Naurex's First Orally Active Molecule, NRX-1074, Demonstrates Statistically Significant Improvement in Depression Scores within 24 Hours in Phase 2 Study for Major Depressive Disorder

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Coverage:
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Forbes

Depression Drug That Works In One Day Passes Key Test

By Luke Timmerman
January 27, 2015

Good drugs for depression have been around for years, but they tend to take weeks to kick in, and don’t work for everyone. Millions of people still need more help.

Now a little biotech company, Naurex, is gathering data that suggests it may have a drug that works faster and better than anything on the market.

Naurex, a private company founded by a Northwestern University professor in Evanston, Ill., is reporting today that an experimental drug with a new biochemical way of working helped push patients out of a major depressive state within 24 hours of getting a single intravenous shot. The company-sponsored study, which enrolled 140 patients at a dozen U.S. medical centers, showed the new drug had no severe side effects and was significantly more effective than a placebo. The difference was both statistically significant–meaning it was unlikely the result of random chance–and clinically meaningful, said Susan McElroy, one of the study’s investigators. The next step is to see if the company can repeat the success in another clinical trial with a once-daily oral pill form of the drug, which could achieve broad use in the real world. If the drug can be consistently shown to work within a single day, it would be a godsend for many patients who currently have to wait weeks to see if they will get any relief.

“If these results can be replicated, they are almost revolutionary. They will change the treatment of depression,” said Dr. McElroy, a study investigator and professor of psychiatry and behavioral neuroscience at the University of Cincinnati College of Medicine.
While millions of people manage depression with generic drugs known as selective serotonin reuptake inhibitors (SSRIs), those molecules tend to take two to six weeks to start working and fail to help millions of patients. Each year, about 6.7 percent of U.S. adults are estimated to experience a major depressive episode—defined as depression that interferes with the ability to work, sleep, study, eat, and enjoy life, according to the National Institute of Mental Health. An estimated 4 million people in the U.S. every year are thought to have depression that persists after treatment with two different SSRI drugs.

Part of what’s intriguing about the Naurex compound is that it doesn’t go down the same tried-and-true biochemical pathway as existing SSRI drugs like sertraline (Zoloft) and paroxetine (Paxil), or a related class of serotonin and norepinephrine reuptake inhibitors (SNRIs) like venlafaxine (Effexor) and duloxetine (Cymbalta). Instead, the Naurex drug is designed to interact with what’s known as the brain’s NMDA receptor, which plays a role in the formation of synaptic connections and memories.

Scientists have known for years that a common anesthetic called ketamine blocks the NMDA receptor, and that it curiously can resolve depression symptoms. That observation has spurred about a half-dozen drugmakers, including Johnson & Johnson, to see if they can develop new anti-depressants that work on the NMDA receptor, but without causing the delusions and hallucinations sometimes seen when people take ketamine in high doses. Because of that troubling effect, ketamine has been abused as a party drug with the street name of “Special K.”

Naurex has developed a variety of drugs that work on the NMDA receptor, with an eye toward tweaking it to get the antidepressant effect without the hallucinations. The drug it is reporting on today, dubbed NRX-1074, is designed, in part, to stimulate the target, rather than shut it down.

The data gathered so far are encouraging, but preliminary. Patients with major depressive disorder were enrolled in the study, based on the standard Hamilton rating score in which medical professionals conduct a detailed interview about depression symptoms. About 72 percent of patients in the study had what was considered to be a clinically meaningful response to the new drug within 24 hours, compared with 39 percent who did that well on a placebo. The difference was statistically significant at the highest of three doses studied, and patients appeared to do best at the highest dose. The magnitude of benefit at that dose seen was about twice as high, after just 24 hours, as what is typically seen with standard antidepressants after four to six weeks, Dr. McElroy, the study investigator, said. Patients weren’t cured. But in practical terms, they went from severe depression to a mild state, she said. Patients with the most severe depression, those who told clinicians they’ve had suicidal thoughts, were excluded from the trial for safety reasons. Detailed results are expected to be presented at a medical meeting, and submitted for publication in a peer-reviewed journal.

As with any small clinical trial, there are a number of caveats to consider. The benefits of the single shot didn’t last long, disappearing at the two-week follow-up visit. The Naurex drug was given in an intravenous form, which can only be administered in a medical facility. The drug is also a peptide molecule. While Naurex has re-engineered it into a more convenient oral pill form, it is a difficult feat of chemistry to make a peptide into a pill. Ensuing studies will need to show that the oral pill works in larger numbers of patients, in repeat doses, at multiple clinical sites, and that it likely offers a benefit beyond existing anti-depressants. The FDA likely will ask the company for long-term follow-up data to assess the safety of a drug that would likely be taken by many people on an ongoing basis.

Naurex is planning to start the next clinical trial of NRX-1074 in April or May, said Norbert Riedel, the company’s CEO. By July, it plans to start another trial of a different drug, rapastinel, that is further along in development,
but which is only available in the IV form, and in combination with existing antidepressants. Naurex is also developing other molecules that interact with the same target, and it hopes they will be useful for more than just depression. The list of potential uses includes dementia and neuropathic pain, Riedel said.

Although Naurex raised $80 million of venture capital last month, it would need more money to run an ambitious slate of clinical trials for multiple neurological disorders. The company is considering going public to take advantage of optimistic investor sentiment toward biotech stocks. “This is not just a depression company. It’s a CNS (central nervous system) company we are building,” Riedel said.

**FierceBiotech**

**The Special K connection: Naurex spotlights another promising NMDA depression drug**

*By John Carroll*

*January 27, 2015*

Just a few months after heralding some strong data for their lead depression drug, Naurex has wrapped a Phase II study of its number two NMDA treatment after getting the positive efficacy data it was looking for—while continuing to set the stage for a possible IPO in its near future.

The Evanston, IL-based biotech turned heads last fall when it rolled out an $80 million financing round. The funding arrived just weeks ahead of positive Phase IIb data for GLYX-13, an NMDA modulator that has been attracting careful attention for a therapeutic approach that is designed to safely hit the same target as ketamine, better known on the street as the party drug Special K.

In this new Phase II study, Naurex's follow-up program for NRX-1074 also breezed past the placebo arm, posting a 7-point improvement over a placebo based on industry-standard HDRS-17 rating scale scores, with an average 14-point reduction over baseline. Investigators used an IV formulation of the drug in order to monitor the drug's performance so it could better choose the right dose for the next oral study, according to Naurex CEO Norbert Riedel.

Riedel noted that the depression effect seen in the drug arm after 24 hours was similar to what you might expect after several weeks on existing treatments. The data suggests that a single dose has a fast impact, then the patient's symptoms return to baseline after about three days, which investigators believe fits the profile for a drug that could be dosed daily.

Depression remains a huge target for the drug developers still left in the field. Placebo effects have torpedoed a whole series of experimental late-stage drugs, pushing big players like AstraZeneca ($AZN) to the sidelines. The standard R&D strategy for depression calls for a slate of late-stage studies in order to scrape up with enough positive data to take to regulators. And existing therapies often offer little more than a crap shoot for patients who often cycle through one drug after the next.
For big pharma players like Johnson & Johnson (JNJ), finding a commercially workable version of ketamine—which has repeatedly demonstrated its ability to rapidly lift depression among a large group of severely depressed and sometimes suicidal patients, but is linked to frequent psychotic episodes—has become a prized goal. The durability of Naurex's GLYX-13 data, which Riedel says is due to the fact that its drugs are NMDA modulators, instead of crude blockers, has stood out.

The goal here is to craft a partial impact on the target, he says, without just slamming the target.

With these two drugs, says Riedel, Naurex has a chance to develop GLYX-13 as a once-weekly therapy for prolonged treatment of patients who don't respond adequately to the drugs now available. And NRX-1074 could be a daily oral drug that is being advanced for first-line use in major depression, where physicians are looking for a quick response. Add in a preclinical program headed for Phase I, he says, and he believes the biotech should have the kind of pipeline needed to stage an IPO, perhaps as early as May or June of this year.

Riedel isn't committing the company to any specific timeline on an IPO, but he also hasn't shied away from expressing his interest in raising cash on the public market. And there's also the chance of doing a deal for the drug as well. But the CEO is concerned that the market shows signs of overheating.

Some biotech valuations, he notes, "are completely out of mind."

With a Phase III program looming for GLYX-13 and its follow-up drug advancing closely behind it, Riedel believes that Naurex can escape the need for recruiting a big patient population. Better drugs that stand out more easily can steer clear of the placebo effects that scuttled so much work in the field. But they will still have to clear a very high regulatory hurdle that has proved fatal to a whole host of drug development programs.

**Medscape**

**Rapid-Acting Antidepressant Shows Promise**

*By Megan Brooks*
*January 27, 2015*

A single dose of an experimental N-methyl-D-aspartate (NMDA) receptor modulator led to statistically significant improvement in depression within 24 hours in a phase 2 study of patients with major depressive disorder (MDD), the neuropharmaceutical company developing the drug said today.

The effect size observed at 24 hours after one intravenous dose of Naurex's NRX-1074 was more than double the average effect size typically seen with most other antidepressants after 4 to 6 weeks of repeated dosing, the company noted in a news release.

"The reductions in depression symptoms we saw from a single dose of NRX-1074 in this study were among the most substantial I have observed in antidepressant clinical development," study investigator Susan McElroy, MD,
A professor of psychiatry and behavioral neuroscience at the University of Cincinnati College of Medicine, in Ohio, said in the release.

"This level of effect will likely have a very positive impact on patients' lives. There is a significant need for treatment options that are able to bring rapid and meaningful benefits to patients struggling with depression. We look forward to continuing to study the benefit of this therapy, including in the upcoming repeat-dose trial," Dr McElroy added.

The randomized, double-blind, placebo-controlled phase 2 study tested the efficacy and safety of a single intravenous dose of NRX-1074 in approximately 140 patients with MDD. The study was conducted at 12 centers in the United States. Patients received 1 of 3 doses of NRX-1074 or placebo.

A clear dose response was observed across the three dose levels tested, the company said.

At the highest and most effective dose, the average reduction in the 17-item Hamilton Depression Rating Scale (HDRS-17) scores at 24 hours was 14 points, with a mean difference from placebo of 7 points ($P = .0029$), they report.

The effect size 24 hours after dosing was 0.88, which is more than two times the effect size seen with most other antidepressant drugs after 4 to 6 weeks of repeated dosing, according to the company.

Nearly three quarters (72%) of patients receiving the highest dose demonstrated a clinically meaningful response at 24 hours (defined as at least a 50% reduction in HDRS-17 score from baseline) compared with 39% of patients given placebo ($P = .038$).

NRX-1074 was well tolerated, with no drug-related serious adverse events reported and no patient dropping out because of adverse events. This safety profile was also observed in earlier phase 1 studies with both intravenous and oral NRX-1074 in healthy volunteers.

The company says results from this phase 2 study using an intravenous formulation of NRX-1074 will guide dose selection for an upcoming phase 2 study that will test repeated dosing with an oral form of the drug.

BioWorld Today
In the Clinic
January 28, 2015

Naurex Inc., of Evanston, Ill. reported that at 24 hours, 72 percent of subjects receiving the highest dose of its NMDA receptor modulator, NRX-1074, in a single-dose phase II study demonstrated at least a 50 percent reduction in their HDRS-17 depression score from baseline, compared to 39 percent of subjects given placebo ($p = 0.038$). Though tested in its oral form during a phase I study, NRX-1074 was given via intravenous administration during the phase II trial, which included 140 people with major depressive disorder. The drug, a
follow-up to Naurex's lead program, rapastinel (GLYX-13), was well tolerated with no drug-related serious adverse events reported and no subjects dropping out of the study due to adverse events. (See BioWorld Today, Dec. 4, 2014.)

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NeuroGram+
Interim note news and topics

By Harry Tracy
January 27, 2015

1) Naurex and NRX-1074
Naurex reported today that the first efficacy trial for NRX-1074, using a single-dose IV administration of a compound that will be delivered orally from now on, established a remarkable degree of immediate impact. At 24 hours post-injection of the highest dose (and unlike GlyX-13, NRX-1074 does not have an inverted-U dose-response curve), the mean reduction in Hamilton scores was 14 points, the effect size was .88. The effect size itself, just 24 hours later, is impressive compared to current antidepressants. It was also pleasantly surprising that 72% of patients receiving NRX-1074 showed a 'clinically meaningful' response, given that in rapastinel/GlyX-13's PhIIb, only about half of the patients appeared to be treatment responsive. The usual caveats--small treatment samples for each of the three doses, 35 patients; just a single-dose readout; IV delivery of this oral compound--do apply, and the data release did not offer anything regarding the durability of the antidepressant response. However, durability is far less important here than it was with IV GlyX-13, for which minimizing the frequency of re-infusion would be an important treatment consideration. These data at 24 hours suggest that once-daily administration would be viable, the sweet spot for an oral antidepressant. The next clinical step (starting this spring) will be a repeated-dose, oral administration trial of NRX-1074, as monotherapy--in contrast to GlyX-13, being developed as an adjunct. As to the next corporate development step, it seems a near-certainty that Naurex will go the IPO route to funding their ambitious clinical development agenda--the question to us is not whether, but when.

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Scrip
Naurex reveals promising data with oral depression candidate

By Sukaina Virji
January 27, 2015

Naurex has presented positive Phase II data with the second depression candidate in its pipeline, NRX-1074, an oral NMDA receptor partial agonist. This follows Phase IIb data reported recently with Naurex's lead program, GLYX-13, which also targets the NMDA receptor (scripintelligence.com, 11 December 2014). Naurex is in the "advantageous position [of having] two complementary late-stage assets with compelling clinical data in depression that can serve different needs in clinical practice. GLYX-13 is being developed as an adjunctive treatment for difficult-to-treat major depressive disorder, while orally available NRX-1074 has the
potential to be an early-line monotherapy," explained Dr Norbert Riedel, president and chief executive officer of Naurex.

"NRX-1074 modulates the NMDA receptor in a similar fashion to GLYX-13, but has a synthetic modification to one of the amino acids, conferring increased potency and oral bioavailability," he told Scrip. "In preclinical models the two compounds both appear to be highly efficacious across a number of CNS disorders."

Naurex is planning two pivotal 6-week, parallel-designed, placebo-controlled Phase III studies of GLYX-13. "The first of these is on track to initiate in the summer of 2015, using our commercial formulation – a rapid bolus injection with a pre-filled syringe. We will provide additional details at that time."

"The reductions in depression symptoms we saw from a single dose of NRX-1074 in this study were among the most substantial I have observed in antidepressant clinical development," said Dr Susan McElroy, a study investigator and professor of psychiatry and behavioral neuroscience at the University of Cincinnati College of Medicine. "We look forward to continuing to study the benefit of this therapy, including in the upcoming repeat-dose trial."

Naurex raised an IPO-sized private financing round last month, an $80m series C (scripintelligence.com, 3 December 2014).

"It was very important for us not to just have very active insider participation, but to bring new investors into the company that are focused on CNS and who are investing in companies at a point in their life and development that are interested in pursuing an IPO next," said Dr Riedel at the time.

"We are evaluating multiple options for funding continued growth and advancement of our pipeline," he added this week.

**Study Details**

At the highest and most effective dose level, the average reduction in HDRS-17 scores at 24 hours was 14 points, with a mean difference from placebo of 7 points (p=0.0029). The effect size, a measure of the magnitude of the drug’s antidepressant efficacy, observed at 24 hours after dosing was 0.88 – more than double the effect size seen with most other antidepressant drugs after four to six weeks of repeated dosing. Clinical response to NRX-1074 was also significantly different from placebo, with 72 percent of subjects receiving the highest dose of the compound demonstrating a clinically meaningful response at 24 hours (defined as at least a 50 percent reduction in HDRS-17 score from baseline) compared to 39 percent of subjects given placebo (p=0.038). A clear dose response was observed across the three dose levels tested. The study utilized an intravenous formulation to inform dose selection for an upcoming repeat-dose Phase 2 study with the oral form.

In the study, which was conducted at 12 clinical centers in the US and enrolled around 140 subjects, NRX-1074 was well-tolerated with no drug-related serious adverse events reported and no subjects dropping out of the study due to adverse events.

The upcoming randomized, double-blind, placebo-controlled multi-dose study will evaluate the efficacy and safety of repeated oral dosing of NRX-1074 administered as a monotherapy to subjects with MDD.

"We expect to start our repeat-dose Phase II trial by mid-2015," added Dr Riedel.
"There is a lot of evidence now from various different molecules that targeting glutamate signaling results in rapid improvement in depression symptoms," noted Datamonitor Healthcare analyst Daniel Chancellor. "The class has a large potential in treatment-resistant patients, which accounts for around one third of patients with major depressive disorder."

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Naurex has been setting the stage for an #IPO. Pipeline advances - $80M crossover round. The works. http://www.fiercebiotech.com/story/special-k-connection-naurex-spotlights-another-promising-nmda-depression-dr/2015-01-27 ...

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Tom Insel & other neurosci heavies call Ketamine THE hottest thing in CNS R&D. Naurex, Cerecor + $JNJ (intranasal) all fast trackd @jasonCRG

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