Zacks Small-Cap Research

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Aevi Genomic Medicine (GNMX-NASDAQ)

GNMX: SAGA Misses Primary Endpoint But Data-Within-Data Warrants Optimism

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

Current Price (03/27/17)	$1.60
Valuation	**$7.00**

OUTLOOK

While disappointing that the SAGA primary endpoint was not met, we believe the data-within-the-data, including meeting statistical significance on the CGI-I and ADHD-RS responder measures (and with what appears to be an obvious dose response) and barely missing significance on the ADHD-RS inattention subscale, indicates that patients did respond favorably to AEVI-001 treatment. This, coupled with no meaningful safety issues (in SAGA or earlier studies) and a history of being used safely in over 1,000 patients provides encouragement that a refined study design, potentially including a higher maximum dose, longer treatment duration and a more selective biomarker, has a reasonable chance of being green-lighted by FDA and eventually demonstrating success in ADHD-RS versus placebo.

As such, we think that there is good reason to believe that the SAGA results may eventually prove not to be the end of the story but only an additional step in development of AEVI-001 which results in a delayed, yet eventual happy ending – perhaps lending alternate suitability to the name of the study.

SUMMARY DATA

52-Week High	**$6.89**
52-Week Low	**$1.50**
One-Year Return (%)	**-63.13**
Beta	**0.74**
Average Daily Volume (sh)	**632,472**
Shares Outstanding (mil)	**37**
Market Capitalization ($mil)	**$59**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**46**
Insider Ownership (%)	**23**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

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

ZACKS ESTIMATES

Revenue
(in '000s of $)

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

Earnings per Share

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

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

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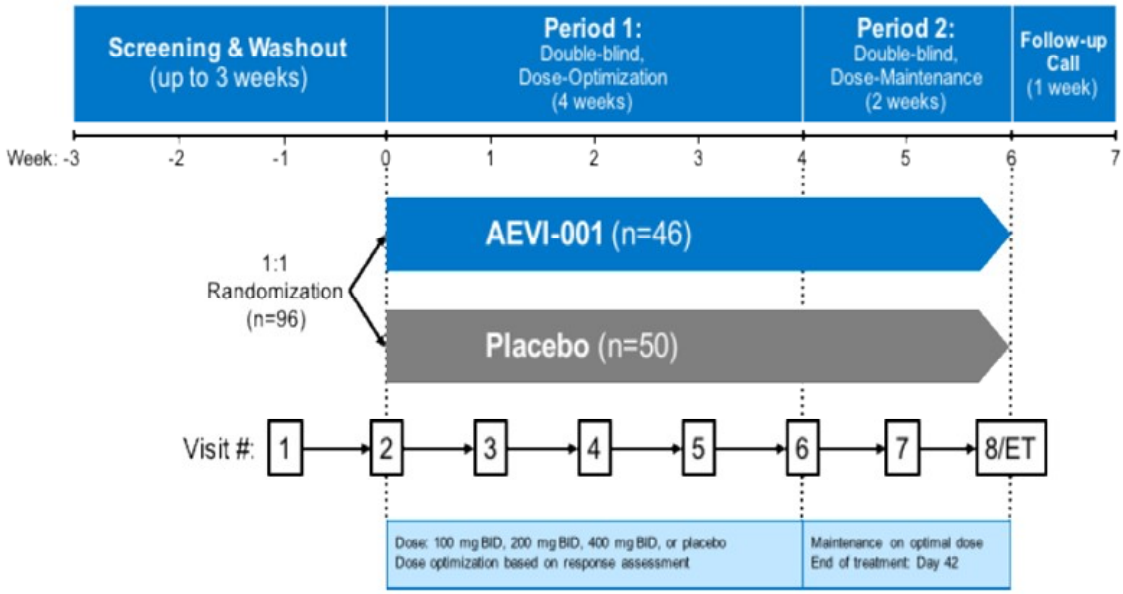
SAGA Results: *Primary Endpoint Missed But Data-Within-The-Data Suggest Reasons To Remain Optimistic*

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:

- anticipated enrollment (n=90)
- double-blinded, randomized 1:1; NFC-1/placebo
- following (up to 3-week) wash-out period patients received
    - placebo or
    - AEVI-001
        - in weekly escalating doses from 100mg BID (i.e. twice/day) to 400mg BID based on tolerability to establish optimized dose
        - after the 4th week patients remain on the optimized dose for 2-week maintenance phase
        - followed by 1 week off-drug for safety observation
- **Endpoints**
    - Primary endpoint is change in ADHD-RS (parent assessment) from baseline of AEVI-001 treated patients versus those receiving placebo
    - Key secondary endpoint is change in Clinical Global Impressions (CGI-I) Scale from baseline
    - Additional measures were also assessed including an ADHD-RS responder analysis (pre-specified improvement of ≥ 30%)

SAGA Design



SOURCE: Aevi Genomic Medicine March Presentation

Results:

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

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

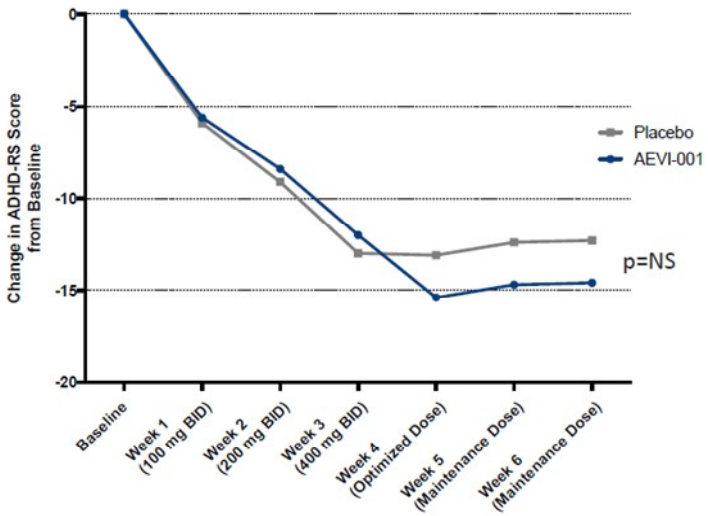
Results showed that the **primary endpoint**, change from baseline in ADHD-RS scores of AEVI-001 patients compared to those receiving placebo, was **not statistically significantly different**. That was the unfortunate news.

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

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

Additional SAGA results details:

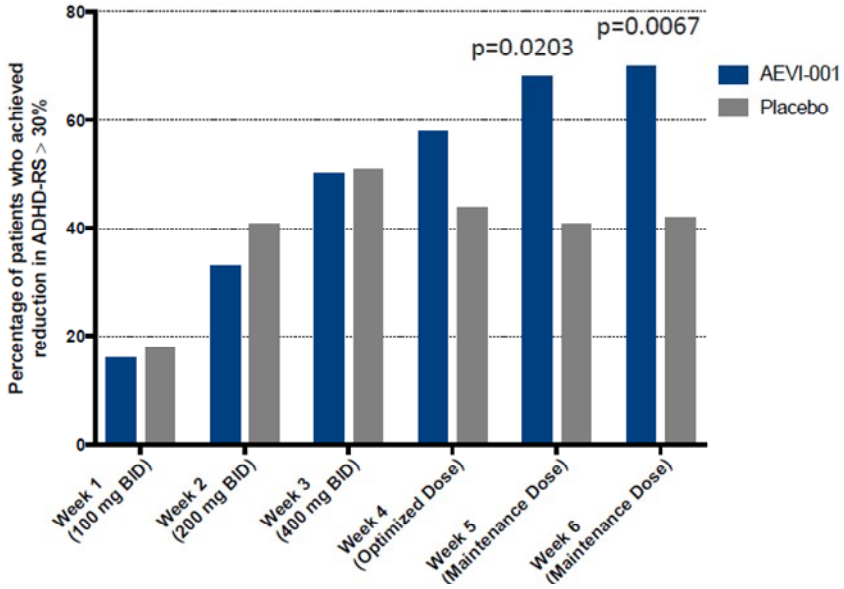
- **ADHD-RS**: While GNMX did not disclose (full data will be at World Congress in late April) the specific ADHD-RS data (i.e. % change in each arm or p-value), they did note that absolute change was approximately 15 in the AEVI-001 arm and ~12 in the placebo group, with separation (although not statistically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



SOURCE: Aevi Genomic Medicine March Presentation

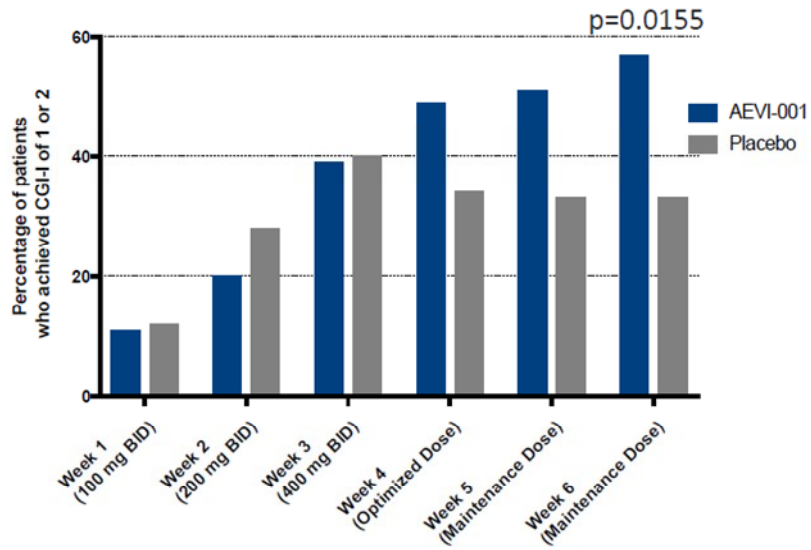
In terms of **ADHD-RS response** (also an oft-utilized measure in ADHD trials), 70% of AEVI-001 subjects showed ADHD-RS decrease of 30% or more, compared to 42% of placebo subjects. The difference **was highly statistically significant** (p=0.0067) at week-6 and also statistically significant at week-5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

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



Aevi Genomic Medicine March Presentation

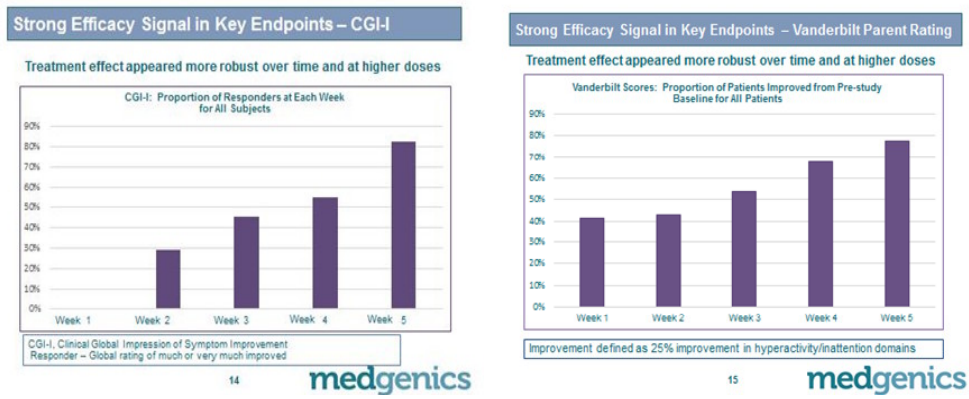
- **CGI-I:** Relative to CGI, also a well-established ADHD-related measure, 57% of AEVI-001 subjects and 33% of those on placebo achieved CGI-I scores or 1 or 2 – the difference **was statistically significant** (p=0.0155). The CGI-I response chart (below) is very similar to that of the ADHD-RS response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



SOURCE: Aevi Genomic Medicine March Presentation

We also remind investors that a similar response was seen in the GREAT study. In GREAT, treatment was dose-escalating from 50mg (BID) to a maximum of 400mg (BID). Dose was escalated weekly. Results showed a **statistically significant dose and time-dependent response** on CGI-I (as well as on

Vanderbilt, the other efficacy-related endpoint) and approximately 80% of AEVI-001 patients responded based on both CGI-I and Vanderbilt. See chart below.



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

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

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

SOURCE Aevi Genomic Medicine March Presentation

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

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

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

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

profile may pave the way for FDA to accept a longer treatment duration and/or higher dose. Higher dose or longer duration could further improve upon the dose response witnessed in both ADHD-RS and CGI-I.

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

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

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

In parallel GNMX expects;

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

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

VALUATION: Value GNMX at $7/share

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Prior to SAGA 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 have now 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, had valued the company at approximately $350M. However, given results of SAGA, we have incorporated a one-year delay to initial revenue as well as handicapped eventual approval by 25% - the combination of which has moved our valuation of GNMX from ~$350M (~$10/share) to $250M (~$7/share).

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

FINANCIAL MODEL

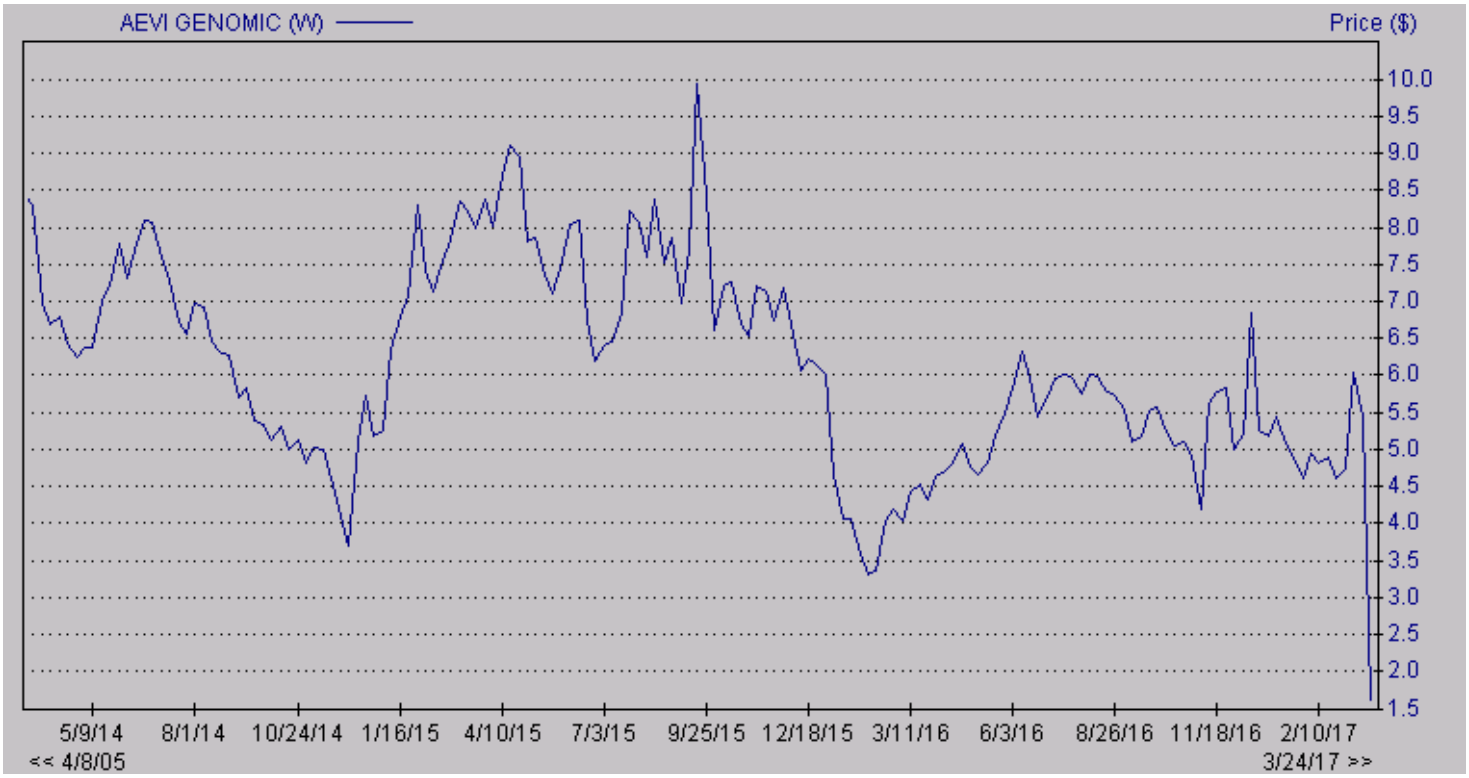
Aevi Genomic Medicine, Inc.

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

Brian Marckx, CFA

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