

## The biggest questions facing gene therapy, the XLMTM community, and Astellas after fourth patient death

by Jason Mast on September 17th, 2021



After three [patients](#) died last year in an Astellas gene therapy trial, the company halted the study and began figuring out how to safely get the program back on track. They would, executives eventually explained, cut the dose by more than half and institute a battery of other measures to try to prevent the same thing from happening again.

Then tragically, Astellas [announced](#) this week that the first patient to receive the new regimen had died, just weeks after administration.

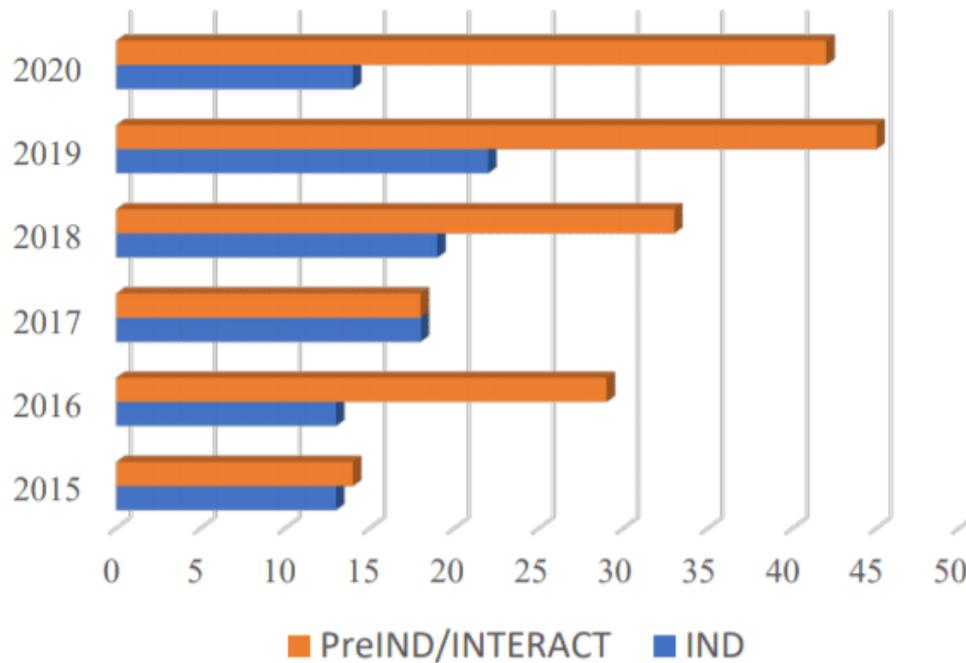
The trial is now back on hold and the future of the therapy, a potential one-time treatment for the fatal muscle-weakening disease X-linked myotubular myopathy, or XLMTM, is in limbo. The death raises new questions about what happened to the four boys and delivers another devastating blow to families who have pinned their hopes on the experimental treatment, known as AT132.

It also raises new questions about the future of gene therapy and particularly about the nanometer-

sized engine that has allowed the field to resurrect itself over the last two decades: [adeno-associated viruses](#), or AAV.

Researchers turned to these harmless viruses after an 18-year-old boy, Jesse Gelsinger, died in a gene therapy trial. Far safer than the previous methods used to shuttle genes into patients, these viruses eventually led to two FDA-approved gene therapies and hundreds of clinical trials that promised one-time treatments for diseases ranging from hemophilia to muscular dystrophy and Parkinson's.

**Growth in AAV trials over the last half-decade (Source: FDA)**



[Click on the image to see the full-sized version](#)

Now, four deaths — the first in three decades of AAV trials to appear as a direct result — point to the viruses' limits. We spoke with gene therapy researchers and a patient leader about what may have happened, what the future holds for this program and how it may affect current and future efforts to develop AAV-based gene therapies for other diseases.

They preached caution, noting the thousands of patients who have safely received AAV and the particular difficulties posed by XLMTM, a condition with an unusually devastating combination of symptoms. But they also noted that much remains unknown, in part because Astellas has been slow to share details since the first death in May 2020.



Federico Mingozzi

“The lack of visibility on what happened is a little bit impairing,” said Federico Mingozzi, CSO of Spark Therapeutics, the first company to develop an approved AAV gene therapy. “I’m sure they are trying to figure things out but everyone else is sort of blinded.”

More details on the trial, the four patients and what studies Astellas has conducted internally could be crucial for all gene therapy researchers, as well as patients and families affected by disorders that might be treated with AAV, said Lindsey George, a gene therapy expert at the Children’s Hospital of Philadelphia.



Lindsey George

“Additional information on these tragic events is critical,” she said in an email.

Astellas declined interview requests but answered emailed questions. A spokesperson demurred on when more details will be available.

“The company’s current focus is to investigate and review all findings with its independent Data Monitoring Committee, Liver Advisory Panel and the ASPIRO site investigators, and will determine the

best venue to provide additional information at the appropriate time,” he said.

## **How could gene therapy have led to these patients’ deaths?**

The short answer is no one knows, although there are theories.

AAV is harmless in low quantities, but as researchers have infused higher amounts, they’ve run into safety issues. Many of those issues occurred in the liver, likely because the organ acts as the body’s filters and AAVs travel directly there after infusion.

A large portion of XLMTM patients have a history of liver issues, putting them at higher risk for hepatic side effects. And because treating the disease requires hitting muscle cells throughout the entire body, Astellas initially used among the highest — if not *the* highest — doses of AAV ever given to humans.

(There is no standard way to measure AAV dose, making comparisons hard, but Astellas’ reported figure of 350 trillion viruses per kilogram is the highest any company has put out.)

That meant researchers had to conduct a balancing act, needing to use a high dose to have an impact on patients who were particularly susceptible to the side effects of high dose therapy.



Terry Flotte

“These patients, they’re just so fragile,” said Terry Flotte, dean of the UMass Chan Medical School and editor of the journal *Human Gene Therapy*. “It just seems like it’s a condition where it’s very hard to thread the needle between safety and efficacy.”

All four boys who passed away cleared basic liver function tests directly prior to administration but had a history of liver disease. The first three boys died of liver failure. Doctors haven’t determined a cause of death for the boy who passed away this month, Astellas said, but he showed signs of liver dysfunction directly after treatment.

Because the newest patient received less than half the virus the first three patients received, it’s tempting to look for alternative explanations. Alison Rocket-Frase, director of the [Joshua Frase Foundation](#), which funded early research that led to AT132, said families have been asking her how a boy could still die on such a low dose.

But even the reduced dose still ranked among the highest ever used in clinical trials, said Nicole Paulk, who runs a gene therapy lab at UCSF. And it's above the level where researchers begin to see more severe side effects across other studies.



Nicole Paulk

“It is still among the top 10 doses of AAV ever given,” she said.

Still, “AAV-induced liver injury” isn’t a sufficient enough answer. In other trials, liver side effects appeared to be a byproduct of an immune response, but Astellas’ investigators say that wasn’t the case here.

So what’s causing it? What’s the exact mechanism? Are there measures, such as steroids or other drugs, that might mitigate it? And are there biological tests doctors might run to decide who can safely receive the therapy?

### **What’s the future of the Astellas therapy, AT132?**

Frase and Paulk said they have been fielding questions from families concerned that Astellas will simply kill the program, a terrifying prospect for those who saw the therapy as their best hope.

“We must learn from this and not allow it to amount to nothing,” Frase said in an email. “We owe it to those families, we owe it to those kids.”

Moving on could indeed be the easiest solution for Astellas, a \$30 billion company that isn’t dependent on the revenue they might get from AT132. But a spokesperson said the company “remained committed” to the program and XLMTM families, and there’s agreement among researchers that they should try to find a way forward.

The reason is simple: The therapy does appear to work.

XLMTM is a devastating disease. Most patients die by 18 months and those who survive can rarely sit or breathe on their own. There are no other therapies. Audentes' early data showed that the first patients given the treatment could soon breathe and sit up on their own; some could even walk.

“Clearly the therapy has the potential to really reverse the disease, in a way that’s amazing and really life-changing,” said Mingozi. “And this is a disease that does not have any other treatments.”

Because of how rapid the disease is, many of the patients would have likely passed away had they not received therapy, Paulk said. One way of looking at the trial is it enrolled 24 children and 20 of them are still alive today, when they likely wouldn’t have been otherwise.

That effectiveness adds another layer of tragedy to the deaths. When it purchased the program in its 2019 buyout of Audentes Therapeutics, Astellas thought it would file for approval in 2020. That timeline was then [pushed](#) back to 2022. Now it’s entirely up in the air.

Some patients who would have received it won’t, especially given that the therapy, should it be approved, will likely come with strict age restrictions to prevent safety issues from recurring.

“Some patients will age out,” Paulk said. “Or they will die waiting.”

There are several ways Astellas could move forward, all of which come with drawbacks. You could, of course, lower the dose even more, Mingozi said. But then you run the risk of giving patients an insufficient amount. And you only get one shot — gene therapies can’t be dosed twice.

“You don’t know if a lower dose is going to be safe and you don’t know if it’s going to be efficacious,” he said. “So what do you do?”

Astellas could exclude all XLMTM patients who have a history of liver failure, but that would exclude many of the boys who might benefit and who face a death sentence without treatment. They could lower the age — the first three patients were some of the oldest and heaviest in the trial, and thus received some of the highest doses — but that runs into the same issue.



Alison Rockett-Frase

In a best-case scenario, further research will show that supportive measures can blunt the liver effects and allow patients to safely receive the therapy; in other trials, generic steroids are used to reduce the risk that the body will mount a dangerous immune response to the virus.

The side effects in those studies, though, were milder.

“It’s hard to imagine that would have made the difference here,” Flotte said.

There is also the option of moving on without giving up. The situation has similarities to when three young cancer patients died in a trial for Juno Therapeutics’ experimental CAR-T therapy, Paulk said. In that case, Juno decided to abandon the program and switch over to a second-generation candidate, ultimately approved this year, that was far safer.

Researchers have been [working](#) on AAVs that traffic more directly to muscle cells. And it’s likely, Paulk said, that Astellas has been working on another candidate.

“It might be that there’s something about the way that Audentes made this [AAV] prep that although it is not bad, it just doesn’t work for this particular indication,” Paulk said, “and we need to figure out what that is and then revamp and try again.”

Such a move, though, would delay approval even longer. And Astellas has not indicated they would go that route.

“AT132 is the current asset in development for XLMTM,” a spokesperson said in response to a question on successor programs. “Astellas Gene Therapies remains committed to the development of AT132 and the XLMTM patient community.”

### **What does this mean for gene therapy as a whole?**

Once again, the short answer is no one knows, in part because it’s still not clear exactly what happened in these patients.

“How the events in the XLMTM clinical trial will impact other AAV work is highly dependent on understanding why the events happened and release of additional information,” George said.

Mostly, though, experts preached caution. Thousands of patients across multiple diseases have now received AAV with minimal side effects. George suggested it’s possible that the doses Astellas used — between 140 and 350 trillion viruses per kilogram — represent the safety ceiling for AAV.

Other companies have gone over that limit, though, particularly for Duchenne muscular dystrophy therapies. And while patients in those studies have seen serious side effects, none have been deadly.

“I think it’s too easy to talk about high vector dose,” Mingoizzi said.

The combination of high dose and liver susceptibility may be somewhat unique to XLMTM. Paulk said there’s no reason for any company to halt plans to start trials for new gene therapies, which have already undergone numerous animal studies. That’s particularly true if you’re injecting into the eye or nervous system, which is safer but only works for a limited set of disorders.

But if a company is developing a new therapy that has to be delivered systemically, they should be re-examining their data just in case, she said. Perhaps, they can go in with a slightly lower dose. Perhaps they could do extra monitoring or conduct liver tests on patients.

With little information, though, it’s hard to justify making substantive changes, she said. And some answers are never going to come: In a trial of 24 patients, there’s only so many conclusions one can draw.

“So the real answer is we need more data,” Paulk said. “But the real answer is also you’re not going to get it.”

### **What does Astellas do now?**

Still, there are specific details researchers want that Astellas knows but has declined to release, including seemingly small but important aspects, like AT132’s manufacturing specs.

Doses for AAV therapies are traditionally measured by the number of viruses containing the therapeutic gene. But that’s not the only thing in the vials patients will receive.

All AAV therapies contain viruses that, because of an imperfect manufacturing process, form around a fragment of DNA or around nothing at all. Depending on the process, so-called empty capsids can comprise between less than 10% to up to 90% of the AAVs in a treatment.

The FDA has [raised concerns](#) that they can increase the total amount of viral protein patients are exposed to. And Astellas has repeatedly declined to disclose how many empty capsids there are, frustrating outside researchers who are trying to make sense of what happened and whether it has implications for other therapies.

“Everybody, everybody needs to see this,” Paulk said. “If we could see some of this stuff, we might be able to knock things off the list of probable causes right away.”

If they find out, the preparation is 99% full capsids, for example, researchers can rule out empties as a concern.

The Astellas spokesperson cited trade secrets for its refusal, saying the company “will not disclose

certain aspects of its manufacturing process as they are proprietary.” But researchers said they can release empty capsid counts without revealing any confidential information about their manufacturing process, as many companies already do.

There are other high-level details about the manufacturing and purification process experts said Astellas could disclose, along with details on the progression of each patient after administration.

Astellas didn’t provide a timeline on getting the trial running but said they will continue to collect clinical information and incorporate it into the investigation, sharing the findings with the study’s academic investigators and data-monitoring committee, along with a group of liver experts it convened.

Some in the XLMTM community, though, would like Astellas to be more public.

“I’d like to see Astellas put all the data on the table, let the gene therapy scientific community weigh in,” Frase, the patient leader, said, “for the good of this community and for the good of gene therapy’s future in general.”

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