

**Jaguar Gene Therapy**  
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To: Members of the Phelan-McDermid syndrome community

From: Jaguar Gene Therapy

### **An Important Update on Jaguar's Investigational Gene Therapy for Phelan-McDermid Syndrome**

Jaguar Gene Therapy is pleased to share that the U.S. Food and Drug Administration (FDA) has cleared our Investigational New Drug (IND) Application for JAG201, a gene therapy for Phelan-McDermid syndrome (PMS) and a genetic form of autism spectrum disorder (ASD). JAG201 aims to deliver appropriate *SHANK3* genetic function via the AAV9 vector to treat the root cause of the disease and improve cognitive, functional and behavioral abnormalities.

We are now focused on planning for a Phase I clinical trial in adults to begin in the United States in the second half of the year. While we are still determining many details, we know this trial will be small and include very specific inclusion/exclusion criteria. We are setting the trial up this way to meet the guidance set forth by the FDA for Phase 1 clinical trials and to ensure we can appropriately evaluate the safety, tolerance and dosage of JAG201. We will continue to keep you updated as we finalize our plans.

We want to extend our gratitude to CureSHANK and the Phelan-McDermid Syndrome Foundation for their partnership. They have provided us with invaluable insights that helped get us to this point. We look forward to continuing to work with them as JAG201 progresses.

We know you likely have questions about next steps concerning JAG201. We have created the following FAQ to do our best to answer the questions that may be at the top of your mind. Please also feel free to reach out directly to us at [patientadvocacy@jaguargenetherapy.com](mailto:patientadvocacy@jaguargenetherapy.com). You can also share your feedback with CureSHANK or the Phelan-McDermid Syndrome Foundation, and they will relay your thoughts to us. We encourage you to visit our [website](#) and follow us on [LinkedIn](#) for the latest information and updates.

Sincerely,  
The Jaguar Gene Therapy Team



## **Frequently Asked Questions**

### **Q: What is gene therapy?**

A: Gene therapy involves delivery of healthy copies of genes into the body with the aim of restoring the function of target cells. Jaguar's gene therapy programs use an adeno-associated viral (AAV) vector-based delivery, meaning AAV functions as a type of vehicle (or vector) to deliver functioning genes into the target cells. AAV has been shown to be an effective vector because it is nonpathogenic (meaning it is not capable of causing illness) but very effective at gaining access to the target cells. To be used as a vector for gene delivery, the viral DNA of AAV is removed and replaced with a gene that is intended to have a therapeutic benefit for a patient suffering from a genetic disease. After the AAV vector delivers its genetic payload to the nucleus of a cell, the gene is then transcribed and translated to produce a functional protein. The gene will persist in the nucleus as an episome, separately from the chromosomes. The patient's body then breaks down and processes the AAV vector.

You can view a brief animated video created by Jaguar for younger audiences that explains gene therapy [here](#).

### **Q: Does gene therapy alter a person's DNA?**

A: This depends on the type of gene therapy utilized. We have specifically selected AAV as a vector in part due to its low likelihood for altering the patient DNA. While AAV vectors primarily deliver a gene to the nucleus which then exists separately from the patient DNA, there have been some cases where the gene inserts into (combines with) patient DNA in human clinical trials. To date, there is no evidence that this has led to development of any disease, including cancer.

### **Q: Are there potential risks associated with AAV vectors?**

A: Vector-associated safety risks have been reported in both animals and human clinical studies of investigational AAV gene therapies, as well as in post-marketing experience with approved gene therapies. Sometimes the immune system overreacts to the vector leading to complications affecting the liver, the brain or your body's ability to form clots. To decrease the likelihood of immune system-linked risks, clinical trials may prescreen for antibodies to AAV vectors and require medicines to decrease the patient's immune response.

### **Q: How does JAG201 work?**

A: *SHANK3* haploinsufficiency leads to synaptic dysfunction, disrupting communication between nerve cells. It causes a reduction of several key neuron receptors and signaling proteins at excitatory synapses, resulting in impaired synapse formation between neurons. Adequate synapse function is essential for neuron-to-neuron communication, which is the basis for learning and cognitive function. JAG201 delivers a functional *SHANK3* minigene\* via an adeno-associated virus serotype 9 (AAV9) vector to target neurons in the central nervous system. The therapy is designed to deliver proper *SHANK3* levels and to durably restore the synaptic function required for learning and memory, which underlie appropriate neurodevelopment and maintenance of cognitive, communicative, social and motor skills.

\*A minigene is a shortened form of the gene that retains the key functional components of the genetic sequence. The *SHANK3* minigene was created by removal of unessential parts of the *SHANK3* gene in order to allow the DNA to fit within the AAV vector.

### **Q: How is JAG201 administered?**

A: JAG201 is administered via a one-time unilateral intracerebroventricular (ICV) injection, that allows delivery of the AAV vector to the entire brain and spinal cord. This involves an injection directly into a cerebral lateral ventricle of the brain.

**Q: What studies have been done to date with JAG201?**

A: Preclinical (animal models) studies are an important and required way new potential treatments are tested before human clinical trials. Promising preclinical data in rodent and non-human primate models of *SHANK3* insufficiency have been generated. Jaguar plans to publish some of these data in the coming months ahead of clinical trial initiation.

**Q: What exactly will JAG201 correct or improve in an individual with PMS?**

A: JAG201 is intended to treat the root cause of the disease and improve cognitive, functional and behavioral abnormalities observed in PMS. The therapy is designed to deliver proper *SHANK3* levels and to durably restore the synaptic function required for learning and memory, which underlie appropriate neurodevelopment and maintenance of cognitive, communicative, social, and motor skills.

**Q: Does JAG201 have the potential to be a cure for PMS?**

A: Our goal with JAG201 is to treat the root cause of PMS. Gene therapy could offer the opportunity to have a lasting impact on the disease including, potentially the associated behavioral, developmental, and cognitive abnormalities observed in individuals with disorders resulting from *SHANK3* mutations or deletions.

**Q: What are the inclusion and exclusion criteria for the trial? Why?**

A: We are still finalizing our criteria for inclusion and exclusion. Our first clinical trial for JAG201 will be a small study in adults and include very specific inclusion and exclusion criteria to meet the guidance set forth by the FDA for Phase 1 clinical trials and to ensure we can appropriately evaluate the safety, tolerance and dosage of JAG201.

**Q: Will you be studying JAG201 in pediatrics in addition to adults? If so, when?**

A: We are focused on following the clearance granted by the FDA, which allows us to study JAG201 in adults to evaluate safety, tolerability and dosage. Our goal is to bring a safe and effective gene therapy treatment to individuals living with Phelan-McDermid syndrome, and we aim for that to include pediatric patients. We will continue to provide updates as the JAG201 program evolves.

**Q: How many adult participants will you enroll in this first trial? Why?**

A: Jaguar is actively working to finalize the proposed protocol for this trial. The first clinical trial for JAG201 is designed to evaluate the safety, tolerability and dosing of the JAG201 treatment. As a safety study and dosing trial designed to inform the future development of JAG201, we are aiming to enroll approximately 3 adult participants in the 2024-2025 timeframe. Depending on the outcomes and learnings from this first trial, we would aim to expand the trial to additional patients in late 2025-2026.

As this is a first-in-human trial, we will monitor safety outcomes in each trial participant closely and anticipate that there may be communications with the FDA after dosing of each participant. These ongoing discussions with the FDA could inform or determine potential changes to study design including enrollment criteria as the trial progresses.

**Q: Where are the clinical trial sites?**

A: We have not yet finalized clinical trial site locations. Our aim is to provide 2-3 locations in different areas of the U.S.

**Q: Is travel reimbursement available for clinical trial participants?**

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A: Participants that enroll in our clinical trial will be provided reimbursement for travel associated with participation in the clinical study.

**Q: What is the screening process for trial enrollment? How much time is required?**

A: We are still determining these details. Inclusion and exclusion criteria will be posted on [clinicaltrials.gov](https://clinicaltrials.gov) and communicated by Jaguar once finalized and approved by the FDA. Interested families will be able to reach out to trial sites directly to express interest and initiate screening for enrollment.

**Q: What is the time commitment overall for participating in the clinical trial?**

A: Details around study visits involved in the clinical trial are still being finalized. However, the evaluation phase of the study will involve multiple visits to the clinical trial site over two years, followed by an additional three years of observation in an open label extension study.

**Q: When in the second half of 2024 do you expect to dose the first patient?**

A: We are working closely with potential clinical trial sites to be in a position to dose our first adult patient in Q4 of 2024. Depending on the outcomes and learnings from this first trial, we would aim to expand the trial to additional patients in late 2025-2026. We anticipate further FDA feedback in Q2 of 2025, at which point we may be able to share more details on criteria for the potential larger clinical trial.

**Q: If my loved one participates in a clinical trial for JAG201, will they be excluded from future clinical trials?**

A: Unfortunately, we do not know the answer to this. It would depend on the goals of future clinical trials and the associated investigational therapies as well as applicable regulatory guidance. We can tell you that AAV9 exposure may lead to development of immune system recognition of the AAV vector that could make future treatment with AAV9 ineffective.

**Q: What is a Phase 1 clinical trial?**

A: In a Phase I clinical trial, a treatment is tested in a small group of people for the first time. The purpose is to study the treatment to learn about safety and identify side effects. To learn more about clinical trials, you can visit <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research>.

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