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To: Members of the Phelan-McDermid Syndrome Community

From: Jaguar Gene Therapy

An Important JAG201 Clinical Trial Update

Jaguar Gene Therapy would like to update the Phelan-McDermid syndrome (PMS) community regarding new developments with JAG201, an investigative gene therapy for Phelan-McDermid syndrome and a genetic form of autism spectrum disorder (ASD). The company has received agreement from the U.S. Food and Drug Administration (FDA) to administer JAG201 to both pediatric and adult patients as part of the initial clinical trial. With this clearance, Jaguar will proceed with dosing pediatric patients (2+ years) with JAG201 and expand into adults (18+ years) following the pediatric cohort. Preclinical data suggest that the administration of the gene therapy early in life provides a clear potential for benefits to be realized, and 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 will open the door to evaluating JAG201 in broader patient populations.

At this time, we are focused on updating our clinical trial plans to dose both pediatric and adult patients. We aim to dose the first pediatric patient in Q12025. When we have the final trial protocol, including inclusion/exclusion criteria, we will share it with you and make it available on ClinicalTrials.gov. We are continuing to work with the Phelan-McDermid Syndrome Foundation and CureSHANK to keep the community informed as our work progresses. Please visit our website for the latest information and updates.

In addition to receiving clearance to dose both pediatric and adult patients, Jaguar also announced it has received Rare Pediatric Disease (RPD) and Fast Track designations from the FDA. RPD is granted for products that treat serious and life-threatening rare pediatric diseases. Fast Track status is granted to therapies that address a high unmet medical need. Both designations provide benefits to the drug developer.

To discuss in more detail the update for the initial JAG201 clinical trial, **please join us for a webinar on Thursday, July 11 at 7 p.m. CT**. Members of the Jaguar team along with Dr. Alexander Kolevzon, Professor of Psychiatry and Pediatrics at the Icahn School of Medicine at Mount Sinai, will be presenting. Time will be reserved for questions. Click here to register. In the meantime, please see the following FAQ.

As always, we extend our gratitude to CureSHANK and the Phelan-McDermid Syndrome Foundation 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 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).

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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: 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.

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.

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.

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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?
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.

Q: Is it possible for a trial participant to be re-dosed?
A: JAG201 is being investigated as a single-ICV administration treatment.

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.

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 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

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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: 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.

Q: Where are the clinical trial sites?
A: We have not yet finalized clinical trial site locations.

Q: What is the screening process for trial enrollment?
A: We are still determining these details. Inclusion and exclusion criteria will be posted on ClinicalTrials.gov and communicated by Jaguar once finalized. Interested families will be able to reach out to trial sites directly to express interest in participating in the study.

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 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?
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: 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

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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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