Jaguar Gene Therapy
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To: Members of the Phelan-McDermid Syndrome Community

From: Jaguar Gene Therapy

UPDATED NOVEMBER 5, 2024 TO INCLUDE APPROACH FOR PRIORITIZING TRIAL-ELIGIBLE INDIVIDUALS.

Update: JAG201 Clinical Study Record Available on ClinicalTrials.gov

Jaguar Gene Therapy would like to inform the Phelan-McDermid syndrome (PMS) community that the JAG201 clinical study record has been published and is now available on ClinicalTrials.gov, a U.S. government website and online database of clinical research studies. You can use this link to read the JAG201 clinical study record.

As is required for all study records, the JAG201 clinical study record includes the following information.

- General information about the study:
  - Study name and description
  - Person or organization responsible for conducting the study (sponsor or investigator)
  - Funding or support for the study
  - Disease or condition studied
  - Estimated study start and completion dates
  - Clinical trial sites
- Specific information about the study:
  - Who can and cannot join (eligibility criteria)
  - Estimated enrollment
  - A description of the intervention(s) that may be given
  - What researchers want to learn and how they will measure it
  - How to contact the study staff

It is important to keep in mind that the initial JAG201 clinical study 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. **Please see the following Frequently Asked Questions for more information**.

As always, we extend our gratitude to the Phelan-McDermid Syndrome Foundation and CureSHANK for their continued partnership.

Sincerely,
The Jaguar Gene Therapy Team

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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 AAV-delivered gene inserts into (combines with) patient DNA in human clinical trials. To date, there is no evidence that AAV-delivered gene therapy 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 screen for antibodies to AAV vectors and require medicines to decrease the patient's immune response. This is one of the reasons the clinical trial includes outcomes measures to evaluate and understand the immune response to treatment.

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 protein 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.

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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 patient's brain using imaging such as MRI or CT 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. Additionally, JAG201 expression is controlled by a neuron-specific promoter to ensure the SHANK3 minigene is only expressed in neuronal cells.

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

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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. These data were used to support our IND application. We are continuing to work to publish additional data from our preclinical studies.

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 protein 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. Results from the initial clinical study will help inform further study development.

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. Results from the initial clinical study will help inform further development of JAG201.

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 evaluating an additional escalated 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

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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.

Q: Will every pediatric trial participant receive the same exact dose? Is it age or weight dependent?
A: 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: The study is not yet open for recruitment, but sites will keep your information on file with the study team for future consideration.

When enrollment begins, it will be done through the trial sites. Following is the contact information for each trial site:

- United States, New York
  Seaver Autism Center at Mount Sinai
  New York, New York, United States, 10029
  Contact: Abby Siegel
  Phone: 212-241-3072
  Email: abigail.siegel@mssm.edu
  Principal Investigator: Alex Kolevzon, MD

- United States, Illinois
  Rush University
  Chicago, Illinois, United States, 60612
  Contact: Aimee Puz
  Phone: 312-942-9841
  Email: aimee_f_puz@rush.edu
  Principal Investigator: Elizabeth B Kravis, MD, PhD

Please visit clinicaltrial.gov for the most current information related to clinical trial sites.

We encourage families with potential interest in participating in JAG201 clinical trials to explore enrolling in the Developmental Synaptopathies Consortium (DSC) natural history study. Given the value of natural history data in providing a historical understanding of the impact of PMS in the individual, JAG201 sites will give preference to enrolling individuals in the first in human study who are participants in the DSC PMS natural history study.

For information on participating in the DSC natural history study, please reach out directly to the following contacts:

- Seaver Autism Center at Mount Sinai
  New York, New York, United States, 10029

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Contact: Abby Siegel
Email: abigail.siegel@mssm.edu

- Rush University
  Chicago, Illinois, United States, 60612
  Contact: Madison Nava
  Email: Madison_T_Nava@rush.edu

Q: What is the screening process for trial enrollment?
A: Following the patient's legally authorized representative (LAR) providing informed consent, patients will undergo screening to determine eligibility for the study. Screening will begin with determination of key eligibility criteria, including genetic status and medical history in addition to a number of baseline assessments. Patients will be evaluated by the study team to determine whether they meet all eligibility criteria and can receive JAG201.

Q: How many participants will you enroll in this first trial? Why?
A: 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 (target of six) with the first participant expected to enroll in the first quarter of 2025 timeframe. Depending on the outcomes and learnings from this first trial, we would aim to expand the trial to enroll additional patients in 2026.

As this is a first-in-human clinical 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: With such a small number of participants in the trial, how will eligible participants be prioritized?
A: Generally speaking, the first cohort of participants will be prioritized by age with the youngest eligible participants given preference. We are prioritizing age because we believe treating individuals that are still actively undergoing development may provide greater potential for evaluating the benefit of JAG201. Additionally, preference will be given to individuals who have participated or are eligible to participate in the Developmental Synaptopathies Consortium (DSC) PMS natural history study. Mount Sinai is currently accepting participants for natural history in the age range of 12-36 months.

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: Mount Sinai in New York and Rush University in Chicago will be the first two clinical sites. Up-to-date study details on ClinicalTrials.gov are posted here: Study Details | JAG201 Gene Therapy Study in Children & Adults with SHANK3 Haploinsufficiency | ClinicalTrials.gov. Additionally, we have begun discussions to potentially expand beyond the two initial sites in the future.

We encourage families with potential interest in participating in JAG201 clinical trials to explore enrolling in the Developmental Synaptopathies Consortium (DSC) PMS natural history study. Given the value of natural history data in providing a historical understanding of the impact of PMS in the individual, JAG201 sites will give preference to enrolling individuals in the first in human study who are participants in the DSC PMS natural history study.

DSC-specific questions may be directed to:

- Seaver Autism Center at Mount Sinai
  New York, New York, United States, 10029
  Contact: Abby Siegel
  Email: abigail.siegel@mssm.edu

- Rush University
  Chicago, Illinois, United States, 60612
  Contact: Madison Nava
  Email: Madison_T_Nava@rush.edu

Q: What are the inclusion and exclusion criteria for the trial?
A: Up-to-date study details, including inclusion and exclusion criteria, are available on ClinicalTrials.gov here: Study Details | JAG201 Gene Therapy Study in Children & Adults with SHANK3 Haploinsufficiency | ClinicalTrials.gov. Our first clinical trial for JAG201 will be a small study and includes 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.

Generally speaking, the first cohort of participants will be prioritized by age with the youngest eligible participants given preference. We are prioritizing age because we believe treating individuals that are still actively undergoing development may provide greater potential for evaluating the benefit of JAG201.

Throughout the clinical phase of the JAG201 program, our goal remains to demonstrate safety, tolerability, dosage and efficacy so the therapy can be considered for approval by the FDA and potentially made available to all individuals with SHANK3 haploinsufficiency. We are dedicated to doing this as rapidly and as safely as possible.

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: Up-to-date study details, including inclusion and exclusion criteria, are available on ClinicalTrials.gov here: Study Details | JAG201 Gene Therapy Study in Children & Adults with SHANK3 Haploinsufficiency | ClinicalTrials.gov. Our first clinical trial for JAG201 will be a small study and includes very specific inclusion and exclusion criteria to meet the

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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: Does an immune response to AAV9 prohibit an individual from participating in the initial clinical trial?
A: Up-to-date study details, including inclusion and exclusion criteria, are available on ClinicalTrials.gov here: Study Details | JAG201 Gene Therapy Study in Children & Adults with SHANK3 Haploinsufficiency | ClinicalTrials.gov. Our first clinical trial for JAG201 will be a small study and includes 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: 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: Up-to-date study details, including inclusion and exclusion criteria, are available on ClinicalTrials.gov here: Study Details | JAG201 Gene Therapy Study in Children & Adults with SHANK3 Haploinsufficiency | ClinicalTrials.gov. Our first clinical trial for JAG201 will be a small study and includes 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 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. Results from the initial clinical study will help inform further development of JAG201.

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.

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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. Results from the initial clinical study will help inform further development of JAG201.

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 2027.

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 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, tolerability and dosing. 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 initiating 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 include 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

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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.

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