India

Underweight *(no change)*

Chemicals - Overall

CRISPR to be used in human therapeutics

- The world's first CRISPR-Cas9 therapy has been approved for human use in the US and UK for treating sickle cell anemia and beta-thalassemia.
- In FY24 budget, a screening plan was launched under the Eliminate Sickle Cell Mission. Currently, India has CRISPR-based therapy at the pre-clinical stage.
- We have previously written about CRISPR-Cas9 that it's a new-age gene editing technology which can be used to edit genes at the DNA level.

CRISPR-based therapy has already received approval for human use

Vertex and CRISPR Therapeutics have developed a CRISPR-based therapy for blood disorders like sickle cell anemia and beta thalassemia. It has received approval in the UK and can get the US FDA approval by Dec 2023F. The CRISPR-Cas9 complex will modify the faulty gene that causes abnormally shaped blood cells, thereby fixing the disease. Most of the patients who were treated using this therapy had normally shaped blood cells in case of sickle cell anemia and did not require blood transfusions in case of beta thalassemia for a year. The only major safety concern associated with this therapy is that it may change some other part of the DNA, potentially causing blood cancer. However, based on the studies carried out by Vertex, the probability of this happening is extremely low.

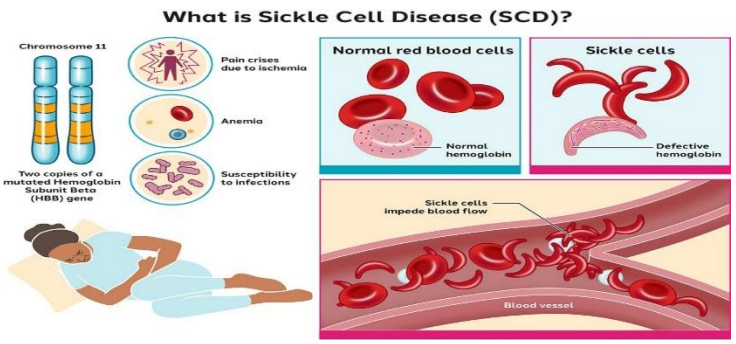
India is also moving to CRISPR for eliminating sickle cell anaemia

The Indian government plans to screen 70m people for sickle cell anemia via the Eliminate Sickle Cell Mission, which was a part of its 2023-24 budget announcements. The Council for Scientific and Industrial Research or CSIR's Institute of Genomics and Integrative Biology (IGIB) has developed a CRISPR-based sickle cell therapy that is currently at the pre-clinical trials stage. If successful, India could provide the therapy at a marginal cost compared to its global counterparts. Laurus Labs has already worked with ImmunoACT to commercialize the CAR-T therapy and collaborated with IIT (Indian Institute of Technology) to develop gene therapies. Laurus Labs could be a potential commercialization partner for CSIR as sickle cell therapy is quite similar to CAR-T cell therapy.

High cost and complexity can restrain the therapy's growth

There isn't any information from the US authorities yet on who will be eligible for receiving the drug, but the UK government has stated that only individuals who are in severe need of treatment or have no other options available will be eligible for this treatment. We are expecting something similar to happen in the US as well. Even though Vertex and CRISPR Therapeutics haven't declared the cost but based on the cost of similar gene therapies, we are expecting it to be at US$2m. Moreover, there will be resistance at the patient level as the treatment is complex and it requires the patient to undergo several weeks of chemotherapy. Scaling up the manufacturing process will be complex, as the patient's cells need to be individually modified for this therapy. Overall, the high cost, complex treatment, and arduous manufacturing process can challenge the market growth for this therapy.

Figure 1: Gene mutation causes sickle-shaped blood cells, thereby leading to debilitating pain and other complications



SOURCE: INCRED RESEARCH, COMPANY REPORTS

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CRISPR to be used in human therapeutics

In a landmark development, CRISPR has forayed into human therapeutics. The UK government has approved the therapy for human use and the US government may also follow suit in the next 15 days or so. It will be primarily used to treat sickle cell anaemia and beta thalassemia. The Indian government also plans to eliminate sickle cell disease from the country by 2047F. In this direction, the CSIR is already developing a treatment method using CRISPR- Cas9.

World's first CRISPR therapy

1. The world's first CRISPR-Cas9-based therapy received approval from the UK government and is expected to receive the US Food and Drug Administration or US FDA approval by Dec 2023F. The therapy has been developed by Vertex and CRISPR Therapeutics.
2. Most of the patients who were treated using this therapy during the clinical trials recovered from sickle cell anaemia and thalassemia, and did not suffer from the complications caused by these disorders for a year.
3. There is a slight chance that the CRISPR can mutate a wrong gene in the body, thereby causing blood cancer, but no such instances were observed during the clinical trials.

UK gives its approval for the world's first CRISPR-based therapy and a FDA expert panel sets the stage for US approval ➤

1. CRISPR Therapeutics' stock price surged after the approval was granted to the world's first CRISPR-based gene-editing therapy. CRISPR Therapeutics and Vertex received approval for their Casgevy, a CRISPR-based treatment. This is a big win for the biotechnology industry, as it is for the first time that CRISPR will be used in humans since its conception over a decade ago.
2. This therapy is called Exa-Cel in the US. It has received the green signal from the US FDA expert panel and is likely to be approved by the US FDA by Dec 2023F.
3. Casgevy will treat blood disorders such as sickle cell anaemia and β-thalassaemia. Sickle cell anaemia causes enfeebling pain and individuals suffering from β-thalassaemia need frequent blood transfusions.
4. The US FDA will also decide on a second sickle cell treatment, a gene therapy by BlueBird Bio, by 20 Dec 2023F.

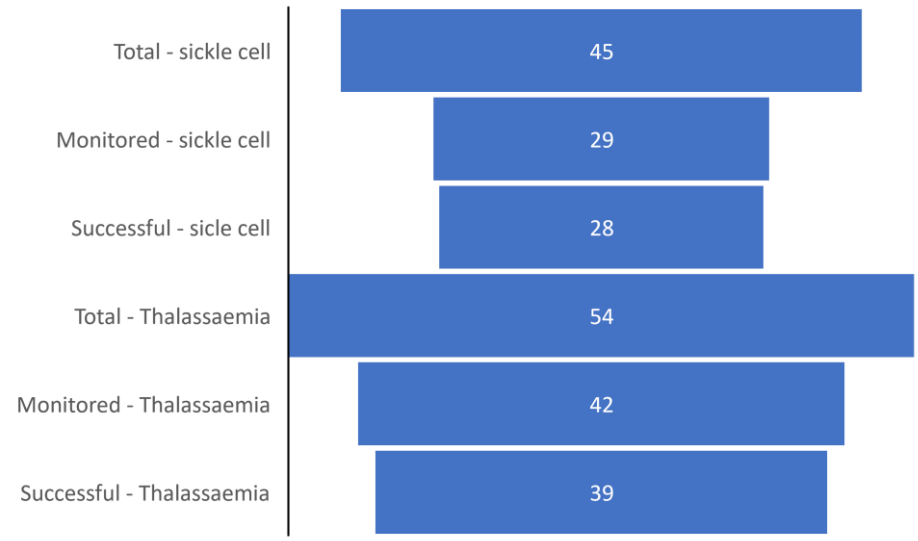
Figure 2: CRISPR Therapeutics' stock price rallies after the UK government gives its nod to use its therapy for sickle-cell disease treatment

SOURCE: INCRED RESEARCH, COMPANY REPORTS

What are the factors that led to the approval? ➤

1. The Medicines and Healthcare Products Regulatory Agency or MHRA's approval was based on the promising results from the clinical trials. The patients were administered with a single dose of the treatment intravenously.
2. In the trial for sickle-cell anaemia, 29 patients out of the 45 patients that were administered the therapy were monitored for a longer term to draw conclusions about the efficacy and safety of the therapy. As many as 28 out of 29 people were completely relieved of the debilitating pain caused by the sickle cell disease for at least a year after the treatment.
3. Clinical trials were also carried out on the individuals suffering from a severe form of β-thalassaemia. Normally, individuals afflicted with this disorder require blood transfusions at least once a month. Out of the 54 patients that received the therapy, 42 patients were monitored for a longer term to draw the conclusions from the trials. As many as 39 out of these 42 patients did not need blood transfusions for at least a year after the treatment and the requirement for blood transfusions for the remaining 3 patients reduced by over 70%.

Figure 3: Results from Casgevy clinical trials



SOURCE: INCRED RESEARCH, COMPANY REPORTS

What are the safety concerns involved with the therapy? ➤

1. Even though most patients who underwent the clinical trials had the desirable effects, there is a concern that CRISPR may accidentally cut a wrong piece of the patient's DNA. This could disrupt the gene and cause blood cancer. Vertex has assessed multiple patients' DNA from its large database to assess the likelihood of such an event. It also plans to monitor the clinical trial patients for the next 15 years.
2. Other than this, the patients who underwent clinical trials experienced a few side effects like fever, nausea, fatigue, and an increased susceptibility to infections but no major safety concerns have been observed.

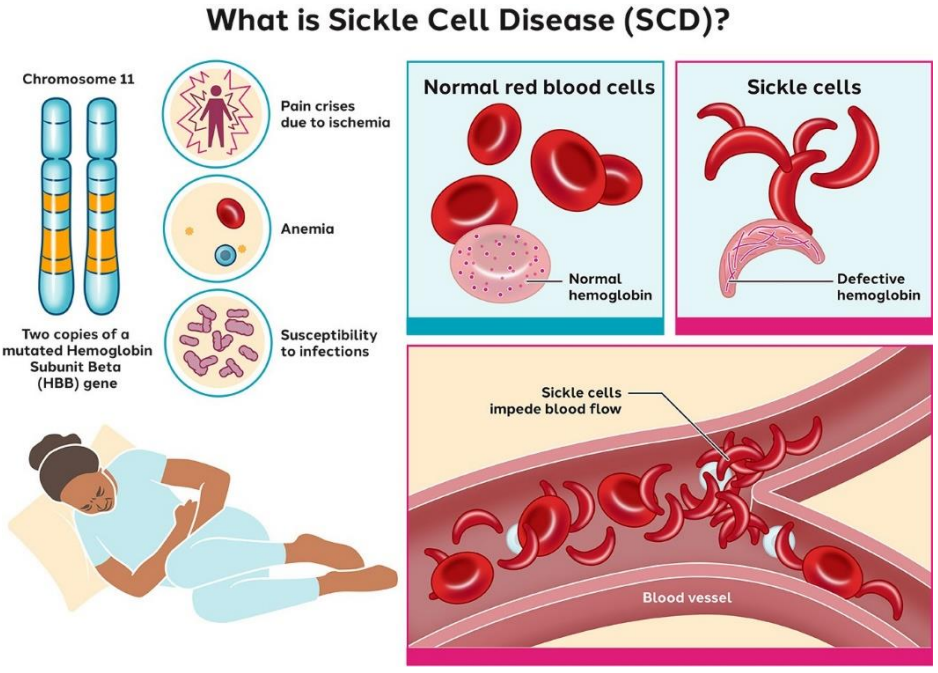
How does the drug work?

1. Sickle cell anemia is caused by gene mutation at the DNA level because of which abnormally shaped blood cells are produced.
2. The CRISPR-Cas9 therapy will connect the faulty mutation and normal shaped cells will be produced.

What is sickle cell anaemia disease?

1. Sickle cell anaemia is caused by gene mutation, which makes the blood cells abnormally shaped like a sickle or crescents. It affects millions of people globally who come from African ancestry.
2. The abnormally shaped blood cells get stuck in blood vessels and cause strokes, organ damage, and instances of debilitating pain as the muscles do not get sufficient oxygen.

Figure 4: Gene mutation causes sickle shaped blood cells, which leads to debilitating pain and other complications

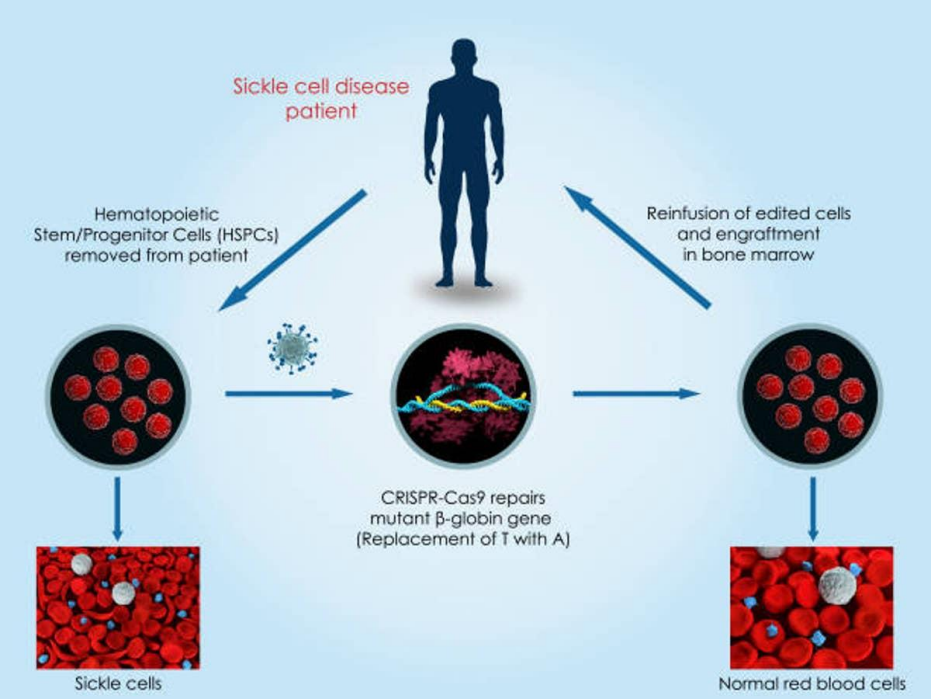


SOURCE: INCRED RESEARCH, COMPANY REPORTS

How does the therapy work?

1. Conventionally, patients can be cured of the sickle cell disease via bone marrow transplant. However, it is a complicated process because it requires finding a donor and taking drugs so that the body doesn't attack the foreign cells.
2. Recently, a few biotech companies have tried to generate novel treatments for sickle cell anaemia. As mentioned earlier, Bluebird Bio will receive the US FDA verdict regarding its gene therapy-based treatment for sickle cell soon.
3. The treatment by Vertex and CRISPR Therapeutics focuses on the CRISPR-Cas9 system. CRISPR can be used to turn certain genes on or off. We have explained the CRISPR technology in depth in our previous report. So far CRISPR has only been used for research purposes, and this will be for the first time that it will be used as a treatment for patients with genetic disease.
4. CRISPR cuts a piece of DNA in bone marrow stem cells for the treatment of sickle cell disease. This allows the block gene to make a form of haemoglobin that is usually produced by the foetus. The foetal gene results in the production of haemoglobin that is not sickle shaped.

Figure 5: Action mechanism of CRISPR sickle cell therapy



SOURCE: INCRED RESEARCH, COMPANY REPORTS

What are the market prospects for this therapy?

1. Based on the eligibility criteria, in the UK, 2,000 people and in the US, 20,000 people will be eligible for this treatment.
2. The high cost of therapy, complex manufacturing process, and onerous treatment procedure may prove to be growth restraints.

Who will receive the therapy? ➤

1. In the UK, the therapy has been approved for individuals over 12 years of age who are suffering from sickle cell disease and are experiencing recurrent debilitating pain, or beta thalassemia serious enough to need regular blood transfusions. Additionally, the clearance is restricted to the patients who cannot receive stem cell transport from a matched donor. According to CRISPR Therapeutics' estimate, 2,000 patients will be eligible for this treatment.
2. In the US, Medicaid and other healthcare providers have expressed their willingness to pay for the therapy. It is likely that children below 12 years of age and senior citizens, for whom the treatment could be risky, will not be eligible for it. Vertex estimates that 20,000 people will be eligible for it.

High price, complicated treatment procedure, and manufacturing could be growth barriers ➤

1. Sickle cell anaemia is highly prevalent in the underprivileged population. Even though Vertex and CRISPR Therapeutics have not yet disclosed the price of their therapy, based on the pricing of previously approved gene therapies, it is estimated that it could approximately cost US$2m per patient. This high pricing will reduce the accessibility of the therapy.
2. The production process is onerous because each patient's cells need to be modified in a sterile environment. Hence, this poses a challenge for Vertex and CRISPR Therapeutics as ramping up the production will be difficult.
3. There can also be a resistance at the patient level. The patients need to go through a chemotherapy process, and also be in a hospital for over a month to undergo the treatment. This will deter the patients from going for the therapy.

What does this mean for India?

1. According to the 2023-24 budget announcements, the Indian government is aiming to eliminate sickle cell anemia in the country.
2. The Council for Scientific and Industrial Research's IGIB currently has pre-clinical trials going on for its CRISPR-Cas9 therapy to treat sickle cell anaemia.

Indian government has introduced an eliminate Sickle Cell Mission and has approved pre-clinical trials ➤

1. The Government of India has targeted the elimination of sickle cell anaemia in the year 2047F, based on its 2023-24 budget announcements. 70m people will be screened for the disease under this mission, making it the largest such exercise globally.
2. CSIR's IGIB is working on its CRISPR CAS-9 therapy for sickle cell disease. The therapy is currently at the pre-clinical trials stage.
3. If successful, India will be able to provide this therapy at a more economical price. The major cost for personalized therapies is the manpower cost, which proves to be a plus point for India. As we have seen with ImmunoAct's CAR-T cell therapy, India can provide these therapies at a 90% lower cost than other nations. As the technology reaches the commercialization stage, Laurus Labs could be a potential partner, as the company has already aided ImmunoAct with its CAR-T cell therapy. The CRISPR-based sickle cell therapy and CAR-T cell therapy are like each other in a lot of ways.

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