Vivoryon Therapeutics N.V. Shares Clinical Development Update Highlighting Progress of N3pE-Amyloid-targeting Small Molecule Varoglutamstat in Alzheimer's Disease

- *Small molecule varoglutamstat, with potential for meaningful safety and ease of use advantages over antibody-based therapies, continues to show encouraging safety data at therapeutic dose of 600 mg twice daily, a dose demonstrated to result in nearly 90% target occupancy*
- *VIVIAD data presented at AAIC 2023 demonstrate that WAIS-IV Coding test as an inclusion criterion successfully ensures recruitment of patients with early AD presenting with evidence of baseline cognitive deficits, enabling a more reliable assessment of potential cognitive improvement after treatment*
- *June 2023 DSMB meeting results with approval to proceed for both VIVIAD and VIVA-MIND*
- *VIVIAD Phase 2b study in Europe on track for final data readout Q1/2024 with safety data from all 259 randomized patients showing no clinical signs of ARIA to date; no additional DSMB meetings required until study completion*
- *VIVA-MIND Phase 2 study in the U.S. steadily progressing, recruitment into second cohort ongoing*
- *Commenced preparations for open label extension study to provide long-term treatment option to patients after completion of treatment under VIVIAD or VIVA-MIND protocol contingent on trial outcome*

Halle (Saale) / Munich, Germany, July 16, 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 a clinical development update highlighting the progress of its unique N3pE-amyloid-targeting small molecule varoglutamstat in Alzheimer's disease (AD). The update included data presented at the Alzheimer's Association International Conference (AAIC), being held July 16-20, 2023, in Amsterdam, the Netherlands. The Company is also providing updates from the ongoing clinical Phase 2 studies VIVIAD in Europe and VIVA-MIND in the U.S.

"In light of the renewed momentum within the Alzheimer's disease drug development space with the first full approval of a potentially disease-modifying medication, I am particularly encouraged by the opportunity to be testing varoglutamstat within our Phase 2 Proof-of-Concept trial," commented Dr. Howard Feldman, Professor of Neurosciences and Director of the ADCS at UC San Diego School of Medicine, and the VIVA-MIND study director. "As a small molecule alternative that can conveniently be taken at home and potentially without comparable risks of brain swelling and bleeding seen with amyloid lowering monoclonal antibodies, varoglutamstat may hold significant advantages in safety and ease of use by patients."

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"As varoglutamstat continues to progress through clinical development, we are very pleased to report that VIVIAD's independent Data Safety Monitoring Board has determined that the VIVIAD study can continue without modifications and no additional meetings will be required until the meeting scheduled at study completion," added Dr. Ulrich Dauer, CEO of Vivoryon. "This is the first time varoglutamstat long-term safety data from patients suffering from Alzheimer's disease with a treatment duration of more than a year and up to two years have been reviewed independently. Our path forward both from a clinical and regulatory perspective is promising and we see the outcomes of this meeting as an important point of validation for our approach. The growing evidence supporting varoglutamstat as a potential novel medicine to treat Alzheimer's disease with a favorable safety profile is incredibly encouraging, particularly as we think about its positioning within the broader treatment landscape. We look forward to reporting on the final data, which we expect to read out in the first quarter of 2024. In tandem, given the excellent progress of VIVIAD, we have decided to initiate preparations for an open label extension study, which, following positive VIVIAD study outcome, could provide a long-term therapeutic option to patients who have been treated under VIVIAD or VIVA-MIND protocols."

Varoglutamstat Clinical Program:

Varoglutamstat is a differentiated investigational small-molecule medicine in development to treat Alzheimer's disease. It is currently being investigated in two large Phase 2 studies, VIVIAD (NCT04498650) in Europe and VIVA-MIND (NCT03919162) in the U.S., where it continues to show evidence of a favorable safety profile at the therapeutic dose of 600 mg twice daily (BID), a dose demonstrated to result in a target occupancy of nearly 90%.

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.

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.

VIVIAD (NCT04498650) 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 259 (final number of randomized participants) subjects with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD).

- **Data from AAIC 2023:** P1-18 / P1-904 Poster #82642 – "VIVIAD, a Phase 2b Study Investigating Varoglutamstat in Patients with MCI or Mild AD: Analysis of Baseline Cognition Data." These data demonstrate that Vivoryon's strategy of recruiting individuals with

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evidence of baseline deficits on the WAIS-IV Coding test, a well-known measure of cognitive function, successfully enriches study cohorts with respect to deficits in attention and working memory, enabling reliable assessment of potential cognitive improvement after treatment.
    - A new enrichment strategy was applied in the VIVIAD study to ensure that study participants exhibited rescuable deficits in attention and working memory at baseline. VIVIAD uses the WAIS-IV Coding test to select patients with rescuable cognitive deficits in the target domains. The study inclusion criteria encompassed a score of at least 0.5 SD (standard deviations) below age-adjusted mean on the WAIS-IV Coding subtest.
    - Approximately 20% of screened patients did not meet the inclusion criteria during screening due to good performance on the WAIS-IV Coding test. In addition, for selecting patients with mild disease, the MMSE cut-off was set at 20, leading to 8% of patients not meeting the inclusion criteria due to falling under this cut-off value.
    - The WAIS-IV Coding test performance shows reasonably good correlation with the measures that comprise the primary outcome, i.e. detection (DET), identification (IDN) and one back test (ONB) of the Cogstate NTB as judged by the Spearman correlation coefficients of 0.27, 0.44, and 0.47, respectively, using the blinded baseline data of all randomized patients.
    - The use of MMSE and WAIS-IV Coding test, together with inclusion criteria based on CSF biomarkers (Abeta and p-tau) are valuable tools in identifying and recruiting patients with MCI or mild AD who already have deficits in working memory and attention.

- **Safety Results:** Data from all 259 randomized patients showed no clinical signs of ARIA at the cutoff date of June 14, 2023. 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, while retaining a similar level of target inhibition at the dosing in both studies.

- After carefully reviewing the updated safety data, the independent Data Safety Monitoring Board (DSMB) decided in its recent meeting on June 22, 2023, that the study should continue as planned and that no additional DSMB meeting will be required until study completion.

- The study is on track for the final data readout in Q1/2024.

- **Open label extension (OLE) study**: Vivoryon commenced preparations for an OLE study to provide a long-term treatment option to patients after completion of treatment under the VIVIAD or VIVA-MIND protocol. The launch of the OLE study is contingent on the outcome of VIVIAD.

VIVA-MIND (NCT03919162) is a complementary Phase 2 study for varoglutamstat conducted in the U.S. which seeks to enroll 180 patients with early AD into the Phase 2a adaptive dose finding portion and enroll a further 234 patients in the Phase 2b portion of the study.

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- **Study Updates:** The first cohort was fully randomized into the study as planned and the study is now recruiting participants into the second cohort, with 19 sites open across the U.S.
    - In its June 12, 2023, meeting, the study's independent DSMB recommended to continue the study without modification, supporting the rationale for accelerated uptitration to 600 mg BID dosing.
    - The Company anticipates a decision on final trial size following the data readout of the VIVIAD study.
    - Vivoryon intends to provide a study update in Q4/2023.

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About VIVIAD
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 with a total of 259 participants and the study was adapted in 2022 to enable an average treatment duration of ~82 weeks. The primary endpoint is a composite of the Neuropsychological Test Battery (NTB) focusing on changes in working memory and attention with secondary endpoints including multiple cognitive, safety and biomarker assessments.

About VIVA-MIND
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 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 2022 to enable all 180 patients in the Phase 2a portion 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.

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

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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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