Glossary of Terms

A

AAV (Adeno-Associated Virus)
A modified virus used as a delivery vehicle in some gene therapies. It is designed to carry genetic material into cells without causing disease. Jaguar Gene Therapy's JAG201 delivers a *SHANK3* "minigene" into the brain via AAV. The minigene is designed to help brain cells make SHANK3 protein and restore function.

Adaptive Behavior
Everyday life skills such as communication, dressing, eating, toileting, and social interaction.

ADI-R (Autism Diagnostic Interview-Revised (ADI-R))
A "gold standard" tool often used to help diagnose autism. It is a standardized, semi-structured interview between a clinician and a caregiver.

ADOS-2 (Autism Diagnostic Observation Schedule, Second Edition)
A "gold standard" tool often used to help diagnose autism. It is a play-based assessment for individuals with autism or suspected autism.

AE (Adverse Event)
Any unfavorable medical symptom or illness occurring during the course of a clinical trial, that may or may not be related to the study drug.

Allele
One of two copies of a gene inherited from each parent. People have two alleles of the *SHANK3* gene: One from their mother and one from their father. In the majority of individuals with Phelan-McDermid syndrome, one copy of *SHANK3* is functional, while the other contains a disease-causing variant or is deleted.

ASO (Antisense Oligonucleotide)
A short, synthetic piece of genetic material designed to change how a gene works. An ASO binds to a specific RNA message inside a cell, which can alter the amount of protein the gene makes. In Phelan-McDermid syndrome, PYC Therapeutics' PYC-002 is an ASO designed to increase the amount of SHANK3 protein produced from the working copy of the SHANK3 gene.

ASD (Autism Spectrum Disorder)
A neurodevelopmental condition involving differences in communication, social interaction, sensory processing, and behavior. Many individuals with PMS also meet criteria for ASD.

B

Behavioral Phenotype
A pattern of behaviors commonly associated with a specific genetic condition.

BID
Taking medication twice a day.

Biomarker
A measurable sign of a biological process, disease, or response to intervention. Biomarkers may come from blood tests, EEG recordings, or other measurements. There are no validated biomarkers in Phelan-McDermid syndrome.

Brain Imaging
Techniques such as MRI that create pictures of the brain to help researchers understand structure and function.

C

Caregiver-Reported Outcome
Information provided by families or caregivers about symptoms, behaviors, quality of life, or functioning.

CIC (Caregiver Impression of Change)
The Phelan-McDermid syndrome-specific CIC is a measure completed by caregivers to capture changes in symptoms associated with Phelan-McDermid syndrome compared to a person's baseline.

Class I Deletion
In Phelan-McDermid syndrome, Class I deletions are smaller deletions including only SHANK3 or SHANK3 in combination with ARSA and/or ACR and RABL2B.

Class II Deletion
In Phelan-McDermid syndrome, Class II deletions are all other deletions that did not qualify as Class I deletions, or in other words, larger deletions beyond SHANK3 and ARSA.

Clinical Trial
A research study that evaluates whether a treatment is safe and effective.

Cognitive Function
Mental abilities such as learning, memory, attention, reasoning, and problem-solving.

D

Deletion
A genetic change that involves missing a segment of DNA. In Phelan-McDermid syndrome, there can be deletions on chromosome 22 of different sizes. See **Class I** and **Class II Deletions**.

DEE (Developmental and Epileptic Encephalopathy)
A term used to describe rare and severe epilepsies that start in early development and are associated with neurodevelopmental disorders, impact daily life, and are often drug-resistant. Phelan-McDermid syndrome is considered a DEE.

DSC (Developmental Synaptopathies Consortium)
A NIH-funded research grant studying disorders that affect synapses, including Phelan-McDermid syndrome. This study is commonly referred to as the “Natural History Study”. Two cycles of funding have been completed, and the third and final cycle will begin in 2026.

Dose Escalation
A clinical trial process where researchers gradually increase medication doses to determine safety.

Double-Blinded
An experimental design when neither the study team or participant know whether the participant is receiving the study drug or placebo. This is a gold-standard method of clinical trials to help eliminate bias and determine treatment effects.

E

ECG (Electrocardiogram)
A relatively non-invasive procedure to examine the electrical signals in the heart. ECGs are often used during clinical trials to help ensure the person is safe to participate and the study drug is not adversely impacting the heart.

EEG (Electroencephalogram)
A relatively non-invasive test that measures electrical activity in the brain. EEGs are commonly used to study seizures in a clinical setting or brain-based biomarkers in a research study.

Efficacy
How well a treatment works.

Endpoint
A specific outcome researchers measure in a clinical trial, such as improvement in communication or behavior.

F

Frameshift Variant
A genetic change that happens when DNA letters (called nucleotides) are inserted or deleted in a way that shifts the gene's instructions. It's like removing a letter from a sentence so that every word after it is read incorrectly. This often causes the cell to stop making the protein too early, resulting in a protein that is shorter than normal and usually does not function properly.

Functional Outcome
A measure of how well a person performs daily activities and participates in life.

G

Gene
A segment of DNA that contains instructions for making proteins. The majority of individuals with Phelan-McDermid syndrome have a deletion or variant in the SHANK3 gene.

Gene Expression
The process by which a gene produces its protein product. The SHANK3 gene produces the *SHANK3* protein.

Gene Therapy
A treatment approach that attempts to add, replace, repair, or regulate genes to improve health. JAG201 is an example of gene therapy.

Genotype
A person's genetic makeup.

Genotype–Phenotype Relationship
The connection between a genetic change and the observable characteristics it causes.

H

Haploinsufficiency
When one working copy of a gene is not enough to produce normal function. Phelan-McDermid syndrome is often associated with SHANK3 haploinsufficiency.

Heterogeneous
Highly variable. Phelan-McDermid syndrome is considered a heterogeneous disorder due to the wide range of skills and abilities among all individuals with Phelan-McDermid syndrome.

Heterozygous
Having inherited two different versions of a particular gene. Phelan-McDermid syndrome is considered heterozygous because individuals only have one deleted or mutated *SHANK3* gene. SHANK3 animal models are sometimes heterozygous, meaning like humans, there is one copy of the healthy SHANK3 gene and one copy of the mutated SHANK3 gene.

Homozygous
Having inherited two identical copies of the same gene. This is extremely rare in humans. However, SHANK3 animal models are sometimes homozygous, or are “knock-out” meaning they do not have any functional copies of the SHANK3 gene.

I

ICV (Intracerebroventricular) injection
Delivers drug or gene therapy directly into the brain’s ventricles, which are filled with cerebrospinal fluid. In JAG201, the *SHANK3* minigene is delivered via ICV.

IGF-1 (Insulin Growth-like Factor 1)
A hormone impacting the effects of growth hormone. NNZ-2591 in Neuren’s Phase 3 trial is a synthetic analog of a metabolite called cyclic glycine-proline of IGF-1.

Informed Consent
A critical part of any research study in which the participant or their legal authorized representative are educated about the study and the risks and benefits of the study. Completing the informed consent process ensures that the participant (or their legal authorized representative) is participating voluntarily and fully understands their options.

Investigational Therapy
A treatment that is still being studied and has not yet received regulatory approval.

IRB (Institutional Review Board)
An administrative ethics committee that reviews, approves, and monitors research involving human subjects. All research studies with human subjects in the United States must be approved by the IRB.

IVIG (Intravenous Immunoglobulin)
An infusion therapy that provides antibodies used in autoimmune and neurological conditions.

J

JAG201
An investigational gene therapy used in Jaguar's Phase 1/2 trial, delivered via AAV, to help restore proper SHANK3 gene function. See **AAV** for more information.

L

Loss-of-Function
A genetic change that reduces or limits the normal function of a gene. In Phelan-McDermid syndrome, most disease-causing *SHANK3* variants are loss-of-function variants.

M

MAC (Medical Advisory Committee)
PMSF's Medical Advisory Committee is made up of physicians who are experts in Phelan-McDermid syndrome. The MAC provides guidance on important treatment considerations for individuals with Phelan-McDermid syndrome.

Mechanism of Action
How a treatment works in the body.

Missense Variant
A genetic change in a single DNA letter (called a nucleotide) that causes the cell to substitute one building block of a protein for another. This is like replacing a letter to change one word, but the overall message stays intact. Some, but not all, missense variants will alter the function of the protein.

Molecular Therapy
A treatment designed to act on specific genes, proteins, or biological pathways.

N

NHS (Natural History Study)
A general term for a research study that follows individuals over time to understand how a condition changes throughout life without experimental treatment. The "Natural History Study" in

Phelan-McDermid syndrome typically refers to the NIH-funded Developmental Synaptopathies Consortium. See **DSC** for more information.

Neuroimmunology
A subspeciality that studies how the immune system interacts with the nervous system. This may be an important area of study in Phelan-McDermid syndrome.

Neuron
A type of cell, “nerve cell”, that sends and receives information throughout the brain and nervous system.

Neurotransmitter
Chemical messengers, or molecules, that allow neurons to communicate. Neurotransmitters are sent across the synapse. Common neurotransmitters are dopamine and serotonin.

NNZ-2591
An investigational treatment by Neuren Pharmaceutics that is currently being studied in a Phase 3 trial for Phelan-McDermid syndrome that aims to improve function. See **IGF-1.**

O

OLE (Open Label Extension)
A phase of a clinical trial following the blinded, placebo-controlled period when all study participants receive active treatment. This allows trial participants to have uninterrupted access to the study drug prior to FDA approval.

ORCA (Observer-Reported Communication Assessment)
A caregiver-report measure assessing communication skills in individuals with rare neurodevelopmental disorders, like Phelan-McDermid syndrome, who typically have significantly impacted verbal abilities.

P

Pathogenic Variant
A genetic change known to cause disease.

Phenotype
The observable traits or characteristics of a person, such as speech ability, behavior, seizures, or developmental level.

Phase 1 Clinical Trial
An early-stage clinical trial primarily focused on safety. Also aimed at determining appropriate dose and understanding how the treatment behaves in the body.

Phase 2 Clinical Trial
A clinical trial focused on safety and preliminary effectiveness.

Phase 1/2 Clinical Trial
Combines the initial safety and dosing tests of Phase 1 with the preliminary effectiveness of Phase 2. JAG201 is a Phase 1/2 study.

Phase 3 Clinical Trial
A large study designed to confirm effectiveness and monitor safety. Typically randomized, double-blinded, placebo-controlled. Results from successful Phase 3 trials may be used to support regulatory approval.

PK (Pharmacokinetics)
The study of how the body absorbs and metabolizes a drug. PK values can help determine whether this is a high enough concentration of the drug in the body to have the desired effect without causing toxicity.

Placebo
A treatment that looks like the investigational therapy but does not contain the active ingredient, and thus should have no medical effect. Used in clinical trials to objectively determine the effectiveness of the study drug.

Placebo-Controlled
In a clinical trial, when, at random, half the participants received study drug and half receive placebo.

PMSA-S (Phelan-McDermid Syndrome Assessment of Severity)
A clinician-rated measure to evaluate the overall severity of symptoms associated with Phelan-McDermid syndrome and its level of impairment on functioning.

PMS-SHANK3 Related
Phelan-McDermid syndrome caused by a pathogenic variant in the *SHANK3* gene or by a deletion that includes *SHANK3* on chromosome 22. These individuals have SHANK3 haploinsufficiency, meaning they have only one working copy of the SHANK3 gene.

PMS-SHANK3 Unrelated
Phelan-McDermid syndrome caused by a deletion (most commonly an interstitial deletion) in the 22q13 region that does not include *SHANK3*. Clinical phenotypes are believed to result from the loss of other genes in the deleted region. Thus, these individuals do not have SHANK3 haploinsufficiency,

Precision Medicine
Medical care tailored to an individual's genetic and biological characteristics.

Primary Endpoint
The main outcome a clinical trial is designed to measure, such as improvement in a specific symptom or skill. It is the key measure researchers use to determine whether a treatment worked. In most clinical trials, the primary endpoint must show a statistically significant improvement for the study to be considered successful.

PYC-002
An investigational RNA-based therapy from PYC Therapeutics designed to increase SHANK3 protein production from the functional copy of the *SHANK3* gene. The goal is to help restore SHANK3 protein levels in people with *SHANK3* haploinsufficiency. See **ASO**.

R

Randomized
In a clinical trial, being put in the placebo group or treatment group, at complete random.

Regression
Loss of previously acquired skills, such as language, motor abilities, self-help skills, or social engagement.

Registrational Trial
Typically a Phase 3 clinical trial that generates critical safety and efficacy data required to support application to the FDA.

Ring chromosome
In Phelan-McDermid syndrome, when deletions on both ends of chromosome 22 cause it to fuse into a circular structure, or ring. Individuals with Ring 22 are at higher risk for Neurofibromatosis Type 2 (NF2).

RNA (Ribonucleic Acid)
A molecule involved in carrying genetic instructions from DNA to produce proteins. ASOs modify RNA rather than DNA.

S

SAC (Scientific Advisory Committee)
PMSF's Scientific Advisory Committee is made up of researchers across the globe who are

experts in Phelan-McDermid syndrome. The SAC provides guidance on research priorities for PMSF.

Screening Period
In research, a period where researchers determine whether you qualify to participate. Within a clinical trial, this includes physical exams, review of medical history, and basic safety lab to determine whether the potential participant meets inclusion/exclusion criteria.

SAE (Serious Adverse Event)
In a clinical trial, if a participant experiences an unfavorable medical event that results in serious outcome, including requiring hospitalization, death, or permanent disability.

***SHANK3* gene**
A gene critical for synapse function. Deletions or variants involving *SHANK3* are the primary cause of most cases of Phelan-McDermid syndrome.

Shank3+/− Mice (SHANK3 Heterozygous Mice)

Laboratory mice with one working copy and one altered or missing copy of the *Shank3* gene. They are widely used as a model of Phelan-McDermid syndrome to study the effects of SHANK3 haploinsufficiency and evaluate potential treatments. Shank3+/− also may depict other heterozygous animal models, like zebrafish or macaque monkeys.

Shank3−/− Mice (SHANK3 Homozygous Knockout Mice)
Laboratory mice that lack both copies of the *Shank3* gene. These mice typically have more severe changes in brain function and behavior than Shank3+/− mice and are used to study the effects of complete SHANK3 loss. While valuable for research, they do not represent most people with Phelan-McDermid syndrome, who usually have one remaining functional copy of *SHANK3*.

SHANK3 protein
The protein product of the *SHANK3* gene that is found throughout the body but especially in the brain and is important in organizing synapses that facilitate the communication between neurons, or brain cells.

Synapse
The connection point where nerve cells communicate with one another.

Synaptopathy
A disorder affecting synapses.

T

Translational Research
Research that moves discoveries from the laboratory toward clinical use.

Titrate
The process of slowly adjusting medication dosage over time to help minimize side effects while maximizing benefit.

V

Variant
A difference in DNA sequence. Some variants are harmless; others can cause disease.

VUS (Variant of Uncertain Significance)
A genetic test finding indicating a DNA change was detected, but there is not enough scientific evidence to determine whether the change is disease-causing (pathogenic) or not.

W

WT (Wildtype)
An animal that has not been genetically modified and serves as the normal comparison group in research. Scientists compare genetically modified animals to wild-type animals to understand how a genetic change or treatment affects health and behavior. For example, Shank3+/− mice vs. WT controls.