Targeting the Putamen with Gene Therapy Leads to Sustained Improvements in Motor and Non-Motor Functions in Children with AADC Deficiency

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- Commentary Published in the European Molecular Biology Organization Journal -

SOUTH PLAINFIELD, N.J., Aug. 23, 2021 /PRNewswire/ -- PTC Therapeutics, Inc. (NASDAQ: PTCT) today announced the publication of a manuscript, "Gene Therapy in the Putamen for Curing AADC Deficiency and Parkinson's Disease," in the European Molecular Biology Organization Journal. The paper describes a pioneering approach that delivers gene therapy to a specific part of the brain called the putamen, which is helping successfully treat a previously intractable, devastating disorder and transforming the lives of children born with AADC deficiency (AADC-d)[1].

"I am excited about what the success of this new approach means for the children and families living with AADC deficiency," said Stuart W. Peltz, Ph.D., Chief Executive Officer, PTC Therapeutics. "AADC deficiency is a terrible, life-shortening condition that requires around-the-clock care. The data reported in this article show that the surgical approach of delivering our novel PTC-AADC gene therapy directly to the putamen robustly produces dopamine in the brain that results in sustained and substantial functional improvements in children with AADC deficiency."

Currently there are no approved disease-modifying therapies for treating AADC-d, and the success of symptomatic treatment using combinations of vitamin B6, dopamine (DA) agonists, and monoamine oxidase inhibitors is very limited, especially in severe cases[2].

The paper, authored by global experts in the United States, Taiwan, France, Germany, and Japan, describes three clinical trials in which AAV2-hAADC was infused into the putamen of children with AADC-d via brain surgery. Prior to treatment, most of the children with AADC-d had never developed muscle control, could not lift their heads, move on their own or talk, and nearly all were bed ridden. Every child in the trials showed significant improvements following treatment with PTC's novel gene therapy, PTC-AADC[1].

The clinical benefits and safety profile of PTC-AADC has been demonstrated across multiple trials, with the first patient dosed more than 10 years ago, in 2010. The trials together represent the largest cohort of AADC-d patients ever studied.

"The remarkable results published have been life-changing for the children we have treated," said co-author and investigator Paul Wuh-Liang Hwu, National Taiwan University Hospital. "Before this treatment, the children with AADC deficiency couldn't lift their heads, but now some can sit and stand with help, and have even begun learning to talk."

AADC deficiency is a debilitating neurological disorder that involve motor dysfunction caused by dopamine deficiencies. Dopamine is a neurotransmitter that is critical for motor and mental development[1]. The studies demonstrate that the restoration of DA synthesis in the putamen via gene therapy using low doses of AAV2-hAADC is well tolerated, leads to sustained improvements in motor and nonmotor symptoms of AADC deficiency, and beneficial for the patients. The novel gene therapy, PTC-AADC was delivered to the putamen because it is more easily accessible via surgery than other sites, and therefore, may result in fewer surgical complications. In neurological disorders such as AADC-d, the putamen is directly impacted by the loss of DA synthesis in the striatum[1].

PTC-AADC is currently under review by the European Medicines Agency's Committee for Medicinal Products for Human Use with an opinion expected in the fourth quarter of 2021.

About aromatic L-amino acid decarboxylase (AADC) deficiency
AADC deficiency is a fatal, ultra-rare genetic disorder that causes severe disability and suffering from the first months of life, affecting every aspect of life – physical, mental, and behavioral[1,2,[3]]. The suffering of children with AADC deficiency is exacerbated by episodes of distressing seizure-like oculogyric crises, which can happen daily and last for hours, causing the eyes to roll up in the head, frequent vomiting, behavioral problems, difficulty sleeping, and life-threatening complications such as respiratory infections and gastrointestinal problems[2,[4],[5],[6]].

Current management options yield limited improvement for the majority of patients with AADC-d.[2] Managing patients with AADC-d requires a multidisciplinary team of specialists and complex coordination of care to address significant health issues, including developmental delays, infections, orthopaedic and cardiac complications, and other comorbidities[2]

While several diagnostic tests for AADC deficiency are available, the condition remains largely undiagnosed or misdiagnosed for other conditions with similar symptoms, such as cerebral palsy and some forms of epilepsy[4,[7]].

About PTC Therapeutics, Inc.
PTC Therapeutics is a science-driven, global biopharmaceutical company focused on the discovery, development and commercialization of clinically differentiated medicines that provide benefits to patients with rare disorders. PTC's mission is to provide access to best-in-class treatments for patients with an unmet medical need, using its ability to globally commercialize products as the foundation to drive investment in a robust and diversified pipeline of transformative medicines. The Company's strategy is to leverage its strong scientific expertise and global commercial infrastructure to maximize value for its patients and other stakeholders. To learn more about PTC, please visit us at www.ptcbio.com and follow it on Facebook, on Twitter at @PTCBio, and on LinkedIn.

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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 release, other than statements of historic fact, are forward-looking statements, including statements regarding: the future expectations, plans and prospects for PTC, including with respect to the expected timing of clinical trials and studies, availability of data, regulatory submissions and responses and other matters; expectations with respect to PTC's gene therapy platform, including any regulatory submissions and manufacturing capabilities; PTC's expectations with respect to the licensing, regulatory submissions and commercialization of its other products and product candidates; PTC's strategy, future operations, future financial position, future revenues, projected costs; and the objectives of management. Other forward-looking statements may be identified by the words, "guidance", "plan," "anticipate," "believe," "estimate," "expect," "intend," "may," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions.

PTC's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes as a result of a variety of risks and uncertainties, including those related to: the outcome of pricing, coverage and reimbursement negotiations with third party payors for PTC's products or product candidates that PTC commercializes or may commercialize in the future; expectations with respect to PTC's gene therapy platform, including any regulatory submissions and potential approvals, manufacturing capabilities and the potential financial impact and benefits of its leased biologics manufacturing facility and the potential achievement of development, regulatory and sales milestones and contingent payments that PTC may be obligated to make; significant business effects, including the effects of industry, market, economic, political or regulatory conditions; changes in tax and other laws, regulations, rates and policies; the eligible patient base and commercial potential of PTC's products and product candidates; PTC's scientific approach and general development progress; and the factors discussed in the "Risk Factors" section of PTC's most recent Quarterly Report on Form 10-Q and Annual Report on Form 10-K, as well as any updates to these risk factors filed from time to time in PTC's other filings with the SEC. You are urged to carefully consider all such factors.

As with any pharmaceutical under development, there are significant risks in the development, regulatory approval, and commercialization of new products. There are no guarantees that any product will receive or maintain regulatory approval in any territory, or prove to be commercially successful, including PTC-AADC.

The forward-looking statements contained herein represent PTC's views only as of the date of this press release and PTC does not undertake or plan to update or revise any such forward-looking statements to reflect actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this press release except as required by law.

[1] Hwu WL, Kiening K, Anselm I *et al*. Gene Therapy in the Putamen for Curing AADC Deficiency and Parkinson Disease'. *EMBO Molec Medicine*. 2021. DOI 10.15252/emmm.202114712. Available at: https://www.embopress.org/doi/10.15252/emmm.202114712. Last accessed August 2021.

[2] Wassenberg T, *et al.* Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. *Orphanet J Rare Dis.* 2017;12(1):12.

[3] Williams K *et al.* Symptoms and impacts of aromatic l-amino decarboxylase (AADC) deficiency: A qualitative study. Poster presented at ISPOR 2021, May 17-20, 2021

[4] Pearson T *et al.* AADC deficiency from infancy to adulthood: Symptoms and developmental outcome in an international cohort of 63 patients. *J Inherit Metab Dis.* 2020 Sep;43(5):1121-1130.

[5] Chien YH, *et al.* 3-O-methyldopa levels in newborns: Result of newborn screening for aromatic l-amino-acid decarboxylase deficiency. *Mol Genet Metab.* August 2016;118(4):259-263.

[6] Buesch K *et al.* Caring for an Individual with Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency: Analysis of Reported Time for Practical and Emotional Care and Paid/Unpaid Help. Poster presented at ISPOR 2021, May 17-20, 2021.

[7] Chien YH, *et al.* 3-O-methyldopa levels in newborns: Result of newborn screening for aromatic l-amino-acid decarboxylase deficiency. *Mol Genet Metab.* August 2016;118(4):259-263

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