How NeuroRx Pharma is Turning Suicidal Ideation Into A Treatable Condition

By **David Rich** - November 30, 2016

It's not often that we cover a private firm at Market Exclusive, as we are geared towards publicly investable companies. However, our staff recently had the privilege of speaking with Chief Commercial and Patient Officer Robert Besthof of NeuroRx, as of now a private company in the suicidal ideation space. Investors should keep one eye out for any word of an initial public offering, which is why we have chosen to cover the company here.

The area of suicide is chronically and perpetually underserved. To even call it an "area" or a "space" is almost a misnomer, because suicidality is actually an exclusionary criterion for practically all psychological clinical trials. Combine that with the difficulty in measuring qualitative as opposed to quantitative psychological endpoints, and you have a surefire way to discourage most biotech companies big or small from even touching suicide indications with a 10-foot pole.

The problem is big and growing. 2014 saw over 40,000 suicides. That's 2.5x the number of people that die of brain cancer each year in the United States. How much coverage does brain cancer get in terms of clinical trials and tight races to approval versus suicide? It's not even a question. It's like asking how much sunlight the dark side of the moon gets versus the light side. And behind it all is the controversial nature of suicide itself. Is it a disease or is it rather

an unfortunate choice? Regardless of the objective answer, getting companies and investors even interested in the field in the first place requires convincing the public that suicidality is a *bona fide* disease,the culmination of which is actual suicide, and therefore treatable with a marketable drug. Those with little to no personal connection to the condition tend to simply and sadly brush it aside as an unfortunate choice rather than a condition.

NeuroRx is an interesting reflection of this unspoken reality. Besthof told us that everyone involved in NeuroRx has a personal connection to suicide, whether of a friend or relative.

How Ketamine Changed the Suicide Landscape

Up until 2012, there were no drugs even known to be capable of treating suicidal ideation specifically. Major depressive disorder (MDD) and to a lesser extent treatment resistant depression (TRD) yes, but depression and suicidality are not the same thing. In fact, all approved MDD medications contain a black box warning of an *increased risk* of suicidality. Just because depression lifts does not mean patients stop considering suicide. In fact, akathisia, the condition of "needing to do *something*" including jumping off a building, is a known and common side effect of MDD medications.

It was one Dr. Carlos Zarate who pioneered the research of low-dose ketamine as in principle effective against suicidal ideation. Ketamine is used as an anesthetic but is also a popular recreational party drug used for its dissociative affects. Dr. Zarate found that low-dose intravenous ketamine can counteract not only depression, but specifically suicidal thoughts as well within 40 minutes and for up to 3 days. There is now a speck of light at the end of the tunnel. The problem is, you can't just administer IV ketamine to suicidal patients every 3 days. Ketamine is known to be extremely addictive and repeated use is known to necrotize brain cells causing lesions in the cortex. So what to do?

Ever since Zarate's pioneering research, a handful of biotechs spanning Big Pharma to startups and even to private NeuroRx have been trying to figure out how to capitalize on ketamine. By and large, the approach has been to modify ketamine's mechanism of action (MOA) and/or method of administration in order to make it less addictive and hopefully prolong its anti-suicidal effects.

NeuroRx is Almost Alone in the Suicide Space

But as we'll soon see, the very term "anti-suicidal effects" is actually misleading with regard to ketamine in terms of what biotechs are pursuing with these drugs. And it's been a difficult road so far with limited success. The furthest along, at least on paper, is the $312B behemoth Johnson & Johnson (NYSE:JNJ). JNJ does have some encouraging Phase II clinical data for its intranasal esketamine – a chemical mirror image of ketamine – and is currently in Phase III. However, besides the issue of addiction and the likely requirement that an intranasal administration be taken in a clinical setting, the elephant in the room here is that JNJ's current esketamine Phase III trial *still* has the exclusion criterion of suicidal ideation. From the file on Clinicaltrials.gov:

> *SINCE THE LAST STUDY VISIT IN THE PARTICIPANT'S PRIOR STUDY, PARTICIPANT HAS SUICIDAL IDEATION WITH INTENT TO ACT PER THE INVESTIGATOR'S CLINICAL JUDGMENT OR BASED ON THE COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)…*

JNJ is however planning a suicide indication for esketamine in the future. While the current Phase III trial for esketamine excludes suicidal ideation, an earlier Phase II trial includes it, but excludes patients with bipolar disorder. JNJ back in August received a Breakthrough Therapy Designation for esketamine for patients with MDD at imminent risk of suicide, and there is a Phase III trial planned. But if and when the current Phase III trial succeeds, even if approved, suicidal patients will still be almost entirely ignored for all intents and purposes, excluding off-label treatment.

Rapastinel, a drug with a modified ketamine-like MOA acquired by Allergan plc Ordinary Shares (NYSE:AGN) from Naurex, has the **same exclusion criterion** regarding suicidality. The indication for Rapastinelonce again is MDD and not suicidality itself.

Just this factor alone makes NeuroRx a fascinating case because while they may have competition in terms of clinical development of ketamine and ketamine-like drugs, that competition is actually on an entirely different plane. In terms of the actual indication of suicidality, NeuroRx is practically all alone.

Cyclurad – The NeuroRx Approach to Suicidality

So what is NeuroRx working on exactly? Unlike its competition at least regarding ketamine development proper, NeuroRx is not seeking to alter ketamine's MOA or method of

administration. Rather, it is seeking to prolong its effect while at the same time reducing the associated danger. And it is doing this in a rather novel way.

Cyclurad is a combination of two FDA approved drugs. The first is D-cycloserine, actually a tuberculosis drug. The second is lurasidone, a drug used as an antipsychotic in bipolar patients. At high doses, D-cycloserine is an NMDA receptor modulator. Ketamine on the other hand is an NMDA receptor antagonist, and it is theorized that D-cycloserine can serve to moderate the clinical activity of ketamine, sort of like a slow-burn effect, reducing the size of the NMDA "flame" and prolonging the duration. This at once may hopefully both prolong the effect and reduce the dissociative side effects.Lurasidone in turn modulates the effect of D-cycloserine, further adding to the slow-burn.

The combination of the two into Cyclurad (the condensed names of cycloserine-lurasidone) is designed to maintain ketamine's effectiveness against suicidal ideation for 6 to 8 weeks, potentially increasing ketamine's effect by a factor of 14 or even more. Going into the clinic every three days to get an infusion of ketamine is impossible and dangerous, but every 6 to 8 weeks may be doable if inconvenient. What happens after that time period is the question, to which a possible answer is psychological reevaluation. This we will have to see as trials progress.

Most importantly though, the indication here is not MDD, but Acute/Elevated Suicidal Ideation/Crisis in Bipolar Depression (ASIBD/ESIBD). This is unique, and for which NeuroRx has no competition. JNJ's planned Phase III trial for esketamine excludes patients with bipolar disorder. Cyclurad, though, is specifically tailored for bipolar patients many of whom are already taking lurasidone anyway. There are 5.7M people in the US suffering from bipolar disorder, 20% of whom will attempt suicide within 5 years. If there was ever a specific target group to treat for suicidality, bipolar patients are Ground Zero.

Early Clinical Results So Far

A small 2015 clinical study published in the **Journal of Psychiatry** found effectiveness for this drug combination in bipolar patients for 8 weeks. In fact, the largest effects seen were immediately after initial ketamine administration and at the 8-week mark. NeuroRxis looking at a pivotal Phase IIb/III trial later this year planning enrollment of 120 bipolar patients with acute suicidal ideation. No more exclusion criteria.

Chances of Approval and Market Size

NeuroRx estimates the market for this combination drug to be between $500M-$960M annually. As for chances of approval, both of the drugs in the Cyclurad combination are already FDA approved, so the main question is safety, and could side effects be any worse than suicide? This is what the upcoming Phase IIb/III trial will attempt to determine. Even at a moderate efficacy level where Cyclurad is only effective on some patients, it would still likely be approved assuming no obvious safety concerns that outweigh the risk/benefit ratio. After all, it will be the only drug even being trialed for suicidality at all, let alone the only one on the market if approved.

After solidifying its intellectual property position **last month**, investors should keep an eye on this one in the event that NeuroRx decides to go public to help fund Cyclurad's upcoming Phase III trial or other "slow-burn" anti-suicidal combinations targeting different disorders deeper down in the pipeline.

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