PureTech's LYT-300 (Oral Allopregnanolone) Demonstrates Oral Bioavailability, Tolerability and GABAA Receptor Target Engagement in Healthy Volunteers

December 19, 2022

RNS Number : 0808K
PureTech Health PLC
19 December 2022

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Orally administered LYT-300 achieved blood levels of allopregnanolone at or above those associated with therapeutic effect.[1] Allopregnanolone is a natural neurosteroid with proven efficacy that is currently only available as a 60-hour intravenous infusion.

Preliminary pharmacodynamic data indicate that oral administration of LYT-300 results in allopregnanolone target engagement with $GABA_A$ receptors, which have been shown to regulate mood and other neurological conditions.

LYT-300 was generally well-tolerated across the trial with no treatment-related severe or serious adverse events observed.

PureTech Health plc (Nasdaq: PRTC, LSE: PRTC) ("PureTech" or the "Company"), a clinical-stage biotherapeutics company dedicated to changing the treatment paradigm for devastating diseases, today announced topline results from the completed, multi-part Phase 1 trial of LYT-300 (oral allopregnanolone).

Topline results announced today show that oral administration of LYT-300 achieved blood levels of allopregnanolone at or above those associated with therapeutic benefit[1] and resulted in exposure-dependent target engagement with γ-aminobutyric-acid type A ($GABA_A$) receptors. Earlier this year, PureTech announced that LYT-300 also demonstrated oral bioavailability of allopregnanolone approximately ninefold greater than third-party reported data with orally administered allopregnanolone.[1] Additional data from the Phase 1 trial will be presented in a scientific forum, and a Phase 1b/2a trial is expected to begin in the first half of 2023.

"Today's results make us very excited about the potential of LYT-300 to unlock the full therapeutic benefit of allopregnanolone, which to date has been limited to a small subset of patients," said Julie Krop, M.D., Chief Medical Officer at PureTech. "Using our proprietary Glyph platform, orally administered LYT-300 has demonstrated a favorable safety profile at allopregnanolone levels that have been shown to be associated with therapeutic benefit. This, along with evidence of exposure-dependent target engagement, brings us one step closer to potentially addressing the needs of patients across a range of neurological and neuropsychiatric conditions."

Allopregnanolone is a natural neurosteroid with well-validated biological effects. It has demonstrated a rapid onset of action for the treatment of depression, as well as the potential to treat other neurological conditions, but its poor oral

bioavailability has limited its therapeutic potential. The United States Food and Drug Administration (FDA) has approved a 60-hour intravenous infusion formulation of allopregnanolone for the treatment of postpartum depression (PPD), though this method of administration has inherent limitations. To overcome this, synthetic oral analogs of allopregnanolone have been developed, though these may not capture the full therapeutic potential of natural allopregnanolone. To potentially harness the broad applicability of this natural neurosteroid through oral administration, PureTech has applied its Glyph™ platform, which is designed to enable the oral administration of certain therapeutics with low oral bioavailability due to first pass metabolism. The Glyph platform has yielded two candidates to date.

72 healthy volunteers were dosed in the multi-part, Phase 1 clinical trial, which was designed to evaluate oral bioavailability, safety and tolerability of LYT-300 across a range of doses, and to inform dose selection moving forward. As part of the trial, single and multiple ascending doses were evaluated along with cohorts to evaluate the effect of food on oral absorption. The impact of LYT-300 on b-EEG and other markers of $GABA_A$ target engagement were also assessed. LYT-300 was generally well-tolerated with no treatment-related severe or serious adverse events observed. Doses have been selected to carry forward into the planned Phase 1b/2a clinical trial.

A second candidate from the Glyph platform, LYT-310, an oral cannabidiol (CBD), is designed to greatly expand the therapeutic application and potential of CBD. LYT-310 has demonstrated a three to fourfold increase in oral exposure versus unmodified CBD in multiple preclinical models, including large animal and non-human primate. This has the potential to translate into improved safety and reduced side effects. Lymphatic transport has also been confirmed in preclinical models, with up to 30% of LYT-310 entering the lymphatics, compared to 5% for unmodified CBD - which further supports the novel Glyph mechanism of enhancing oral bioavailability. LYT-310 is expected to enter the clinic in Q4 of 2023.

About LYT-300

LYT-300 is a clinical therapeutic candidate that is in development as a potential treatment for a range of neurological and neuropsychological conditions. Developed using PureTech's Glyph™ technology platform, LYT-300 is an oral prodrug of natural allopregnanolone. An intravenous formulation of allopregnanolone is approved by the United States Food and Drug Administration and administered as a 60-hour infusion for the treatment of postpartum depression. Allopregnanolone is a positive allosteric modulator of γ-aminobutyric-acid type A ($GABA_A$) receptors and has been shown to regulate mood and other neurological conditions. PureTech completed a Phase 1 clinical trial of LYT-300 in 2022, which demonstrated oral bioavailability, tolerability and $GABA_A$ receptor target engagement in healthy volunteers. Allopregnanolone is a neuroactive steroid and positive allosteric modulator (PAM) of $GABA_A$ receptors. Unlike benzodiazepines, allopregnanolone can provide both transient and longer-term normalization of overactive neural circuits because it also acts at GABA receptors outside of synapses.[2] Dual intra- and extra-synaptic GABA PAMs have been shown to not only improve sleep,[3] but also mood.[1]

About the Glyph™ **Platform**

Glyph is PureTech's synthetic lymphatic-targeting chemistry platform which is designed to employ the lymphatic system's natural lipid absorption and transport process to enable the oral administration of certain therapeutics. Glyph reversibly links a drug to a dietary fat molecule, creating a novel prodrug. The linked fat molecule re-routes the drug's normal path to the systemic circulation, bypassing the liver and instead moving from the gut into the lymphatic vessels that normally process dietary fats. PureTech believes this technology has the potential to (1) enable direct modulation of the immune system via drug targets present in mesenteric lymph nodes and (2) provide a broadly applicable means of enhancing the bioavailability of certain orally administered drugs that would otherwise be limited by first-pass liver metabolism. PureTech is accelerating development of a Glyph portfolio that leverages validated efficacy, prioritizing highly characterized drugs to evaluate the ability of the Glyph technology to improve oral bioavailability or lymphatic targeting. PureTech's lead Glyph therapeutic candidate, LYT-300 (oral allopregnanolone), completed a Phase 1 clinical trial in 2022, and a Phase 1b/2a clinical trial is expected to begin in the first half of 2023. A second therapeutic candidate, LYT-310 (oral cannabidiol), is expected to enter the clinic in Q4 of 2023. PureTech has

a robust intellectual property portfolio that includes licensed patents as well as wholly owned patents, covering the Glyph technology platform, which is based on the pioneering research of Christopher Porter, Ph.D., and his research group at the Monash Institute of Pharmaceutical Sciences at Monash University. The Porter Research Group and collaborators have published research in Nature Metabolism, Angewandte Chemie and the Journal of Controlled Release supporting the Glyph platform's ability to directly target the lymphatic system with a variety of therapies.

About PureTech Health

PureTech is a biotherapeutics company dedicated to changing the treatment paradigm for devastating diseases. The Company has created a broad and deep pipeline through the expertise of its experienced research and development team and its extensive network of scientists, clinicians and industry leaders. This pipeline, which is being advanced both internally and through PureTech's Founded Entities, is comprised of 28 therapeutics and therapeutic candidates, including two (Plenity® and EndeavorRx®) that have received both U.S. FDA clearance and European marketing authorization and a third (KarXT) that will soon be filed for FDA approval, as of the most recent update by the Company. All of the underlying programs and platforms that resulted in this pipeline of therapeutic candidates were initially identified or discovered and then advanced by the PureTech team through key validation points based on unique insights in immunology and drug development.

For more information, visit www.puretechhealth.com or connect with us on Twitter @puretechh.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation those statements that relate to our expectations around timelines and key milestones associated with clinical trials for LYT-300, the therapeutic potential of LYT-300, the potential for improved tolerability associated with LYT-310 as compared to unmodified CBD, that such potential improved tolerability and oral dosing could expand the therapeutic application of CBD across a wider range of age groups and indications, our expectations regarding the Glyph™ technology platform including the potential for new treatment applications, the applicability of preclinical results to human subjects, our product candidates and approach towards addressing major diseases, and our future prospects, developments, and strategies. The forward-looking statements are based on current expectations and are subject to known and unknown risks, uncertainties and other important factors that could cause actual results, performance and achievements to differ materially from current expectations, including, but not limited to, those risks, uncertainties and other important factors described under the caption "Risk Factors" in our Annual Report on Form 20-F for the year ended December 31, 2021 filed with the SEC and in our other regulatory filings. These forward-looking statements are based on assumptions regarding the present and future business strategies of the Company and the environment in which it will operate in the future. Each forward-looking statement speaks only as at the date of this press release. Except as required by law and regulatory requirements, we disclaim any obligation to update or revise these forward-looking statements, whether as a result of new information, future events or otherwise.

1) Brexanolone NDA 211371 Multi-disciplinary Review and Evaluation, FDA CDER, 2018.
2) Ghit, A., Assal, D., Al-Shami, A.S. Hussein D.E.E. GABAA receptors: structure, function, pharmacology, and related disorders. J Genet Eng Biotechnol 19, 123 (2021). https://doi.org/10.1186/s43141-021-00224-0
3) Bullock, A., Kaul, I., Li, S., Silber, C., Doherty, J., & Kanes, S. J. (2021). Zuranolone as an oral adjunct to treatment of Parkinsonian tremor: A phase 2, open-label study. Journal of the neurological sciences, 421, 117277. https://doi.org/10.1016/j.jns.2020.117277

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