Vivoryon Therapeutics N.V. Provides Comprehensive Progress Report for Ongoing Varoglutamstat Clinical Program Following R&D Event and VIVA-MIND DSMB Dose Decision

- *Both VIVIAD and VIVA-MIND progressing at 600mg twice daily with oral administration following two independent positive DSMB decisions*
- *Varoglutamstat demonstrates very encouraging safety data with no evidence of drug-related ARIAs at therapeutic dose of 600mg twice daily, a dose demonstrated to result in nearly 90% target occupancy*
- *On track to report final VIVIAD Phase 2b readout in Q1/2024*
- *Commenced preparations for open label extension study to provide long-term treatment option to patients after completion of treatment under VIVIAD or VIVA-MIND*
- *Company to participate at upcoming Jefferies London Healthcare Conference taking place November 14-16, 2023*

Halle (Saale) / Munich, Germany, October 26, 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 comprehensive overview of the progress of the ongoing clinical development of varoglutamstat, an orally administered novel small molecule. Varoglutamstat's mid to late-stage clinical studies, VIVIAD and VIVA-MIND, evaluating its potential to treat early Alzheimer's disease (AD), are comprised of a broad range of key primary and secondary endpoints covering cognition, function and neuronal connectivity.

"The breadth and significance of data collected thus far from varoglutamstat's clinical development program further expands our understanding of early AD pathology and treatment. With independent DSMB dose decisions for both of our ongoing Phase 2 studies across multiple geographies and different titration regimens, varoglutamstat, has been cleared from a safety and tolerability standpoint to proceed with the highest investigated dose of 600mg twice daily. By evaluating varoglutamstat in two parallel clinical studies with varying efficacy endpoints, we can meaningfully support our regulatory strategies and provide a clear picture of the cognitive changes potentially resulting from treatment on study. Utilizing a stepwise methodology for clinical development, we have been able to create a statistically robust trial setting in VIVIAD with the intent of VIVA-MIND designed to confirm the findings of VIVIAD," said Frank Weber, M.D., CEO of Vivoryon. "Building upon the positive findings from the SAPHIR Phase 2a study, we have meticulously designed VIVIAD and VIVA-MIND, grounded in the understanding that N3pE-Abeta presence has been identified in and beyond

Vivoryon Therapeutics N.V.
www.vivoryon.com
Weinbergweg 22
06120 Halle (Saale)
Germany
contact@vivoryon.com

plaques, in the synaptic space of neurons and within their cell walls. Varoglutamstat has shown convincing results of neuronal recovery after only 12 weeks of treatment, which supports our belief in the advantages of this mechanism of action to substantially reduce the production of N3pE-Abeta, rather than increase the clearance once synthesized and deposited in the plaque. Together, SAPHIR, VIVIAD and VIVA-MIND culminate in an immensely comprehensive Phase 2 clinical development program in early AD conducted so far with a planned total of nearly 800 patients. The program is further supported by varoglutamstat's Fast Track designation granted by the FDA. Vivoryon is committed to improving the daily lives of patients with early AD and their families and we look forward to our imminent, final study readout from VIVIAD in the first quarter of 2024 at which point we intend to share final topline data, with the full dataset to be presented at a subsequent medical meeting."

Varoglutamstat Clinical Program

The clinical development program of varoglutamstat in early AD is based on a strong scientific rationale rooted in Vivoryon's research and discovery activities in conjunction with support from leading academic partners and scientific organizations worldwide. 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 additional positive impact on tau pathology. Preclinical data supports the N3pE-Abeta hypothesis with the following key highlights:

- Pyroglutamate-modified Abeta (N3pE-Abeta) is a trigger of toxicity and disease pathology in AD and there is a strong rationale for targeting N3pE-Abeta to create a tailored AD therapy.
- Experimental data show that N3pE-Abeta has very different physio-chemical properties compared to other Abeta variants, including its potential to form highly toxic oligomers and fibrils together with non-modified Abeta variants.
- Strong preclinical evidence supports the hypothesis that reducing N3pE-Abeta formation by inhibiting the enzyme QPCT, has the potential to change the course of progression of AD.

Varoglutamstat is a differentiated investigational small-molecule medicine in development to treat early AD. As an orally administered treatment which can conveniently be taken at home, varoglutamstat holds significant advantages in ease of use by patients. Importantly, in line with its mode of action, safety data to-date indicate that varoglutamstat could potentially come without comparable risks of brain swelling and bleeding (ARIA) seen with amyloid lowering mAbs. It is currently being investigated in two large Phase 2 studies, VIVIAD (NCT04498650) in Europe and VIVA-MIND (NCT03919162) in the U.S. The two studies taken together enable a deep and robust understanding of the effect of varoglutamstat on cognition and daily function of patients with early AD, capturing a range of key primary and secondary efficacy endpoints. In addition, VIVALONG (the open label extension study) will allow for the potential

Vivoryon Therapeutics N.V.
www.vivoryon.com
Weinbergweg 22
06120 Halle (Saale)
Germany
contact@vivoryon.com

confirmation of the long-term safety and health outcome benefits of varoglutamstat after patients have completed the double blinded studies VIVIAD and VIVA-MIND. The study will also help to generate relevant pharmacoeconomic data.

VIVIAD

VIVIAD (NCT04498650) is a state-of-the-art Phase 2b study being conducted in Europe and is designed to evaluate the safety, tolerability, and efficacy of varoglutamstat in 259 subjects with mild cognitive impairment (MCI) and mild AD. The primary endpoint, which is a combination of three elements of the Cogstate neuropsychological test battery (NTB), called "Cogstate 3-item scale," includes Identification, Detection and One Back tests and evaluates attention and working memory domains over 48-96 weeks. Key secondary efficacy endpoints include in hierarchical order: Cogstate Brief Battery (CBB, 4-item scale), the full Cogstate NTB (8-item scale), the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q), and electroencephalogram (EEG).

- The objective of the Cogstate 3-item scale (Identification, Detection, One Back) as the primary endpoint is to confirm the positive findings on working memory and attention observed in the SAPHIR study.
- The CBB (3-item scale plus One Card Learning), which is the first secondary endpoint, is marketed as Cognigram and has approval as a medical device by the U.S. Food & Drug Administration (FDA) and multiple other regulatory authorities to assess cognition in early AD patients.
- The full Cogstate NTB (8-item scale) enables an assessment of outcome on various cognitive domains.
- Th A-IADL-Q is a fully validated and sensitive scale to measure the impairment of daily function in patients with early AD.
- The EEG captures change in large scale neuronal and synaptic activity. Theta power has been selected as a key secondary endpoint because it is well correlated to working memory and has been shown to increase (worsen) in AD.

Formal testing for significance will begin with the Cogstate NTB 3-item scale and continue until the first endpoint does not show a p value of <=0.05. Furthermore, there will be additional exploratory analysis for domains such as working, executive and episodic memory and language via the Winterlight Labs speech assessment. In sum, the analysis provides a detailed performance assessment of varoglutamstat across key relevant cognitive performance parameters.

The end of the active treatment phase in VIVIAD is estimated to occur by year end 2023, which is then followed by a period of safety follow up visits and rigorous data and statistical analysis. Vivoryon remains on track to share final topline data in the first quarter of 2024 and the full dataset at a subsequent medical meeting.

Vivoryon Therapeutics N.V.
www.vivoryon.com
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VIVA-MIND

VIVA-MIND (NCT03919162) is an ongoing Phase 2 study for varoglutamstat being conducted in the U.S., complementary to Vivoryon's VIVIAD Phase 2b study being conducted in Europe. VIVA-MIND 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.

- In July 2023, the Company announced that the first cohort of the study was fully randomized as planned and is now recruiting participants into the second cohort with 21 sites open across the U.S. The primary endpoint of the study is evaluating Clinical Dementia Rating scale Sum of Boxes (CDR-SB) over a 72-week treatment period. In addition to evaluating safety, key secondary efficacy endpoints include ABC score, quantitative EEG-relative theta wave power, FAQ (Functional Activities Questionaire) Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13) and Neuropsychiatric Inventory.
- While the Cogstate NTB applied in VIVIAD and the CDR-SB used in VIVA-MIND are distinct and very different scales with each having a specific strength, there has been a positive correlation established between both scales.[1]
- Recently, Vivoryon shared a positive DSMB dose decision recommending that the highest dose of varoglutamstat 600mg twice daily (BID) be selected for the remainder of the trial, based on a quarterly safety review and subsequent analysis of treatment-emergent adverse events of special interest (AESI) pertaining to skin and subcutaneous tissue disorders and hepatobiliary disorders, as well as target occupancy and plasma pharmacokinetic (PK) data.
- With VIVA-MIND, the Company has confirmed the feasibility of an up-titration protocol to the final dose of 600mg BID which is accelerated compared to the ongoing VIVIAD Phase 2b study.

VIVALONG

In July 2023, Vivoryon announced that it commenced preparations for an open-label extension (OLE) study, now termed "VIVALONG," to provide a long-term treatment option to patients after completion of treatment under the VIVIAD or VIVA-MIND protocol.

- The launch of VIVALONG is contingent on the outcome of VIVIAD.
- Pending VIVIAD results, Vivoryon plans to assess the long-term treatment of varoglutamstat including positron emission tomography (PET) imaging and other key safety and efficacy endpoints.

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[1] Maruff et al.; BMC Pharmacology and Toxicology 2013

Vivoryon Therapeutics N.V.
www.vivoryon.com
Weinbergweg 22
06120 Halle (Saale)
Germany
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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.

For more information, please contact:

Investor Contact
Stern IR
Julie Seidel
Tel: +1 212-698-8684
Email: julie.seidel@sternir.com

Media Contact

Trophic Communications
Valeria Fisher
Tel: +49 175 8041816
Email: vivoryon@trophic.eu

Vivoryon Therapeutics N.V.
www.vivoryon.com

Weinbergweg 22
06120 Halle (Saale)
Germany

contact@vivoryon.com