A New Era for "BUBBLE BOY" DISEASE

Sven Kili, M.D., head of gene therapy development at GlaxoSmithKline, talks about the company's gene therapy to treat a very rare immune system disorder, which recently received EU approval.

Children born with a specific immune disorder — severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), sometimes called bubble boy disease — do not have a healthy, fully functioning immune system and as a consequence are unable to fight off everyday, common infections.

Now these children in Europe have a new option: an individualized treatment approach that uses their own gene-modified stem cells to correct the root cause of the disease.

In May, GlaxoSmithKline received European marketing approval for Strimvelis, the first ex-vivo — meaning it is prepared outside the body in a laboratory before being administered back to the patient — stem-cell gene therapy to treat patients with ADA-SCID. Strimvelis (autologous CD34+ cells transduced to express ADA) is the first corrective gene therapy for children to receive regulatory approval anywhere in the world.

GSK developed Strimvelis in collaboration with Fondazione Telethon and Ospedale San Raffaele.

"We are using state-of-the-art technology to create an individualized medicine for each ADA-SCID child, based on the child's own cells," says Sven Kili, M.D., head of gene therapy development at GlaxoSmithKline. "The ADA gene is fully humanized. The benefit of using the child's own cells as a starting material for the medicine is that it provides the child with a cell match. Strimvelis is administered only once and doesn't rely on a third-party donor, so there's no risk of immune incompatibility causing rejection — graft versus host disease, which is a fairly common side effect of a bone marrow transplant treatment."

The approval was based on data collected from 18 children treated with Strimvelis. A 100% survival rate at three years post-treatment with Strimvelis was seen.

"Once a child is accepted for treatment, about one month before treatment, bone marrow stem cells will be collected from the child as a precaution in case of any unforeseen problems that could occur during the treatment and follow-up phase," Dr. Kili says. "Five days before treatment, the child is admitted to San Raffaele Hospital in Milan, Italy."

He says a new collection of stem cells is taken from the patient's bone marrow and the stem cells are taken to the cell processing center where a correct copy of the ADA gene is inserted using a viral vector. The cells are then suspended in a sterile saline solution. Meanwhile three and two days before treatment, the child receives a pre-treatment low dose of chemotherapy with busulfan to improve engraftment of the gene-corrected stem cells in the child's bone marrow.

Dr. Sven Kili

"After treatment, the child remains in isolation for about one and a half months to protect him or her against infection while his or her immune system begins to build back up," Dr. Kili says. "Once well enough, the patient is discharged from the hospital but remains in Milan for up to two months as an outpatient and has frequent follow-up visits in the clinic with the San Raffaele team."

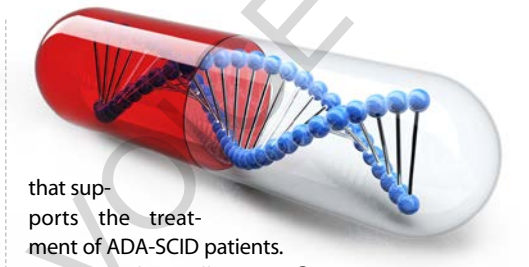
Dr. Kili says overall, the safety findings in the pivotal study were in line with those expected in children with ADA-SCID who have undergone treatment with low-dose chemotherapy and who are undergoing immune recovery. Of the 39 serious adverse events reported, 62% were infections, with the most common being device-related infections, for example from the central venous catheter (CVC) used during the treatment.

"As this branch of medicine is relatively new, we will monitor 50 children for 15 years after treatment via a Strimvelis product registry," he says.

As Strimvelis was the first marketing authorization application submitted anywhere in the world for an autologous, ex vivo, stem cell gene therapy, it presented an interesting challenge for both regulators and GSK.

"Despite many sections of the submission being unprecedented, the positive opinion was received within 11 months from submission, which was 10 months faster than the average time required for advanced therapies approved within the EU to date," Dr. Kili says.

He says the company's next goal is to seek marketing approval of Strimvelis outside of the EU. For the United States, the timing is dependent on a number of factors, including amassing the data required by the FDA and establishing a supply chain that supports the treatment of ADA-SCID patients.



Strimvelis will cost €594,000 ($665,000). Because Strimvelis is administered via a single infusion, pricing it using traditional means presents a challenge, Dr. Kili says.

"We have aimed to price Strimvelis in such a way as to create value for the patients receiving the drug," he says. "Our priority in pricing Strimvelis has been to make the one-time treatment cost for the medicine affordable and sustainable for healthcare systems in Europe through established payer mechanisms, to ensure that patients with this ultra-rare disease can access the treatment."

Dr. Kili says the price of €594,000 is significantly lower than long-term enzyme replacement therapy alone, which can cost from €3 million to €4.2 million over a 10-year period, which could be the only other viable option for these patients.

"Given the extreme rarity of ADA-SCID, payers have indicated to us that Strimvelis is likely to be funded on a case-by-case basis without the need for a potentially complicated pricing arrangement," Dr. Kili says. "This is due to the extremely low patient numbers."

GSK is offering payers a risk-share agreement. Dr. Kili says there are certain limited conditions primarily linked to efficacy under which GSK may agree to refund certain costs for Strimvelis for a limited period of time in Italy.

"Within the Italian healthcare system, risk-sharing agreements routinely form part of reimbursement agreements for approved specialty medicines so this is no different for Strimvelis, which is also a specialty medicine that has been approved for reimbursement by AIFA," he says.

He noted, however, that GSK will not recoup its investment in the development of Strimvelis, but sees this as a way to gain experience in developing and commercializing additional therapies. The gene therapy platform is currently being used for two other rare disease development programs: Metachromatic Leukodystrophy, which impacts one in 40,000 to 160,000 people worldwide, and Wiskott-Aldrich syndrome, which occurs in one and 10 cases per million males worldwide. Both programs are currently in pivotal clinical trials. PV

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