A devastating skin condition could soon get its first medication, as the frontiers of gene therapy expand

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By Andrew Joseph

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Aaron Owens, who has a painful genetic skin blistering condition called epidermolysis bullosa, is seen at Foothill Park in Milpitas, Calif. *Constanza Hevia for STAT*

Wounds have been a constant fact of Aaron Owens' life. His skin is so fragile that friction that would be trivial to others — rolling over in bed, weight shifting against the seat as the car turns — could scrape off his tissue. He didn't like being in public sometimes because people would stare at the boy covered in bandages.

When he enrolled in a clinical trial a few years ago, the teenager didn't know which wound on his body was treated with the experimental medication, and which was dosed with a placebo. This trial wasn't like so many others where some enrollees get the drug in question and others get a sham dose. Rather, Owens received both, but on different wounds.

Soon, though, Owens noticed that portions of skin in some areas started to heal, and heal faster and stronger than he had experienced in his lifetime contending with these wounds. It was a clue that, maybe, the medication was working.

Owens, an 18-year-old high school student, has epidermolysis bullosa, or EB, a genetic condition that causes the skin to be so exquisitely delicate that it's likened to a butterfly wing. In severe cases, even slight touches lead to blisters that can form persistent wounds. The accumulated scarring can fuse fingers and toes together. People live in constant pain.

The therapy that Owens received, called B-VEC and developed by Krystal Biotech, could soon be available to many more patients. The Food and Drug Administration will decide by next month whether to approve it, and analysts and experts say they expect the treatment, which succeeded in the clinical trials that Owens participated in, to receive the green light.

For Owens, who has continued to receive B-VEC through an extension of the trial, the healing has meant he can sleep knowing he won't wake up with a reopened wound. It's easier to walk longer distances now because blisters aren't reforming on his legs. He still wears bandages as a protective measure, and still has some wounds that he has to deal with, but when he's out in public, people no longer just see someone in pain.

"I used to have wounds on my back the size of a piece of paper," Owens said. "Like 70% of my back was completely raw. Now it's 100% healed. I can sleep on my back. I don't have to worry about so much pain and blood in the shower. It's more than life-changing. It's easier to do everything."

The potential approval of B-VEC, also called Vyjuvek, is notable not just because it would be the first medicine that targets the root genetic cause of EB, which is normally addressed just with wound care, infection prevention, and pain management. B-VEC is a gene therapy, which uses a harmless virus, called a vector, to ferry a corrected version of the gene that's mutated in patients into particular cells.

B-VEC — which is dripped onto wounds from a syringe — would be the first topical gene therapy and the first for a skin condition, demonstrating the potential of the approach for similar genetic diseases. It would also be the first gene therapy that would be repeatedly given to patients. Gene therapy is often described as a "one-and-done" treatment: you get the healthy gene into cells and they are good to go. But

some cells, like skin cells, don't stick around for all that long, so need a regular replenishment of the healthy gene.

"It's really a remarkable thing, correcting the gene just through this procedure," said Peter Marinkovich, a Stanford dermatologist and one of the investigators in B-VEC's trials.

EB is a group of diseases, differentiated based on the root mutations and in which layer of skin blisters form. B-VEC is specifically for people with dystrophic EB, who have faulty versions of the gene that encodes the protein type VII collagen, or C7. The protein acts like an anchor that binds the layers of tissue together. With a mutated version, the layers are like separate plies of tissue paper. They can't withstand much before tearing.

B-VEC works by delivering healthy copies of the gene, equipping those cells to churn out normal C7 — to make "what's otherwise not there," said Amy Paller, a dermatologist at Northwestern University, who has consulted for Krystal and other companies working on EB therapies. With the corrected protein, the cells can help the skin start to heal, and may make it less susceptible to blistering or opening up going forward.

The FDA is set to make its decision by May 19. The decision date was scheduled for February, but was pushed back after the agency said it needed more time to review manufacturing information the company submitted. Analysts still anticipate approval.

Krystal estimates 3,000 people in the United States have dystrophic EB. This would be the Pittsburgh-based company's first approved product.

A Phase 3 trial of B-VEC, which included 31 patients 1 year and older, showed that 67% of wounds treated weekly with the medicine were healed completely at six months, compared to just 22% of those dosed with placebo. Wounds treated with B-VEC also seemed to stay healed for longer, and patients reported reduced pain as well, according to the trial data, which were published in the New England Journal of Medicine.

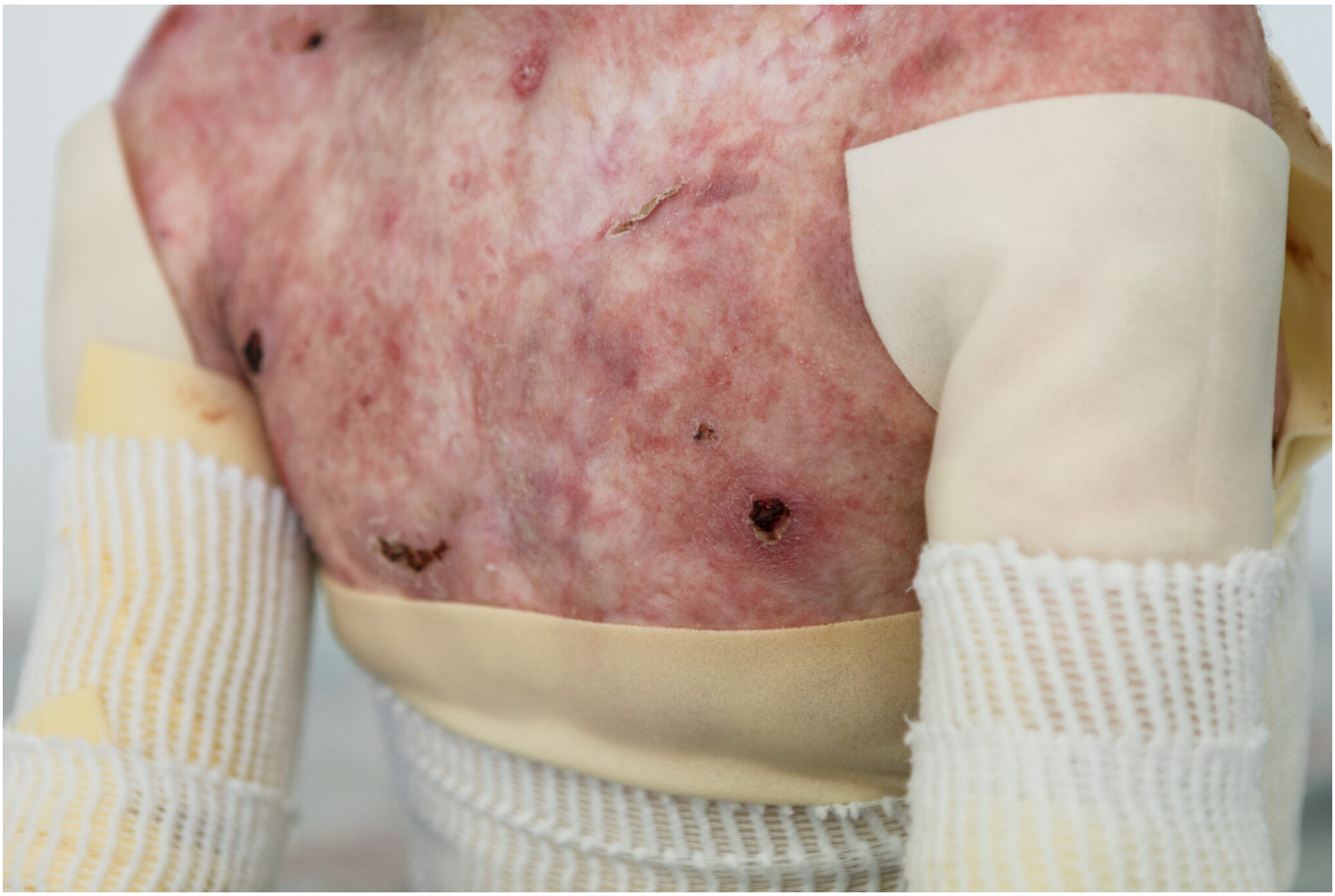
"There's nothing that reverses the cause of disease and blistering," said Aimee Payne, a dermatologist at the University of Pennsylvania, who has consulted for drug companies but not Krystal. "Wound care prevents these wounds from bleeding, sticking to your clothing, causing immense pain, but it's just symptom management. This has the potential for complete healing of skin."

B-VEC's design distinguishes it from gene therapies already on the market. While other products typically rely on an adeno-associated virus as their vector of choice, an AAV can only haul comparatively small genes into cells. The C7 gene is a much bigger payload, so scientists needed something with more towing power.

Enter herpes simplex virus type 1, which has a carrying capacity some 30 times greater than an AAV. You may be more familiar with it as the cause of cold sores, but tweaks made to the virus prevent it from replicating or causing disease after delivering the gene to skin cells. The success of B-VEC in trials

highlights how different vectors could broaden the conditions gene therapies can successfully treat, and which types of tissues they can reach.

"Delivery is such a tough problem that there's not going to be one magic bullet" — one vector that will work for all cells and diseases, said David Schaffer, a bioengineer at the University of California, Berkeley, who works with companies developing different vectors.



Owens' EB causes his skin to be so exquisitely delicate that it's likened to a butterfly wing. *Constanza Hevia for STAT*

One burgeoning issue with gene therapies is their typically seven-figure price tags, which have stoked debate about how society can afford such treatments as more head to the market. Companies have justified the prices by arguing these are one-time treatments with benefits that last for years.

In an interview with STAT, Krystal CEO Krish Krishnan wouldn't discuss B-VEC's potential price ahead of the FDA's decision. But he said looking at approved gene therapies may be the wrong model. Because B-VEC's going to be repeatedly given, in effect it's more like a different type of medicine called an enzyme replacement therapy. These involve giving patients versions of the enzymes, or proteins, that they can't make. Krishnan said Krystal has been making that comparison in its conversations with insurers.

"A lot of drugs have been previously approved in those areas," Krishnan said. "If you position us not as a one-and-done gene therapy and much more like enzyme replacement or protein replacement, that conversation gets a lot easier with the payer."

In filings, the company has stated that, "While not disease-modifying, current treatment is estimated to cost between $200,000 and $400,000 annually per patient in the United States." Analysts have forecasted the potential price as in the $400,000 per year range.

While analysts expect B-VEC's approval, there are several open questions about the details. There are recessive and dominant forms of dystrophic EB, based on how many copies of the mutated gene a patient has, and it's not clear if the approval will be for all patients or for those with the recessive form, who made up the vast majority of trial participants.

The FDA will also likely weigh in on whether the therapy has to be applied in a clinic — as in the clinical trials — or if it can be done at home by a visiting nurse, which has been allowed during the extension of the clinical studies. Advocates say that at-home treatment could make it simpler and smoother to get the treatment to more patients.

Such a therapy would typically be applied when people have their wounds cleaned and bandages changed, a process that can take several hours, cause immense pain, and is much easier done in the comfort and with the routine of home — not in a clinic, said Brett Kopelan, the executive director of the patient advocacy group Debra and whose 15-year-old daughter has EB.

"I have to torture my child three days a week in order to keep her safe," Kopelan said about doing her regular bandage changes. Still, he said, if the approval limits the therapy to clinics, many patients will still be motivated given that there are no other targeted treatments. "People will do whatever they need to do to get this."

In addition to tracking how durable the wound healing is, experts will be watching what happens as patients continue to receive doses in the long run. One concern with repeated delivery of a gene therapy is that the immune system could start to recognize the vector and pounce, neutralizing the therapy. While there were clues in the trial that the patients' immune systems were starting to detect the virus, there was no sign of a response that hurt effectiveness. It's possible that the herpes virus is a stealthier vector than other viruses, or that dropping it onto the skin doesn't elicit as powerful of an immune response as injecting a gene therapy would.

There are hopes, too, that starting treatment with B-VEC early could have long-term benefits beyond healing wounds. Perhaps there will be less scarring, and patients' fingers and toes won't fuse. Patients with EB also develop certain skin cancers at high rates; squamous-cell cancers are the leading cause of death in adults with dystrophic EB. Doctors will be tracking to see if therapies like B-VEC, by restoring C7 expression, can stave off some of those cases.

B-VEC is not the only EB treatment that could reach patients soon. Companies including Abeona Therapeutics and Castle Creek Biosciences are also developing therapies, using different approaches, that are making progress toward regulatory approval.

For Kopelan, the possibility of having multiple therapies underscores how much progress has been made in just a few years. He can now envision a potential future of kids born with EB who have normal life spans, less defined by pain and disability.

“When my kid was born, 15 years ago, there were basically no clinical trials,” he said. “There was academic research, but nothing translational. Here we are now with such a plethora of different avenues being explored that in the long run will allow us to have very complementary approaches we can use together.”

“Early on, I didn’t necessarily think I was working for my child’s life,” he said about his advocacy. “But now I am. It’s been a huge sea change.”

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