COMPANY NOTE

Initiating Coverage

USA | Healthcare | Biotechnology

July 28, 2014

Jefferies

Minerva (NERV)

Initiating At Buy – First-In-Class Schizophrenia Opportunity

BUY

Price target $10.00

Price $6.78

EQUITY RESEARCH AMERICAS

Key Takeaway

We see Minerva as an undervalued neuropsychiatric company with two drugs in Phase 2 development that each address huge market opportunities. MIN-101 already has proof-of-efficacy and strong safety data and could be the first schizophrenia drug to address negative symptoms, while MIN-117 is earlier and risky but could pay off if it shows compelling efficacy in refractory depression.

In July 2014, Jefferies acted as the sole bookrunner in the initial public offering of NERV common shares.

Bull Case: Multiple Drugs For Big Indications. Relative to its modest market cap, Minerva has multiple unpartnered programs in Phase 2 development targeting large market opportunities. Minerva has already generated positive Phase 2a data for MIN-101 that shows a favorable effect on negative symptoms of schizophrenia (e.g., social withdrawal, isolation), a significant unmet medical need that current schizophrenia drugs do not address. Even 5% penetration of the schizophrenia prescription market could yield $2+ billion in sales. We would also highlight management's deep experience in conducting schizophrenia trials. Separately, Minerva is advancing MIN-117 into Phase 2 proof-of-concept trials for major depression, an equally large market. Phase 1 programs for MIN-202 and MIN-301 in insomnia and Parkinson's represent free call options.

Bear Case: Investors Perceive High Clinical Risk In These Indications. There have been questions raised on the strength of the efficacy signal and the high dropout rate in the MIN-101 Phase 2a study and the risk that the MIN-101 Phase 2b trial will fail to show a compelling efficacy signal on negative symptoms. There is competition developing schizophrenia drugs treating both positive and negative symptoms. The exclusivity period for MIN-101 could be short as 2026 and as long as 2034. We see MIN-117 as riskier given the early stage of development and lack of proof-of-concept.

Upcoming Catalysts. The critical Phase 2b data for MIN-101 in schizophrenia will be available in 1Q16, with Phase 2a data for MIN-117 in 1H16 pending funding. The Phase 1 trial of MIN-202 in insomnia could be a positive catalyst in 2H14 that would be upside to our valuation.

Valuation/Risks

We reach our $10 PT through a sum-of-the parts DCF of $7.50 MIN-101 + $1.50 MIN-117 + $1 cash. NERV is subject to standard biotech risks including clinical, regulatory, and commercial.

USD	Prev.	2012A	Prev.	2013A	Prev.	2014E	Prev.	2015E
Rev. (MM)	--	0.0	--	0.0	--	0.0	--	25.0
EV/Rev								2.7x
EPS								
Mar	--	--	--	--	--	(0.43)A	--	--
Jun	--	--	--	--	--	(0.43)	--	--
Sep	--	--	--	--	--	(0.38)	--	--
Dec	--	--	--	--	--	(0.55)	--	--
FY Dec	--	(0.47)	--	(0.63)	--	(1.82)	--	(1.43)
FY P/E		NM		NM		NM		NM

Financial Summary

Net Debt (MM):	($56.0)
Long-Term Debt (MM):	$0.0

Market Data

52 Week Range:	$7.54 - $5.57
Total Entprs. Value (MM):	$68.1
Market Cap. (MM):	$124.1
Insider Ownership:	NA
Institutional Ownership:	NA
Shares Out. (MM):	18.3
Float (MM):	3.9
Avg. Daily Vol.:	NA

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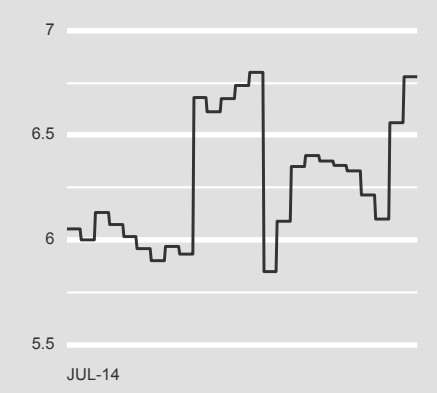
Price Performance



Minerva Neurosciences Inc.

BUY: $10 Price Target

THE LONG VIEW

Scenarios

Target Investment Thesis

- MIN-101 could offer benefit for negative schizophrenia symptoms
- Negative symptoms represent a major unmet need – modest penetration could yield $1.1b in peak U.S. sales
- MIN-101 exclusive through 2026
- MIN-117 is a high-risk / high-reward opportunity in addressing antidepressant failures
- Target Price: $10 ($7.50 MIN-101 + $1.50 MIN-117 + $1 cash)

Upside Scenario

- With strong benefit on positive and negative symptoms MIN-101could be multi-billion opportunity
- Vast market opportunity for MIN-117 if it shows differentiating characteristics
- MIN-101 exclusive through 2031
- Takeout potential if either drug works
- Target Price: $19 ($14 MIN-101 + $4 MIN-117 + $1 cash)

Downside Scenario

- MIN-101 trial design changes could be negative
- MIN-101 may not show benefit for positive symptoms limiting opp
- MIN-117 may not find partner and is too costly for NERV to develop
- High likelihood MIN-117 fails
- MIN-101 exclusive through 2021
- Target Price: $1 ($1 cash)

Long Term Analysis

Revenue (millions)

N/A

Source: Company Reports, Jefferies LLC

Long Term Financial Model Drivers

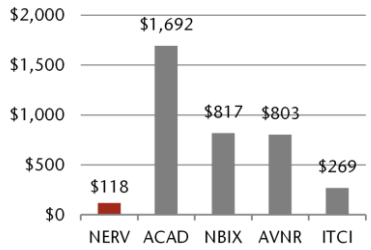
Earnings CAGR	**+45%**
Revenue Growth (2019-2022 CAGR)	**+53%**

Other Considerations

With several eagerly anticipated product launches, anemic pipelines at large cap pharma, and an increasingly conservative FDA stance, we believe small and mid-cap biotech could lead sector performance in 2014. We see a premium placed on late-stage and marketed products. M&A interest could also factor into the performance of the sector, particularly among small-cap and mid-cap companies with later stage programs.

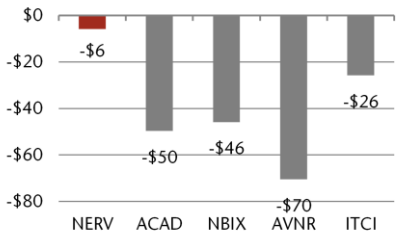
Peer Group

Group EVs



Source: Jefferies LLC

Net Income



Source: Jefferies LLC

Recommendation / Price Target

Ticker	Recommendation	PT
NERV	BUY	$10
ACAD	BUY	$38
AVNR	HOLD	$5
NBIX	BUY	$21
ITCI	NC	NA

Catalysts

- 2H14: MIN-202 Ph1b data
- 1H16: MIN-117 Phase 2 data
- 1H16: MIN-101 Phase 2b data

Company Description

Minerva Neurosciences Inc. (NERV, $10) is a Cambridge, MA-based company focused on developing neuropsychiatry therapeutics. Minerva's lead product candidate MIN-101 is a 5-HT2A/Sigma2 antagonist in Phase 2 development for the treatment of schizophrenia. NERV is also developing MIN-117, an antagonist of 5-HT1A and 5-HTT receptors and both serotonin and dopamine, for major depressive disorder (MDD).

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Executive Summary

Minerva Neurosciences Inc. (NERV) is a Cambridge, MA-based company focused on developing neuropsychiatry drugs. Minerva's lead product candidate, MIN-101, is a 5-HT2A/Sigma2 antagonist in Phase 2 development for the treatment of schizophrenia. MIN-101 is differentiated from conventional antipsychotics as it was developed to be effective against negative symptoms (e.g., social withdrawal, isolation, mood flatness) with the potential to also improve positive symptoms (e.g., hallucinations and delusions) that are targeted by current approved antipsychotics. We expect data from the Phase 2b trial for MIN-101 in 1H16 and believe MIN-101 could be approved by 2019, leading to peak sales of $3+b. Minerva is also developing MIN-117, an antagonist of 5-HT1A and 5-HTT receptors and both serotonin and dopamine, for major depressive disorder (MDD). Although the antidepressant space is crowded and saturated with generics, conventional anti-depressants can take weeks to have an effect and have a high failure/relapse rate. Minerva believes MIN-117 could be differentiated by fast onset of action and potential to treat patients that have failed previous lines of antidepressants. We believe MIN-117 could reach market by 2020 leading to peak U.S. sales of $2+b. Minerva has two other products in early Phase 1 or preclinical development: MIN-202, an orexin-2 antagonist for primary and secondary insomnia, and MIN-301, an ErbB4 activator for Parkinson's disease.

Valuation

We value Minerva entirely on prospects for MIN-101 and MIN-117, which we expect to reach the market in 2019 and 2020, respectively. We build our market models for both schizophrenia and depression from historical prescription data as reported by IMS. For MIN-101, we model peak 2025 share of only 6% in the U.S. and 3% of the EU of all antipsychotics prescribed for schizophrenia (we assume roughly 50% of all antipsychotic use is in schizophrenia). We are assuming a launch price of $1,140 per month in the U.S. and $650 per month ex-U.S. We model a U.S. and rest-of-world (ROW) partnership with tiered net royalties of 17-22%. We equally weight a base case exclusivity scenario of 2026 with an extended exclusivity scenario of 2033. We assume a 55% probability of success for MIN-101. For MIN-117, we model 3% penetration of the antidepressant market in the U.S. and 1% penetration ex-U.S. We are assuming a price of $484 per month in the U.S. and $164 per month ex-U.S. We model a U.S. partnership with tiered royalties of 8-15% and ROW partnership with tiered royalties of 6-13%. We estimate a 25% probability of success with MIN-117. Our $10 price target is based on a discounted-cash-flow, sum-of-the-parts model of $7.50 MIN-101 + $1.50 MIN-117 + $1 net cash.

Exhibit 1: NERV Sum-Of-The-Parts Valuation

	Prob of Success	NPV - 2026	NPV - 2033	Blended	Per Share
MIN-101	55%	$163,058	$361,559	$144,270	$8
MIN-117	25%	$104,764	$176,438	$35,150	$2
Net cash				$17,671	$1
Total NPV				**$197,091**	**$10**
Shares	19,175				

Source: Jefferies estimates, company data

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Risks

Risks include the standard early-stage biotech risks: clinical, regulatory, and commercial. In addition, specific risks to MIN-101 and MIN-117 are discussed in the next section of our report. For MIN-101, there is the risk that the Phase 2b trial will fail to show efficacy on negative symptoms and we note changes to the trial design could help or hinder its likelihood to succeed. Further, we are unsure whether there will be a significant impact on positive symptoms, which could have implications for both clinical trial risk and the commercial opportunity. Further, there is the competitive risk posed by other schizophrenia drugs in development such as ITI-007. Exclusivity for MIN-101 is uncertain: MIN-101 is protected by a composition of matter patent through only 2021, and as such, the minimum exclusivity will result from standard Hatch-Waxman protection for a new chemical entity (effectively 6.5 years following a 30-month stay) through 2026. There is a pending method of use patent that could provide additional protection through 2031 and may even be extended with patent term extension into 2034, but there is a risk that this patent will not be defensible and that generic entrants could come to market sooner than expected. We believe the development program of MIN-117 is risky, as we have no efficacy data in depression yet, and at this time, advancement into Phase 2 trials is contingent on partnering or finding additional funds, as the IPO proceeds were insufficient to advance both MIN-101 and MIN-117 in parallel.

Key Controversies

Controversy #1: How strong are the Phase 2a data for MIN-101? We believe the major concern with the Phase 2a data for MIN-101 is the strength of the efficacy signal on negative symptoms, the key differentiating feature of the drug, particularly when comparing the per-protocol completer (PPC) analysis with the intent-to-treat (ITT) analysis. Ninety-six patients were randomized in the trial, 84 patients were dose titrated and made it to the first evaluation on day 6 (ITT population), but only 30 completed the study. For the per-protocol completer analysis, there was a statistically significant effect observed on the negative symptom five-factor PANSS score (-7.5 vs. -3.2, p=0.0178). In the ITT population, the negative score reduction was also nominally statistically significant but the magnitude of the benefit was smaller (-1.4 vs. -0.1, p=0.045). Using the less robust three-factor PANSS score, MIN-101 demonstrated similar, near-significant reduction in negative symptoms in both the PPC and ITT analyses at p=0.058 and p=0.062, respectively.

Our Take: Efficacy signal is encouraging - new trial design should enhance future outcomes. We are encouraged by the efficacy signal in the Phase 2a study. First, the trial did reach statistical significance on both a PPC and ITT basis, and although the magnitude of the effect is smaller on ITT, we believe that this provides sufficient evidence to move forward into the next study. To this end, Minerva's data on negative symptoms is stronger than what Roche (ROG VX, CHF267, Buy) observed with bitopertin in Phase 2 (-1.8 vs. placebo in a per-protocol completer analysis, and -1.35 in the ITT population). Second, patients on MIN-101 had continuing improvement in negative symptom PANSS scores over time, and the placebo effect in the placebo arm looks like it is just starting to wear off and reverse right around the end of the Phase 2a study. This would suggest more robust data in the Phase 2b trial as treatment is extended from three months to six months. Third, Minerva expects a lower dropout rate in the Phase 2b trial due to trial

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design changes (enrolling patients with less severe schizophrenia and less severe positive symptoms), coupled with a better statistical powering (200-250 patients vs. 100 patients in the Phase 2a). Thus, we think that investors could take a reasonable bet that the Phase 2b study will show a benefit on negative symptoms.

Controversy #2: Do the changes in the Phase 2b trial help or hurt? We have looked closely at the design of the upcoming Phase 2b study and compared to the Phase 2a design to evaluate the risk in replicating the outcome. There are several changes being implemented: the dosing of MIN-101 (from twice daily to once daily), the duration of treatment (from three months to six months), the hospitalization period (from 28 days to 8-10 days), and the patient population (from all-comers to a predominantly negative symptoms population, and from 100 patients to 255 patients). Arguments could be made on both sides whether the net effect of these changes enhances or reduces the risk of a positive outcome.

Our Take: We generally do not like a lot of changes, but the net effect should be positive. In evaluating drugs, one of the key parameters we monitor is the number of changes being implemented from proof-of-concept to confirmatory trial. The MIN-101 Phase 2b program contains several changes, which would normally increase the risk of the outcome, compounded by the high historical failure rate of schizophrenia trials in negative symptoms. That said, we note that many of these changes are being implemented to try to lower the risk of the trial, and ultimately, we would rather see these changes be implemented at the Phase 2b stage than during the Phase 3 trials. We also point to a key strength of the management team in their deep experience in schizophrenia; the chief medical officer of Minerva ran a contract research organization devoted to the operational execution of clinical trials for 30+ drugs in schizophrenia. Below, we outline each of the changes in detail.

Patient population: The key change is that the Phase 2b trial will enroll patients with either prominent or predominant negative symptoms, whereas the Phase 2a trial was relatively heterogeneous and reflected the general schizophrenia population. In the Phase 2a trial, those patients who dropped out had higher baseline positive symptom scores. For instance, there was a 3.2 point difference between the ITT population and completers in the MIN-101 arm. Completers had an average positive symptom score below 19 at baseline, similar to the patient entry criteria in the Phase 2b study. There are multiple ways to refine the Phase 2b population to a more homogeneous group with negative symptoms. Generally, screening for patients who score highly on the negative subscale (predominant negative symptoms) would allow for Minerva to recruit from a broader schizophrenia population. In this case, Minerva's entry criteria will allow only those patients into the trial with a negative subscore of greater than 22 points. The company estimates that the baseline average will be 28 points. The PANSS positive subscale will also need to be below 19 at study entry. This has been endorsed by our physician consultants and represents a stricter set of predominant negative criteria, sacrificing recruitment speed to some degree for a higher quality, more homogeneous patient pool. This will have two potentially beneficial effects. First, the company hopes that Phase 2b patients may have more negative relative to Phase 2a (target of 28 on the PANSS negative subscale vs. 24 in the Phase 2a study), with the assumption that it may be easier to show a treatment benefit in patients who suffer from the sought-after condition. Second,

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placing a ceiling on the maximum positive symptom score at entry could result in lower positive scores at baseline (target of 19 or less in Phase 2b vs. 21 in the Phase 2a study) and a lower relapse/dropout rate. Secondarily, the company believes that its entry criteria will skew the overall population to generally less severe schizophrenics. The total PANSS at baseline in the Phase 2a study was 89 in the MIN-101 arm, a very high score relative to historical studies, which may have increased the dropout rate. For comparison, the arms for bitopertin Phase 2b trial had PANSS between 78 and 80. The CATIE trial, which tried to compare the efficacies of multiple antipsychotics, had an average PANSS of 76. In fact, the MIN-101 Phase 2a population was close to the severity of patients enrolled in studies of long-acting depot antipsychotics (the Invega Sustenna trials had PANSS ranging between 85 and 92). This makes sense, as usually the most severe patients require depot injections. The size of the trial will also be increased from 100 patients in Phase 2a to 255 patients in Phase 2b. This will increase the company's power to detect a difference in efficacy between the two arms.

Hospitalization: One key change in the protocol will be to shorten the period of hospitalization at the start of the study from 28 days in the Phase 2a study to 8-10 days in the Phase 2b study. This long hospitalization in Phase 2a was a safety measure since patients were being washed off all other schizophrenia medication during the course of the study, but may have contributed to a "caregiver" effect on the efficacy endpoints. The shorter hospitalization period in Phase 2b may have the benefit of reducing some of the placebo effect observed in the Phase 2a study, allowing the curves to separate to a greater and faster extent. However, the shorter hospitalization may also increase the risk of early discontinuations due to relapse. Minerva believes that the less severe patient target population and the dominance of negative symptoms relative to positive symptoms may help compensate for the increased risk of potential relapses. Separately, Minerva does not expect to use a placebo lead-in period, where all patients are administered placebo and patients who see a high "response" are removed from the randomized pool. The company believes this would be unnecessary given the long duration of the trial and the rigorous patient screening process both should limit the placebo effect.

Dosing and duration: Minerva is changing the dosing in the study. In the Phase 2a study, patients were titrated to 32 mg twice daily. In the Phase 2b study, patients will receive 64 mg once daily in an extended release formulation. Bioequivalence work is under way to confirm equivalent total drug exposure for the new formulation, although with a smoother exposure level (lower Cmax and higher Cmin). Any differences in pharmacokinetics could increase the risk of replicating a positive outcome, but we do not view this as a major risk to the trial. There will be an additional dose studied, 32 mg once per day, in addition to the 64 mg daily dose from Phase 2a. The change in dosing may also have a favorable effect on the QT prolongation profile of the drug by lowering the Cmax. The treatment period in the Phase 2b trial will also be extended from three months to six months. Efficacy will be assessed at both month 3 and 6. We see this as a positive change in the trial design, as the Phase 2a curves suggest that the MIN-101 arm may experience continued improvements in efficacy beyond month 3 while the placebo arm may rebound back toward baseline if followed for longer. Either of these trends would favorably impact the data in Phase 2b.

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Controversy #3: Does MIN-101 affect positive symptoms? Should a monotherapy trial be run? One key point that will need to be clarified in the upcoming Phase 2b trial is the effect of MIN-101 on positive symptoms. Minerva notes a trend towards improvement in positive symptoms late in the three-month treatment period of the Phase 2a trial and management believes that a longer trial would show an eventual benefit on positive symptoms. In the per-protocol completer population, the effect on positive symptoms was -3.0 vs. -4.9 in placebo at day 28 ($p<0.05$ favoring placebo), but had reversed to -4.2 for MIN-101 vs. -3.9 for placebo by day 84 (p = not significant). In the ITT population, the placebo score showed a reduction in positive scores greater than MIN-101 for the entirety of the study, but the gap was closing by day 84 (0.4) vs. day 28 (1.9). The data raise three questions: will MIN-101 have a favorable effect on positive symptoms with longer-term followup? Does MIN-101 have an early unfavorable effect on positive symptoms and what are the implications for development? Should MIN-101 be used as monotherapy or in combination with an atypical antipsychotic to treat positive symptoms?

Our Take: We assume MIN-101 works on negative symptoms only and likely to be used in combination with atypicals. At this point, we are not certain if MIN-101 will show an effect on positive symptoms and believe its role will be largely in the treatment of negative symptoms. Because of very small patient numbers, it is also possible that MIN-101 could have no effect on positive symptoms either early on or over time. The early unfavorable separation in positive symptom scores may lead to questions around the potential for heightened acute exacerbations in the upcoming monotherapy study, but we do not believe that this will play a major role in the dropout rate as both arms of the Phase 2a trial showed an improvement in positive symptoms relative to baseline and the target patient population for Phase 2b will be optimized for patients who do not have significant positive symptoms at baseline.

Nonetheless, there are signs of positive symptom benefits for MIN-101. There were improvements in the positive subscale score over time in the MIN-101 arm. Schizophrenia-related treatment-emergent AEs (TEAEs) were less frequent in the MIN-101 arm (6 patients) compared to placebo (12 patients). Additionally, the number of withdraws due to lack of efficacy and/or worsening of schizophrenia was less in the MIN-101 arm (9 patients) than placebo (16 patients). If MIN-101 actually had a deleterious effect on treating positive symptoms, we would have expected the schizophrenia-related withdrawals and TEAEs to skew in the opposite direction. Overall, the number of psychiatric disorder-related TEAEs was the same for both arms at 22 each.

From a commercial standpoint, the most likely scenario where MIN-101 has a neutral effect on positive symptoms could limit the drug to adjunctive therapy for stable patients already on atypical antipsychotics, an important setting which we believe will have to be studied prior to approval. This would be the same population that was targeted by the failed compounds for Roche and Targacept (TRGT, $3.92, NC). Even in this more restricted population, we believe the drug would have multibillion dollar potential based on the size of the schizophrenia population. There could also be some use as monotherapy in patients suffering primarily from negative symptoms.

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Controversy #4: Does MIN-101 carry a cardiac toxicity risk? MIN-101 is associated with modest QTc prolongation. QTc prolongation can lead to rare fatal ventricular arrhythmias and sudden cardiac death. This has been a historically sensitive issue for the FDA. In the early Phase 1 trials, QTc prolongation of 21.6 msec was observed at doses of 48 mg twice daily. This is the reason why Mitsubishi (MTZXF, $14.55, NC) discontinued development of MIN-101. In Minerva's Phase 2a trial, lower doses were tested and the mean QTc prolongation was 7.75 msec at 32 mg twice daily vs. placebo over the course of the 84 day study. No QTc measurement was over 480 msec, an absolute threshold considered to be concerning. These measurements were taken at maximum drug concentration levels on office visits (patients took their daily dose while at the investigator's office).

Our Take: The magnitude of QTc prolongation with MIN-101 should be acceptable to regulators. We do not see the QTc prolongation as a major issue for MIN-101 for several reasons. First, the magnitude (7.75 msec) falls below the range where the FDA becomes concerned (>10 msec), although this may still need to be confirmed in the context of a thorough QT study, which the company has yet to conduct. Second, this particular division of the FDA has a history of approving drugs with some modest or even bigger QTc effects, including many antipsychotics with less differentiated profiles than MIN-101. Third, the company is switching to an extended release, once daily formulation (64 mg once daily instead of 32 mg twice daily), which will reduce the Cmax by 4-6 fold relative to the immediate release formulation while maintaining overall daily exposure levels. Since QTc prolongation is dose-dependent, this should mitigate the QTc profile of the drug.

Controversy #5: Will Intra-Cellular's (ITCI, $13.72, NC) ITI-007 offer a better profile than MIN-101? ITCI's ITI-007 is a 5-HT2A receptor antagonist, dopamine phosphoprotein modulator, glutamatergic phosphoprotein modulator, and serotonin reuptake inhibitor being developed for multiple indications at various doses. ITI-007 has completed Phase 2 trials in schizophrenia, demonstrating antipsychotic efficacy in a randomized, double-blind, placebo and active controlled trial in patients with an acutely exacerbated episode of schizophrenia. In its four arm (60 mg ITI-007, 120 mg ITI-007, active control 4 mg Risperdal, and placebo), 335-patient Phase 2 study (of which 311 were in the ITT primary analysis population), ITI-007 at the lower dose (60 mg once daily) met the pre-specified primary endpoint, improving symptoms associated with schizophrenia as measured by a statistically significant and clinically meaningful decrease in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to Day 28 (p=0.017 versus placebo in the ITT patient population). The trial also met key secondary outcome measures related to efficacy on PANSS subscales and safety. The Phase 2 showed a differentiating response for ITI-007 60 mg on negative symptoms versus both placebo and 4 mg Risperdal. Additionally, ITI-007 improved some negative symptoms that Risperdal did not improve and also did not worsen some negative symptoms that Risperdal worsened versus placebo (e.g., blunted affect).

ITI-007 was also shown to improve pro-social behavior, with a statistically significant effect versus placebo and a non-statistically significant but favorable trend versus Risperdal. Notably, the higher dose, 120 mg once daily, did not reach statistical significance. The company has hypothesized that sedation, the most frequent side effect

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in the 120 mg dose group, interfered with the ability to detect an efficacy signal. Approximately 32.5% of subjects randomized to 120 mg ITI-007 experienced sedation/somnolence, compared to 21% of subjects randomized to Risperdal, 17% of subjects randomized to 60 mg ITI-007, and 13% randomized to placebo. Thus, the company has hypothesized that nighttime dosing (the Phase 2 used morning dosing) may be more appropriate for testing the 120 mg dose. Importantly, only 19% of patients discontinued the Phase 2 trial and 7% completed but were lost to follow-up, which is better than Minerva's Phase 2a, where only 31% of the 96 patients that were initially randomized completed the trial.

In contrast to the Risperdal arm of the trial, 60 mg of ITI-007 was effective with no difference from placebo on weight change parameters, prolactin levels, extrapyramidal symptoms (EPS) or akathisia. There were no clinically significant changes in cardiovascular function (no QTc prolongation and unlike Risperdal, did not cause sustained increases in heart rate). Thus, preclinical studies and initial clinical trials demonstrate that ITI-007 has shown evidence of addressing the symptoms of schizophrenia without causing cardiovascular and metabolic abnormalities, or motor impairments and the company is currently planning confirmatory later-stage clinical trials.

Our Take: MIN-101 likely to have more pronounced efficacy on negative symptoms than ITI-007. While the Phase 2 data for 60 mg is encouraging, the lack of a dose response necessitates confirmation of the initial signal with additional randomized trials. The company plans to position ITI-007 as a stand-alone therapy, but we believe that MIN-101 has the potential to be used in combination with atypical antipsychotics to offer an even more potent degree of activity on positive and negative symptoms. ITI-007's effect on negative symptoms appears to be inferior to MIN-101 on an absolute basis, even in predominantly negative patients (-0.34 points vs. -1.7 points for MIN-101), and there was limited efficacy with ITI-007 on negative symptoms in the overall population. Thus, in the key population of predominantly negative symptom stable patients, we would expect MIN-101 to be the drug of choice. On safety, MIN-101 appears to offer a strong side effect profile in line or better than ITI-007, including a lack of dopaminergic side effects seen with atypical antipsychotics, no weight gain, no prolactin increase, no sedation, and a reasonable cardiovascular safety margin.

Controversy #6: Are negative symptoms too difficult to study? The failures of Roche's bitopertin and TRGT's TC-5619. MIN-101 is thought to work via a dual mechanism of action as a blocker of 5-HT2A and sigma2. Notably, it is non-dopaminergic, which is the issue with most atypical antipsychotics causing side effects such as sedation, weight gain, EPS, and cognitive impairment. MIN-101 has thus far demonstrated evidence that it could be a potential treatment of negative symptoms (for which there is no approved therapy) and early studies have shown that MIN-101 could improve cognitive abilities and insomnia, in addition to potentially having a longer-term improvement in positive symptoms. Given this profile, MIN-101 is quite different than Roche's bitopertin and TRGT's TC-5619, which both recently failed clinical trials.

In December 2013, Targacept announced failure of its Phase 2b trial of TC-5619, an oral α7 agonist, following positive data from a Phase 2a study showing a 10-point improvement in negative symptoms. In its 477-patient Phase 2b study run in the U.S. and

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Eastern Europe in combination with antipsychotics, the company failed to show a benefit in either negative symptoms or cognitive function. The primary endpoint was SANS at 24 weeks. Unlike the prior Phase 2a trial that did not have a threshold SANS score, the Phase 2b trial required a PANSS negative symptom subscale score >20. In the Phase 2b trial, subjects in placebo arm and both doses showed consistent but similar improvements in negative symptoms. Improvement in the SANS score was 15.4 for placebo and 14.7 and 17.5 in high and low dose arms, respectively. Baseline was approximately 70.

Roche's bitopertin is a glycine reuptake inhibitor that specifically inhibits glycine transporter type-1 (GlyT-1) in glial cells. Based on mixed Phase 2 trial results, in which there was an inverse dose response (10 mg dose was efficacious but 60 mg was not) and a marginal effect on negative symptoms in both ITT and per protocol analyses, Roche initiated six Phase 3 studies under a special protocol assessment (SPA) from the FDA. Three trials were in patients with predominant negative symptoms with doses of 5mg, 10mg and 20mg. The other three trials were in patients who were sub-optimally controlled on their current medication. However, in January 2014, Roche reported that two of the negative symptom trials did not meet their primary endpoints of PANSS NSFS. Additionally, the Roche quarterly earnings press release in April 2014 disclosed that one of the sub-optimally controlled studies also failed its endpoint (PANSS PSFS), and following a futility analysis of the remaining three trials, an additional two were discontinued. The remaining trial, NightLyte, in sub-optimally controlled schizophrenia continues, but we have low expectations for success.

Our Take: Negative symptoms have been tough to improve, but recent failures hold little relation to MIN-101. While the recent failures in schizophrenia highlight the challenges of drug development in this indication, we would point out that both TC-5619 and bitopertin are different mechanistic approaches relative to MIN-101. TC-5619 had been heavily scrutinized for an unusual demographic in the positive Phase 2a study (2/3 Indian, 1/3 black). In addition, we note that Roche's high profile failure was based on weak Phase 2 data. Thus, we do not see these failures are providing any read-through to MIN-101.

Controversy #7: How much risk is there in the MIN-101 patent portfolio? MIN-101 currently has a composition of matter patent that expires in 2021 (with potential for up to five years of extension) as well as a pending method of use / treatment patient that would expire in 2031. Patent term extension of the method of use patent would create exclusivity through 2033/2034. We currently assume product launch in 2019, at which point there would be at least 6.5 years of exclusivity based on the minimum Hatch-Waxman exclusivity if five years plus an extension for a stay related to patent litigation.

Our Take: We weight both scenarios equally to derive our valuation. Given the inherent risk in method of use patents, we currently use both exclusivity scenarios (2026 vs. 2033) with equal weight. That said, the size of the market opportunity makes MIN-101 a compelling asset at current valuations even in the worst case scenario of a generic launch in 2026. For EU markets, we assume a minimum of 10 years of data exclusivity post approval.

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Controversy #8: MIN-117 Is A Potentially Differentiating Therapy For Depression, But Still Early. Based on preclinical and Phase 1 data, the company has hypothesized that MIN-117, an NCE being studied for the treatment of major depression disorder (MDD), could be differentiated from currently approved MDD therapies. Given data from studies in healthy volunteers showing a sleep benefit associated with MIN-117 versus placebo, it is possible that MIN-117 could improve sleep in patients with MDD. Further, MIN-117 was found to be safe and well tolerated in healthy volunteers. While the drug had a safe and tolerable profile in healthy volunteers, it has not yet been tested in MDD patients and thus it is unclear if it will have a better side effect profile than currently approved anti-depressants (i.e., weight gain, sedation, and sexual dysfunction). That said, if it is successful in demonstrating efficacy while also providing a benefit to sleep and a lack of effect on weight gain, sedation and sexual dysfunction, MIN-117 could be a promising drug in a very large market (>$5b currently). Lastly, preclinical data has suggested that MIN-117 could have a faster onset of action versus currently marketed therapies. Most marketed products have an onset of action within two weeks, whereas MIN-117 could potentially be active within a few days. While we do not yet have any data on MDD patients and thus attribute a low probability of success to the program in our current model, MIN-117 could prove to be a differentiated therapeutic option in a very large MDD market.

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MIN-101

Background: Negative Schizophrenia Symptoms Are A Major Unmet Need. Schizophrenia affects about roughly 1% of the world population. The disease represents a substantial burden to public health resources, as schizophrenic patients are often unemployed, homeless, or incarcerated. The symptoms of schizophrenia have historically been divided into three categories using the Positive and Negative Syndrome Scale (PANSS): positive, negative, and general psychopathology. Positive symptoms are the most commonly known manifestation of schizophrenia and include delusions, hallucinations, and hostility. Negative symptoms deal with a lack of emotion, withdrawal and a blunted affect. In more recent evaluations of schizophrenia (with some controversy), there are PANSS with five factors to also attempt to assess cognition symptoms. The expanded five factors are: positive, negative, activation, dysphoric, and autistic.

The symptoms are heterogeneous in the schizophrenia population and often differ by age. At the beginning of schizophrenia onset, typically in the 20s, there are more frequent and severe episodes of positive symptoms. These episodes begin to dissipate with age. However, negative symptoms and cognitive impairment continue throughout the patient's life, and patients remain a burden on the healthcare system. There are many drugs indicated for schizophrenia in the antipsychotic class. The older agents, such as haloperidol and fluphenazine, are known as typical antipsychotics while the newer class drugs, including Risperdal, Zyprexa, Seroquel, and Abilify, are atypical antipsychotics. The vast majority of these drugs are now genericized; Invega, Abilify, and long-acting Seroquel remain branded. Approved antipsychotics, when effective, are used to treat the positive symptoms of schizophrenia. Although some patients respond well to single-drug regimens, a psychiatrist may need to prescribe a cocktail of antipsychotics to find an effective therapy to manage the positive symptoms. Unfortunately, there continue to be no effective therapies to treat the negative and cognitive symptoms of schizophrenia. Atypical antipsychotics are often used to treat other psychiatric indications, such as major depressive disorder and bipolar disorder. Off-label usage is prevalent for atypicals as well. For example, often atypical antipsychotics are used to treat psychosis related to Parkinson's and Alzheimer's despite having a black box warning for an increased risk in elderly patients with dementia.

Background on MIN-101. MIN-101 is a Minerva's lead oral drug candidate for the treatment of schizophrenia, specifically negative symptoms and cognition. MIN-101 has completed a Phase 2a trial and a Phase 2b trial is expected to begin in 4Q14. The drug rights were acquired from Mitsubishi in 2007. Minerva has worldwide rights to MIN-101, aside from a few Asian countries (China, Japan, India, South Korea).

Pharmacology. Atypical antipsychotics inhibit the D2 dopamine receptor, as well as serotonin (5-HT2A) receptors. Unlike typical antipsychotics that only inhibit D2, the atypical class bind less tightly to the receptor and also dissociate rapidly after binding. This allows for transient occupation of receptors and more normal dopamine levels. As a result, atypicals tend to have lower rates of adverse events such as movement disorders (extrapyramidal symptoms and tardive dyskinesia). The 5-HT2A binding could also reverse some of the D2 blockade and normalize dopamine. Risperdal is a strong inhibitor of 5-

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HT2A (Ki = 0.15 nM) as well as D2 (Ki = 3.77), while Zyprexa is slightly weaker. Abilify is actually a partial agonist of both D2 (Ki = 0.34 nM) and 5-HT1A, while having 5-HT2A antagonism (Ki = 3.4 nM).

Unlike atypical and typical antipsychotics, MIN-101 does not act as a dopamine antagonist and rather, works as both a 5-HT2A and a sigma-2 antagonist. The 5-HT2A antagonism is already found with atypical antipsychotics, including Risperdal, Zyprexa, and Seroquel. Sigma-2 inhibition may be responsible for more of the negative symptom and cognition-related improvements that Minerva expects MIN-101 to have. However, the role of sigma-2 on schizophrenia is still somewhat unclear. MIN-101 is highly selective for 5-HT2A (Ki = 5.2 nM), sigma-2 (Ki = 8.2 nM), and alpha-1 adrenergic receptors (Ki = 14.4 NM). MIN-101 has substantially less affinity for sigma-1 (Ki = 253.8) and no affinity (Ki > 1000 nM) for dopamine, muscarinic, cholinergic, and histaminergic receptors.

MIN-101 is metabolized through multiple pathways in the liver including CYP2D6, CYP3A4 and CYP2C19. 60% of the drug is metabolized through CYP2D6. We see this as an advantageous aspect of the MIN-101 profile as the multiplicity of metabolic pathways lessens the likelihood for drug-drug interactions and exacerbation of QTc prolongation.

Preclinical Efficacy Data. Studies of MIN-101 were conducted in a rat model using phencyclidine (PCP) to induce negative symptoms. In the study, the number of seconds of social interaction were measured over a 10-minute period in rats treated with nothing, PCP alone, PCP plus MIN-101, PCP plus Risperdal, and PCP plus Zyprexa. The animals treated with MIN-101 saw improvements in social interaction that were significantly greater than animals treated only with PCP. In fact, rats treated with the high dose of MIN-101 (1 mg/kg) had nearly the same level of social interaction as normal rats. In the rats treated with Risperdal or Zyprexa, there were marginal improvements in social interaction but none were significant.

Preclinical Safety Data. From a toxicology standpoint, MIN-101 has been tested in a variety of species in repeated dose studies (in rats for 4 weeks up to 300 mg/kg, 13 weeks up to 60 mg/kg, and 26 weeks up to 60 mg/kg, and in cynomolgus monkeys for 4 weeks up to 30 mg/kg, 13 weeks up to 20 mg/kg and 39 weeks up to 20 mg/kg). At the highest dose in the monkeys, there were some signs of movement disorders, decreases in body weight, decreases in hemoglobin, and QTc prolongation. All changes were reversible upon discontinuation of treatment. These data suggest a significant safety margin for human dosing, with this dose in monkeys representing a 20-30x window over the highest human dose being taken forward.

Phase 1 Data. MIN-101 was studied by Mitsubishi in 200 patients in five Phase 1 trials involving healthy volunteers and one Phase 1 trial in schizophrenic patients. Overall, safety and tolerability for MIN-101 was roughly comparable to placebo, with no extrapyramidal symptoms, tardive dyskinesia, or weight gain. Further, patients did not see a rise in prolactin levels, which can lead to sexual dysfunction and infertility. However, one study that included a higher dose group (48 mg BID) was discontinued due to QTc prolongation of 21.6 msec, a level that would normally trigger a high degree of regulatory concern. Because of the QTc results, Mitsubishi discontinued the program and

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then licensed the compound to Cyrenaic Pharmaceuticals, which became Minerva. Further discussion of QTc data is below in the Phase 2a results.

Phase 2a Trial Results. Minerva conducted a Phase 2a trial in 96 schizophrenic patients with severe symptoms. Patients had been hospitalized following an acute episode. These patients suffered from positive, negative, and cognitive symptoms, and had not responded to previously prescribed medication. Patients were tapered off of current antipsychotic therapy (roughly 3 to 9 days, and up to 3 weeks) during hospitalization and given three days of placebo lead-in. Patients were then randomized to MIN-101 or placebo and remained in the hospital for an additional 14 days. Patients were then released from the hospital and followed for an additional 10 weeks of therapy. Patients treated with MIN-101 were titrated during the inpatient stay, starting at 8mg BID to 32mg BID (or maximal tolerated dose) over six days. The primary endpoint was the global PANSS score and subscores at 28 days, although equally important were the secondary endpoints of PANSS scores at 84 days.

Patients had baseline PANSS of 89.4 (+/- 16.1) and 87.5 (+/- 15.5) in the MIN-101 and placebo arms, respectively. Positive subscale scores were 21.4 and 20.2 in the MIN-101 and placebo arms, respectively. Negative subscale scores were 23.8 and 24.3 in each respective arm. Notably, these patients were not required to have predominant negative symptoms. For comparison, relative to the Roche bitopertin Phase 2 trial, patients in the MIN-101 trial had significantly higher total PANSS scores (88 vs. 79-80), lower negative symptom scores (24 vs. 26-27), and higher positive symptom scores (20-21 vs. 17-18). Thirty out of the 96 patients completed the trial, and 84 patients were included in the ITT analysis (not all patients made it through titration to the first assessment).

The change in total five-factor PANSS (as measured by least-squares mean) at day 84 were 24.1 for MIN-101 and 17.9 for placebo, based on the per protocol analysis. The reduction in negative symptom scores continued to improve over time, as did the placebo-adjusted improvement based on the PPC analysis. At day 28, the reduction was 6.3 points for MIN-101 vs. 5.0 for placebo. At day 84, this increased to 7.5 points for MIN-101 vs. 3.2 for placebo. Further, at day 84, the result was statistically significant (p=0.0178). Given the high dropout rate, the magnitude in the ITT population was less, with a negative symptom reduction at Day 84 of 1.4 points compared to 0.1 for placebo. This result was still nominally statistically significant at p=0.045.

On positive symptoms, both the ITT and PPC at day 28 showed an unfavorable effect for MIN-101 relative to placebo. MIN-101 actually was worse than placebo by 1.9 points (3.0 vs. 4.9) for positive symptoms at day 28. However, this trend reversed by day 84 and MIN-101 showed a 0.3 point improvement in positive symptoms relative to placebo (4.2 vs. 3.9). In the ITT population, MIN-101 was numerically worse than placebo at day 84 (1.4 vs. 1.8), although the gap was narrowed from day 28 (1.3 vs. 2.3). Importantly, the MIN-101 arm showed a continued improvement in positive symptoms after the hospitalization placebo effect had passed.

On other endpoints, MIN-101 showed a non-significant improvement in activation symptoms of approximately 2 points relative to placebo (p=0.08). Dysphoric and autistic scores were roughly in line with placebo as well. Minerva also saw improvements in

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motor speed, verbal fluency, and verbal memory based on the BACS (Brief Assessment of Cognition in Schizophrenia) test. MIN-101 also resulted in immediate improvements in sleep architecture and normalization of slow wave sleep.

Generally, adverse events were in line with placebo, and were dissimilar to adverse events for atypical antipsychotics. Of note, MIN-101 had fewer TEAEs defined as "schizophrenia" (6 patients vs. 12 patients). However, numerically more patients were agitated (6 vs. 3) and suffered from insomnia (6 vs. 4).

Notably, there was some modest QTc prolongation in patients receiving MIN-101. As a reminder, QTc prolongation is a marker for potentially fatal arrhythmias and sudden death. No patient in the MIN-101 arm reached the 480 msec or 500 msec QTc absolute interval that acts as a cutoff for substantially higher risk of heart problems. One patient in the placebo group went above 480 msec. The mean change in QTc over the course of the study was 7.75 msec for MIN-101 relative to placebo. The mean change at specific time points of day 6, 14, and 28 were 11.5, 11.7 and 11 msec, respectively. We note that all measurements were taken at maximum concentration levels by having patients administer drug at the investigator's site on the day of the QTc assessment. From a regulatory standpoint, we believe a mean QTc prolongation less than 10 msec will be seen as low risk, a mean QTc prolongation between 10-20 msec as a risk warranting regulatory consideration, and a mean QTc prolongation above 20 msec as a high regulatory risk. Although Minerva will likely have to run a thorough QT study of MIN-101, as has been standard for all drugs of late, we are not particularly concerned with the QT prolongation. An analysis of QT prolongation in antipsychotics showed a range of from 5 msec (haloperidol) to 20 msec (Geodon). This division of the FDA has a history of accepting some modest QTc prolongation for antipsychotics, and we note that MIN-101 would likely have an additional advantage of a highly differentiated clinical profile in being the first antipsychotic to treat negative symptoms. At the time, Geodon was approved with a 20 msec QTc prolongation, there were already several approved atypical antipsychotics, including Zyprexa, Risperdal and Seroquel. Notably, both Risperdal (12 msec) and Seroquel (15 msec), two of the most widely prescribed antipsychotics, have shown increases in QTc in contemporary studies that are similar to or greater than MIN-101.

Phase 2b Design. The Phase 2b trial is expected to begin in 4Q14 and Minerva believes that it can have top-line results in 1H16. Before the trial can begin, Minerva is optimizing a once-daily (QD) 64mg formulation with an equivalent area under the curve as the 32mg twice daily dose. For a potentially noncompliant population, we believe the once daily formulation is particularly advantageous. The study is expected to enroll 255 patients in multiple centers in Europe (40-50 sites), compare the 64mg QD dose and a 32mg QD dose of MIN-101 to placebo, and have a treatment duration of six months. Entry criteria will differ substantially from the Phase 2a trial and should help lower the dropout rate seen in that trial. The prior trial only recruited unstable patients who had recently suffered an acute episode and ceased to respond to previous medication. Rather, the patients in this study will be more stable with lower positive symptom scores at baseline, although still poor responders to previous prescribed medication. Like the Phase 2a trial, patients will discontinue their previous medication for eight days before the trial begins. Additionally, Minerva does not expect to have a placebo lead-in period. Importantly,

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Minerva will be recruiting patients with predominant negative symptoms, which will give them a much higher likelihood of success. Entry into the study will require negative symptom scores above 22 (Minerva predicts baseline means of 28 points vs. 24 points in the Phase 2a study) and positive symptom scores less than 19 (vs. 21 in the Phase 2a study). This should lower the likelihood of an acute episode that would be counted as a treatment failure. Lastly, the inpatient portion of the trial will be for 8-10 days, rather than the 28 days of hospitalization in the first trial. Coupled with the longer treatment duration (6 months vs. 3 months), we expect that the placebo effect will be much lower in the Phase 2b trial.

The primary endpoint will be the PANSS negative score at 3 months and 6 months. Mixed model for repeated measures will be used as the primary statistical analysis method, the same analysis used for the Phase 2a data and the method accepted by the FDA for psychiatric trials. Minerva will also look at the effects of MIN-101 on sleep architecture and other potential indications based on the pharmacodynamics assessments of patient subgroups.

Future Phase 3 Development Pathway. Minerva will run 2-year carcinogenicity studies and complete manufacturing requirements concurrent with the Phase 2b study. Both of these should complete at the same time as or shortly after the Phase 2b readout. If Phase 2b data are positive, Minerva plans to run three Phase 3 trials following results from the Phase 2b trial in 1H16. There will be at least one monotherapy trial, likely recruiting a similar patient population as the Phase 2b trial. There would also likely be a trial of MIN-101 as add-on therapy in patients with who are stable on their atypical antipsychotics. The third Phase 3 trial would either be a second monotherapy trial or a second add-on trial, likely guided by the results from the Phase 2b trial. We would guess that a positive result in the ITT population of the Phase 2b study would give Minerva the confidence to only need a single monotherapy trial in Phase 3.

Assuming that each Phase 3 trial would require 18 to 24 months to complete, Minerva believes that it could potentially file MIN-101 before 2019. With a priority review, MIN-101 could enter the market in mid-2019. We believe this is the most likely scenario and model a MIN-101 entry for this time. There are potential accelerated scenarios: in the most aggressive scenario, MIN-101 could reach the market by 1H17 if the Phase 2b data were overwhelmingly positive to warrant a breakthrough designation, fast-track approval process, and no need for a Phase 3 program. There is also the possibility of being able to file with six-month Phase 3 data under breakthrough designation, supplementing the application at a later time with long-term safety follow-up. In this scenario, MIN-101 could be filed by mid-2017 and approved in the beginning of 2018. We believe the latter two scenarios are unlikely even if the data from Phase 2b is very positive. Given the failures of bitopertin and TC-5619, we believe that a large Phase 3 program will be necessary to confirm MIN-101's impact on negative symptoms.

MIN-101 Commercial Opportunity. According to WHO, 24m people suffer from schizophrenia worldwide, with 3.5m patients in the U.S. and 3m in the five major EU markets. Data from literature suggests that patients with predominantly negative symptoms represent at least 20%-30% of the overall patient population and 37% in patients >45 years of age. Further, approximately half of the number of patients with

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schizophrenia experience sleep disorders, which further exacerbates positive and negative symptoms of schizophrenia.

There are currently numerous therapies approved for the treatment of schizophrenia, but these options primarily treat positive symptoms. To date, there are no current treatments specifically approved for the treatment of negative or cognitive symptoms. Additionally, approved treatments for schizophrenia generally come with significant side effects including sedation, involuntary movements, prolactin increase, metabolic syndrome, cognitive impairment, sleep disorders and weight gain. A combination of severe side effects and the lack of efficacy on negative and cognitive symptoms contribute to a real world high rate of treatment discontinuation of 60%-80% over the course of 18 months. Thus, there still remains a need for novel therapies with reduced side effects.

Patients are often first diagnosed with schizophrenia in conjunction with the onset of positive symptoms, such as hallucinations or delusions, and are first prescribed either conventional first-generation antipsychotic therapy or more commonly a second-generation atypical antipsychotic therapy. Both therapies are effective at managing the positive symptoms, but can exacerbate negative symptoms. Key products such as Thorazine and Largactil (chlorpromazine) and Haldol (haloperidol) represent first-generation typical antipsychotic medications. In 2013, there were 6m prescriptions for typical antipsychotics dispensed in the United States. The market has shifted to atypical antipsychotics due to improved safety. Key products in the atypical antipsychotic class include Clozaril (clozapine), Risperdal (risperidone), Seroquel (quetiapine), Zyprexa (olanzapine) and Abilify (aripiprazole). Notably, none of these treatments addresses negative or cognitive symptoms of the disease, which can lead to non-compliance, treatment discontinuation, and lack of social functioning. There were 51.5m prescriptions written for atypical antipsychotics in 2013, which represents a $35+ b market on a branded dollar basis. We assume that ~50% of these prescriptions, or ~$17b in branded equivalent sales, are related to the treatment of schizophrenia or schizoaffective disorder.

Minerva's planned commercial strategy is to market MIN-101 in the U.S. and EU with its own sales force. That said, management has stated that they will consider regional partnerships. In the U.S., the company guided to 100 sales reps to cover the large centers that treat schizophrenic patients in addition to eight case managers to help manage patient compliance as well as regional managers. The company also expects roughly 100 sales reps would be sufficient to cover Europe. While this is management's stated goal, we have taken a more conservative approach and assumed a global partnership strategy for our modeling purposes. Under the agreement with Mitsubishi, Minerva would owe Mitsubishi a low-double-digit percentage of any milestones and a low 30% portion of any royalties received under a partnership with a third party. We have accounted for this in our valuation.

Competition

ITI-007. ITCI's ITI-007 is a 5-HT2A receptor antagonist, dopamine phosphoprotein modulator, glutamatergic phosphoprotein modulator, and serotonin reuptake inhibitor being developed for multiple indications at various doses. ITI-007 has completed Phase 2 trials in schizophrenia, demonstrating antipsychotic efficacy in a randomized, double-

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blind, placebo and active controlled trial in patients with an acutely exacerbated episode of schizophrenia. In its four-arm (60 mg ITI-007, 120 mg ITI-007, active control 4 mg Risperdal, and placebo), 335-patient Phase 2 study (of which 311 patients were in the ITT primary analysis population), ITI-007 at the lower dose (60 mg once daily) met the pre-specified primary endpoint, Positive and Negative Syndrome Scale (PANSS) total score, from baseline to Day 28. 60 mg ITI-007 lowered total PANSS by a mean of 13.2 points compared to 7.4 points for placebo (p=0.017 versus placebo in the ITT patient population). The trial also met key secondary outcome measures related to efficacy on PANSS subscales and safety. The Phase 2 showed a differentiating response for ITI-007 60 mg on negative symptoms versus both placebo and 4 mg Risperdal. ITI-007 improved negative symptoms by 0.34 at 60 mg in a subgroup of patients with prominent negative symptoms. Additionally, ITI-007 improved some negative symptoms that Risperdal did not improve and also did not worsen some negative symptoms that Risperdal worsen versus placebo (e.g., blunted affect).

ITI-007 was also shown to improve pro-social behavior, with a statistically significant effect versus placebo and a favorable trend versus Risperdal. Notably, the high dose ITI-007 arm did not reach statistical significance, which ITCI hypothesized was driven by sedation, the most frequent side effect at the 120 mg dose, interfering with the ability to detect an efficacy signal. 32.5% patients on 120 mg ITI-007 experienced sedation/somnolence, compared to 21% on Risperdal, 17% on 60 mg ITI-007, and 13% on placebo, leading the company to suggest that nighttime dosing rather than morning dosing may be more appropriate for evaluating high-dose ITI-007. Only 19% of patients discontinued the Phase 2 trial (7% completed but were lost to follow-up), which is a far higher completer rate than in the MIN-101 Phase 2a trial, where only 31% of randomized patients completed the trial. In contrast to Risperdal, low-dose ITI-007 was effective with no difference from placebo on weight, prolactin levels, extrapyramidal symptoms (EPS), or akathisia. Notably, there were no clinically significant changes in cardiovascular function, with no QTc prolongation, and unlike Risperdal, ITI-007 was not shown to cause sustained increases in heart rate. ITCI is currently planning confirmatory later-stage clinical trials.

ITI-007 is being positioned as a stand-alone therapy with differentiated activity as compared to Risperdal and a better safety profile. Specifically, ITI-007 shows effect on positive symptoms that is comparable to Risperdal ($p<0.05$ versus placebo on the PANSS positive subscale at day 28), but also demonstrated an improvement in certain negative symptoms while not worsening other negative symptoms that were negatively affected by Risperdal. Thus, we feel ITI-007 could be a viable option for patients with predominant positive symptoms who do not respond well to existing atypical antipsychotics. However, its effect on negative symptoms appears to be inferior to MIN-101 on an absolute basis, even in predominantly negative patients (-0.34 points vs. -1.7 points for MIN-101 on an intent to treat basis). Thus, in the key population of predominantly negative symptom stable patients or as an add-on to an atypical antipsychotic, we would expect MIN-101 to be the drug of choice. Additionally, MIN-101 appears to cause less sedation than ITI-007, which may mimic some aspects of negative symptoms. Sedation was seen in 33% of patients on the 120mg dose of ITI-007, compared to 17% in the 60mg arm and 13% in the placebo arm. Somnolence was seen in only 9% of patients in the MIN-101 arm.

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TC-5619. Although development was recently discontinued after it failed to show efficacy in a Phase 2b trial, Targacept's TC-5619 is an oral α7 agonist that was expected to have efficacy against negative symptoms and cognitive dysfunction from schizophrenia. Nicotinic acetylcholine receptors (nAChR) are wide expressed throughout the nervous system and the α7 subtype is one of the most abundant in the brain. Decreased α7 receptor binding has been seen in schizophrenia patients and α7 appears to play a role in auditory response, specifically P50 auditory gating. TC-5619 is highly selective for α7, and adding nicotine to TC-5619 increased acetylcholine potentiation. Trials showed that nicotine administration resulted in normalization of abnormal gating in both animal models and schizophrenia patients and TRGT believes increasing α7 agonism can normalize both dopamine and glutamate, leading to improvements in positive and negative symptoms, as well as less cognitive impairment.

The Phase 2a trial compared dose-escalated TC-5619 (1mg, 5mg, 25mg each for 4 weeks each) against placebo in 200 patients who were stable on either Risperdal or quetiapine for 2 months before screening and had minimal positive symptoms. Patients were recruited from 12 sites in India and 7 in the United States. Notably, the population was roughly two-thirds Indian and one-quarter African American. At Week 12, TC5619 demonstrated significant reductions compared to placebo on the primary endpoint change in Groton Maze Learning (GML), with a trend towards better efficacy in the US-based patients. Efficacy was driven by the tobacco users (p=0.002), who made up roughly 50% of the trial population, whereas non-users were roughly in-line with placebo. On the Scale for the Assessment of Negative Symptoms (SANS) secondary endpoint, TC-5619 showed a significant roughly 10-point decline from baseline and a 4-point improvement from placebo (p=0.015) with efficacy improving over the 12 week study. Tobacco users also fared better than non-users, with roughly an 11 point decline in SANS. TRGT believes concomitant nicotine usage could: a) increase the number of receptors affected by TC-5619, b) increase blood-brain barrier penetration, and c) co-activate α4.

The Phase 2b trial compared two doses of TC-5619 (5mg and 50mg) to placebo in 456 patients who had a PANSS negative symptom subscale score >20. The primary endpoint for this 24-week trial was SANS. In December 2013, TRGT announced negative top-line results for the trial with subjects in placebo arm and both doses showing similar improvement in negative symptoms. Specifically, SANS score improvements from a baseline of roughly 70 were 15.4 for placebo and 14.7 and 17.5 in high- and low-dose TC-5619 arms, respectively. Based on the trial, TRGT terminated both its schizophrenia and Alzheimer's TC-5619 programs.

Bitopertin. Roche's bitopertin is a first-in-class glycine reuptake inhibitor that specifically inhibit glycine transporter type-1 (GlyT-1) in glial cells that recently failed a Phase 3 trial in schizophrenia. Bitopertin was thought to improve negative symptoms by selectively modulating glycine reuptake and improving N-methyl-D-aspartate (NMDA) receptor dysfunction.

The Phase 2 proof-of-concept study evaluated 10mg, 30mg, and 60mg doses of bitopertin in 323 patients with predominant negative symptoms, as defined by a 40+ score on 14-item PANSS for negative and cognitive factors and ≤28 on the positive symptom score items. In the ITT population, the 10 mg dose showed near-significant

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reductions in the primary endpoint, PANSS negative symptom factor score (NSFS), with a 1.35 point reduction from a baseline score of 25.8 (p=0.07) and a similar responder p-value (58% vs. 44% for placebo; p=0.08). The 10mg arm showed a significant improvement over placebo on the CGI Negative Symptom endpoint (p=0.02) and 30.9% of patients believed they were much improved compared to 16.9% on placebo. There were also non-significant improvements in the positive symptom score, total PANSS score, and cognition/functional endpoints. Notably, the 30mg dose showed generally less efficacy than the 10mg arm and the 60mg dose was comparable to placebo. Roche believes that the lack of efficacy with the increasing dose is due to the level of occupancy of the GlyT-1 receptor, as animal models suggested that low-to-moderate occupancy resulted in higher efficacy. The number of patients who withdrew from the study was also greater in the 30mg/60mg arms at 9% compared to 1% for 10mg and placebo.

Following these results, Roche received a special protocol assessment (SPA) from the FDA and initiated six Phase 3 trials, three of which were in patients with predominant negative symptoms and three of which were in patients who were sub-optimally controlled on their current medication. In January 2014, Roche reported that two of the negative symptom trials did not meet their primary endpoints of PANSS NSFS. In April, Roche mentioned that one of the sub-optimally controlled studies also failed its endpoint of PANSS PSFS, and following a futility analysis of the remaining three trials, an additional two were discontinued. The remaining trial, NightLyte, in sub-optimally controlled schizophrenia continues.

Patent Protection. MIN-101 currently has a composition of matter patent that expires in 2021. We believe this patent could be eligible for up to five years of patent-life extension, potentially extending composition-of-matter protection through 2026. Minerva has patent applications pending that seek to provide additional protection for method of use / treatment, which would expire in 2031, if granted. One of these patents may be extended by up to five years of patent term extension. We believe the most logical one to extend is the 2031 patent. This would be eligible for extension until 2034. The worst case scenario would be 6.5 years of exclusivity through 2026 based on Hatch-Waxman exclusivity. We currently take the conservative approach in our model, assuming generic entry in mid-2026 in the United States. For EU markets, we assume 10 years of exclusivity post-approval in 2020.

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MIN-117

MIN-117 is a Minerva's oral drug candidate for the treatment of major depressive disorder (MDD). MIN-117 has completed a Phase 1 study in healthy volunteers and a Phase 2b trial is expected to begin in late 2014-1H15. Minerva licensed MIN-117 from MTPC and has rights to the drug candidate in the U.S. and EU.

MIN-117 Pharmacology. MIN-117 is a novel drug candidate that acts through multiple mechanisms on several receptors associates with the control of mood. It is a small molecule antagonist on 5-HT1A receptors (a specific subtype of serotonin receptor) and also acts as an inhibitor of both serotonin and dopamine reuptake. When 5-HT1A is blocked, anxiety and mood can be regulated and the increase in amounts of serotonin and dopamine in the brain are thought to result in an improvement in mood. Currently, MIN-117 is being developed by Minerva for the treatment of major depressive disorder (MDD).

Existing MIN-117 pre-clinical and clinical pharmacology data from healthy volunteers administered higher doses than the anticipated therapeutic dose indicate that the MIN-117 therapeutic doses may demonstrate a favorable safety profile. The potential for rapid onset of action versus serotonin selective reuptake inhibitors (such as Prozac, Zoloft, and Lexapro that can take up to four weeks to begin working) is due to the 5-HT1A auto receptor and dopamine reuptake inhibitor. In addition, currently available therapies have several side effects, including cognitive impairment, sexual dysfunction and sleep disorders that can lead to discontinuation of therapy. Thus far, MIN-117 has demonstrated a lack of these side effects in animals and healthy human volunteers, but the drug has yet to be studied in MDD patients.

MIN-117 Preclinical Data. Preclinical 3-month toxicology studies of MIN-117 have been completed in both rodents and non-rodents demonstrating the potential for favorable safety and tolerability in the intended human therapeutic doses. In preclinical depression models in rodents, MIN-117 was shown to have a positive impact on mood. In a mild chronic stress model that simulates depression by measuring the degree to which an animal is chronically stressed by the reduction in its sucrose intake, very low doses of MIN-117 reversed the suppression of sucrose intake by animals. Animals receiving MIN-117 exhibited a rapid increase in sucrose intake, which reached statistical significance after one week of MIN-117 administration as compared to baseline measurements. In the same study, animals receiving Imipramine (an approved antidepressant), however, did not exhibit increased sucrose intake until after three weeks of dosing. This supports the company's hypothesis that MIN-117 has a positive impact on stress and could have a more rapid onset of action than currently approved therapies.

Other pre-clinical studies using PET imaging suggest that MIN-117 targets the key brain serotoninergic pathways involved in depression. Results showed an increase of serotonin and dopamine after a single dose of MIN-117, unlike the reference antidepressant Lexapro which induced only a modest and transient increase.

Further, the effects on cognition and sexual function were also investigated in animal models. Unlike a number of currently marketed drugs that impair cognitive skills and sexual function, pre-clinical studies suggest MIN-117 may not have these side effects.

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After one week of dosing, rats receiving Paxil (an approved antidepressant) had a statistically significant increase in time to first mount with intromission (a measure of sexual function in rats) compared to rats receiving of MIN-117 (in three different doses) and placebo, suggesting sexual impairment for Paxil and lack of impact on sexual function of MIN-117. MIN-117 was shown to preserve sexual function as compared to Paxil ($p<0.05$) at both one week and two weeks.

Lastly, MIN-117 was demonstrated to have a statistically significant effect on immediate memory as compared to placebo under stress.

MIN-117 Phase 1 Data. MIN-117 (in doses above the expected therapeutic dose) has been tested in two Phase 1 trials in healthy subjects, completed in 2005 by MTPC and 2009 by Sonkei. The primary endpoint of these studies was to assess the safety and tolerability of MIN-117 and secondary endpoints included pharmacokinetics (PK) and pharmacodynamics (PD). As part of the PD analysis, one study assessed the impact of MIN-117 on sleep as measured by polysomnography (objective measures of sleep) and the Leeds Sleep Evaluation Questionnaire. This study also explored the impact of MIN-117 on mood (measured by the Profile of Mood Disorders), emotion (measured by the Emotional Visual Analogue Scale), and cognitive function (measured by the Flanker/EEG task). A total of 50 subjects were randomized, of which 47 completed the study per the protocol. Based on the PSG analysis, statistically significant improvements compared to placebo were found in the density of ocular movements during REM sleep (at both the 3 and 7.5 mg dose) as well as the number of ocular movements during rapid eye movement (REM) sleep (at the 7.5 mg dose). It has been hypothesized that this ocular activity in REM sleep may be an indication of early onset of therapeutic benefit, which would be a differentiating feature versus approved therapies for MDD. This study further found that MIN-117 did not have a negative impact on mood, emotion, cognitive function or sleep in healthy volunteers.

MIN-117 had a significant effect on REM density (the number of eye movements per hour of sleep) evaluated after two weeks of administration of placebo, a therapeutic dose of a reference antidepressant (20 mg/day of Lexapro) and 3 mg/day of MIN-117 in the Phase 1 study of healthy volunteers. As sleep may be a predictive parameter of drugs in MDD patients, an increase in REM density in the study results may indicate potential therapeutic effects in MDD subjects. MIN-117 had a statistically significant increase in REM density as compared to placebo, whereas Lexapro (an approved antidepressant) did not. Because this occurred after two weeks of dosing, this effect may indicate that MIN-117 has a faster effect on MDD when compared to Lexapro.

In addition, based upon the Phase 1 studies, MIN-117 appears to have a favorable safety and tolerability profile at anticipated therapeutic dose levels that does not include many of the side effects experienced by patients taking existing MDD pharmacologic therapies including cognitive impairment, sexual dysfunction, sleep disorders, and weight gain. While adverse events, such as nervous system and gastrointestinal events, did occur in subjects, the incidence of the observed adverse events (even at the highest doses of MIN-117) was generally comparable to placebo. In one trial that included Lexapro as a control, it was shown to have a higher incidence of certain adverse events as compared with MIN-117. PK parameters also indicated that once a day administration may be possible.

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MIN-117 Phase 2 Plans. The next step will be evaluation of the safety and efficacy of MIN-117 in MDD patients in a Phase 2b study expected to begin in late 2014-1H15. This will be a randomized, double-blind, parallel group, placebo-controlled study to evaluate two fixed doses (0.1 and 0.5 mg) in 450 MDD patients. The primary endpoint will be efficacy in reducing depressive symptoms as measured by the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score over 6 weeks of treatment versus placebo. Secondary endpoints will be onset of antidepressant response over two weeks of treatment (as measured by MADRS total score) and reduction in depressive symptoms over 6 weeks of treatment measured by change in baseline in Clinical Global Impression severity and improvement scale (CGI-S and CGI-I). The company also plans to assess effects on sexual dysfunction, cognition, anxiety, and sleep. Assuming funding can be obtained for this study in a timely fashion, results for the Phase 2b are expected by in 1H16. In future studies, the company also intends to look at MIN-117 in combination following failure of another SSRI/SNRI.

MIN-117 Future Development and Timeline. Minerva does not currently have the financial resources to move forward with clinical development of MIN-117 based on IPO proceeds, and plans to seek alternate sources of funding for the Phase 2a study including a potential partnership. We have assumed that both debt financing and a partnership are signed in 2015 to move forward with the Phase 2b program. If data are positive, the company expects to do a minimum of two Phase 3 studies including a six week treatment study as well as a one year study. Minerva currently expects to begin Phase 3 studies in 2H16, followed by commercialization by the end of 2019.

Commercial Opportunity & Partnering. It is estimated that sales of branded drugs for depression totaled $5b in the U.S. and the five major EU markets in 2012. Many of the most popular drugs are generic, and thus, the market from a volume basis is significantly larger. There were a total of 287.2 million antidepressant prescriptions in the last 12 months, according to IMS Health. On a branded dollar basis, this would represent up to a $60b market opportunity in the U.S. alone. The market for first-line treatment of depression is crowded and inexpensive due to the availability of generic therapies. However, there is a large number of patients who do not respond to first-line treatment or only partially respond, and thus, there is also a large market for second-line or combination therapies. That said, recent launches for second-line depression or MDD have been modest, but we believe these are specific to these molecules. Brintellix has been developed as a monotherapy and is one of the most recent competitors approved by the FDA for use as a second-line therapy. Brintellix has generated 65k prescriptions since its launch in November 2013, yielding sales of ~$18m. Viibryd, another drug approved for major depressive disorder, has generated annual sales of $199m (+22% Y/Y). Issues with both drugs include the perception of lack of differentiation from the largely generic SSRI class, despite claims of enhanced activity via different pathways, and side effects including gastrointestinal and sexual dysfunction.

In the MDD patient population, less than half of patients receiving first-line drug treatment for depression enter into remission. Of those that do achieve remission, 30%-50% will relapse and greater than one-third of patients fail to respond to two or more successive lines of antidepressant therapy. Patients with treatment-resistant major depression often require treatment with several antidepressants, such as an SSRI or SNRI,

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combined with an antipsychotic or mood stabilizer such as Seroquel (quetiapine) and Abilify (aripiprazole), or Topimax (topiramate). That said, while these drugs improve efficacy, they also have side effects including motor symptoms, sedation, lack of concentration, and weight gain. In addition to side effects, antidepressants generally do not begin to take effect until a few weeks after initiating treatment, with noticeable improvement occurring beyond four weeks.

MIN-117 Intellectual Property. Minerva has an issued composition of matter patent (6,720,320) expiring in August 2020 in the United States. Further, the company just received issuance of a method of use patent expiring in January 2034 that covers a pharmaceutical composition with MIN-117's structure for the treatment of depression, sleep or cognitive impairment. Pending clinical trial outcomes, the company also hopes to achieve protection related to the dosing schedule to treat depression, methods covering low dose, rapid onset methods of use to treat depression without sexual dysfunction, and methods of treatment using biomarkers based on sleep parameters. In terms of the worst case exclusivity scenario, given that it is a new chemical entity, MIN-117 will be eligible for Hatch-Waxman exclusivity, which would provide a minimum of 6.5 years of exclusivity. European patents provide protection through May 2020, though we would expect a minimum of10 years of exclusivity in EU markets following approval.

MIN-117 Competition. The first generation of antidepressants includes predominately MonoAmineOxydose-Inhibitors (MAOIs) and tricyclic molecules. MAOIs are effective because they are active on most of the neurotransmitter systems involved in mood disorders, but the efficacy comes with various side effects that prevent broad usage. The most severe side effect associated with MAOIs is the cardiovascular impact and severe blood pressure variations requiring strict diet regulation. Tricyclic antidepressants are effective because they also have a large spectrum of effects on several neurotransmitters. However, this broad activity causes severe side effects, such as sedation, weight gain and autonomic nervous system dysregulation, like hypotension, dry mouth, and glaucoma. These side effects prevent tricyclic molecules from being used as a first line therapy and are typically reserved for severe and resistant patients who do not respond to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs).

Currently, the most prescribed antidepressants are SSRIs and SNRIs. The SSRIs generally function by blocking the reuptake of serotonin. SSRIs may lead to varying levels of weight gain and impairment of cognitive skills and sexual function. SNRIs have an effect on noradrenergic neurotransmitter systems in addition to the effect on serotonin reuptake. This added pharmacological activity improves the efficacy over SSRIs but doesn't improve their safety and tolerability profile. In some cases, the SNRIs have a worse safety and tolerability profile compared to SSRIs, in particular with respect to cardiovascular side effects.

By the time of MIN-117's launch (estimated to be in 2019), most antidepressants will be generic including Forest's Lexapro/Cipralex (escitalopram), Pfizer's (PFE, $30.19, Buy) Zoloft (sertraline), GlaxoSmithKline's (GSK LN, 1,423p, Hold) Paxil/Seroxat (paroxetine), Eli Lilly's (LLY, $63.78, Hold) Prozac (fluoxetine), Forest's Viibryd (vilazodone), Pfizer's Effexor (venlafaxine), Pfizer's Pristiq (desvenlafaxine), Eli Lilly's Cymbalta (duloxetine),

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AstraZeneca's (AZN LN, 4,392p, Hold) Seroquel (quetiapine) and Bristol-Myers Squibb's (BMY, $49.39, Hold) Abilify (aripiprazole).

MIN-117 may have a faster onset of action, fewer side effects than existing treatments, and could benefit non- or partial-responders. That said, there are also a number of products in development that could compete with MIN-117. Lundbeck's (LUN DC, DKK126.60, Buy) Vortioxetine (Brintellix), an SSRI with additional 5-HT receptor modulation activity, has been developed as a monotherapy and was recently approved by the FDA for use as a second-line therapy. Brintellix has been shown to have fewer side effects, in particular less impact on cognition, than existing therapies, although it does not show improved efficacy on depressive symptoms. In addition, Eli Lilly's edivoxetine, a norepinephrine reuptake inhibitor, and Naurex's GL4X-13 and AstraZeneca's AZD6765, both targeting the NMDA receptor, are expected to have a faster onset of therapeutic effect as compared to currently available therapies.

MIN-117 License Agreement with MTPC. Minerva licensed MIN-117 from MTPC for global rights, excluding the majority of Asia (Minerva does not have rights to China, Japan, India, and South Korea). Under its license for MIN-117, Minerva is required to make milestone payments upon the achievement of commercial milestones up to $47.5m. If Minerva sells the rights to the license, the licensor will be entitled to a percentage of milestone payments in the low teens and a percentage of royalties received by Minerva in the low double digits. However, Minerva is required to initiate either a Phase 2a or Phase 2b study in MDD by the end of April 2015. Minerva may elect to extend the timeline to achieve the milestone in one year increments by making an extension payment of $0.5m, the number of which is unlimited.

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MIN-202

MIN-202 is Minerva's orexin-2 antagonist being developed for the treatment of primary and secondary insomnia. Orexin works through two receptors, OX1R and OX2R, both of which modulate addiction and impulse behavior. OX1R is primarily involved in suppressing motion/REM sleep regulation and wake promotion, whereas OX2R is primarily involved in wake-promotion and non-REM sleep regulation. Minerva notes that there are 53m patients suffering from insomnia in the U.S., EU5, and Japan with annual prescription drug sales of $2.7b. The company reported Phase 1a data and entered a Phase 1b trial in 20 patients with major depressive disorder (MDD) who had secondary insomnia in December 2013. Minerva expects to report these data by YE14. In 2H14, Minerva plans to start a second Phase 1b trial focusing on primary insomnia, which it expects to read out in late 2015-early 2016, and a 10-day pharmacokinetic/safety study in healthy volunteers. Minerva intends to use about $5m in proceeds from their offering to fund continued development of MIN-202 through Phase 1.

Preclinical and Phase 1 Data. In 2011, Janssen enrolled a single-ascending-dose trial of MIN-202 in 57 young males, 38 of whom were included in the PK analysis. The study found good safety and tolerability and noted that the time to maximum tolerated concentration was 30 minutes with some dose-dependent sedative effects lasting 4-6 hours. Janssen noted that the PK/PD profile enabled sleep induction and maintenance without a major impairment of daytime performance. Janssen also evaluated the effects of MIN-202 on alertness using the Stanford Sleepiness Scale (SSS) showing a dose-proportionate increase in sedation levels. In preclinical testing, Janssen demonstrated a good safety profile during a one-month toxicology study in rodents evaluating biological and clinical aspects. The data from these studies suggests that MIN-202 acts in a desired manner to achieve deep non-REM sleep and increasing the duration of non-REM sleep without impairing REM sleep. MIN202 was shown to decrease the time to onset of non-REM sleep and increase the amount of non-REM sleep during a two-hour period in rodents with no significant impact on REM sleep, which Minerva believes is indicative of potentially favorable effects on sleep.

Partnership Details. Minerva has a co-development license with Janssen in which Minerva has EU sales rights (including Switzerland, Lichtenstein, Iceland and Norway) paying Janssen a royalty, whereas Janssen has ex-EU rights paying Minerva a royalty and Minerva has first right of negotiation to ex-EU rights. Under the terms of their agreement, Minerva is responsible for 40% of the development costs, capped at $5m from the date of the license though Phase 1b and animal toxicology studies and $24m through the completion of Phase 2. Janssen has the right to opt out after certain milestones including the completion of a single-day Phase 1 clinical trial in MDD with no further obligations to fund development, at which point Minerva would gain rights to North America and owe Janssen a reduced royalty in the mid-single digits. Minerva has the right to terminate the Janssen license following Phase 1b data in patients with insomnia and certain toxicology studies subject to payment of a termination fee of $3.0m, after which Minerva would be entitled to mid-single digit royalties. Janssen will supply all product, but Minerva will have rights to manufacture/contract a third-party manufacturer if approved in their territory. Minerva will pay $22m upon closing of the offering and quarterly royalties in the high single digits in their territories, and in exchange, Janssen will pay high single digit royalties

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on aggregate net sales outside the EU. We currently do not model any contribution from MIN-202 in our model, and it remains upside to our current valuation.

IP. Patent protection includes EP 2491038 A1 which claims compositions of matter that encompass MIN-202 and other orexin receptor modulators and methods of using these compositions to treat diseases, including those mediated by orexin receptor activity, which should extent patent coverage through October 2030 at least.

Competition. A key differentiating factor for MIN-202 is that it only targets the OXR2 receptors. Current therapies for insomnia primarily target the gamma-aminobutyric acid A (CABA-A) receptor signaling including benzodiazepines and GABA-A receptor modulators.

Ambien (zolpidem) is one of the leading insomnia agents in the market and functions by positively modulating GABA to increase sleep drive leads to abnormally high levels of REM sleep and a decrease in deep sleep. Minerva believes MIN-202 offers equal to superior efficacy to Ambien with normal levels of REM sleep, no residual sedation or daytime impairment, normal motion suppression, no alcohol interaction, and no abuse potential.

Merck's (MRK, $58.15, Hold) Survorexant (MK-4305) functions as an antagonist for both OXR1 and OXR2 and is thought to function by blocking the wake drive and believed to offer better safety and tolerability than GABAergic drugs such as Ambien. Minerva believes there are potential concerns with dual antagonism including abnormal REM sleep, muscle tone impact, vivid nightmares, and excessive daytime sleepiness while driving. Survorexant is currently under FDA review.

Almorexant was being developed by Actelion (ATLN VX, CHF110.80, Buy) in collaboration with Glaxo. Almorexant is a similar dual orexin receptor antagonist, which showed significant improvements in sleep parameters in animal models and patients with insomnia. The companies halted development of almorexant following undisclosed safety concerns in 2011.

GSK's SB-649868 is an orexin receptor antagonist, being developed for the treatment of insomnia. SB-649868 is a selective antagonist of the OX1/OX2 receptors. In an early single-dose, placebo-controlled crossover study comparing '868 (10mg or 30mg) with Ambien, '868 was shown to increase total placebo-adjusted sleep time by 17 and 31 minutes for 10 and 30mg doses respectively v. 11 minutes with Ambien. Both doses of 868 showed a benefit in latency to persistent sleep (i.e., sleep onset) and latency to REM sleep, whereas Ambien failed to show an improvement in sleep onset. Wake after sleep onset was reduced by 15 minutes in the 30mg dose. Slow wave sleep (SWS) and electroencephalogram (EEG) power in non-REM sleep were not affected by either dose of 868, whereas SWS was increased after Ambien. REM sleep duration was increased with 30mg 868 and reduced after Ambien. There is currently no information on GSK's website indicating the status of SB-649868 development, and our colleagues on the pharma team speculate that the program was discontinued following the safety concerns with almorexant. However, we see these data as a sign of confirmation of the mechanism of targeting orexin to treat insomnia.

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MIN-301

MIN-301 is Minerva's ErbB4 activator which is currently in preclinical development for the treatment of Parkinson's disease. MIN-301 is a soluble recombinant form of Neuregulin-11 (NRG-11), a 27 kDa polypeptide encompassing the extracellular soluble domain amino acid sequence of NRG-1beta1. Minerva believes that MIN-301 has disease-modifying ability in neurodegenerative diseases including a slowing of the onset and improvement of brain function in Parkinson's disease. Notably, MIN-101 crosses the blood-brain barrier and a one month toxicology study supported a safe profile. In Parkinson's disease models 6-OHDA, MPTP – MIN301 shows neuroprotection against toxin inducing lesions and induces neurorestoration after delayed administration. Further, MIN-301 is thought to improve cognitive function (according to the Morris Watermaze test) and preserves the sleep-wake cycle. Potential for other indications including psychotic disorders, multiple sclerosis, and traumatic brain injury. Minerva expects to complete IND enabling studies around YE14 to enable begin a Phase 1 trial in 1H15 in healthy volunteers and a Phase 1b proof-of-concept trial in Parkinson's patients in 2H15/1H16. Minerva acquired rights to MIN-301 through its acquisition of Mind-NRG which had acquired rights from ProteoSys. The company intends to use $0.8m from its current offering to bund pre-clinical development of MIN-301 and $0.7m to pay for the ProteoSys License Fee, but the company expects to raise additional money prior to entering clinical development

Parkinson's Background. Parkinson's is caused by the death of dopamine-generating cells – it is thought to be progressive and incurable leading to lower quality of life, disability, loss of speech, mobility, and cognitive abilities and is associated with a lower life expectancy. Parkinson's is thought to impact roughly 2.4m patients in the US, EU5, and Japan and is expected to increase with the aging baby-boomer generation, as the prevalence of the disease increases from 1% in patients over 60 to 4% in patients over 80.

Preclinical Data. MIN-301 demonstrated activity in the 6-OH-dopamine and the 1-methyl-4-phenyl-1, 2, 3, 6 tetrahydropyridine (MPTP) animal models of Parkinson's disease, both of which are considered key models for Parkinson's-like syndromes. MIN-301 has been shown to restore motor function in non-primate models with a positive effect on cognition, including faster rodent speed on a treadmill that suggests better correlation and endurance. Minerva noted that the improvement in motor function occurred without the preservation of TH cells that is seen with existing treatments – suggesting that the mechanism of action may not be entirely caused by the preservation of dopaminergic TH cells. Minerva believes that MIN-301 may have positive effects on oxidative stress and metabolism, noting that ATP levels increase in a dose-dependent manner following administration. A one month toxicology studies, including a dose 50x higher than predicted therapeutic levels, showed a good safety profile. Because MIN-301 targets neurological deficits, Minerva believes it could be used as a monotherapy and complementary therapy for later stage disease. Further, Minerva believes that MIN-301 may be useful in other indications such as Alzheimer's disease, MS, schizophrenia, stroke, and traumatic brain injury. Minerva is currently planning pre-clinical studies in primate models of Parkinson's disease to confirm the results observed in non-primate animals and validate certain biomarkers in human trials.

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IP. MIN-301 is protected by four families of patents including ones that cover claims for certain isolated neuregulin-beta isoforms and methods of using these as diagnostic indicators. The issued patents will expire no earlier than 2/9/21 with an additional patent expiring no earlier than 1/20/22. The second patent family includes methods of screening for agents that increase or decrease the level of a specific neuregulin-beta isoform – these will not expire before 12/16/22 with two pending EU applications expected to expire no earlier than 8/6/22. A third patent is based on PCT international publication and have claims directed at the medical use for a specific neuregulin isoiform, and also covers compositions comprising of neuroregulin isoform and further drugs. A fourth patent family is based on PCT application WO 2011/147981 A2 and has claims directed to a polypeptide composition, a pharmaceutical composition based on the polypeptide, use of the polypeptide to treat neurological conditions and diagnostic methods. In the U.S. and the EU, MIN-301 would likely qualify for 12 years of biologics exclusivity at a minimum.

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Initial Public Offering

On 7/1/14, NERV completed an initial public offering of 5,454,545 shares of common stock at $6/share, with net proceeds of ~$31M. Jefferies served as the sole bookrunner.

Management

Rogerio Vivaldi, MD, MBA - President and CEO. Dr. Vivaldi has been involved in commercializing more than 20 pharmaceutical products across multiple indications. Prior to Minerva, he was SVP and Head of the Rare Diseases Business Unit at Genzyme and was previously head of Genzyme's Renal and Endocrinology Unit. Previously, he led the establishment of Genzyme's business operations in Brazil and served as President of Genzyme Latin America. He received his MD from Medical School Rio de Janeiro University and his MBA from Federal University of Rio de Janeiro.

Remy Luthringer, PhD - EVP and Head of R&D. Dr. Remy Luthringer has been involved in the development of more than 150 active molecules for clinical trials in the CNS. Previously, Dr. Luthringer served as CMO for Index Ventures. He was also the head of the FORENAP Institute for Research in Neurosciences and Neuropsychiatry in France. Dr. Luthringer has extensive experience in clinical psychiatric practice and holds a PhD in neurosciences and clinical pharmacology.

Geoff Race, FCMA, MBA - EVP and CFO. Prior to his current role, Mr. Race served as a consultant for the development of MIN-101 and MIN-117. He has previously served as CEO of Funxional Therapeutics and CFO at PanGenetics B.V. He is a Fellow of the Chartered Institute of Management Accountants and earned his MBA from Durham University Business School.

Joseph Reilly - Chief Business Officer. Mr. Reilly was most recently VP, Head of Commercial Strategy and Operations at Genzyme. In more than a decade at Genzyme, he also served as VP of Global Business Operations, VP of Commercial Operations and VP of Finance in the Rare Diseases Division. Mr. Reilly holds a BS and MS in Finance from Boston College.

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NERV: Historical and Projected Revenue and Earnings

December 31 Fiscal Year ($000s, except per share)	2012A	2013A	1Q14A	2Q14E	3Q14E	4Q14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
MIN-101 Sales	-	-	-	-	-	-	-	-	-	-	-	15,479	221,239	751,234	1,589,771
U.S.	-	-	-	-	-	-	-	-	-	-	-	11,150	161,607	550,462	1,173,029
EU	-	-	-	-	-	-	-	-	-	-	-	4,328	58,550	186,135	370,208
ROW	-	-	-	-	-	-	-	-	-	-	-	-	1,082	14,637	46,534
U.S. Royalties to Minerva	-	-	-	-	-	-	-	-	-	-	-	2,676	38,786	136,129	317,369
ROW Royalties to Minerva	-	-	-	-	-	-	-	-	-	-	-	1,039	14,312	48,185	100,018
MIN-117 Sales	-	-	-	-	-	-	-	-	-	-	-	-	189,406	629,527	1,278,142
U.S.	-	-	-	-	-	-	-	-	-	-	-	-	189,406	512,823	943,290
ROW	-	-	-	-	-	-	-	-	-	-	-	-	-	116,704	334,852
U.S. Royalties to Minerva	-	-	-	-	-	-	-	-	-	-	-	-	17,047	46,667	102,628
ROW Royalties to Minerva	-	-	-	-	-	-	-	-	-	-	-	-	-	8,169	23,440
Total Royalties	-	-	-	-	-	-	-	-	-	-	-	3,715	70,144	239,151	543,455
Milestones	-	-	-	-	-	-	-	25,000	-	15,000	100,000	175,000	150,000	100,000	100,000
Other	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Revenue	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**25,000**	**-**	**15,000**	**100,000**	**178,715**	**220,144**	**339,151**	**643,455**
Payments to Mitsubishi	-	-	-	-	-	-	-	2,500	-	1,500	10,000	19,601	45,983	113,217	232,230
R&D	550	501	485	1,000	4,000	5,500	10,985	32,000	45,000	50,000	40,000	55,000	75,000	100,000	125,000
SG&A	443	1,799	1,836	2,200	2,600	3,500	10,136	12,163	13,623	15,258	17,088	19,139	21,436	24,008	26,889
Income from Operations	(993)	(2,300)	(2,321)	(3,200)	(6,600)	(9,000)	(21,121)	(21,663)	(58,623)	(51,758)	32,912	84,975	77,725	101,926	259,335
Other Income	0	2	-	1	35	25	61	257	152	389	792	1,423	2,235	2,979	3,790
Other Expenses	(1)	(89)	(315)	(72)	-	(650)	(1,037)	(2,600)	(2,600)	(2,600)	-	-	-	-	-
Pre-Tax Income	(994)	(2,387)	(2,636)	(3,271)	(6,565)	(9,625)	(22,097)	(24,007)	(61,071)	(53,968)	33,704	86,397	79,960	104,906	263,125
Tax Expense	-	-	-	-	-	-	-	-	-	-	12,470	31,967	29,585	38,815	97,356
Tax Rate	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	37%	37%	37%	37%	37%
Net Income	(994)	(2,387)	(2,636)	(3,271)	(6,565)	(9,625)	(22,097)	(24,007)	(61,071)	(53,968)	21,233	54,430	50,375	66,091	165,769
Diluted shares outstanding	3,381	4,838	6,903	8,521	18,478	18,678	13,145	18,278	21,778	30,378	36,146	36,538	36,932	37,331	37,742
Net Loss per share	$ (0.29)	$ (0.49)	$ (0.38)	$ (0.38)	$ (0.36)	$ (0.52)	$ (1.68)	$ (1.31)	$ (2.80)	$ (1.78)	$ 0.59	$ 1.49	$ 1.36	$ 1.77	$ 4.39
Options Expense	588	656	302	400	500	600	1,802	2,072	2,383	2,741	3,152	3,625	4,168	4,794	5,513
EPS with Options Expense	$ (0.47)	$ (0.63)	$ (0.43)	$ (0.43)	$ (0.38)	$ (0.55)	$ (1.82)	$ (1.43)	$ (2.91)	$ (1.87)	$ 0.50	$ 1.39	$ 1.25	$ 1.64	$ 4.25

Source: Company data, Jefferies Group LLC estimate
July 25, 2014

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Please see important disclosure information on pages 34 - 37 of this report.

NERV: Historical and Projected Changes in Financial Position

December 31 Fiscal Year ($000s)	2012A	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Cash flows from operating activities											
Net loss	**(994)**	**(2,387)**	**(22,097)**	**(24,007)**	**(61,071)**	**(53,968)**	**21,233**	**54,430**	**50,375**	**66,091**	**165,769**
Adjustments to reconcile used in operating activities:											
NOL Utilization	-	-	-	-	-	-	12,470	31,967	29,585	38,815	-
Amortization of debt discount recorded as interest expense	-	36	-	-	-	-	-	-	-	-	-
Change in fair value of derivative	-	0	-	-	-	-	-	-	-	-	-
Unrealized foreign exchange loss	-	20	-	-	-	-	-	-	-	-	-
Interest expense	-	23	-	-	-	-	-	-	-	-	-
Changes in operating assets and liabilities											
Accounts receivable			-	-	-	-	-	-	(11,837)	(34,002)	(86,944)
Prepaid expenses	25	(6)	-	-	-	-	-	-	-	-	-
Accounts payable	-	538	-	-	-	-	-	-	-	-	-
Accrued expenses and other liabilities	59	(383)	-	-	-	-	-	-	-	-	-
Net cash used in operating activities	(909)	(2,159)	(22,097)	(24,007)	(61,071)	(53,968)	33,704	86,397	68,123	70,904	78,825
Cash flows from investing activities:											
Equipment purchases	-	(3)	(5)	(10)	(20)	(20)	(20)	(20)	(20)	(20)	(20)
Cash acquired in business acquisition	-	631	1,168								
Net cash provided by investing activities	-	628	1,163	(10)	(20)	(20)	(20)	(20)	(20)	(20)	(20)
Cash flows from financing activities											
Proceeds from issuance of convertible promissory notes	-	1,300	-	-	-	-	-	-	-	-	-
Proceeds from options exercises			6,023	-	-	1,898	2,610	3,445	4,421	5,558	6,878
Proceeds from follow on offerings	900	1,850	30,764	-	64,155	116,461	-	-	-	-	-
Debt issuance/repayment			20,000			(20,000)					
Stock issuance costs	-	-	-	-	-	-	-	-	-	-	-
Net cash provided by financing activities	900	3,150	56,787	-	64,155	98,359	2,610	3,445	4,421	5,558	6,878
Net (decrease) increase in cash and cash equivalents	(9)	1,619	35,852	(24,017)	3,064	44,370	36,294	89,822	72,524	76,441	85,683
Beginning of period	**209**	**200**	**1,818**	**37,671**	**13,654**	**16,718**	**61,088**	**97,382**	**187,204**	**259,728**	**336,169**
End of period	**200**	**1,818**	**37,671**	**13,654**	**16,718**	**61,088**	**97,382**	**187,204**	**259,728**	**336,169**	**421,852**

Source: Company data, Jefferies Group LLC estimate

July 25, 2014

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NERV: Historical Condensed Balance Sheets

(000s)	12/31/2012	12/31/2013	3/31/2013	Pro forma 3/31/2013
Assets				
Cash and cash equivalents	200	1,818	2,141	32,905
Prepaid expenses	9	1	46	46
Total current assets	209	1,819	2,187	32,951
Equipment	-	3	31	31
In-process research and development	-	19,000	34,200	34,200
Goodwill	-	7,918	15,104	15,104
Deferred public offering costs	-	434	-	-
Other assets	-	-	1,615	1,615
Total assets	**209**	**29,175**	**53,138**	**83,902**
Liabilities				
Accounts payable, accrued expenses, and other c	190	1,348	5,052	5,052
Convertible promissory notes	-	58	333	333
Total current liabilities	190	1,407	5,384	5,384
Deferred tax liability	-	7,589	13,669	13,669
Total liabilities	**190**	**8,995**	**19,053**	**19,053**
Stockholders' equity	**19**	**20,180**	**34,085**	**64,849**
Total liabilities and stockholders' equity	**209**	**29,175**	**53,138**	**83,902**

Source: Company Reports, Jefferies Group LLC
July 25, 2014

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Company Description

Minerva is focused on developing neuropsychiatry drugs. Minerva's lead product candidate, MIN-101, is a 5-HT2A/Sigma2 antagonist in Phase 2 development for the treatment of schizophrenia. MIN-101 is thought to be differentiated from conventional antipsychotics as it was developed to be effective against negative symptoms. NERV is also developing MIN-117, an antagonist of 5-HT1A and 5-HTT receptors and both serotonin and dopamine, for major depressive disorder (MDD). NERV believes MIN-117 could be differentiated by fast onset of action and potential to treat patients that have failed previous lines of antidepressants. NERV has two other products in early Phase 1 or preclinical development: MIN-202, an orexin-2 antagonist for primary and secondary insomnia, and MIN-301, an ErbB4 activator for Parkinson's disease.

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Company Specific Disclosures

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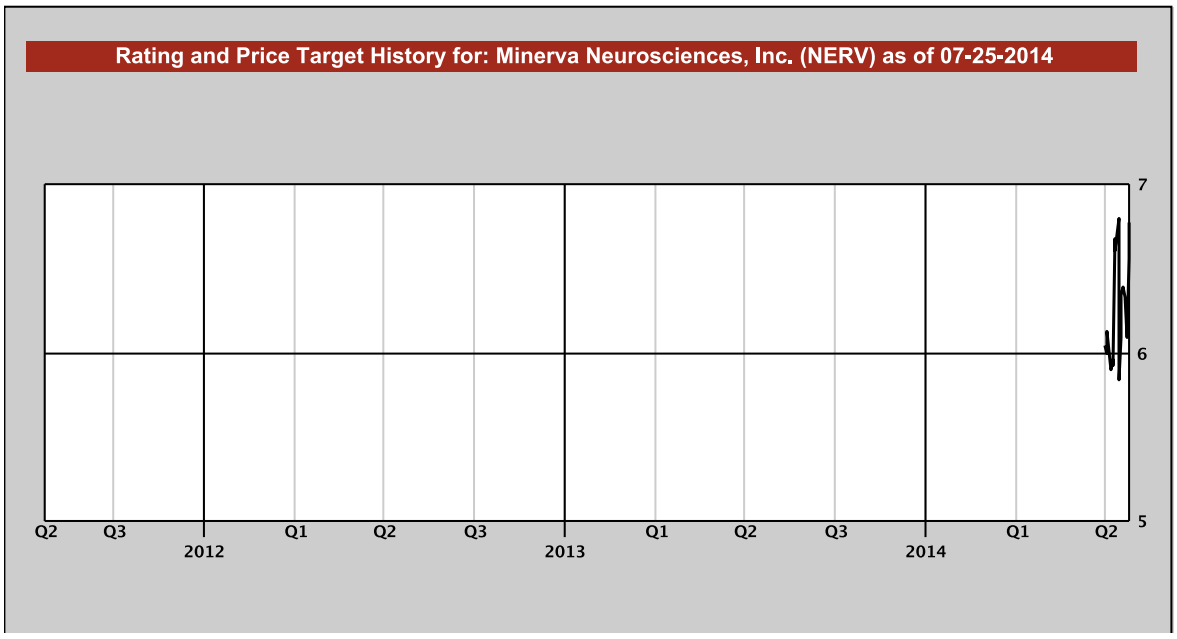
- ACADIA Pharmaceuticals Inc. (ACAD: $20.62, BUY)
- Actelion (ATLN VX: CHF110.80, BUY)
- AstraZeneca PLC (AZN LN: p4,392.00, HOLD)
- Avanir Pharmaceuticals (AVNR: $5.22, HOLD)
- Bristol-Myers Squibb (BMY: $49.39, HOLD)
- Eli Lilly & Co. (LLY: $63.78, HOLD)
- GlaxoSmithKline Plc (GSK LN: p1,423.00, HOLD)
- Lundbeck (LUN DC: DKK126.60, BUY)
- Merck & Co. (MRK: $58.15, HOLD)
- Neurocrine Biosciences (NBIX: $13.53, BUY)
- Pfizer, Inc. (PFE: $30.19, BUY)
- Roche (ROG VX: CHF267.00, BUY)



Distribution of Ratings

Rating	Count	Percent	IB Serv./Past 12 Mos. Count	IB Serv./Past 12 Mos. Percent
BUY	957	51.40%	250	26.12%
HOLD	757	40.66%	121	15.98%
UNDERPERFORM	148	7.95%	8	5.41%

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