Vivoryon Therapeutics N.V. Presents Key Phase 2b Data at AAIC 2022 Showing that Varoglutamstat is Well Tolerated at Doses with High Target Inhibition, Highlighting Unique Opportunity in AD

- *Safety data from 181 patients show no on-target toxicity and no clinical signs of ARIA*
- *Therapeutic dose of 600 mg varoglutamstat given twice daily selected by the Data Safety Monitoring Board is known to result in a target occupancy of nearly 90%*
- *Data validate clinical development strategy designed to overcome limitations of AD drug development with varoglutamstat as early intervention, disease-modifying AD therapy with a unique N3pE-targeting mode of action*
- *Breakfast and networking event with webcast scheduled for August 2, 2022*, at 7:15 am PDT (4:15 pm CEST)

HALLE (SAALE) / MUNICH, GERMANY, July 31, 2022 – 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 announced detailed results of the completed parallel group, dose-finding part of its European Phase 2b study VIVIAD (NCT04498650). The data were presented at the prestigious Alzheimer's Association International Conference (AAIC) in San Diego in a poster presentation by Dr. Michael Schaeffer, Vivoryon's CBO.

The presentation titled "VIVIAD, A Phase 2b Study Investigating Varoglutamstat in Patients with MCI and Mild AD: Dose Selection and Preliminary Safety Results" (poster P1-403, abstract 69290) included data that led to the independent Data Safety Monitoring Board's (DSMB) decision to select the highest dose investigated in the study (600 mg twice daily (BID)) as the final dose to be administered in the second part of the study. All data remain blinded outside the DSMB.

The safety data showed that varoglutamstat was well tolerated with only 14% of overall reported adverse events (AEs) considered to be potentially related to study treatment. All of the AEs were gastrointestinal, general, or related to the nervous system or skin. Only four patients (2.2%) experienced serious AEs (SAEs) and only two patients (1.1%) discontinued the study. 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 (NCT02389413; 15% SAEs, 33% discontinuation), while retaining a similar level of target inhibition.

A total of 110 (60.8%) patients reported treatment emergent adverse events (TEAEs), the majority of which (66%) was rated as not related to study treatment, with 20% not assessable. Overall, most AEs were defined as mild (67%) or moderate (31%). The DSMB decision on the selected dose moving forward was based on data at the cut-off date, May 17, 2022. At data

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cut-off, 181 patients, 91 of which had completed the 24 weeks visit, had been randomized into the study at 600 mg, 300 mg or placebo.

Notably, no clinical signs of on-target toxicity, such as amyloid-related imaging abnormalities (ARIA), a side effect frequently reported for antibody-based AD treatment approaches, were observed. The safety results to date further substantiate the potential of varoglutamstat as a monotherapy and as an interesting component of combination therapies, including with anti-Abeta antibodies. Vivoryon is currently investigating this approach in preclinical studies, one of which will also be presented at AAIC today (poster P1-457, abstract 69050, see https://bit.ly/3JglkN9).

“Safety of all participants in our clinical studies is paramount to us, and has been a critical breaking point for many therapeutic candidates in the AD field. That is why we could not be happier with these interim VIVIAD data, which are exactly the outcome we had hoped for,” said Dr. Michael Schaeffer, CBO of Vivoryon. “With the selected dose of 600 mg BID we believe we have a stand-alone safety profile for varoglutamstat while maintaining high target engagement, which is a critical factor in enabling disease modification. Target occupancy is only marginally lower than that achieved in our SAPHIR Phase 2a study. These combined results strengthen our belief that both VIVIAD and our ongoing U.S. study, VIVA-MIND, have the potential to build on the SAPHIR results, which already reported a number of significant changes in AD-related parameters, most notably significant improvement of working memory. At the same time, the new 600 mg dose significantly reduces any potential safety concerns.”

“These highly encouraging safety results represent a crucial milestone on our path to clinical proof of concept of varoglutamstat’s unique N3pE-targeting mechanism of action in AD, which is not limited to Abeta pathology, but addresses all hallmarks of AD including tau pathology, neuroinflammation and synaptic impairment,” commented Dr. Ulrich Dauer, CEO of Vivoryon. “Varoglutamstat is, to our knowledge, the first small molecule and only project in clinical development selectively targeting the *de novo* production of neurotoxic N3pE-Abeta and modulating neuroinflammation via CCL2. After a number of setbacks our industry has faced, we are confident that based on our data to date we have selected not only the right target with the right underlying mode of action (MOA), but also the right drug candidate to modify this target and the right clinical trial design to change the devastating reality of AD. We wholeheartedly thank all patients, trial sites and investigators and look forward to reporting more data in 2023.”

VIVIAD is actively enrolling patients at 22 study centers in five European countries and will continue to evaluate its primary and secondary outcome measures, which include multiple cognitive, safety and biomarker endpoints. Vivoryon remains on target to report final data for the study in the second half of 2023.

Details on the VIVA-MIND-study design will be presented in an oral presentation at AAIC later this week (Tuesday, August 2, 2022, 9:45 am – 9:55 am PDT (6:45 pm – 6:55 pm CEST), abstract 365197,“A novel, efficient and seamless Phase 2A-2B design to test varoglutamstat in early AD: the VIVA-MIND study”).

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Webcast Information: Breakfast and Networking Event at AAIC

Vivoryon will host a webcasted breakfast and networking event on August 2, 2022 at 7:15 am PDT (4:15 pm CEST), available at https://bit.ly/3uFGTjU. For in-person attendance, please RSVP at Eva.Hoffmann@vivoryon.com.

About Varoglutamstat

Varoglutamstat (PQ912) is a differentiated oral small-molecule targeting the toxic Abeta species N3pE which is being developed as disease-modifying therapy and is designed to target AD pathology upstream of Abeta-antibody focused approaches. Varoglutamstat blocks the enzyme glutaminyl cyclase (QPCT) and its isoenzyme QPCTL. QPCT catalyzes the formation of N3pE amyloid, a particularly neurotoxic variant of Abeta peptides, which is only found in AD patients and not present in the brains of healthy individuals. N3pE amyloid in the brain acts as a seeding element for Abeta aggregation, thus providing a starting point for plaque formation. It has been described to correlate with the cognitive ability of AD patients. Beyond Abeta pathology, varoglutamstat has also been shown to impact synaptic impairment. Through a second mode of action, the inhibition of full CCL2 maturation via QPCTL, varoglutamstat modulates pro-inflammatory signaling and tau pathology, thereby simultaneously addressing multiple hallmarks of AD. Data from the completed Phase 2a SAPHIR study of varoglutamstat (NCT02389413) provided important safety information and also showed first evidence of the disease-modifying capabilities of varoglutamstat, most importantly with statistically significant changes from baseline in working memory as an important cognitive ability after only 12 weeks of treatment.

Vivoryon has received Fast Track designation for varoglutamstat in early AD by the U.S. Food and Drug Administration (FDA) and is currently in clinical Phase 2 development with studies ongoing in Europe (VIVIAD, NCT04498650) and the U.S. (VIVA-MIND, NCT03919162). Varoglutamstat has not yet been approved by any regulatory authority and the safety and efficacy have not yet been established.

About Vivoryon's Clinical Development Strategy

In an effort to maximize the probability of success, Vivoryon's clinical development strategy is uniquely crafted to overcome the limitations of AD drug development. Both VIVIAD (NCT04498650) and the ongoing U.S. Phase 2a/b VIVA-MIND study (NCT03919162) have been carefully designed to enable a thorough validation of the novel mode of action (MOA) of varoglutamstat. The VIVIAD study builds on data from the completed SAPHIR Phase 2a study (NCT02389413) with the option to establish new and meaningful surrogate endpoints for AD, as called for by the U.S. Food and Drug Administration's (FDA) current draft guideline for AD. Building on the key data obtained from SAPHIR and VIVIAD, VIVA-MIND is designed to add approvable endpoints to the overall Phase 2 data set, with a Phase 2a portion designed to render additional proof of concept data and to minimize the risk of later-stage program failure. In summary, this strategy will enable Vivoryon to deliver a thorough characterization of varoglutamstat in extended Phase 2 studies before advancing towards a potential pivotal Phase 3 study or, if supported by the combined data from both studies, potentially applying for an accelerated approval path.

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About VIVIAD
VIVIAD (NCT04498650) is a state-of-the-art multi-center, randomized, placebo-controlled, double-blind, parallel group dose finding Phase 2b study in patients with mild cognitive impairment (MCI) and mild AD. The study seeks to enroll approximately 250 patients. Objectives are to evaluate the long-term efficacy, safety and tolerability of oral varoglutamstat. A composite neuropsychological test battery (NTB) score will be administered throughout the study in order to assess cognitive efficacy. Additionally, a set of exploratory read-outs including cognitive tests, functional electroencephalogram (EEG) and the analysis of new molecular biomarkers in the cerebrospinal fluid (CSF) will be used to evaluate the compound's effect on disease pathology. Secondary endpoints include long-term safety and tolerability of varoglutamstat and its efficacy on brain activity, cognition and activities of daily living. Within the parallel group, dose-finding part of the study, the first 90 patients were randomized 1:1:1 (600 mg / 300 mg or placebo, all BID) and treated for at least 24 weeks. An independent Data Safety Monitoring Board (DSMB) unblinded the data for a safety analysis and recommended 600 mg BID as the final dose to be administered in the second part of the study. All subjects randomized to the treatment arm will be treated at the selected dose of 600 mg BID moving forward and will continue treatment for 48-96 weeks, dependent on study entry date. The data remain blinded outside of the DSMB. Details on the study background and design have been published in the Journal "Alzheimer's Research & Therapy".

About VIVA-MIND
VIVA-MIND (NCT03919162) is Vivoryon's combined Phase 2a/b U.S. study for varoglutamstat in patients with early AD. VIVA-MIND seeks to enroll 180 patients into the Phase 2a adaptive dose finding part which will investigate a range of 150 mg to 600 mg twice daily. If predefined criteria are fulfilled in an interim futility analysis, the trial will pass a stage-gate into the Phase 2b part, 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 primary endpoint for this study is CDR-SB (clinical dementia rating scale - sum of boxes), an established approvable endpoint measuring a combination of cognitive abilities and activities of daily living. The study is 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).

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

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available small molecule inhibitors for various indications including cancer, inflammatory diseases and fibrosis. http://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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