First PRIZM Study Participant Enrolled in Tisento Therapeutics' Open-Label Extension Study in MELAS

Participants Who Complete Treatment in Global Phase 2b PRIZM MELAS Study Are Eligible to Enroll

CAMBRIDGE, Mass., August 20, 2025 – Tisento Therapeutics today announced that the first participant has enrolled in the company's open-label extension study in MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes). The extension study (NCT06961344) is evaluating the long-term safety and tolerability of zagociguat in individuals with MELAS who complete treatment in the global Phase 2b PRIZM study, which is expected to complete screening in the next months. The extension study is intended to provide uninterrupted access to zagociguat for clinical trial participants for up to two years and evaluate the long-term safety of zagociguat.

"We're pleased to reach the important milestone of enrolling the first PRIZM study participant into our open-label extension study," said Peter Hecht, Ph.D., chief executive officer of Tisento. "Enthusiastic engagement by MELAS patients and physicians is powering momentum in our development program, and we look forward to completing PRIZM enrollment in the next few months."

The PRIZM study is actively enrolling in the U.S., Canada, Australia, United Kingdom, Italy, and Germany, and interested individuals are encouraged to discuss participation with their physician. PRIZM is evaluating the impact of zagociguat treatment on fatigue, cognitive performance, and other key aspects of MELAS. The clinical outcome assessments and endpoint strategy for the PRIZM study were informed by Tisento's interview study in which individuals living with MELAS described the symptoms and impacts of the disease that are most important to them. Participants who complete treatment in PRIZM have the opportunity to enroll in the open-label extension study.

About the PRIZM Study

PRIZM – a **P**hase 2b **R**andomized, Placebo-Controlled Trial **I**nvestigating **Z**agociguat in **M**ELAS – is evaluating the efficacy and safety of oral zagociguat 15 mg or 30 mg compared to placebo when administered once-daily for 12 weeks in participants with genetically and phenotypically defined MELAS. The PRIZM study has a crossover design, with two 12-week treatment periods separated by a 4-week washout period. All participants will receive zagociguat during one of the 12-week periods and placebo during the other. Participants who complete treatment in the study have the opportunity to enroll in an open-label extension study.

The global PRIZM study is now enrolling approximately 44 participants at mitochondrial disease centers of excellence in the U.S., Italy, Germany, United Kingdom, Australia, and Canada. For more information, please visit www.tisentotx.com/prizm or ClinicalTrials.gov (NCT06402123). Interested individuals can also reach out to their physicians for participation details.

About Zagociguat

Zagociguat is a once-daily, oral, clinical-stage investigational medicine with potential to positively impact both peripheral and central nervous system manifestations of mitochondrial diseases. Zagociguat

stimulates soluble guanylate cyclase (sGC), an enzyme that is found in virtually every cell in every tissue of the body and is part of a system of cellular mechanisms that control critical physiological functions including neuronal function and blood flow.

A first-in-class, brain-penetrant sGC stimulator, zagociguat is hypothesized to rebalance dysregulated cellular pathways in MELAS. By restoring cellular functions that support mitochondria, zagociguat may help restore mitochondrial energy production and physiological function.

In a Phase 2a study in patients with MELAS, zagociguat exhibited a favorable safety profile, exposure throughout the body including in the central nervous system, and improvements in neuronal function, mitochondrial function, and blood flow in the brain. Zagociguat is currently being evaluated as a treatment for MELAS in the Phase 2b PRIZM study.

Zagociguat received Fast Track designation from the U.S. Food and Drug Administration for the treatment of MELAS. Fast Track is a process designed to facilitate the development and potentially expedite the review of medicines to treat serious conditions and fill an unmet medical need, with the goal of getting important new drugs to patients earlier.

For more information, visit www.tisentotx.com/our-science.

About Tisento Therapeutics

Tisento Therapeutics, a privately held biotech company, is developing novel medicines to treat diseases with significant unmet need, beginning with MELAS and other genetic mitochondrial diseases. *Ti sento* means “I hear you” in Italian; our approach to innovation begins with listening to patients and then channeling what we learn into decisive actions that shape our research and clinical programs.

Tisento is guided by a high-caliber internal team of biopharma veterans and an extensive external network of expert physicians, patient advocacy groups, researchers, industry-leading vendors, and other close collaborators who are partners in our mission to develop meaningful treatments for mitochondrial diseases.

Learn more at our website, www.tisentotx.com, or connect with us on LinkedIn, Facebook, X (@tisentotx), or Bluesky.

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