Aruvant Sciences
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One-time gene therapy for sickle cell disease

Aruvant is developing ARU-1801, a one-time, potentially curative gene therapy for sickle cell disease and β-thalassemia. In an ongoing clinical phase 1/2 study, ARU-1801, administered with only reduced intensity conditioning, has provided stable reductions in disease burden and opioid dependence.

Sickle cell disease (SCD) is a progressively debilitating and life-threatening inherited red blood cell (RBC) disorder that causes a patient's oxygen-carrying RBCs to become abnormally inflexible and sickle-shaped upon deoxygenation. SCD causes anemia, frequent pain attacks and life-threatening acute complications such as vaso-occlusive crises. Furthermore, SCD shortens lives, with the median life expectancy for patients with SCD being just 42 years for males and 48 years for females.

Aruvant Sciences is a private clinical-stage gene therapy company focused on developing and commercializing transformative therapies for patients with severe hematological conditions. The company's near-term focus is on SCD, with a subsequent expansion into β-thalassemia. Aruvant's lead candidate, ARU-1801, consists of autologous cells that are genetically modified with a lentiviral vector that encodes a novel, highly potent anti-sickling γ-globin. ARU-1801 was designed to address the limitations of current curative treatment options, such as low donor availability and the need for more toxic, intensive chemotherapy conditioning regimens for stem cell transplants. The investigational therapy aims to restore normal RBC function through increasing levels of hemoglobin F (HbF) by increasing γ-globin protein levels (Fig. 1). γ-globin is a subunit of fetal hemoglobin, the primary form of hemoglobin in early life. Fetal hemoglobin exhibits a one and a half to two times higher oxygen affinity than normal adult hemoglobin, hemoglobin A (HbA). By enhancing the oxygen-carrying capacity of RBCs, the sickling process is prevented.

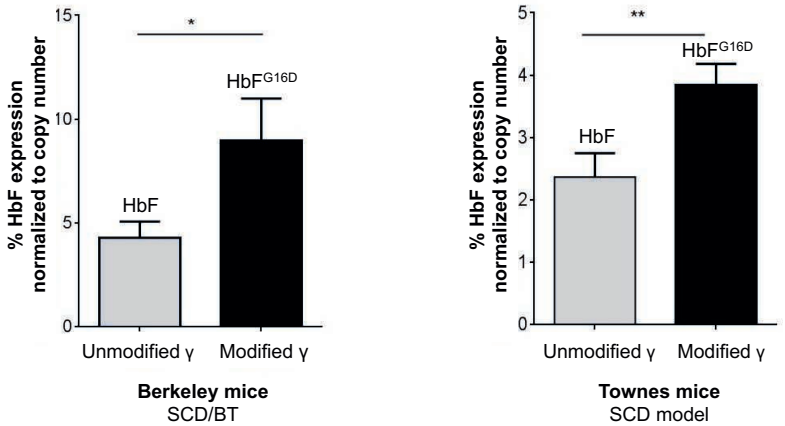

Fig. 1 | Aruvant's potentially curative gene therapy ARU-1801. ARU-1801 leverages a modified γ-globin, called γ(G16D), to produce a modified HbF called HbF^{G16D}. The γ(G16D) mutation results in higher HbF production per vector copy number relative to endogenous γ-globin. Significant improvement was seen in both the Berkeley (*$P < 0.05$) and Townes (**$P < 0.01$) mouse models.

A potent modified γ-globin

ARU-1801 uses a modified γ-globin to create a one-time, highly potent autologous treatment for SCD and β-thalassemia that requires only reduced intensity conditioning (RIC) for engraftment. ARU-1801 leverages a proprietary lentiviral vector to deliver a gene encoding a modified γ-globin, called γ(G16D), into a patient's own stem cells ex vivo. γ(G16D) was designed to have a higher affinity for α-globin, with the intention of outcompeting the mutated β-sickle chains and increasing fetal hemoglobin formation. Comparative studies of vector encoding γ(G16D) versus unmodified γ-globin show a higher proportion of fetal hemoglobin circulating in the bloodstream with γ(G16D) relative to unmodified, endogenous γ-globin.

Unlike other investigational gene therapies for SCD, the higher potency of γ(G16D) allows ARU-1801 to be transplanted using a lower, non-myeloablative dose of chemotherapy. Other gene therapies require the use of high-intensity myeloablative conditioning regimens to ensure sufficient engraftment to prevent sickling, typically resulting in lengthy hospital stays and a host of potentially serious short-term and long-term complications.

"We believe ARU-1801 has the potential to dramatically change the disease trajectory in patients with SCD and β-thalassemia," said William Chou, CEO of Aruvant. "The opportunity to receive a potentially curative gene therapy with a lower, less toxic dose of chemotherapy would provide a meaningful difference to individuals living with SCD."

Possible expedited development pathway for ARU-1801 in SCD

Preliminary clinical data to date from an ongoing phase 1/2 study in SCD patients have shown durable reductions in disease burden. Patients have shown stable levels of anti-sickling fetal hemoglobin levels at 21–29% of total hemoglobin for 15–21 months after treatment. Clinically, ARU-1801 has thus far resulted in reductions in vaso-occlusive crises and disease-related hospitalizations as well as discontinuation of daily opioid use. The US Food and Drug Administration (FDA) has granted orphan drug designation and rare pediatric disease designation to ARU-1801 for the treatment of SCD.

According to Chou, "side effects from conditioning chemotherapy such as infertility and long hospital stays often dissuade patients with blood disorders from choosing a curative therapy option. The ability to administer ARU-1801 through reduced intensity conditioning may open up the possibility of gene therapy to a broader group of patients."

Reaching beyond SCD

SCD is only one blood disorder that can benefit from Aruvant's modified fetal hemoglobin–based gene therapy. The company is already working on applying ARU-1801 to the treatment of β-thalassemia.

β-thalassemia is an inherited red blood cell disorder characterized by reduced or nonexistent production of functional β-globin, compromising the production of functional hemoglobin. Patients with the disorder suffer from anemia, which can cause weakness and fatigue. Aruvant is developing ARU-1801 as a therapy designed to boost levels of functional fetal hemoglobin in β-thalassemia patients and restore normal red blood cell function.

"At Aruvant, we are now focused on scaling up manufacturing and seeking alignment with the FDA and the European Medicines Agency for pivotal studies in both SCD and β-thalassemia," said Chou. "We believe we have a product that can change patients' lives; we come to work with a singular focus to successfully, rapidly, bring ARU-1801 to the many patients in need."

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