Preclinical Data from iECURE's GTP-506 Demonstrates Potential for the Treatment of Ornithine Transcarbamylase (OTC) Deficiency

- *Nonhuman primate (NHP) data demonstrates stable insertion of therapeutic gene using an ARCUS nuclease one year after dosing*
- *OTC-deficient mice treated using iECURE's approach were protected against lethal hyperammonemia upon high-protein diet challenge*
- *Data presented at the International Conference on Ureagenesis Defects and Allied Conditions 2022*

PHILADELPHIA—October 19, 2022 – **iECURE**, a gene editing company focused on developing therapies that utilize mutation-agnostic *in vivo* gene insertion, or knock-in, editing for the treatment of liver disorders with significant unmet need today announced that data presented at the International Conference on Ureagenesis Defects and Allied Conditions 2022 by its research collaborators led by James Wilson, MD, PhD, at the University of Pennsylvania's Gene Therapy Program (GTP), showed stable insertion of the therapeutic gene one year post-dosing in newborn and infant macaques and potential signs of efficacy in mouse Ornithine Transcarbamylase (OTC) Deficiency knock out models.

"Gene therapy approaches for disorders of metabolism in the liver, in which a therapeutic gene exists outside of human chromosomes, have thus far been unsuccessful in babies, as the rapidly dividing liver cells lose expression of the therapeutic construct over time," said Wilson, the Rose H. Weiss Professor and Director, Orphan Disease Center; a professor of Medicine and Pediatrics, and director of the Gene Therapy Program (GTP) at the University of Pennsylvania. "Therefore, we believe knocking-in a healthy copy of a gene may be the most effective method to treat devastating diseases like OTC. The one-year data readout in newborn and infant macaques shows stability of gene insertion in an animal model that is closely related to humans, which provides hope that we may see similar stability when we enter the clinic."

iECURE's approach to gene editing for its initial programs, including OTC deficiency, relies on the delivery of twin adeno-associated virus (AAV)-based vectors carrying different payloads. GTP-506 comprises two vectors, an ARCUS® nuclease vector (GTP-506A) targeting gene editing in the well-characterized PCSK9 gene locus and a therapeutic donor vector (GTP-506D) that inserts the OTC gene to provide the desired genetic correction. [1] The cut in the PCSK9 site serves as the insertion site for the therapeutic gene, providing a potential path to permanent expression of a healthy gene.

In the study presented by Lili Wang, PhD, of the University of Pennsylvania's GTP, potential efficacy of GTP-506 was demonstrated in an OTC-deficient mouse model. Injection of GTP-506A and GTP-506D in newborn mice efficiently knocked-in the human OTC minigene. Mice with the knocked-in gene were challenged with a high protein diet and were protected from lethal hyperammonemia.

Long-term stability of the edited genome in nonhuman primates was demonstrated in newborn and infant macaques. Previously, data was presented showing efficient *in vivo* insertion in newborn NHPs as evidenced by biopsy three months post procedure. In the follow up data, 12-month biopsies continued to demonstrate construct stability, with transduction efficiency up to 28.2% as measured by in-situ hybridization (ISH). This is well above the expected threshold for clinical benefit. Notably, efficient targeted insertion was achieved in macaques up to three months of age, and studies of older infants are

ongoing. Thus far, AAV vector injection has been well tolerated, and there was no evidence of liver histopathology in any ARCUS-treated animals.

“The approach we are taking to execute *in vivo* gene editing has never been done before in a clinical setting, so the evidence of gene insertion stability as well as tolerability are critical to moving forward in patients,” said Joseph Truitt, Chief Executive Officer of iECURE. “Having already secured both Orphan Drug and Rare Pediatric Disease Designations from the FDA, we are very excited with the results so far and are currently working to launch a first-in-human study next year.”

About OTC Deficiency
OTC deficiency, the most common urea cycle disorder, is an inherited metabolic disorder caused by a genetic defect in a liver enzyme responsible for detoxification of ammonia. Individuals with OTC deficiency can build-up excessive levels of ammonia in their blood, potentially resulting in devastating consequences, including cumulative and irreversible neurological damage, coma and death. The severe form of the condition emerges shortly after birth and is more common in boys than girls. The only treatment for early onset severe OTC deficiency is a liver transplant. Currently available medical therapies do not correct the disease, and do not eliminate the risk of life-threatening symptoms or crises.

About ARCUS
iECURE has partnered with Precision BioSciences to leverage the ARCUS Nuclease for gene insertion in OTC and other diseases. ARCUS is a proprietary genome editing technology discovered and developed by scientists at Precision BioSciences. It uses sequence-specific DNA-cutting enzymes, or nucleases, that are designed to insert, delete, or repair disease-causing DNA in living cells and organisms.

About iECURE
iECURE is a gene editing company focused on developing therapies that utilize mutation-agnostic *in vivo* gene insertion, or knock-in, editing for the treatment of liver disorders with significant unmet need. We believe our approach has the potential to replace and restore the function of a dysfunctional gene by knocking-in a healthy copy, regardless of mutation, to offer durable gene expression and long-term, potentially curative, therapeutic benefit. Our management team has extensive experience in executing global orphan drug and gene therapy clinical trials and successfully commercializing multiple products. We intend to leverage our team’s core strength in research and development strategy to identify what we believe to be the most suitable target and modality for our product candidates to address particular liver diseases. We are collaborating with the University of Pennsylvania’s Gene Therapy Program, or GTP, led by James M. Wilson, M.D., Ph.D., to utilize GTP’s world-class translational expertise and infrastructure, which has helped generate our initial pipeline of potential product candidates. For more information, visit ***iecure.com*** and follow on ***LinkedIn***.

Financial Disclosure
The University of Pennsylvania (Penn) and Dr. Wilson each hold equity interests in iECURE. Penn also receives significant sponsored research support from the Company, and both Penn and Dr. Wilson stand to benefit from licensing revenues received from iECURE based on successful technology development and commercialization of the technologies licensed from Penn. Dr. Wilson serves as Chief Scientific Advisor for iECURE.

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[1] iECURE has licensed the ARCUS® nuclease from Precision BioSciences for four gene insertion programs including OTC, CTLN1 and PKU.