Vivoryon Therapeutics N.V. Presents Preclinical Evidence of Combination Therapy Potential for Varoglutamstat in AD at AAIC 2022

- *Data underscore the unique potential of Vivoryon's N3pE-focused strategy in mono- and combination therapy settings in AD*
- *Combination treatment of aducanumab and varoglutamstat achieves additive effect on Abeta pathology, indicating feasibility of dose reduction to improve safety of Abeta antibody-based AD treatments*
- *Further evidence demonstrating potential benefit of a combination therapy designed to simultaneously make use of two different and independent molecular N3pE-related MoAs: small molecule based QPCT/L inhibition and anti-N3pE-immunotherapy*
- *Additional data from murine analog of PBD-C06 highlight differentiated safety profile vs. other anti-Abeta antibodies at N3pE amyloid-lowering concentrations*
- *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 the presentation of preclinical data on the Company's N3pE amyloid-targeting molecules at the prestigious Alzheimer's Association International Conference (AAIC) in San Diego. The results underscore the unique potential of Vivoryon's N3pE amyloid-targeting therapeutic strategy in both mono- and combination therapy settings in Alzheimer's disease (AD).

Background:

Vivoryon pursues two different approaches to target N3pE amyloid. Firstly, the Company is developing varoglutamstat, an oral small molecule inhibitor of glutaminyl cyclase (QPCT) and its isoenzyme QPCTL, currently in Phase 2 clinical studies in Europe (NCT04498650) and the U.S. (NCT03919162). Safety data from different Phase 1 and 2 clinical studies of varoglutamstat, including the ongoing Phase 2b study VIVIAD (poster P1-403, abstract 69290; PR on key results here https://bit.ly/3BlhEHU), show no on-target toxicity and no clinical signs of ARIA (amyloid-related imaging abnormalities), the major severe side effects of antibody-based AD therapies. Secondly, in an effort to overcome the limitations of existing anti-Abeta antibody-based approaches, Vivoryon is developing the monoclonal antibody PBD-C06. PBD-C06 is specifically designed to bind to and remove neurotoxic N3pE amyloid from the brain. The antibody is optimized with respect to low immunogenicity and low ARIA-inducing potential.

N3pE amyloid (pGlu3-Abeta) is a toxic form of Abeta that leads to faster aggregation and seeding of plaques. This pivotal role in the development and progression of AD makes it an important therapeutic target. Formation of N3pE amyloid is catalyzed by the enzyme QPCT,

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which is expressed predominantly in the brain's learning and memory centers. Toxic N3pE amyloid correlates with cognitive (MMSE) status in patients suffering from AD and is not found in healthy individuals.

Preclinical Data on Vivoryon's Molecules Presented at AAIC 2022

Poster P1-457 / Abstract 69050: "Exploring Combination Therapies in AD: Additive Effects of the QPCT Inhibitor Varoglutamstat and Aducanumab on Abeta Pathology and Biomarkers In Vivo"

Vivoryon recently published data demonstrating that a combination of the QPCT/L inhibitor varoglutamstat and the N3pE amyloid-specific antibody PBD-C06 had an additive effect on lowering of N3pE amyloid *in vivo (Hoffmann et al., https://doi.org/10.3390/ijms222111791)*. Building on these results, the Company analyzed whether a similar additive effect could be achieved when combining varoglutamstat with the Abeta-plaque-specific antibody aducanumab in a double transgenic mouse model overexpressing a variant of the human amyloid precursor protein (APP) and human QPCT (APPSLxhQC). The animals were treated with either varoglutamstat, chimeric aducanumab (chAdu) or a combination of both for 16 weeks. Brains were analyzed for accumulation of total Abeta, N3pE amyloid and the AD-related biomarkers neurogranin, BACE-1 and YKL-40.

Single agent treatment with either varoglutamstat or chAdu significantly reduced the accumulation of N3pE and total Abeta in brain of APPSLxhQC mice. As anticipated, the effect for chAdu appeared to be more pronounced on total Abeta, while varoglutamstat mediated a stronger decrease in N3pE amyloid. The combination of both agents led to a stronger decrease of both N3pE amyloid and total Abeta, with a Bliss combination index (CI) near 1 suggesting an additive effect of both treatments in this setup.

Importantly, and in line with its secondary mode of action, modulating the CCL2 axis, varoglutamstat significantly reduced brain levels of YKL40, an inflammatory marker (-27%), which corroborates results from Vivoryon's completed Phase 2a study SAPHIR (NCT02389413).

Taken together, the results presented at AAIC support the hypothesis of a potential benefit of a combination therapy designed to simultaneously target two different and independent molecular pathways, namely reducing N3pE amyloid production by QPCT/L inhibition and clearing existing Abeta deposits through anti-N3pE-immunotherapy. For example, therapeutic regimens aiming at an initial antibody-mediated Abeta clearance followed by long-term suppression of N3pE amyloid formation and inflammation by varoglutamstat ("treat and maintain") could be envisioned.

"Alzheimer's disease is a very complex disease state which may require us to work together as a field to combine different therapeutic interventions for the highest benefit of patients as is the standard of care in many other complex diseases. The additive effect of varoglutamstat and Abeta-targeting antibodies we have described to date for our own PBD-C06 and aducanumab underscores this concept and highlights the unique positioning of

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varoglutamstat as a drug candidate that offers strong potential both as a monotherapy and in combination," commented Dr. Michael Schaeffer, Vivoryon's CBO. "While our focus will very much remain on developing varoglutamstat as a monotherapy, we are excited that the further preclinical characterization of our lead candidate continues to expand its therapeutic depth and the potential for its application in a variety of therapeutic settings."

Poster P1-04 / Abstract 67892: "Therapeutic Efficacy of the Murine Precursor to PBD-C06: a Novel CDC-Mutant Anti-pGlu3Abeta mAb"

A study led by Cynthia Lemere, Ph.D., Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, analyzed the therapeutic efficacy of 07/2a-k, a novel murine precursor to PBD-C06, Vivoryon's N3pE amyloid-targeting monoclonal antibody, in comparison to 3D6-L, a murine analog of the classical anti-Abeta antibody bapineuzumab in two AD mouse models (aged APP/PS1 mice and aged APP/PS1;hApoE4 mice). The group had previously demonstrated reductions in plaques and cognitive deficits using the PBD-C06 precursor 07/2a. The novel version, 07/2a-k, is a CDC-mutant version to avoid complement system activation to reduce vascular-related inflammation associated with anti-amyloid antibodies. The data presented at AAIC include a dosing and a therapeutics study.

In the dosing study (APP/PS1 mice treated weekly from 12-13.5 months of age), treatment with the PBD-C06 precursor 07/2a-k had no effect on biochemical levels of Abeta and did not change overall Abeta levels, but significantly reduced N3pE amyloid plaque load in the hippocampus, a region essential for learning and memory at two different doses (300 µg, $p<0.0005$; 600 µg, $p<0.005$).

In the therapeutics study (APP/PS1;E4 mice treated weekly from 16 to almost 20 months of age), 07/2a-k had no effect on biochemical or pathological measures of Abeta, but modestly improved memory in the Novel Object Recognition (NOR) task, while having no effect in the Barnes maze task. Importantly, 07/2a-k did not induce any micro- or macrohemorrhages. The bapineuzumab analog 3D6-L lowered Abeta levels (biochemically and N3pE amyloid plaque load), increased movement of the mice in the NOR, but had no benefit on cognition in either the NOR or Barnes maze test. In contrast to 07/2a-k, 3D6-L induced a high number of micro- and macrohemorrhages.

"Safety is a main concern in antibody-based AD therapies, as anti-amyloid antibodies, e.g. bapineuzumab, are associated with ARIA involving vasogenic edema and microhemorrhages in AD patients, especially in ApoE4 carriers," commented Cynthia Lemere, Brigham and Women's Hospital and Harvard Medical School. "Both Vivoryon's PBD-C06 and the murine precursor 07/2a-k we tested in this study have been designed with a site-specific CDC mutation to prevent complement system activation and, thus, could potentially reduce inflammation and ARIA. Our data presented at AAIC confirm that 07/2a-k treatment lowered N3pE amyloid levels in the hippocampus, a region essential for learning and memory in APP/PS1 mice and also had a modest cognitive benefit without eliciting microhemorrhages in aged APP/PS1;APOE4 mice. Based on these encouraging results, we look forward to further investigating the potential of 07/2a-k in earlier disease stages."

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Vivoryon is conducting a number of preclinical studies to further characterize PBD-C06 and evaluate its differentiation from other Abeta antibodies. PBD-C06 is partnered with Simcere Pharmaceuticals, Ltd., for development in Greater China.

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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 PBD-C06
PBD-C06 is Vivoryon's preclinical stage N3pE amyloid-targeting monoclonal antibody. Seeking to overcome the limitations of existing anti-Abeta antibody-based approaches, PBD-C06 is specifically designed to bind to and remove neurotoxic N3pE amyloid from the brain. The antibody is optimized with respect to low immunogenicity and low potential to induce amyloid-related imaging abnormalities (ARIA). In particular, PBD-C06 is a CDC-mutant antibody, avoiding complement system activation to potentially reduce vascular-related inflammation associated with anti-amyloid antibodies. In preclinical studies, PBD-C06 has not only shown the ability to reduce N3pE amyloid, but also to significantly improve cognitive deficits in aged Alzheimer's mice. Moreover, no evidence was found of increased microhemorrhages under treatment with PBD-C06.

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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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