

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's 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 dysfunction at the synapses, or interaction points between neurons, disrupting communication between nerve cells. It causes a reduction of several key neuron receptors and signaling proteins, 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 will be administered via intracerebroventricular (ICV) injection. ICV administration is an injection directly into the brain using a catheter, or tubing, into a space known as the lateral ventricle which contains cerebrospinal fluid (CSF).

Humans have one ventricle in each hemisphere of the brain, and JAG201 will be injected into one ventricle. A neurosurgeon, who is experienced at performing this type of surgery, will perform the procedure in an operating room (OR) and will know how to guide the catheter into the right space by looking at pictures taken of the participant's brain using magnetic resonance imaging (MRI) before the procedure. This method was selected to allow delivery of JAG201 directly to the target cells in the brain and central nervous system and is supported by the preclinical studies conducted with JAG201 to evaluate its benefit and safety profile in animals.

Q: How do you get the AAV to go to the desired location (i.e., to the cells lacking in SHANK3)? Does it go to the entire brain?

A: JAG201 will be administered via intracerebroventricular (ICV) injection. ICV administration is an injection directly into the brain using a catheter, or tubing, into a space known as the lateral ventricle which contains cerebrospinal fluid (CSF). Humans have one ventricle in each hemisphere of the brain, and JAG201 will be injected into one ventricle. This method was selected to allow delivery of JAG201 directly to the target cells in the brain and central nervous system and is supported by the preclinical studies conducted with JAG201 to evaluate its benefit and safety profile in animals.

Q: Has intracerebroventricular (ICV) administration of AAV been done in humans before? What is known about how those patients fare in the long term?

A: Yes. There are multiple investigational AAV-based gene therapy treatments currently in clinical testing that are administered via a one-time ICV injection. These studies are ongoing and long-term data and outcomes in these individuals are pending. Outside of gene therapy, ICV administration is utilized for short-term and long-term delivery of FDA-approved medicines directly to the brain and CNS. According to published research, more than 20,000 procedures are done annually in the U.S.ⁱ

To learn more about gene therapy routes of administration, including ICV, please visit ASGCT's [Lunch & Learn](#) on the topic.

Q: Will immune system suppression be required for the administration of JAG201?

A: Short-term immune suppression will be required and is standard for AAV-based investigational gene therapy treatments to prevent immune reaction to delivery of the gene therapy.

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.

Q: Has Jaguar presented any preclinical data for JAG201?

A: Yes. In May 2024 at the Annual Meeting of the American Society of Gene & Cell Therapy (ASGCT), Jaguar presented the first preclinical efficacy data for JAG201 following a single intracerebroventricular (ICV) injection in mice. The proof-of-concept (POC) data show that in a mouse model of *SHANK3* deficiency, which mimics many of the features of humans with loss of one functional *SHANK3* gene, JAG201 treatment resulted in significant improvements in neurobehavioral outcomes involving measures of restorative sleep, motor and explorative behavioral deficits, and motor-coordination deficits vs. untreated control animals lacking both copies of *SHANK3*. Additionally, JAG201 treatment resulted in widespread and persistent delivery of *SHANK3* throughout the brains of treated animals, suggesting that these

neurobehavioral improvements can be sustained over time following a single ICV treatment with JAG201. You can view the data here on Jaguar's [website](#) under the SHANK3 section.

Q: Can you share the results you saw in non-human primate and mouse studies?

A: To date, we have presented two sets of preclinical data. You can see the published information here on our [website](#) under the SHANK3 section. We are continuing to work to publish additional data from our preclinical studies.

Q: Can you provide any of the preclinical data used for the IND application?

A: To date, we have presented two sets of preclinical data. You can see the published information here on our [website](#) under the SHANK3 section. These data were used to support our IND application.

Q: What exactly is JAG201 designed to 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: How can you control for over-expression of SHANK3?

A: The *SHANK3* minigene is under the regulation of the human synapsin 1 promoter, which limits expression to neuronal cells.

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: Will the effect of JAG201 be durable over time? Do brain cells/neurons die?

A: Given the low potential for cellular division in the brain, we expect that a one-time JAG201 ICV gene delivery will have lasting, long-term durability in neurons. Neurons are generally non-dividing, compared to another target tissue such as the liver, which has a higher rate of cell turnover.

Q: Do you anticipate the lower dose in the initial clinical trial to be effective?

A: We have selected an initial dose for the first human clinical trial that we believe will be both safe and effective based on preclinical studies in animals. We are also including an additional higher dose to ensure we identify the safest and most effective dose coming out of the trial.

Q: Why will dosing be done one at a time?

A: JAG201 will be evaluated in humans for the first time ever in this initial clinical study. While we propose to test a dose that was well tolerated in animals, we plan to dose one patient at a time to allow for thorough safety evaluations of individual patients. If the gene therapy is determined to be well tolerated in the first patient, then the next patient can proceed with dosing. This approach is not unusual and is generally done for at least the first few patients that receive a particular dose in a gene therapy clinical trial. It allows a Sponsor (in this case, Jaguar) and the FDA to make necessary adjustments to the clinical trial and dosing of subsequent patients if a safety concern arises.

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Q: Will every pediatric trial participant receive the same exact dose? Is it age or weight dependent?

A: Every individual participating in a pediatric age cohort will receive the same dose. We have selected two doses for two cohorts to use in the initial clinical trial that we believe will be both safe and effective based on preclinical studies in animals.

Q: Is it possible for a trial participant to be re-dosed?

A: JAG201 is being investigated as a single-ICV administration treatment.

Q: How do I enroll my child in the initial clinical trial?

A: Trial enrollment will be done through the trial sites. Once the clinical trial protocol including inclusion/exclusion criteria are finalized, families who are interested in enrolling their loved ones can reach out directly to trial sites to express their interest. If the clinical research team at a trial site believes your child is a good candidate for the trial, a screening process will be initiated.

Given the value of natural history data in providing a historical understanding of the impact of PMS in the individual, Mount Sinai and Rush will give preference to enrolling individuals who are participants in the Developmental Synaptopathies Consortium (DSC) PMS natural history study.

Jaguar will make announcements when the trial protocol including inclusion/exclusion criteria is final and available on ClinicalTrials.gov. We encourage you to stay in touch with the Phelan-McDermid Syndrome Foundation and CureSHANK as they will have the latest information about the trial.

Q: What is the screening process for trial enrollment?

A: We are still determining these details.

Q: How many 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 a small number of participants, approximately three, with the first participant expected to enroll in the Q12025 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 participants. These ongoing discussions with the FDA could inform or determine potential changes to study design including enrollment criteria as the trial progresses.

Q: Will Jaguar be reaching out directly to specific families about participating in the initial clinical trial?

A: No. Enrollment for the initial clinical trial will be done through the trial sites.

Q: Will the first clinical trial be limited to the U.S.?

A: The first clinical trial will be limited to sites within the U.S. Patients will be expected to attend visits in person throughout the duration of the trial. Visits are anticipated to be more frequent earlier in the trial and less frequent after year 1.

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Q: Where are the clinical trial sites?

A: We are actively working to complete site startup activities at Mount Sinai in New York and Rush University in Chicago. We will post up-to-date study details on ClinicalTrials.gov as soon as we are ready to begin enrollment. Additionally, we have begun discussions to potentially expand beyond the two initial sites in the future.

Given the value of natural history data in providing a historical understanding of the impact of PMS in the individual, Mount Sinai and Rush will give preference to enrolling individuals who are participants in the Developmental Synaptopathies Consortium (DSC) PMS natural history study.

Site specific questions may be directed to:

- Mount Sinai: Abby Siegel (abigail.siegel@mssm.edu) and Dr. Alex Kolevzon (alexander.kolevzon@mssm.edu)
- Rush University: Giulia DiMarco (Giulia_DiMarco@rush.edu), Dr. Elizabeth M Berry-Kravis (Elizabeth_Berry-Kravis@rush.edu), Dr. Latha Soorya (Latha_Soorya@rush.edu). Elizabeth Fitts (Elizabeth_L_Fitts@rush.edu) may be contacted for any Rush University DSC-related questions

Up-to-date contact information will be posted to ClinicalTrials.gov, once we are ready to begin enrollment.

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

A: We are still finalizing our criteria for inclusion and exclusion. Our first clinical trial for JAG201 will be a small study 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.

Jaguar will make announcements when the trial protocol including inclusion/exclusion criteria is final and available on ClinicalTrials.gov. We encourage you to stay in touch with CureSHANK and the Phelan-McDermid Syndrome Foundation as they will have the latest information about the trial.

Q: If my child has a specific medical condition or device (e.g., seizures, ventricular shunt), will it prohibit him/her from participating in the initial clinical trial?

A: We are still finalizing the inclusion/exclusion criteria for the initial clinical trial. Once it is finalized, the research teams at trial sites will work directly with families to determine whether a loved one is eligible for the trial. Enrollment will be done through the trial sites.

Jaguar will make announcements when the trial protocol including inclusion/exclusion criteria is final and available on ClinicalTrials.gov. We encourage you to stay in touch with the Phelan-McDermid Syndrome Foundation and CureSHANK as they will have the latest information about the trial.

Q: Does an immune response to AAV9 prohibit an individual from participating in the initial clinical trial?

A: We are still finalizing the inclusion/exclusion criteria for the initial clinical trial. Once it is finalized, the research teams at trial sites will work directly with families to determine whether a loved one is eligible for the trial. Enrollment will be done through the trial sites.

Jaguar will make announcements when the trial protocol including inclusion/exclusion criteria is final and available on ClinicalTrials.gov. We encourage you to stay in touch with CureSHANK and the Phelan-McDermid Syndrome Foundation as they will have the latest information about the trial.

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Q: You have said you will be including pediatric individuals with small deletions and loss-of-function mutations in the initial clinical trial. Can you be more specific about the size of deletions and the kinds of mutations?

A: We are still finalizing the inclusion/exclusion criteria for the initial clinical trial. We can tell you that we are planning to enroll patients with Class 1 deletions, which include only *SHANK3* or *SHANK3* in combination with *ARSA* and/or *ACR* and *RABL2B* as defined by the Developmental Synaptopathies Consortium. Loss-of-function mutations include frameshifting and stop variants that result in absent protein or truncated non-functional protein.

Q: Will JAG201 help those with larger deletions or other mutations not included in the initial clinical trial? What about a ring chromosome?

A: We believe JAG201 has the potential for benefit in all patients with *SHANK3* haploinsufficiency.

Q: Will trial participants need to stop their ongoing medications during the trial?

A: Participants will be allowed to continue maintenance medications as long as they are on a stable dose for the 3 months leading into the trial.

Q: Will trial participants need to change (i.e., discontinue, decrease or increase) their ongoing therapy services (e.g., ABA, speech, occupational, etc.) during the trial?

A: No. Participants will be allowed to continue in ongoing therapy services. The level of intervention must remain stable for at least 3 months prior to the start of the trial.

Q: Will you be studying JAG201 in both adults and pediatrics?

A: Our goal is for JAG201 to be studied in both adult and pediatric patients.

Q: Why have you updated your study to start with pediatric patients instead of adults?

A: Our preclinical data suggest that the administration of the gene therapy early in life provides a clear potential for benefits to be realized. Key opinion leaders think intervening earlier in a patient's course of illness to address the underlying deficits caused by the *SHANK3* deficiency while individuals are still actively undergoing development will provide a greater potential for benefit. Our hope is that potential early success in the pediatric population may open the door to evaluating JAG201 in broader patient populations.

Q: Does this mean you don't believe treatment with JAG201 will have a benefit in adults?

A: We believe JAG201 has the potential for benefit in both pediatric and adult patients.

Q: When will you begin dosing adults in the clinical trial?

A: We don't know exactly when adults could be dosed as part of the clinical trial. Timing will depend on when pediatric patients are dosed and data from those trial participants can be evaluated. Based on outcomes and learnings from these first patients, dosing in adults could occur as early as 2026.

Q: If someone 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

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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>.

Q: Do you have any clinical trial applications for JAG201 with MHRA, EMA or other regulatory bodies outside the U.S.?

A: Having received IND clearance from the U.S. Food and Drug Administration (FDA), we are currently in the process of planning our first clinical trial in the U.S. No additional expansion is being planned at this time as we prioritize our regulatory pathway in the U.S.

Q: Can you recommend a site/company/physician/lab for my loved one to be tested for a SHANK3 gene mutation or deletion?

A: We are not in a position to recommend care or testing for your loved one. We encourage you to speak with your loved one's physician to discuss potential genetic testing options.

Q: What genetic test does my loved one need to determine if he/she has SHANK3 mutation or deletion?

A: Examples of genetic tests that can diagnose both mutations and deletions including Whole Exome Sequencing, Chromosomal Microarray and genetic panels that sequence the SHANK3 gene.

Q: What is Rare Pediatric Disease designation, and why is it important?

A: The FDA grants Rare Pediatric Disease designation for serious and life-threatening rare pediatric diseases. Under this program, companies are eligible to receive a priority review voucher for a subsequent marketing application for a different product following approval of a product with rare pediatric disease designation. The priority review voucher may be used by the sponsor or sold or transferred. This program is meant to stimulate drug development for rare pediatric diseases.

Q: What is Fast Track designation, and why is it important?

A: The Fast Track program is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to patients earlier. Fast Track addresses a broad range of serious conditions. A therapy that receives Fast Track designation is eligible for more frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval, among other benefits.

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ⁱ Sekula RF, Cohen DB, Patek PM, Jannetta PJ, Oh MY. Epidemiology of ventriculostomy in the United States from 1997 to 2001. *Br J Neurosurg.* 2008 Apr;22(2):213-8. doi: 10.1080/02688690701832084. PMID: 18348016.