Maze Therapeutics Presents Preclinical Data Highlighting Potential of APOL1 Inhibitor Program as a Treatment for Chronic Kidney Disease

November 4, 2022

Significant Reductions of Disease Manifestations in Proprietary Mouse Renal Model of APOL1-Mediated Kidney Disease Observed

New Research Shows APOL1 p.N264K Variant Associated with Reduced Risk of Chronic Kidney Disease and End Stage Kidney Disease Among Carriers of APOL1 High-risk Variants

SOUTH SAN FRANCISCO, CA., Nov 4, 2022 – Maze Therapeutics, a company translating genetic insights into new precision medicines, today announced new research highlighting the potential of its APOL1 inhibitor program as a treatment for chronic kidney disease (CKD) and describing the role of APOL1 variants in causing and protecting from kidney disease. The findings will be presented today, November 4, 2022, from 10:00 a.m. to 12:00 p.m. ET during a poster session at the American Society of Nephrology's 2022 Kidney Week. Kidney Week is being held November 3-10, 2022, in Orlando, FL.

Apolipoprotein L1 (APOL1) is a protein that in humans is encoded by the APOL1 gene. Genetic variants of the gene (G1 and G2) are associated with increased risk for a spectrum of progressive kidney diseases in people of African ancestry. While there are no targeted therapies to address the underlying cause of disease available today, recent human genetic findings suggest that pharmacologic inhibition of APOL1 pore function may treat APOL1-mediated kidney disease. Maze is advancing an APOL1 small molecule inhibitor program, with preclinical data demonstrating dose dependent responses to treatment and supporting its potential as a treatment for certain APOL1-mediated kidney diseases. In addition, Maze Therapeutics and collaborators with the Million Veteran Program and Vanderbilt University have identified a critical genetic variant in APOL1 that provides protection from the development of CKD.

"The collective data we and our partners are presenting at this year's ASN meeting represent a tangible application of how the power of human genetics and an understanding of genetic variants can potentially transform the lives of patients and their caregivers," said Jason Coloma, Ph.D., chief executive officer of Maze. "Our scientific team deftly moved from variant discovery to preclinical proof-of-concept with key genetic insights and understanding informing our drug development. Through our Compass Platform, human genetics analyses and variant functionalization, our team established a better understanding of the mechanism of APOL1 toxicity and used these insights to create an exceptionally active compound that we aim to take to the clinic next year."

Detailed findings from the research include: In collaboration with the Million Veteran Program and Vanderbilt University, Maze has identified and characterized the role and mechanism of a genetic variant in APOL1– p.N264K. Through this research, the presence of the p.N264K variant was determined to suppress the risk for kidney disease and slow progression to end stage renal disease. In experiments conducted by Maze Therapeutics, the p.N264K variant reduces conductance of ions through the APOL1 pore and thereby suppresses the toxicity of APOL1 to kidney cells. These studies are the first of their kind to demonstrate the protective role of p.N264K and its mechanism of action in blocking APOL1 pore-function, reducing the toxicity of APOL1 high-risk mutations with clear clinical significance.

The second poster outlines preclinical data from Maze's APOL1 program to date. Maze is advancing a small molecule that inhibits APOL1 pore function, reducing APOL1 mediated toxicity and offers a potentially disease-modifying treatment option for people with APOL1-mediated CKD. In the data presented today, Maze researchers evaluated its APOL1 inhibitor in several in vitro systems and in a proprietary BAC-Tg G2-HOM mouse renal model in which albuminuria, a condition associated with kidney disease characterized by abnormal protein presence in the urine, was induced.

Findings showed that administration of MZ-301:

- Potently blocked APOL1 and prevented APOL1-mediated killing of trypanosomes in a parasite viability assay
- Inhibited APOL1-dependent cytotoxicity in vitro in human podocytes and reduced APOL1 ion conductance in APOL1-overexpressing cells
- Led to dose dependent resolution of albuminuria in the APOL1 kidney disease mouse model

"The findings presented today highlight the potential to offer a disease-modifying therapy for over a million people who suffer from APOL1-mediated CKD," said Eric Green, M.D., Ph.D., chief scientific officer of Maze. "Together with our collaborators, we now have a better understanding of APOL1's role in kidney disease. With variant functionalization and the application of our Compass Platform, we have been able to translate that understanding into a potential treatment for CKD. We believe the compound that we are developing could specifically address the underlying mechanism of disease and potentially reduce the rate of CKD

progression. These new findings, built on a strong genetic foundation and validated through translational models, provide critical insight into developing a potentially safe and potent oral treatment for a broad patient population suffering from various forms of APOL1 mediated CKD.”

ASN Poster Presentation Details
Session: Genetic Diseases: Models, Mechanisms, Treatments
Title: Genetic Inhibition of APOL1 Pore Forming Function Prevents APOL1 Kidney Disease
Date & Time: November 4, 2022, from 10:00 a.m. to 12:00 p.m. ET
Location: Exhibit Hall, Orange County Convention Center, West Building

Session: Genetic Diseases: Models, Mechanisms, Treatments
Title: MZ-301 Is a Small Molecule Inhibitor of APOL1 Pore Function That Attenuates Albuminuria in a Mouse Model of APOL1-Mediated Kidney Disease
Date & Time: November 4, 2022, from 10:00 a.m. to 12:00 p.m. ET
Location: Exhibit Hall, Orange County Convention Center, West Building

About Maze Therapeutics
Maze Therapeutics is a biopharmaceutical company applying advanced data science methods in tandem with a robust suite of research and development capabilities to advance a pipeline of novel precision medicines for patients with genetically defined diseases. Maze has developed the Maze Compass™ platform, a proprietary, purpose-built platform that combines human genetic data, functional genomic tools and data science technology to map novel connections between known genes and their influence on susceptibility, timing of onset and rate of disease progression. Using Compass, Maze is building a broad portfolio of wholly owned and partnered programs. Maze is based in South San Francisco. For more information, please visit mazetx.com, or follow us on LinkedIn and Twitter.

Contacts:
Jillian Connell, Maze Therapeutics
jconnell@mazetx.com
650.850.5080

Media:
Katie Engleman, 1AB
katie@1abmedia.com