Vivet Therapeutics to Present Key Findings on its Gene Therapy Program for Cerebrotendinous Xanthomatosis at the American Association for the Study of Liver Diseases Annual Meeting

- *Gene therapy program VTX-806 demonstrated normalization of toxic bile acid metabolites in blood, liver, tendons and brain in a CTX mouse model for the first time, holding promise for curative treatment*
- *Long term characterization of B6.129-Cyp27a1$^{tm1El\ t}$/J CTX mouse model showed measurable motor alterations similar to those described in CTX patients validating model for translation*

Paris, France, November 14, 2024 – Vivet Therapeutics ("Vivet"), a clinical stage biotech company developing novel and long-lasting gene therapies for rare inherited liver metabolic disorders, today announces that it will be presenting key pre-clinical findings for VTX-806, its gene therapy program for the treatment of Cerebrotendinous Xanthomatosis (CTX), at The Liver Meeting presented by the American Association for the Study of Liver Diseases (AASLD), being held in San Diego, CA from 15-19 November.

CTX is a rare neurodegenerative disease caused by mutations in the *CYP27A1* gene, which affect the body's ability to metabolize cholesterol and bile acids. It is characterized by a buildup of cholestanol in the blood, which can accumulate in different tissues like the brain, tendons, eyes, and arteries. If left untreated, this can lead to debilitating consequences and a poor prognosis affecting a patient's lifespan.

The oral presentation entitled: **"Liver-directed gene therapy normalizes toxic bile acid metabolite levels in the blood and brain of mice with cerebrotendinous xanthomatosis"** will be presented by Co-Founder and Chief Scientific Officer, Dr Gloria Gonzalez-Aseguinolaza on Monday 18 November. It details the development and optimization of its gene therapy program, VTX-806, an adeno-associated virus (AAV) vector with high potency and low immunogenicity designed to reinstate *CYP27A1* enzymatic activity, which is impaired in CTX patients.

The study was conducted to optimize an AAV vector using an expression cassette containing liver-specific promoter, CpG-depleted *CYP27A1* sequences to prevent the potential activation of an innate immune response and different regulatory sequences. The optimized expression cassettes were tested ***in vitro*** and AAV8 vectors were generated with the selected sequences and tested ***in vivo*** in a CTX mouse model, resulting in the findings highlighted below:

- ***In vitro*** *and* ***in vivo*** *results demonstrate higher CYP27A1 expression with VTX-806*
- ***VTX-806*** *restores normal levels of circulating 7αC4, expression of hepatic bile acid synthesis-related genes, and corrected hepatomegaly*

- *Results demonstrate for the first time that liver-directed AAV gene therapy can normalize levels of toxic metabolites in the brain, liver and tendons*

The poster presentation entitled: **"Long-term metabolic, phenotypic, and neuropathological characterization of the *Cyp27a1*$^{-/-}$ mouse model of cerebrotendinous xanthomatosis"** details the findings highlighted below:

- *When compared to normal "wild type" mice, CTX mouse model had lower body weight, enlarged livers, higher levels of transaminases in their blood, and expression of enzymes Cyp7a1 and Cyp3a11- the latter being the mouse equivalent of the human enzyme CYP3A4*
- *The CTX mouse model also showed higher levels of harmful bile acids in their blood and brains that increased with age*
- *The CTX mouse model – in particular the females – showed signs of ataxia, similar to that seen in people with CTX*

This is the first study describing motor alterations in a CTX mouse model, similar to those reported in CTX patients, and progressive accumulation of toxic metabolites.

Dr Jean-Philippe Combal, Co-Founder & Chief Executive Officer at Vivet Therapeutics added, "*Our preclinical findings for VTX-806 further demonstrate its enormous potential as a valuable alternative treatment option for the curative treatment of CTX. These outcomes come at a transformative stage for Vivet as we refocus our efforts and progress toward key inflection points for our VTX-PID and VTX-806 programs. VTX-PID is advancing in a Phase 1 study, aimed at depleting neutralizing antibodies, with initial results already acquired and more due in 2025. We continue to develop novel and long-lasting gene therapies for rare inherited liver metabolic disorders, which have the potential to transform the current standard of care and treat broader patient populations.*"

Details of the oral and poster presentations are as follows:

Presentation Title: Liver-directed gene therapy normalizes toxic bile acid metabolite levels in the blood and brain of mice with cerebrotendinous xanthomatosis
Presenter: Dr Gloria Gonzalez-Aseguinolaza, Co-founder and CSO at Vivet Therapeutics
Date and Time: Monday 18 November, at 08:00-9:30 PST
Abstract Parallel Session: From Bench to Bedside: State of the Art Diagnostics and Therapeutics in Genetic and Metabolic Liver Disease
Presentation Number: 0230

Oral Presentation Authors: *A Molina1,2,‡, L Trigueros-Motos 3,‡, G Pérez1,2, M Molina1,2, I Marcilla-García1,2, L Neri3, A Douar4, JP Combal4, B Tamarit4, C Bouquet 4, P Krasniqi 5, A Lamazière5, 6, R Hernandez-Alcoceba1, G González-Aseguinolaza1,2,3,**

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Poster Presentation Title: Long-term metabolic, phenotypic, and neuropathological characterization of the Cyp27a1-/- mouse model of cerebrotendinous xanthomatosis
Poster (4476): Long-term metabolic, phenotypic, and neuropathological characterization of the Cyp27a1-/- mouse model of cerebrotendinous xanthomatosis
Date and Time: Monday 18 November, at 08:00 – 17:00 PST
Abstract Parallel Session: Metabolic and Genetic Disease
Poster Presentation Number: 4476
Location: Poster Hall C

Poster Presentation Authors: *L Trigueros-Motos[3,‡], A Molina[1,2,‡], G Pérez[1,2], I Marcilla[1,2], M Molina[1,2], L Neri[3], D Moreno-Luqui[1,2], A Douar[4], JP Combal[4], A García-Osta [1,2], M Cuadrado-Tejedor [1,2], B Tamarit[4], C Bouquet[4], G Despres[5], P Krasniqi[5], A Lamazière[5, 6], R Hernandez-Alcoceba[1], G González-Aseguinolaza[1,2,3,*]*

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About Vivet Therapeutics

Vivet Therapeutics is a private, clinical-stage biotech company developing novel and long-lasting gene therapies for rare inherited metabolic conditions, including Wilson's Disease. Vivet's gene therapy platform uses recombinant adeno-associated viruses (rAAVs) as vectors and has initiated two clinical programs and four pre-clinical assets to date. Its most advanced program VTX-PID, is aimed at depleting Neutralizing Antibodies (NAbs) levels for a given AAV serotype and is advancing in a Phase 1 dose escalating study in Nabs+ subjects. Its Leading pre-clinical program VTX-806, for the treatment of Cerebrotendinous Xanthomatosis (CTX), received ODD by the EC in September 2024 and is demonstrating its potential as an alternative treatment option for patients affected by the burden of CTX.

Vivet Therapeutics was founded in 2016 by CEO Dr Jean-Philippe Combal and CSO Dr Gloria Gonzalez-Aseguinolaza and is led by a highly experienced management team with deep expertise developing gene therapies and orphan drugs.

Vivet Therapeutics is backed by international life science investors including Novartis Venture Fund, Roche Venture Fund, HealthCap, Pfizer Inc., Columbus Venture Partners, Ysios Capital,

Kurma Partners and Eurazeo. In 2019, key investor Pfizer contributed a €45M investment to collaborate with Vivet in recognition of its scientific expertise and innovative technology platforms.

For more information, please visit www.vivet-therapeutics.com - Follow us on LinkedIn @Vivet Therapeutics and Twitter @Vivet_tx