Relmada Therapeutics, Inc.
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Relmada Therapeutics: delivering medicines for depression and central nervous system disorders

Relmada Therapeutics is developing REL-1017, a phase 2, noncompetitive *N*-methyl-D-aspartate receptor antagonist for the treatment of depression and Rett syndrome.

As many as 65 million Americans will experience at least one episode of depression in their lifetime[1]. Unfortunately, currently approved antidepressant drugs take several weeks to show effectiveness. Nearly two-thirds of patients do not respond to first-line treatment and one-third fail to respond to up to fourth-line treatment, leaving some 10 million patients with treatment-resistant depression[2].

Relmada Therapeutics, a publicly traded specialty pharmaceutical company, is set to address this considerable unmet need with REL-1017 (dextromethadone or D-methadone), a noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist, currently in a phase 2 trial for the treatment of depression.

NMDARs appear to be abnormally activated in depression. Whereas traditional antidepressants (such as selective serotonin reuptake inhibitors, serotonin–noradrenaline reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors) operate slowly, targeting the serotonin, noradrenaline and dopamine-activated pathways, NMDAR antagonists are thought to act rapidly by correcting the imbalance between inhibitory GABAergic and excitatory glutamatergic activity in the brain cortical microcircuits[3]. In addition, by inducing expression of the neuroprotective brain-derived neurotrophic factor (BDNF), NMDAR antagonists appear to produce a sustained antidepressant response, promoting synaptic plasticity and increasing the number of synaptic connections, which are decreased in depression and chronic stress.

The anesthetic ketamine was the first NMDAR antagonist to show rapid and sustained antidepressant effects[4,5], and the US Food and Drug Administration (FDA) recently approved esketamine for treatment-resistant depression. However, its rapid and efficacious antidepressant activity is offset by the significant rate of psychotomimetic and dissociative adverse events, and by the requirement of in-clinic administration by trained and specialized clinical staff. "These critical issues limit esketamine access and clinical utility," explained Ottavio V. Vitolo, senior VP, head of research and development and CMO at Relmada.

Introducing REL-1017

What sets REL-1017 apart is that, in addition to being a noncompetitive NMDAR antagonist with an affinity for the ketamine-binding site (**Fig. 1**), it has excellent oral bioavailability with acceptable safety and tolerability profiles devoid of psychotomimetic and dissociative adverse events. "REL-1017 has a fast-acting and long-lasting therapeutic, physiological effect in animal studies, but with virtually no opioid activity or ketamine-like toxicities at the expected therapeutic doses—as shown in our phase 1 clinical studies," said Vitolo[6].

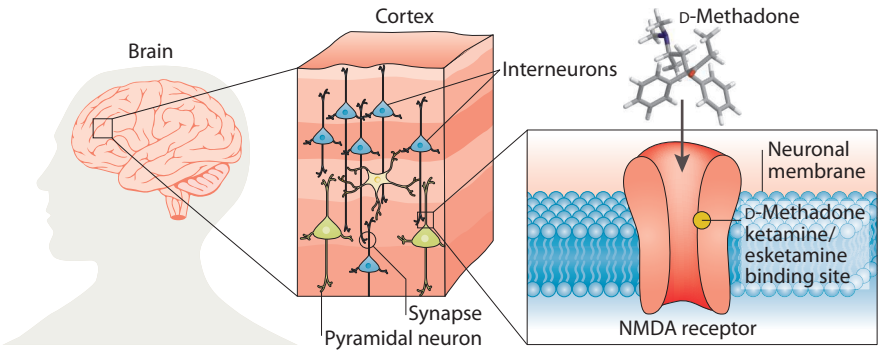

Fig. 1 | REL-1017 mechanism of action. The noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist has affinity for the NMDAR ketamine and esketamine binding site.

Results from preclinical studies demonstrate that REL-1017 is rapidly efficacious (within 24 hours) in four different animal behavior models of depression and stress-induced depression, similar to ketamine. It also appears to improve synaptic plasticity, increasing the expression of important synaptic proteins and improving neuronal function. Individuals treated with REL-1017 in the multiple-ascending-dose study showed plasma BDNF levels between 2 and 17 times greater than pretreatment levels—an increase that began by day 2 and persisted throughout the 10-day trial.

Relmada is currently evaluating the tolerability, safety and antidepressant efficacy of a seven–day treatment of REL-1017 in patients with major depressive disorder who have not responded to traditional antidepressants in a phase 2a clinical trial; the FDA has granted REL-1017 fast-track designation for the adjunctive treatment of depression. "Findings to date are compelling, confirming that this new chemical entity has the potential to be a safer and equally efficacious treatment alternative to ketamine with the potential for long-term neuroprotective effects," said Vitolo. "Methadone, of which D-methadone forms 50%, has been around for 40 years, so we are confident that our safety and tolerability data is cogent."

Moreover, the neurotrophic effects of NMDAR antagonists could be beneficial for the treatment of a range of psychiatric and neurological disorders associated with a variety of cognitive, neurological and behavioral symptoms. Indeed, REL-1017 also has significant potential in multiple additional central nervous system conditions, including movement disorders and Rett syndrome, a rare neurological disorder affecting approximately 15,000 people in the US for which there is no approved treatment.

Partnering aspirations

Relmada is currently focused on developing REL-1017 for the treatment of depression, and results from the phase 2a trial (expected later in 2019) will inform the design of new drug application (NDA)-enabling studies. The company is open to consider collaboration, including codevelopment or out-licensing partnerships for multicentre phase 3 trials, scale-up and commercialization.

"We are looking for partners to realize the enormous potential of REL-1017, a highly compelling product opportunity," said Sergio Traversa, Relmada CEO. "This once-a-day, oral medication, which works like ketamine but without its adverse effects, is set to be a best-in-class treatment for depression and transformative for millions of patients and their families."

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