# Vivoryon Therapeutics N.V. Provides Progress Update on Varoglutamstat Clinical Development for the Treatment of Alzheimer's Disease

- *VIVIAD Phase 2b study in Europe on track for final data readout Q1/2024*
- *Data from all 259 randomized patients presented at AD/PD show no on-target toxicity and no clinical signs of ARIA, broadening evidence for potential of varoglutamstat in AD to overcome the safety challenges of other drug classes*
- *Coding enrichment strategy successfully applied for improved baseline assessment of rescuable deficits in attention and working memory in the study cohort*
- *VIVA-MIND Phase 2 study in the U.S. steadily progressing and enrolling at 18 sites; status update expected in 2H/2023*
- *DSMB provided unanimous recommendation to continue VIVIAD without modification to dosing regimen, supporting rationale for accelerated uptitration to 600 mg BID dosing*

**Halle (Saale) / Munich, Germany, March 28, 2023** – Vivoryon Therapeutics N.V. (Euronext Amsterdam: VVY; NL00150002Q7) (**Vivoryon**), a clinical stage company focused on the discovery and development of small molecule medicines to modulate the activity and stability of pathologically altered proteins, today provided an update on both clinical studies of its lead candidate, varoglutamstat, a small molecule medicine in development for the treatment of Alzheimer's disease (AD), VIVA-MIND (NCT03919162) and VIVIAD (NCT04498650). Furthermore, the Company presents updated safety data from its European Phase 2b study, VIVIAD, at the 2023 International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders (AD/PD) in Gothenburg, Sweden.

"We are pleased to report that both of our ongoing studies are progressing steadily, and we continue to broaden the overall data package for varoglutamstat with consistently positive incremental results," commented Dr. Ulrich Dauer, CEO of Vivoryon. "Varoglutamstat is strongly positioned as a differentiated oral, outpatient small molecule that has the potential to significantly impact the AD treatment landscape and address ongoing unmet need. Designed to modulate all major hallmarks of AD including Abeta aggregation, neuroinflammation and tau pathology, and also enabling improvement of synaptic function, varoglutamstat captures the key features of a novel drug that has already exhibited a favorable safety profile with no signs of ARIA side effects. We are incredibly encouraged by what we have been able to report to date, and we see a unique opportunity for ultimately realizing the promise of a widely accessible treatment option in AD with the realistic potential to reach the millions of patients in need."

Vivoryon is pursuing a unique and highly differentiated approach to AD treatment, with a meticulously designed clinical development strategy. Grounded in the discovery that the


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enzyme glutaminyl cyclase (QPCT) catalyzes formation of the neurotoxic Abeta variant N3pE- Abeta, a key driver of AD pathology, Vivoryon is pioneering small molecule-based therapies to block this disease pathway. Varoglutamstat is designed to prevent N3pE- Abeta formation, rather than aiming to clear existing plaques, making it an intervention upstream of other approaches such as monoclonal antibodies (mAbs). Through a second mode of action, varoglutamstat also modulates neuroinflammation via the CCL2 pathway, which, in turn, has an impact on tau pathology.

“We are extremely encouraged by the exceptionally low discontinuation rates in both of our studies,” added Dr. Michael Schaeffer, CBO of Vivoryon. “Vivoryon is acutely focused on lessening the burden of AD for both patients and their families. As we are addressing an elderly patient population, we know how important it is to design a drug that is convenient. These patients typically have to live with and manage many different health conditions at the same time, which heavily impacts their everyday lives. Many feel overwhelmed by the sheer number of medicines they have to take every day and it is therefore our goal to make taking varoglutamstat as easy and convenient as possible. By investigating options to further optimize the formulation of our tablets, we feel that we have the unique chance to facilitate adherence to the correct dosing in our clinical studies and beyond.”

**Clinical development of varoglutamstat**

Following a meticulously designed clinical development strategy, varoglutamstat was shown to be well-tolerated in both a completed first-in-human Phase 1 study in over 200 participants and the subsequent first-in-patient Phase 2a study, SAPHIR (NCT02389413), which enrolled 120 patients suffering from early AD. Importantly, after only 12 weeks of treatment, this study showed evidence of improving not only pathological hallmarks, but also synaptic function and connectivity, cognition, memory and attention in AD patients, including statistically significant changes from baseline in working memory.

Building on these encouraging results, Vivoryon based the selection of endpoints for both VIVIAD and VIVA-MIND on the outcome of SAPHIR, as well as on the regulatory draft guidelines for AD drug development introduced by FDA and EMA in 2018. With these two complementary studies, the Company intends to assess if potential cognitive improvements in patients in the European VIVIAD study will translate into an established clinical endpoint in patients in the U.S. VIVA-MIND study.

**VIVIAD: European Phase 2b study in patients with mild cognitive impairment and mild AD**

VIVIAD is a state-of-the-art Phase 2b study being conducted in Europe and designed to evaluate the safety, tolerability and efficacy of varoglutamstat in 250 subjects with mild cognitive impairment (MCI) and mild AD compared to placebo over the course of 48 to 96 weeks of treatment. The highest dose investigated in the study (600 mg twice daily) was selected by an independent Data Safety Monitoring Board (DSMB) as final dose after the dose-escalation portion of the study. Enrollment was completed and the study was adapted to enable longer average treatment duration of participants (anticipated average treatment duration ~82 weeks) in the third quarter of 2022. The primary endpoint is a composite of the



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Neuropsychological Test Battery (NTB) focusing on changes in working memory and attention with secondary endpoints including multiple cognitive, safety and biomarker assessments.

***Highlights from AD/PD poster titled, VIVIAD, a Phase 2b study investigating varoglutamstat in patients with MCI and mild AD: Update on interim blinded safety results (Poster P0315/#2631)***

- As of the data cut-off date of January 5, 2023, over 100 of the 259 participants randomized into the study had been treated for 48 weeks or more
- Varoglutamstat showed no on-target toxicity and no clinical signs of brain swelling or hemorrhages (ARIA), a clearly limiting class side effect of Abeta antibodies
- Overall, varoglutamstat was well tolerated in the study to date, with all of the adverse events (AEs) (except for COVID-19 infections) being gastrointestinal, general, or related to the nervous system or skin. Only 14 serious AEs (SAEs) have been reported
- A low number of treatment emergent adverse events (TEAEs) was observed, only 18% of which were considered to be potentially related to study treatment
- The occurrence of AEs normalized per 100 visits is stable at 31 and as few as 19 participants (6.5%) discontinued the study, with only six (2.3%) discontinuing due to AEs
- Both the total number of SAEs and the discontinuation rate were considerably lower than the respective numbers at the 800 mg BID varoglutamstat dose in Vivoryon's completed Phase 2a SAPHIR study (15% SAEs, 33% discontinuation), while retaining a similar level of target inhibition at the dosing in both studies
- Data from these participants corroborate the beneficial safety data reported previously for varoglutamstat, with no on-study deaths, no on-target toxicity and no clinical signs of ARIA observed
- A new coding enrichment strategy was applied to ensure that the majority of participants exhibited rescuable deficits in attention and working memory at baseline, enabling reliable assessment of potential cognitive improvement after treatment
- Only five of the 259 participants exhibited normal performance on cognitive tests of the CogState NTB at baseline, demonstrating that the strategy of recruiting individuals with evidence of baseline deficits can be an effective method of enriching a study cohort

Vivoryon remains on track to report the final data readout from the VIVIAD study in the first quarter of 2024.

**VIVA-MIND: U.S. Phase 2a/b in patients with early AD**

VIVA-MIND is a complementary Phase 2 study being conducted in the U.S., coordinated by the Alzheimer's Disease Cooperative Study (ADCS) at the University of California San Diego (UCSD) School of Medicine and supported by the National Institute on Aging (NIA), part of the National Institutes of Health (NIH) with a $15 million grant (NIA award number R01AG061146). The study seeks to enroll 180 patients into the Phase 2a adaptive dose-finding portion with the Phase 2b portion, enrolling an additional 234 patients treated at the selected


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dose for at least 72 weeks, with a total of 414 patients being treated on stable doses of varoglutamstat for 18 months. The VIVA-MIND design was adapted in the third quarter of 2022 to enable all 180 patients to be treated for at least 72 weeks, allowing for the opportunity to progress seamlessly to a potential Phase 3 study. The flexible study design is aimed at increasing the probability of success by broadening option space for adjustments in clinical development based on learnings from VIVIAD and other developments in the field. The primary endpoint for this study is clinical dementia rating scale - sum of boxes (CDR-SB), an established approvable endpoint measuring a combination of cognitive abilities and activities of daily living. Secondary efficacy endpoints include quantitative EEG theta power, ADAS-Cog 13 and others. Exploratory endpoints include mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA), quantitative EEG alpha power, relative QPCT activity in CSF and others.

***Highlighted study updates:***

- Study is ongoing and continuing to recruit patients at 18 sites across the U.S. Vivoryon expects the first cohort to be fully randomized into the study within the second quarter of this year
- Focus on overcoming the challenges historically impacting AD drug development with a uniquely designed study, serving as a complementary to VIVIAD and following a specific dosing scheme implemented to investigate the feasibility of an accelerated uptitration regimen
- Objective to reach the 600 mg BID dose, the final dose selected in the VIVIAD study, without requiring slow uptitration to reduce the overall burden on patients and study sites
- The study's independent Data Safety Monitoring Board (DSMB) has recently provided the unanimous recommendation to continue the study without modification
- Study design allows to potentially transform VIVA-MIND into a Phase 3 study and include further patients beyond the currently planned 414; the decision on actual size will be taken after the readout of the VIVIAD study

Vivoryon expects to provide the next update on the VIVA-MIND study in the second half of 2023.

"As a neurologist confronted with the severe impact this devastating disease has on peoples' lives on a daily basis, I am very pleased to see the progress being made in Vivoryon's varoglutamstat studies and the hope that this new treatment might offer to patients," commented Dr. Howard Feldman, Professor of Neurosciences and Director of the ADCS at UC San Diego, and the VIVA-MIND study director. "While there remains much to be done in terms of research and development for safe and effective disease-modifying therapies that are widely available to patients, I believe that varoglutamstat represents a new approach to reducing the pathological events in AD. The complementary studies, VIVIAD and VIVA-MIND, present a strong clinical path forward for varoglutamstat. It is encouraging to see the VIVA-MIND trial receive its most recent DSMB recommendation for the trial to continue forward based on their most recent safety review of March 13, 2023."

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**About Vivoryon Therapeutics N.V.**
Vivoryon is a clinical stage biotechnology company focused on developing innovative small molecule-based medicines. Driven by our passion for ground-breaking science and innovation, we strive to change the lives of patients in need suffering from severe diseases. We leverage our in-depth expertise in understanding post-translational modifications to develop medicines that modulate the activity and stability of proteins which are altered in disease settings. Beyond our lead program, varoglutamstat, which is in Phase 2 clinical development to treat Alzheimer's disease, we have established a solid pipeline of orally available small molecule inhibitors for various indications including cancer, inflammatory diseases and fibrosis. www.vivoryon.com

***Vivoryon Forward Looking Statements***
*This press release includes forward-looking statements, including, without limitation, those regarding the business strategy, management plans and objectives for future operations of the Vivoryon Therapeutics N.V. (the "Company"), estimates and projections with respect to the market for the Company's products and forecasts and statements as to when the Company's products may be available. Words such as "anticipate," "believe," "estimate," "expect," "forecast," "intend," "may," "plan," "project," "predict," "should" and "will" and similar expressions as they relate to the Company are intended to identify such forward-looking statements. These forward-looking statements are not guarantees of future performance; rather they are based on the Management's current expectations and assumptions about future events and trends, the economy and other future conditions. The forward-looking statements involve a number of known and unknown risks and uncertainties. These risks and uncertainties and other factors could materially adversely affect the outcome and financial effects of the plans and events described herein. Actual results, performance or events may differ materially from those expressed or implied in such forward-looking statements and from expectations. As a result, no undue reliance should be placed on such forward-looking statements. This press release does not contain risk factors. Certain risk factors that may affect the Company's future financial results are discussed in the published annual financial statements of the Company. This press release, including any forward-looking statements, speaks only as of the date of this press release. The Company does not assume any obligation to update any information or forward-looking statements contained herein, save for any information required to be disclosed by law.*

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