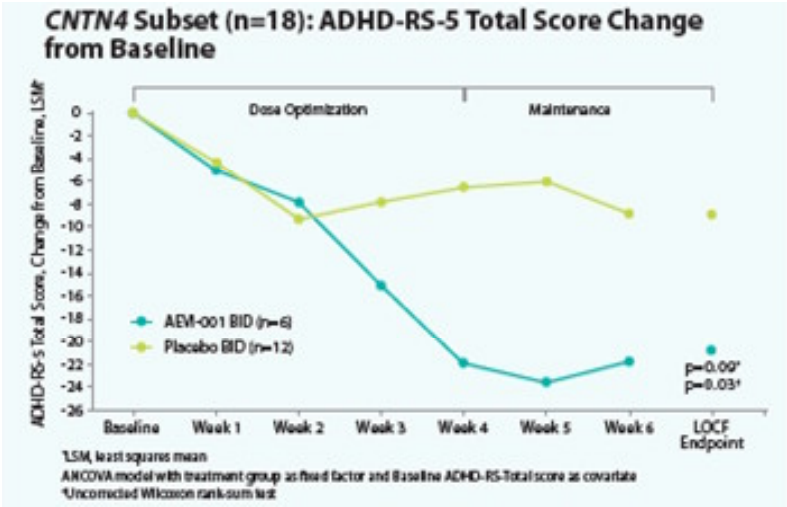


SOURCE Aevi Genomic Medicine. Poster, World Congress on ADHD

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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