Zacks Small-Cap Research

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Medgenics Inc (MDGN-AMEX)

MDGN: Waiting On Edge of Seat, NFC-1 Data Later This Year

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	06/08/2014
Current Price (02/17/16)	$3.81
Target Price	**$11.00**

OUTLOOK

Recent neuroFix acquisition brought high-potential NFC-1 candidate. Ph 1 data looks very encouraging. This could move rapidly through development and be the first commercialized product - could address both ADHD and orphan indications. Add'l positive data, expected in 2016, we think could be a needle-mover to the share price.

Meanwhile,TARGT biopump moving from EPO to CNS related targets. MDGN expects to initiate preclinical work on $TARGT_{CNS}$ later this year.

Other shots on goal include newly inlicensed GeneRide technology as well as other new programs that could come online.

SUMMARY DATA

52-Week High	**$10.25**
52-Week Low	**$3.09**
One-Year Return (%)	**-45.75**
Beta	**0.55**
Average Daily Volume (sh)	**138,204**
Shares Outstanding (mil)	**33**
Market Capitalization ($mil)	**$125**
Short Interest Ratio (days)	**8.80**
Institutional Ownership (%)	**22**
Insider Ownership (%)	**27**
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 2016 Estimate	**N/A**
P/E using 2017 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)
2015	0 A	0 A	0 A	0 A	0 A
2016	0 E	0 E	0 E	0 E	0 E
2017					0 E
2018					0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.36 A	-$0.24 A	-$0.66 A	-$0.25 A	-$1.51 A
2016	-$0.31 E	-$0.31 E	-$0.28 E	-$0.27 E	-$1.16 E
2017					-$1.11 E
2018					-$0.97 E

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

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Q4 Results 2015, Operational Update

Medgenics reported fourth quarter 2015 financial results and provided a comprehensive operational update on the conference call.

On the financial side, Q4 operating expenses were significantly tempered from Q3 and G&A was well below our number. The difference related to lower professional fees and stock-based compensation. We are modeling incremental growth in operating expenses in 2016 (all related to G&A) but estimating R&D roughly flat, representing increased clinical activity with NFC-1 (in both ADHD and 22q11.2 Deletion Syndrome) and some incremental spend in $TARGT_{CNS}$, offset by the non-recurring NFC-1 acquisition cost (of $8M booked in Q3 2015) as well as conclusion of the $TARGT_{EPO}$ program. We also continue to incorporate some cushion in OpEx related to new programs that may come online during the year. The $53M in cash on the balance sheet as of the end of 2015 should provide a sizeable runway and potentially enough to move NFC-1 into pivotal studies.

On the operational front, the $TARGT_{EPO}$ program, which was the company's main focus prior to the NFC-1 acquisition, has been wrapped up. While MDGN indicated that they were pleased with the efficacy signal observed in the ESRD study and had fairly recently indicated that they intended to move towards EPO-related orphan targets such as beta thalalassemia, peritoneal dialysis, myelodysplastic syndrome and others, these will now take a back-burner as resources and focus moves to other programs - most notably of which is NFC-1 in ADHD and 22q11.2 DS but also TARGT in (yet to be fully determined) CNS targets.

There was writing on the wall that EPO-orphans might be relegated to back-burner following the NFC-1 acquisition so the shift is not a surprise, and in our opinion, is a wise move given the already compelling data in ADHD and the potential that both the ADHD and 22q11.2 DS programs could be fast-moving (and potentially less expensive and lower risk than $TARGT_{EPO}$).

Regarding the NFC-1 programs, data is expected later this year in both ADHD and 22q11.2

- **NFC-1**
    - In September MDGN acquired neuroFix Therapeutics, LLC and its lead candidate NFC-1, a compound targeting CNS disorders associated with mutations of the metabotropic glutamate receptors (mGluRs). Initial investigated indications are ADHD and 22q11.2 Deletion Syndrome, although other CNS diseases may also be pursued. See refresher below for info on the deal and NFC-1 including clinical data to-date

    - ADHD:
        - Positive phase I data (NFC1-GREAT) in ADHD presented at AACAP meeting in October
        - Due to efficacy observed in phase I study, 20 of 30 patients chose to remain in long-term
        - Will conduct non-interventional study in order to;
            - Identify individuals with tier 1 and 2 mutations (i.e. – those most likely to respond to NFC-1 therapy). Will genotype 1k subjects. Results will be used to facilitate enrollment of phase 2/3 study. Enrollment has commenced
            - Confirm that 20%-30% of child ADHD is influenced by mGluR signaling
            - Initiate study sites that will be used in phase 2/3 study
        - Phase 2/3 ADHD study
            - Expected to initiate this year, with initial data in 2H
            - Primary efficacy endpoints will be ADHD RS (parent assessment) and CGI-I
            - We think the phase 2/3 data, assuming it supports what was seen in ph 1, could be catalyst for the stock price as this should provide much more insight into the potential of NFC-1 in both ADHD and 22q11.2
        - Phase 3 study: assuming positive results in ph2/3, will move to confirmatory phase 3 study

    - 22q11.2 Deletion Syndrome:
        - Given the rarity of incidence and lack of any effective treatment, it's possible (assuming demonstrated NFC-1 effectiveness) this could be a quick-moving regulatory orphan candidate
        - Received IND (January 2016) to initiate phase 1/2 indication and dose finding study

- This initial study is expected to parse out the first (of potentially other follow-on) indication - which MDGN noted could be related to ADHD, anxiety or mood disorders
- Still shooting for initial read-out around mid-2016
- If the phase 1/2 study results are positive, MDGN may be able to go straight to a pivotal, regulatory approval-supporting

And while the TARGT EPO program is shelved (at least for the time being), MDGN will continue to pursue their biopump platform in potential CNS-related applications. They expect to initiate preclinical work on $TARGT_{CNS}$ in the second half of 2016.

REFRESHER: NFC-1 Acquisition, Clinical Data

In September 2015 MDGN acquired neuroFix Therapeutics, LLC and its lead candidate NFC-1, a compound targeting CNS disorders associated with mutations of the metabotropic glutamate receptors (mGluRs). Initial focus will be on Attention Deficit Hyperactivity Disorder (ADHD), where Phase 1 data showed promising results and 22q11.2 Deletion Syndrome, a rare condition also associated with mGluR mutations and one which may offer orphan status opportunities (both specifically for 22q11.2 Deletion Syndrome as well as associated indications).

This is the first opportunity to come from MDGN's relationship with CHOP

neuroFix was founded by Dr. Hakon Hakonarson, Director of the Center for Applied Genomics at CHOP, in order further develop NFC-1. Prior to MDGN's acquisition, neuroFix licensed certain technology related to ADHD and other neurological and neuropsychological indications from CHOP.

Terms of the deal;

- $8M in cash and common stock
- additional payments of up to $450M upon achievement of certain milestones (development, regulatory and sales) related to an oral formulation of NFC-1 and any new chemical entity (NCE) developed covering the same indication (specifics in terms of exactly what this relates to and what the triggers are were not disclosed)
- sales royalties based on tiered rates ranging from mid-to-high single digits depending on the product or NCE
- $25M for each FDA approved indication beyond the initial indication

Terms of License Agreement between neuroFix and CHOP;

- up to $1.5M in regulatory and sales milestones for each FDA approved indication using IP covering the agreement
- sales royalties based on a fluctuating rate in the low single digits - which adjust downward based on the extent of third party royalties
- $100k or less in annual maintenance fees
- a percentage (ranging from mid-single digits to mid-teens) of any sublicense income (ex-sublicensed sales by a certain party in Japan)
- this license agreement terminates upon the later of the expiration of certain CHOP patent rights and January 1, 2025, at which time neuroFix owns the covered licensed rights

Metabotropic Glutamate Receptors (mGluRs)

The amino acid glutamate is the most prominent excitatory neurotransmitter in the brain. It binds to mGluRs which are involved in the modulation of synaptic transmission and neuronal excitability in the central and peripheral nervous system. Genetic mutations of genes within the mGluR network have been associated with certain conditions including ADHD, anxiety disorders, schizophrenia and other neuropsychiatric disorders.

Research conducted by Dr. Hakonarson and colleagues indicated that mutations in the mGluR gene network are associated with a 10x higher rate of ADHD. They found that disruptions specifically to GRM1 (glutamate receptor, metabotropic 5), GRM3, GRM 7 and GRM8 were associated with ADHD.

NFC-1 GREAT Study

neuroFix, in collaboration with CHOP, conducted a Phase 1, 30-patient, single arm study at Thomas Jefferson University (Philadelphia) assessing NFC-1 in adolescents with ADHD. Inclusion criteria included professionally

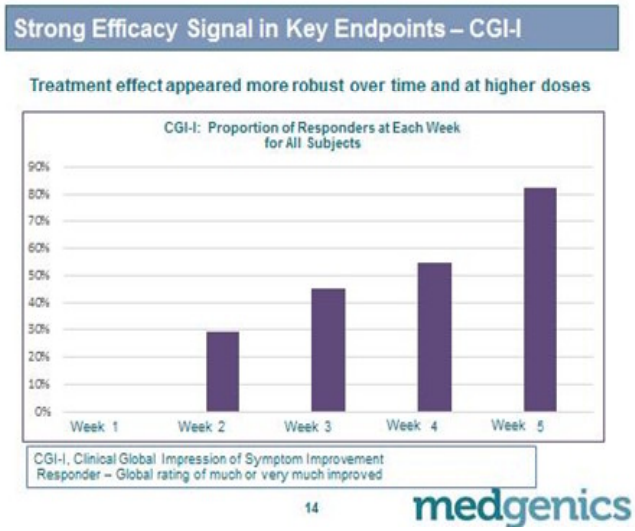
diagnosed with ADHD and genotyped as having disruptions to the mGluR network. The background of the enrolled population had certain symptoms which could be considered particularly challenging to effectively treat including;

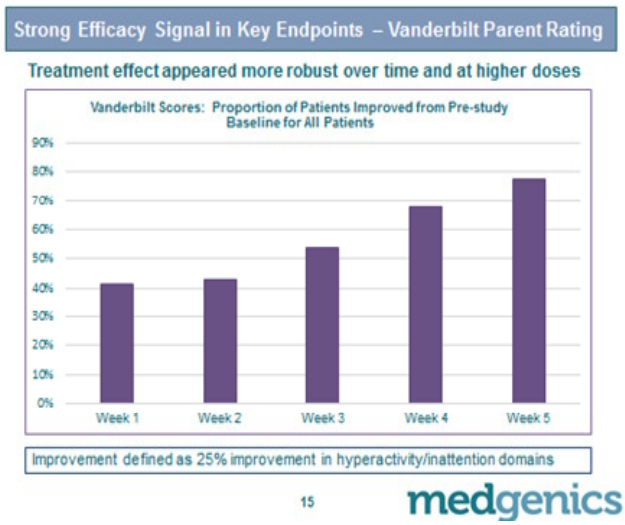
- 73% had severe ADHD (CGI-S>5, on a scale of 1=normal to 7=extremely ill)
- 67% had co-morbid psychiatric conditions such as anxiety, ODD and insomnia
- 30% were on antipsychotics and/or antidepressants
- 70% had been previously treated with ADHD drugs (with presumably little benefit)

One-week run-in on placebo was followed by four weeks of active treatment. Treatment was dose-escalating from 50mg (x2/day) to a maximum of 400mg (x2/day). Dose was escalated weekly. Patients were blinded, clinicians were not. Primary endpoint was safety, secondary endpoint efficacy measures were standard ADHD assessments including Vanderbilt and Clinical Global Impressions (CGI) scores.

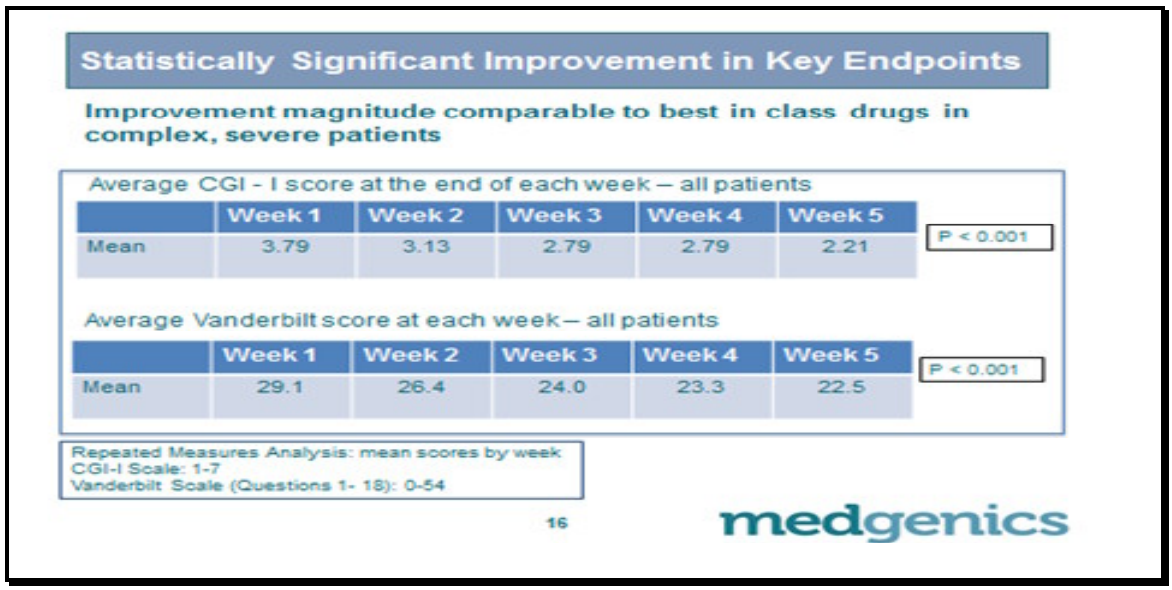
Full results will be presented at AACAP in late October in San Antonio. Management also provided a glimpse of the data on the call announcing the transaction which included;

- dose and time-dependent response on both the CGI-I and Vanderbilt measures
  - over 80% of patients responded to NFC-1 treatment on Vanderbilt measure at week 5
  - just under 80% of patients responded NFC-1 treatment on CGI-I measure at week 5
  - Repeated measure analysis showed statistically significant response on both measures over time and at higher doses
- Mutations to "tier 1" genes (i.e those in the mGluR receptors) and "tier 2" genes (i.e. those that encode proteins that influence mGluR but are not in the receptors) showed much higher response rates compared to "tier 3" genes (more distant from the receptors and therefore likely to show lower response)
- Excellent safety with no treatment related serious adverse events
- 20 of the 30 patients chose to continue to receive NFC-1 therapy in an ongoing long-term safety trial. As management noted in their presentation, this is clearly a positive vote of confidence in the efficacy of NFC-1 given that there's a significant hassle involved in coming to the clinic on a regular basis to receive treatment (i.e. - it's unlikely patients/parents would continue if they experienced no positive effect)





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.



We note that there is the risk of unintended bias in the CGI-I score given that the clinician was not blinded in this study (management noted that the clinician is highly qualified in ADHD assessment, which we acknowledge is likely a mitigating factor). Risk of bias, however, is not relevant with Vanderbilt which is a parent-rated assessment as the parents were blinded in the study - and both CGI-I and Vanderbilt demonstrated dose and time dependent response, indicating that NFC-1 is effective in ADHD treatment. The planned upcoming Phase 2/3 will be double-blinded and therefore will not be at risk of bias.

Phase 2/3 Study

Given the more pronounced response in tier 1 and tier 2 gene mutations, which are believed to account for approximately 20% of the ADHD population, this will be an inclusion criteria in the Phase 2/3 trial. MDGN is still in process of putting the specific trial design together but expects;

- primary efficacy endpoints to be ADHD RS (parent-assessment) and CGI-I
- is expected to serve as the pivotal trial (although a Phase 3 confirmatory trial is anticipated)
- aiming to initiate in near term with initial data in H2 2016

Anticipated enrollment is 90 – 100 subjects. Will be controlled, randomized, double-blind and powered for statistical significance - as such we think the initial data read-out could provide a lot more insight into the efficacy of NFC-1 in ADHD.

ADHD Market Is Attractive: *Positive Phase 2/3 Data Could Be a Needle-Mover to Share Price*

ADHD could be a hugely attractive market for MDGN and a genetic-based therapy including the significant size of the market, ambiguity of diagnosis and unmet need for therapies which are more effective and have less problematic side effect profiles.

- ~6M children (ages 3 - 7) are diagnosed with ADHD in the U.S. This equates to ~10%
- ADHD is the most common neurobehavioral disorder diagnosed in the U.S.
- No definitive test exists to diagnose ADHD - all ADHD diagnoses are arbitrary based on subjective assessment
- Stimulants such as Adderrall (amphetamine and dextroamphetamine), Vyvanse (lisdexamfetamine) and ritalin (methylphenidate) account for over 90% of ADHD prescriptions. These drugs are associated with significant side effects including risk of addiction, irritability and difficulty sleeping, among others. They are highly regulated due to their risk of addiction. These stimulants do not always address all of the underlying symptoms which often can include anxiety and psychotic disorders - mGluR mutations have been associated with other psychiatric conditions which means NFC-1 may be able to address not only ADHD but other of these conditions as well

Unlike stimulants NFC-1 (MDGN has not identified the molecule as additional IP is still being locked down) does address the underlying cause of ADHD. In addition, diagnosis (of mGluR mutations) is genetically-based, not arbitrary. It also (in clinical trials to-date, which includes a 1,000+ patient study in vascular dementia), has shown an excellent side-effect profile. And 10% - 20% of the entire U.S. ADHD market is ~600k - 1.2M people -

which is very significant for a company of MDGN's size, particularly given that the benefits of NFC-1 over stimulants should offer the opportunity for premium pricing. We think it is conceivable that mGluR+ADHD could easily represent a multi-billion dollar market opportunity. As such, if the planned Phase 2/3 study confirms what was demonstrated in Phase 1, **we think this could be a needle-mover to the share price.**

22q11.2 Deletion Syndrome: *Orphan Opportunity for NFC-1 to Address Related Psychological Disorders*

22q11.2 Deletion Syndrome is a relatively rare disease with incidence (per *The International 22q11.2 Foundation Inc.*) estimated at one in every 1,000 live births - which equates to about 4,000 new cases every year in the U.S (~130k worldwide). We have not been able to find an estimate of prevalence rates, although management noted on the call that U.S. prevalence is believed to be approximately 75k - 100k.

22q11.2 Deletion Syndrome is characterized by the deletion on the long arm of one pair of chromosome 22 (region 1, band 1, sub-band 1). The disorder can affect most systems in the body and is associated with serious physical and neuropsychological problems including cardiovascular issues, cleft palate, abnormal facial features, immune disorders and behavioral, psychotic and anxiety disorders (including ADHD). And while many of the physical problems such as heart defects and cleft palate can be addressed by traditional medical intervention such as surgery, there are no current therapies available to address the psychological disorders. It is estimated that about 30% - 40% of individuals with 22q11.2 Deletion Syndrome will eventually progress to schizophrenia.

And mGluR mutations appear to play a roll in 22q11.2 Deletion Syndrome with over 90% of 22q11.2 Deletion Syndrome patients having at least one mGluR network related deletion. In fact two patients in the Phase 1 ADHD study had 22q11.2 mutations (one deletion and one duplication), both of which, per the company's presentation, reported "significant symptom improvement in both CGI-I and Vanderbilt" and both patients continue in the long-term safety trial.

So MDGN will look to capitalize on the potential affect of NFC-1 in 22q11.2 Deletion Syndrome and expects to initiate a Phase 1/2 indication and dose finding study in the near term with data expected around the middle of this year. Received IND in January 2016 to begin this study. The initial study is expected to parse out the first (of potentially other follow-on) indication - which MDGN noted could be related to ADHD, anxiety or mood disorders.

MDGN thinks a 22q11.2-related indication could be fairly fast-moving and ahead of mGluR+ADHD. Given the rarity of incidence and lack of any effective treatment, it's possible (assuming demonstrated NFC-1 effectiveness) this could be a quick-moving regulatory orphan candidate. While we caution that it's too early to jump on a bandwagon at this point (although positive results from 2 of 2 patients in the GREAT trial is encouraging), if the initial P1/2 study is positive, MDGN thinks they can go directly to a pivotal, regulatory approval-supporting study.

Given the benefits of orphan status (potentially massive pricing power, extended exclusivity, tax credits, fast-track regulatory advantage, etc) and no effective therapies that address the symptoms (much less the underlying cause), this could be a home-run type of candidate for MDGN (although remember, royalties and, potential milestones, will apply). And the beauty is, assuming enrollment in the study(ies) is not a challenge (CHOP is the leader in 22q11.2 research which presumably will facilitate this), evidence of efficacy (or not) may not be a long wait.

Value MDGN at $350M, Maintain Buy Recommendation

We continue to see fair value at approximately $350M or ~$11/share. Further successful progression through the development pathway should provide for additional de-risking and potential upside to our current $11/share target price.

FINANCIAL MODEL

Medgenics, Inc.

	2015 A	Q1E	Q2E	Q3E	Q4E	2016 E	2017 E	2018 E	2019 E
Total Revenues	$0.0	$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	$0.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Margin	-	-	-	-	-	-	-	-	-
SG&A	$12,954.0	$4,414.0	$4,387.0	$3,356.0	$2,788.0	$14,945.0	$15,444.0	$15,925.0	$16,324.0
% SG&A	-	-	-	-	-	-	-	-	
R&D, net of grants	$23,614.0	$5,618.0	$5,715.0	$5,912.0	$6,117.0	$23,362.0	$26,687.0	$24,661.0	$23,781.0
% R&D	-	-	-	-	-	-	-	-	
Operating Income	($36,568.0)	($10,032.0)	($10,102.0)	($9,268.0)	($8,905.0)	($38,307.0)	($42,131.0)	($40,586.0)	($40,105.0)
Operating Margin	-	-	-	-	-	-	-		
Financial expense, net	($1,407.0)	($12.0)	($17.0)	($22.0)	($16.0)	($67.0)	$0.0	$0.0	$0.0
Total Other Income (Expense)	($1,407.0)	($12.0)	($17.0)	($22.0)	($16.0)	($67.0)	$0.0	$0.0	$0.0
Pre-Tax Income	($37,975.0)	($10,044.0)	($10,119.0)	($9,290.0)	($8,921.0)	($38,374.0)	($42,131.0)	($40,586.0)	($40,105.0)
Tax expense (benefit)	$17.0	$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	($37,992.0)	($10,044.0)	($10,119.0)	($9,290.0)	($8,921.0)	($38,374.0)	($42,131.0)	($40,586.0)	($40,105.0)
YOY Growth	*106.1%*	*-45.5%*	*13.4%*	*52.7%*	*-46.0%*	*1.0%*	*9.8%*	*-3.7%*	*-1.2%*
Net Margin	-	-	-	-	-	-	-	-	*#DIV/0!*
EPS	($1.51)	($0.31)	($0.31)	($0.28)	($0.27)	($1.16)	($1.11)	($0.97)	($0.91)
YOY Growth	*58.2%*	*-22.0%*	*9.4%*	*-150.5%*	*1.0%*	*-23.4%*	*-4.6%*	*-12.4%*	*-6.1%*
Diluted Shares O/S	25,078	32,900	33,000	33,100	33,200	33,050	38,016	41,800	44,000

Brian Marckx, CFA

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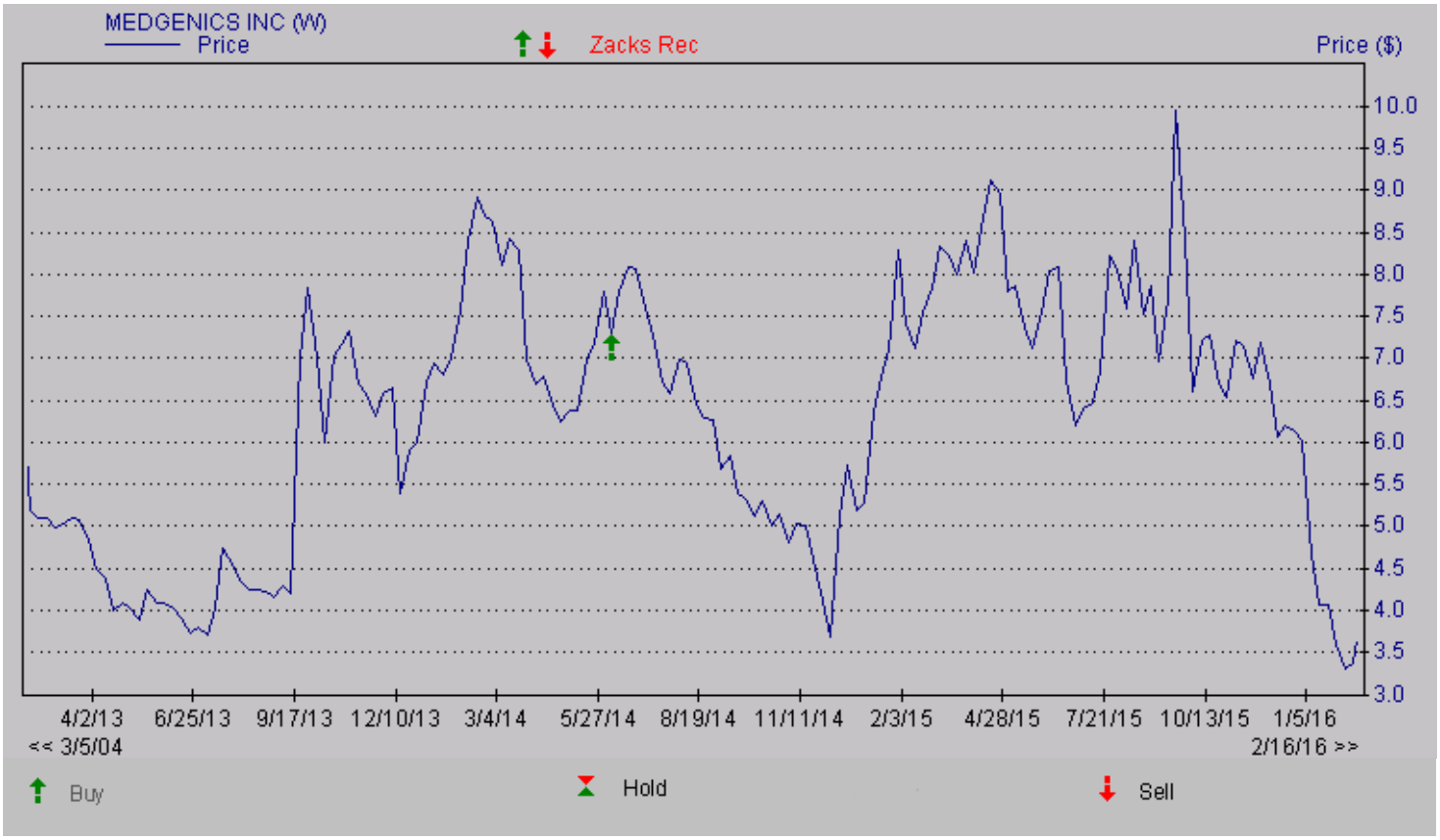

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Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 24.7%, Hold/Neutral- 52.1%, Sell/Underperform – 17.4%. Data is as of midnight on the business day immediately prior to this publication.