SCRIP
CITELINE COMMERCIAL

08 Sep 2023 | **Analysis**

Schizophrenia, Depression And Neuropathy: What's Coming In 2024

by Elizabeth Cairns

The following four neurological products are likely to reach market next year. Carving out sales will be an entirely different problem.

Drugs that act on the nervous system are notoriously difficult to bring to market, with unpredictable placebo responses scuppering many a late-stage trial. But there are some sparks in the darkness, and Biomedtracker has pinpointed four psychiatric or neurological products that are likely to buck the trend and reach market next year.

Some of the most emphatic victories seen in the extremely hard to treat indication of schizophrenia have been won by *Karuna Therapeutics, Inc.*'s combo therapy KarXT, and if it is approved next year, as is expected, it would usher in the first new mechanism to treat the disease in decades.

KarXT is a coformulation of the M1/M4-preferring muscarinic agonist xanomeline with trospium chloride, a peripheral muscarinic receptor antagonist. The idea is that trospium cancels out xanomeline's peripheral side effects but, since it cannot cross the blood-brain barrier, does not hamper xanomeline's effect in the brain.

PANSS down

In its two pivotal trials, EMERGENT-2 and -3, both in acutely psychotic hospitalized adult patients with schizophrenia, KarXT produced statistically significant reductions on the Positive and Negative Syndrome Scale (PANSS) total score of 9.6 and 8.4 points, respectively (Also see "*Karuna Three-For-Three As Another KarXT Schizophrenia Trial Hits Primary Endpoint*" - Scrip, 20 Mar, 2023.).

This compares well with many other antipsychotics. The label for *Johnson & Johnson*'s now-generic Risperdal (risperidone) claims simply that it was "generally superior to placebo on several PANSS measures" in its pivotal trials. The label for the current biggest-selling branded schizophrenia product, J&J's long-acting pill Invega Sustenna (paliperidone palmitate), just says that it was "superior to placebo on the PANSS at all doses".

Karuna plans to submit an NDA for KarXT in schizophrenia in the next few months, so an FDA approval decision ought to come in 2024. Data from two Phase III long-term safety and tolerability trials are also expected next year.

Another Phase III trial, ARISE, will evaluate the safety and efficacy of KarXT as an adjunctive treatment in adults who have an inadequate response to their current antipsychotic therapy, which is likely to better reflect how the drug would be used in the real world, if approved.

The agent has a drawback in its twice-daily administration versus the once-daily or longer schedules of available schizophrenia therapies. But it is still considered biopharma's most valuable unpartnered asset, with *Evaluate Omnium* placing its net present value at $8.3bn.

Sleepless Nights

A new mechanism could make its debut next year in depression, too. J&J is developing seltorexant, a hypocretin/orexin 2 receptor antagonist, for patients with major depressive disorder and insomnia.

Two Phase III trials are ongoing, one head-to-head against *AstraZeneca PLC*'s Seroquel XR (quetiapine extended-release tablets) in 720 patients and another, 588 patients strong, against placebo. Data from both could come this year.

However, another Phase III trial was terminated in 2022 after an interim analysis, though J&J did not say whether this was due to concerns over efficacy or safety.

In a Phase IIb trial in MDD patients with sleep disturbances, seltorexant allowed a statistically significant reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score at week three but not at week six, suggesting that effects could taper over time. Although seltorexant showed only modest efficacy as an adjunctive treatment in this study – specifically at the lowest dose – the drug's target population is SSRI/SNRI-inadequate responders, a challenging population to treat.

In a smaller Phase IIb study versus Seroquel, J&J's therapy permitted greater improvement in

MADRS score and a lower treatment-related discontinuation rate than the control after six months' treatment. Discontinuation rates were similar in the two arms.

Should the two ongoing Phase III studies come up trumps, J&J could submit an NDA before the end of 2023, with the intention of a 2024 launch. But the terminated study remains a mystery, and therefore, perhaps, a red flag.

Expansion

Intra-Cellular Therapies, Inc. first obtained approval for Caplyta (lumateperone) in schizophrenia, in 2019, and expanded into bipolar disorder, specifically bipolar depression, two years later. Now it hopes to add a claim for MDD, and much will depend on the three near-identical placebo-controlled Phase III trials currently underway.

Like other atypical antipsychotics, Caplyta modulates both serotonin and other monoamines, particularly dopamine, although its exact mechanism of action is unknown.

In the Phase III Study 403 trial, Caplyta was explored as a monotherapy in MDD as well as bipolar I and II. In this combined patient population, Caplyta demonstrated a statistically significant reduction of 5.7 points on the MADRS total score compared with placebo at week six, and a 5.9-point reduction over placebo in the MDD subpopulation.

Interestingly, despite the drug's success as a monotherapy in MDD, the three Phase III studies are assessing Caplyta as an adjunctive treatment. Each is in 470 patients who have not responded well to other antidepressants; all are assessing MDRS score change at six weeks. Two of these trials, known as 501 and 502, are set to finish this year, with the third, 505, likely to read out towards the end of 2025. A larger, longer, open-label study in MDD will conclude in the middle of next year.

Intra-Cellular has indicated that it plans to file an sNDA in 2024, and an approval decision could come the same year. Bearing in mind the trials' design, however, Caplyta could well be relegated to refractory patients.

Convenience

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disorder of the peripheral nerves characterized by increasing sensory loss and weakness associated with loss of reflexes.

Takeda Consumer Healthcare Co. Ltd.'s HyQvia is a formulation of recombinant human hyaluronidase and immunoglobulins, which is infused under the skin into fatty subcutaneous tissue. It is intended as a maintenance therapy in adult patients with CIDP, and if it is approved, as it cold be next year, it will become the first monthly subcutaneous immunoglobulin injection on the market. It employs *Halozyme Therapeutics, Inc.*'s ENHANZE technology to enable high levels of the immunoglobulins to enter the bloodstream.

In the pivotal Phase III ADVANCE-CIDP 1 trial, HyQvia, administered every four weeks to most patients, showed a significant reduction in relapse rate compared with placebo, and the product is now filed with regulators.

Takeda's argument is convenience. The current standard of care for CIDP is intravenous immunoglobulin, which must be administered over several hours every three weeks and carries the risk of side effects including injection site reactions, nausea, and headaches. But the immunoglobulin market is long established and dominated by *CSL Limited* and *Grifols, S.A.*, and convenience – plus, Takeda hopes, better efficacy thanks to the concentrated formula – might not be enough to take share from the entrenched players.