FOR PATIENT DISCUSSIONS

What are genes?
Genes are inherited from our parents and make us unique. They are responsible for things like eye color and the color and texture of our hair. Genes are made of strands of a molecule called DNA and are housed in chromosomes. There are about 25,000 genes in most cells of the human body. Each gene contains a “blueprint” for the manufacture of a protein; proteins perform numerous functions. The Fanconi anemia proteins are responsible for repairing damage to genetic material (DNA) in cells throughout the body. A mutation or change in a normal gene can lead to a disorder, like Fanconi anemia (FA).

What is gene therapy?
For many diseases, gene therapy is considered experimental, which means that it has not been proven to be helpful or a regular treatment for that disease. However, it does offer the potential to substantially improve or possibly cure diseases that are caused by mutations in a single gene. In the gene therapy used in this trial, the correct gene is put into the patient’s stem cells (blood forming cells) with the intent of enabling them to work correctly.

What is the purpose of this study?
The purpose of this study is to determine whether gene therapy in FA is safe and can be used to prevent and treat bone marrow failure in patients with Fanconi anemia, complementation Group A (FA-A). Gene therapy will involve placement of an intact (non-mutated) copy of the FANCA gene (Fanconi anemia causing gene) inside blood stem cells. To do this, blood stem cells are collected from a patient and genetically modified in a specialized manufacturing laboratory by introducing a good copy of the FANCA gene using a lentiviral vector (this process is called “transduction”). The corrected stem cells are then given back to the patient without using any medication, such as chemotherapy, to remove existing bone marrow cells.

How is FA currently treated?
Current treatment medications such as androgens may help to raise blood counts to safe levels. These treatments do not work for everyone, are associated with side effects, and the benefits are sometimes only for a short time. The only available therapy that can possibly cure the blood portion of the disease is bone marrow transplantation (BMT). This procedure involves medications such as chemotherapy that kill a patient’s existing blood forming and immune cells followed by an infusion of blood stem cells from a donor to replace the patient’s bone marrow. This is usually done when the patient’s own bone marrow is not working any more or if there is evidence of blood cancers, such as leukemia, because there are many associated risks and side effects.

How may this investigational gene therapy help my child?
We hope that this investigational gene therapy will prevent bone marrow failure in your child but we don’t know for sure if it will. However, we can share that as of October 2018, this therapy has been given to 6 children, with long-term follow-up available for 4 of them. Results from these 4 patients have been promising and show that the gene-corrected stem cells are growing in the bone marrow and making new red blood cells, white blood cells, and platelets, commonly referred to as engraftment.
**How is the mobilization and apheresis process performed?**

Normally, stem cells live in the bone marrow and there are not many in the bloodstream. To increase the availability of stem cells in the blood, medications called granulocyte colony-stimulating factor (GCSF) and plerixafor will be given by a subcutaneous injection, which is an injection that goes just under the skin, for 5-6 days to make more of the stem cells in your child’s bone marrow move (temporarily) into the bloodstream. Blood tests will be done each day to check and see if there are enough stem cells in the bloodstream to collect. Under anesthesia, a special intravenous tube called a leukapheresis catheter will be placed in a large vein in the chest or groin area. When a patient is ready to undergo collection of stem cells, the catheter will be hooked up to an apheresis machine which collects stem cells from the blood and returns the other cells and blood back to your child. The process takes several hours and you can stay with your child during the procedure. Your child will be carefully monitored. It is likely that 2 of these procedures will be necessary to collect enough stem cells; these procedures will be performed on consecutive days. It is likely that the intravenous leukapheresis catheter (apheresis catheter) will be required for 2-3 days, after which time it will be removed. As part of the apheresis procedure, transfusion of platelets and possibly red blood cells will be required (likely on the second day of apheresis). It is likely that any blood product transfusions required will be given only around the time of the apheresis procedure (and that they will not be required subsequently).

**What are the side effects from the gene therapy?**

In any research study where a new therapy is being tested, there is a chance the patient may get sick from the new treatment. With a gene therapy, there is a small chance that the patient may get an infection or an allergic reaction. Older gene therapies that used a different type of vector called a gamma-retroviral vector, to deliver the correct gene, caused leukemia in some of the patients who received these therapies. The current FA trial uses a lentiviral vector (LV). It is believed that lentiviral vectors are not likely to cause cancer and more than 150 patients have received gene therapy with these vectors for various disorders over recent years without any leukemias identified. We will monitor patients carefully to evaluate whether any of these side effects develop. You should also know that some of the tests or other medicines we give your child during this process may make him/her feel sick or have other side effects. This therapy has been given to 6 pediatric patients with long-term follow-up available for 4 of them. To-date, no serious side effects associated with the infusion of gene-corrected cells have been reported.

**Has this study been approved?**

This study has been approved by relevant health authorities, including the US Food and Drug Administration (FDA) and the Spanish Health Authority (AEMPS), and the individual Institutional Review Boards at the clinical centers where the study will be conducted. Health authorities, like FDA, is responsible for ensuring that the study is scientifically sound and appropriate to do with children. The IRB is responsible for ensuring the safety of all patients who agree to participate.

**Can my child receive other therapies while enrolled in the clinical trial?**

Since the therapy in the trial is still experimental, it is important to make sure that the all the effects of the treatment are fully understood. Thus, no other treatments that may affect the bone marrow function are allowed if your child continues to participate in the trial until the 3-year study period is over. Should you decide to pursue another therapy, withdrawal from the trial is permitted at any time with no penalty.

**How does this study differ from other studies in FA using oral medicines to prevent cell stress or cancer?**
Studies looking at medications that may prevent cancer or reduce the stress on blood cells are using medications that are approved for other conditions, and there is evidence from laboratory studies that these drugs can reduce cell stress or reduce chemical processes that lead to cancer formation. The specific effects in FA are not known, and it not known if these therapies will prevent cell damage or for how long. These medications are believed to be generally safe. Gene therapy is intended to reverse the root cause of the blood portion of FA, by providing blood stem cells with an intact (non-mutated) FANCA gene. Similarly, it is not proven whether gene therapy will prevent bone marrow failure or other long-term blood complications in FA; it is believed that if there is a positive effect on blood cells, this is likely to increase over time, and that the benefit could be durable since healthy blood stem cells can generate blood over the course of someone’s entire life.

Gene therapy will involve more direct inconvenience in the short-term relative to an oral medication, since it will involve hospitalization for approximately one week, and will involve stem cell collections which require a large intravenous catheter, two apheresis procedures and possible platelet and red blood cell transfusions. These procedures will not be ongoing, and once a gene therapy patient has received the infusion of gene-corrected cells, they will likely leave the hospital over the following 1-2 days and will not require ongoing medications. Gene therapy patients will be asked to participate in ongoing follow-up visits to enable assessment of blood, bone marrow, and other health-related parameters. The follow-up is not likely to involve more frequent evaluations than would be performed during other studies or as part of normal, non-experimental care.

The gene therapy is intended to prevent bone marrow failure, but will there be a risk that the remaining, non-corrected blood stem cells transform to leukemia over time? It is hoped that gene therapy will enable a sufficient number of blood stem cells to grow in the bone marrow and blood so that a patient will not experience subsequent bone marrow failure. It is likely that some non-corrected HSCs will persist over time. It is hoped that the presence of the gene-corrected blood and bone marrow cells will reduce the stress on these non-corrected cells, so that they may be less likely to transform into leukemia, but the existence or extent of this reduction in stress and leukemia is not known. We will try to study this as part of the gene therapy trial. (It has been shown that FA mosaic patients who have normal blood counts are unlikely to develop leukemia or other blood cancers).

Is gene therapy going to be available for patients who have other FA subtypes, such as FANCC or FANCG? What about the very rare subtypes? The gene therapy program started in FANCA (complementation group A) because the majority of FA patients are part of this subtype. It is planned that once a reasonable degree of improvement is seen in the FANCA study, programs will be developed for the other common complementation groups (FANCC and FANCG). If these appear successful (safe and corrective of the blood component of FA) then we will work with the FDA and other health authorities to understand if there is a way to develop more customized programs for the very rare subtypes.