

What is a Clinical Trial?

A clinical trial, also called a clinical research study, tests an investigational medicine or treatment in a population of volunteers. All new drug products go through the clinical study process, so participants play a very important role in advancing medicine for present and future generations.

About the pheEDIT Clinical Trial

The pheEDIT clinical trial is designed to evaluate the safety and effectiveness of Homology's one-time *in vivo* gene editing candidate HMI-103 in adults with phenylketonuria (PKU) due to phenylalanine hydroxylase (PAH) deficiency.

What is PKU? PKU is a rare, inherited inborn error of metabolism caused by mutations in the *PAH* gene responsible for breaking down phenylalanine (Phe) that is contained in protein. The current standard of care is a highly restrictive diet, but it is not always effective, and there are currently no treatments available that address the genetic defect in PKU. If left untreated, PKU can result in progressive and severe neurological impairment. PKU affects approximately 16,500 people in the U.S., and an estimated 300 newborns are diagnosed each year.

What is HMI-103? HMI-103 is designed as a one-time administration to specifically integrate a functional *PAH* gene into the genome using the natural DNA repair process of homologous recombination. HMI-103 is developed to maximize the expression of functional phenylalanine hydroxylase (PAH) in liver cells and thus restore the natural biochemical pathway that metabolizes Phe. In addition to expression, the integration is designed to correct the cell by inactivating at least one of the mutated genes and enable that correction to persist through cell division. Below is a description of how HMI-103 is designed to work.

Step 1:

A patient would receive a one-time intravenous (I.V.) administration of HMI-103 consisting of functional copies of the *PAH* gene surrounded by long DNA sequences homologous to a specific location in the genome (homology arms).

Step 2:

HMI-103 is designed to target the cells in the liver, where PAH activity is required to metabolize Phe normally.

Step 3:

HMI-103 is designed to enter liver cells and deliver the functional *PAH* gene to the nucleus. Through the body's natural DNA repair process of homologous recombination, in some cells the functional *PAH* gene could integrate into the genome to the exact location where it is needed.

Step 4:

The functional *PAH* gene could then create functional PAH protein that metabolizes dietary Phe, potentially restoring the normal biochemical pathway.

This approach is under investigation as a potential treatment for adult patients with PKU.

What is the pheEDIT Clinical Trial?

The Phase 1 pheEDIT trial is a dose-escalation study designed to evaluate up to three doses of HMI-103. The trial is expected to enroll up to 9 patients ages 18-55 years old who have been diagnosed with PKU due to PAH deficiency. In addition to safety endpoints, the trial plans to measure plasma Phe changes. Over time, Homology plans to evaluate HMI-103 in the pediatric PKU population, once positive safety and efficacy is established in adults.

What Does Participation in the pheEDIT Trial Involve?

Screening Period: The trial will include a screening period to ensure participants meet the eligibility criteria to enroll in the study.

Study Period: Following a single I.V. administration of HMI-103, participants will be observed periodically for 2 years.

Follow-Up Period: Patients will be observed less frequently for additional years.