Gate Neurosciences Publishes Data Highlighting Novel Mechanism of Lead Rapid-Acting Oral Antidepressant and Provides Business Update

- *New publication highlights novel and differentiated NMDA receptor mechanism, and rapid and long-lasting antidepressant activity with lead clinical program, Zelquistinel*
- *Supports further development of Zelquistinel in a Phase 2 confirmatory study in Major Depressive Disorder, with expected initiation in early 2023*
- *Company highlights business update, recent and upcoming clinical milestones, and additions to advisory network, after emerging from stealth last month*

INDIANAPOLIS, September 29, 2022 — Gate Neurosciences today announced the results of research, published in the International Journal of Neuropsychopharmacology, supporting the mechanism of action and clinical foundation of Zelquistinel – the company's lead oral program in Phase 2 development – as a rapid-acting, long-lasting and safe antidepressant.

Publication highlights robust preclinical profile and novel mechanism for lead Phase 2 clinical program, Zelquistinel

The peer-reviewed manuscript spotlights Zelquistinel's novel mechanism and pharmacology by which it elicits rapid and long-lasting antidepressant effects. Zelquistinel was shown to positively modulate NMDA receptors (NMDARs) and enhance synaptic plasticity in the hippocampus and medial prefrontal cortex. A single dose of the molecule demonstrated a dose-dependent antidepressant-like response within one hour of administration that was sustained for more than 7 days. The studies highlighted in the publication build upon a robust underlying translational data package and predictive dose model that is consistent across Gate's class of NMDAR modulators.

Zelquistinel's potential as an oral pill was confirmed by its high bioavailability and brain exposure, and also shows 1000-fold greater potency and a longer plasma half-life compared to its precursor molecule Rapastinel (GLYX-13). In terms of safety, Zelquistinel lacked the sedative, ataxic, and motor impairment effects that are typically observed with NMDAR antagonists and notably, it reversed NMDAR antagonist side effects upon co-administration.

These data highlight Zelquistinel's novel, potent, and highly differentiated mechanism of action with potential for a significantly improved safety profile compared to other NMDAR-targeted antidepressants in development for depressive disorders.

"Zelquistinel's mechanism of action represents a novel pharmacological approach which may help address patient needs in the treatment of depression," said Maurizio Fava M.D., Psychiatrist-in-Chief at Massachusetts General Hospital, and a key advisor to Gate Neurosciences. *"The upcoming Phase 2 study seeks to navigate the known challenges of conducting trials in psychiatry to confirm efficacy in Major Depressive Disorder."*

Business Update

Since its inception in 2019, Gate Neurosciences has assembled and advanced a clinical-stage pipeline of next-generation central nervous system therapies, as previously highlighted when the company emerged from stealth-mode in August 2022. Alongside the previously detailed Zelquistinel, Apimostinel and Rapastinel programs acquired from AbbVie, the company has also acquired exclusive rights to preclinical mGlu2/3 receptor antagonists from Eli Lilly which it is currently developing for sleep disorders, and is advancing a preclinical-stage Insulin Growth Factor 2 Receptor (IGF2R) program for cognitive disorders in collaboration with Northwestern University.

Recent Milestones

- Completed financings totaling $25M from life science-focused investors, including Innoviva, Luson Bioventures, Biocrossroads, and ThornApple Capital, among others
- Appointed new Board of Directors member Sarah Schlesinger M.D., a leading clinical investigator and chair of the Institutional Review Board at Rockefeller University, and member of the Board of Directors of Innoviva, Inc.
- Successfully advanced Investigational New Drug (IND) Applications for lead clinical programs
- Initiated a Phase 1b clinical study exploring human target engagement biomarkers with 2nd generation injectable NMDAR program Apimostinel, in development for acute severe depression
- Established extensive scientific and clinical advisor network, including leading psychiatrists across top institutions in the US
- Hosted an R&D Day event at the 2022 ASCP Annual Meeting: “Update on NMDAR Modulators for Depressive Disorders”
- Published in several peer-reviewed journals highlighting novel NMDAR mechanism and antidepressant activity of lead programs. The full list of publication can be found at gateneuro.com/publications.

Upcoming Milestones

- First patient dosed in a single- and repeat-dose Phase 1b safety and EEG (electroencephalography) target engagement biomarker study of Apimostinel in 40 healthy volunteers in Q4 2022 with topline readouts expected in Q1 2023.
- Initiation of a confirmatory Phase 2 study of Zelquistinel in subjects with major depressive disorder (MDD) in early 2023, with topline readout expected mid-2024.

- Advancement of Rapastinel (GLYX-13) into investigator-led studies in collaboration with multiple leading research hospitals, under the FDA's Expanded Access Program, beginning in 2023

Key Additions to Advisory Network

Gate Neurosciences has continued expanding its network of 20+ scientific and clinical advisors from top psychiatry institutions across the US, who are providing encouraging perspectives on the company's NMDA receptor modulator portfolio. Recent key additions include:

- Maurizio Fava, M.D., Psychiatrist-in-Chief at Massachusetts General Hospital
- Alan Schatzberg, M.D., Director of Mood Disorders Center and former Chair of Psychiatry at Stanford, and 136th president of the American Psychiatric Association
- Thomas Laughren, M.D., Former Director for the Division of Psychiatry Products at the FDA

NMDAR Modulator Portfolio: Data Highlights & Mechanistic Understanding

The core scientific focus of Gate's pipeline is addressing synaptic dysfunction, the hallmark disease biology of many cognitive and psychiatric disorders, by enhancing synaptic plasticity and normalizing brain signaling. NMDARs play an essential role in synaptic plasticity and are the targets of an emerging class of rapid-acting antidepressants. Considerable recent progress has been made, along with a suite of publications, clarifying the underlying mechanisms various NMDAR-targeted molecules.

Gate Neurosciences' lead programs are highly differentiated from other NMDAR-targeted antidepressants by acting through positive modulation instead of antagonism. Gate's molecules positively modulate NMDAR activity on glutamatergic neurons to enhance synaptic plasticity and elicit antidepressant activity. In contrast, antagonists act through NMDARs located on GABA interneurons, causing a profound 'burst' of neurotransmitters and accompanying dissociative side effects, before indirectly stimulating downstream effects on synaptic plasticity.

Gate's novel approach represents a more direct mechanism for enhancing natural neuronal plasticity processes, with the potential for a significantly improved safety profile. Recent literature highlighting Gate's novel mechanism can be found on its website.

Key data highlights from the company's lead NMDAR programs include:

- Zelquistinel: 3rd generation oral NMDAR modulator
    - Development as a rapid, durable, and well-tolerated chronic oral therapy to address more than 17 million Americans with MDD
    - Supported by a robust, de-risking translational data package across ~350 patients, including consistent target engagement and EEG biomarkers, safety, and clinical antidepressant efficacy

- A Phase 2a exploratory dose-finding study in MDD (n=251) showed that Zelquistinel 10mg delivered once-weekly was generally safe and well-tolerated, and demonstrated statistically significant differences from placebo on MADRS change from baseline at multiple timepoints over the study

- Apimostinel: 2nd generation IV NMDAR modulator
    - Development as an acute injectable procedure for the rapid reduction of depressive symptoms in millions of Americans with acute depressive episodes
    - Molecule is 1000-fold more potent than precursor compound Rapastinel, and is the most potent compound in Gate's class of NMDAR modulators
    - A Phase 2a proof-of-concept study in MDD (n=151) showed that a single dose of Apimostinel 10mg was generally safe and well-tolerated with no ketamine-like side effects, and demonstrated a 5.4-point difference from placebo on HDRS-17 change from baseline at 24-hours (p=0.0034) and a 74% response rate (p=0.0067), among the largest seen to-date within the class of rapid antidepressants

Early Stage Research and Development Highlights

- Company continues to advance preclinical programs towards IND milestones in 2023
    - GATE-102: oral mGlu2/3 receptor antagonist for hypersomnia
    - GATE-301: IGFBP2 mimetic for neurodegenerative and neurodevelopmental disorders
    - GATE-252: 4th generation oral NMDAR modulator for cognitive disorders
- Company established cutting-edge research operations at Northwestern University's Falk Center for Molecular Therapeutics led by Dr. Joseph Moskal Ph.D., the original inventor of Gate's NMDAR platform
    - Collaborating with leading research institutions with access to world-class laboratory facilities, equipment, and capabilities
    - Advancing development of objective biomarkers for mood disorders, including novel methods to identify and predict patient responder subsets
    - Advancing early research into growth-factor signaling and other novel drug targets of interest that enhance neuronal function and synaptic plasticity

"We are excited about the momentum Gate Neurosciences has gathered heading into the remainder of the year, along with our upcoming clinical milestones for our lead programs" said Mike McCully, President & CEO of Gate Neurosciences, *"I believe our next-generation portfolio has true transformative potential for patients suffering from neuropsychiatric and cognitive disorders."*

About Gate Neurosciences
Gate Neurosciences is a precision medicine biotechnology company focused on advancing next-generation CNS treatments that address growing needs in mental health. The company is developing a portfolio of novel mechanisms of action that enhance synaptic function to address neuropsychiatric and neurocognitive diseases, including major depressive disorder (MDD). Using learnings from extensive clinical, preclinical, and translational data and a better understanding of CNS development challenges, the company is advancing its clinical pipeline using evidence-driven, precision psychiatry approaches.

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