Maze Therapeutics Announces Positive First-in-Human Results from Phase 1 Trial of MZE782, Establishing Proof of Mechanism for a Potent, Oral SLC6A19 Inhibitor with Potential to Treat Phenylketonuria (PKU) and Chronic Kidney Disease (CKD)

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Phase 1 data in healthy volunteers exceed expectations and support best-in-class potential, enabling Phase 2 advancement for both intended indications of PKU and CKD

Dose-dependent urinary amino acid excretion demonstrated across all SAD and MAD cohorts, including up to a 42-fold increase in urinary phenylalanine (Phe) excretion, a well-validated biomarker for PKU and predictive for CKD

Dose-dependent initial eGFR dip similar to SGLT2 inhibitors observed, supporting a potential kidney protective effect in CKD

Well tolerated across all doses with an excellent safety profile and no serious adverse events observed

Phase 2 trials in both PKU and CKD expected to initiate in 2026

Maze to host investor conference call and webcast today at 8:30 am EDT

SOUTH SAN FRANCISCO, Calif., Sept. 11, 2025 (GLOBE NEWSWIRE) -- Maze Therapeutics, Inc. (Nasdaq: MAZE), a clinical-stage biopharmaceutical company developing small molecule precision medicines for patients with kidney and metabolic diseases, today announced positive clinical results from the Phase 1 healthy volunteer study of MZE782, an oral small molecule targeting the solute transporter, SLC6A19. MZE782 has potential to be a best-in-class therapy for patients with PKU, an inherited metabolic disorder, and a first-in-class therapy for patients with CKD.

“These first-in-human results for MZE782 mark an important milestone, demonstrating an excellent safety profile, robust target engagement and compelling pharmacodynamic effects, consistent with our therapeutic hypothesis,” said Harold Bernstein, M.D., Ph.D., president of R&D and chief medical officer of Maze. “The rapid and profound increase in urinary phenylalanine excretion confirms SLC6A19 inhibition in healthy individuals that we anticipate will translate to meaningful reductions in plasma phenylalanine levels in patients with PKU, based on the biology of this transporter.”

“We also observed dose-dependent changes in eGFR in healthy individuals with MZE782, similar to those seen with SGLT2 inhibitors, suggesting a potential beneficial effect on kidney physiology in CKD patients. We look forward to advancing MZE782 into Phase 2 studies in both PKU and CKD in 2026,” Dr. Bernstein continued. “These findings also serve as important clinical validation of our Compass platform. MZE782 is the third clinical program to come out of our Compass platform, further demonstrating our ability to harness the power of human genetics to develop small molecule precision medicines designed to transform the lives of patients with kidney and metabolic diseases.”

Study Design

The Phase 1 trial of MZE782 was a randomized, double-blind, placebo-controlled study evaluating single ascending doses (SAD) and multiple ascending doses (MAD) of orally administered MZE782 in 112 healthy adult volunteers. The study included 56 participants in the SAD, 40 participants in the MAD and 16 participants in the food effect cohorts. Each SAD and MAD cohort included eight participants randomized 6:2 (MZE782: placebo). The SAD doses ranged from 30 to 960 mg. The MAD doses, with dosing once or twice daily for seven days, ranged from 120 to 240 mg twice daily and 120 to 720 mg once daily. One food effect cohort included eight participants administered 480 mg MZE782 or placebo (6:2) with a high-fat meal. The second food effect cohort included eight participants administered 480 mg MZE782 fasted or with a low-fat meal in a crossover design.

The primary objective was to evaluate the safety and tolerability of single and multiple ascending oral doses of MZE782 in healthy volunteers. Secondary and exploratory endpoints included pharmacokinetics, food effect, pharmacodynamic measures of target engagement, specifically urinary excretion of phenylalanine (Phe) and glutamine (Gln) as predictive biomarkers of SLC6A19 inhibition and disease control, and estimated glomerular filtration rate (eGFR).

Safety and Tolerability Profile

MZE782 was well tolerated across all doses in all cohorts. There were no serious adverse events (SAEs), no severe adverse

events and no treatment-related adverse events (TRAEs) leading to discontinuation. In the SAD portion of the study (n=56), there were a total of three TRAEs reported that were all mild in severity and not seen at the higher doses. Headache was reported in two patients (4%) and diarrhea was reported in one patient (2%). There were no TRAEs reported in the MAD portion of the study. No clinically relevant changes in vital signs, laboratory tests or ECGs were observed.

Pharmacokinetics (PK)

MZE782 demonstrated a favorable plasma PK profile after single and multiple oral doses. Oral administration was associated with consistent absorption, with a t_{max} of six hours and a half-life of 11 hours. Exposure increased proportionally with dose, and steady-state was achieved by Day 3. This is supportive of a once- or twice-daily dosing regimen to be evaluated in Phase 2.

Pharmacodynamics (PD)

Neutral Amino Acid Excretion

MZE782 produced dose-dependent increases in 24-hour urinary excretion of the neutral amino acids Phe and Gln across both SAD and MAD cohorts, confirming target engagement and SLC6A19 inhibition.

A 39-fold increase in urinary Phe excretion over 24 hours was observed with a single dose of 960 mg of MZE782. A 42-fold increase in urinary Phe excretion over 24 hours on Day 7 was observed in the 240 mg twice-daily dose cohort.

A 55-fold increase in urinary Gln excretion over 24 hours was observed with a single dose of 960 mg of MZE782. A 68-fold increase in urinary Gln excretion over 24 hours on Day 7 was observed in the 240 mg twice-daily dose cohort.

Estimated Glomerular Filtration Rate (eGFR)

All participants in the MAD cohorts of the Phase 1 study were assessed for changes in eGFR. MZE782 demonstrated a dose-dependent initial eGFR dip over seven days of dosing that was similar in magnitude to what has been observed in patients initiating SGLT2 and RAAS inhibitors. With other renoprotective therapies, this initial dip is correlated to a slower rate of eGFR decline and better preservation of kidney function over longer periods of time in CKD patients. The combined 240 mg BID cohorts (n=12) demonstrated a change of -11.5 mL/min/1.73m^2 after seven days of dosing, compared to a change of -2.5 mL/min/1.73m^2 in the matched placebo cohort (n=4). This initial eGFR dip rapidly reversed following the end of dosing as assessed at Day 11, strongly suggestive of a drug-related effect on eGFR.

Next Steps

Maze plans to initiate two Phase 2 proof-of-concept trials of MZE782, evaluating plasma Phe reduction in PKU and proteinuria reduction in CKD in 2026.

Conference Call and Webcast

Maze will host a conference call and webcast with members of the executive team today at 8:30 am EDT to discuss the data.

To access the call, please dial (877) 407-3982 (domestic) or (201) 493-6780 (international) and provide the Conference ID 13755793 to the operator.

To access the live webcast and subsequent archived recording of this and other company presentations, please visit the Investors section of Maze's website. The archived webcast will remain available for replay on Maze's website for 90 days.

About MZE782
MZE782 is an investigational, potent, selective, oral inhibitor of SLC6A19, a sodium-dependent neutral amino acid transporter expressed in the small intestine and kidney proximal tubule that plays a key role in the absorption and reabsorption of neutral amino acids, including Phe. MZE782 is being advanced in two indications: PKU and CKD. In PKU, SLC6A19 enables Phe uptake from the gut and reabsorption in the kidney – two key contributors to elevated plasma Phe levels in patients with deficient PAH activity. Inhibiting SLC6A19 with MZE782 offers a genotype- and PAH-agnostic, oral approach to lowering plasma Phe by limiting its entry into circulation. In CKD, SLC6A19-mediated reabsorption has the potential to contribute to metabolic overload in the proximal tubule of the kidney. Blocking this transporter may therefore reduce the burden of amino acids and toxins, potentially slowing disease progression. The potential mechanism is complementary to, as well as distinct from, SGLT2 inhibition. Loss-of-function mutations in SLC6A19, as seen in Hartnup disease, a generally benign condition, support the potential safety of SLC6A19 inhibition and reinforce the therapeutic rationale for MZE782. In the Phase 1 clinical study in healthy volunteers, MZE782 demonstrated an excellent safety profile, sustained urinary neutral amino acid excretion as well as potential to improve kidney filtration.

About Maze Therapeutics
Maze Therapeutics is a clinical-stage biopharmaceutical company harnessing the power of human genetics to develop novel small molecule precision medicines for patients with kidney and metabolic diseases. Guided by its Compass ™ platform, Maze pursues genetically validated targets by integrating variant discovery and functionalization to discover and advance small molecule programs with first- or best-in-class potential. Maze's pipeline is led by MZE829, a dual-mechanism APOL1 inhibitor in Phase 2 development for APOL1-mediated kidney disease (AMKD), and MZE782, a SLC6A19 inhibitor advancing to Phase 2 with the

potential to treat both phenylketonuria (PKU) and chronic kidney disease (CKD). Maze is headquartered in South San Francisco. For more information, please visit mazetx.com, or follow the company on LinkedIn and X.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements reflect the current beliefs and expectations of management. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including, without limitation, statements concerning the company's future plans and prospects, any expectations regarding the safety or efficacy of MZE829, MZE782 and other candidates under development, the ability of MZE829 to treat AMKD or other indications, the ability of MZE782 to treat CKD, PKU or other indications, the planned timing of the company's clinical trials, data results and further development of MZE829, MZE782 and other therapeutic candidates, and the ability to drive financial results and stockholder value. In addition, when or if used in this press release, the words "may," "could," "should," "anticipate," "believe," "estimate," "expect," "intend," "plan," "predict" and similar expressions and their variants, as they relate to the company may identify forward-looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Although the company believes the expectations reflected in such forward-looking statements are reasonable, the company can give no assurance that such expectations will prove to be correct. Readers are cautioned that actual results, levels of activity, safety, performance or events and circumstances could differ materially from those expressed or implied in the company's forward-looking statements due to a variety of factors, including risks and uncertainties related to the company's ability to advance MZE829, MZE782 and its other therapeutic candidates, obtain regulatory approval of and ultimately commercialize the company's therapeutic candidates, the timing and results of preclinical studies and clinical trials, the company's ability to fund development activities and achieve development goals, its ability to protect its intellectual property, general business and economic conditions, and risks related to the impact on its business of macroeconomic conditions, including inflation, volatile interest rates, tariffs, instability in the global banking sector, and public health crises. Further information on potential risk factors that could affect the company's business and its financial results are detailed under the heading "Risk Factors" included in the documents the company files from time to time with the U.S. Securities and Exchange Commission, including the company's Annual Report on Form 10-K and Quarterly Reports on Form 10-Q. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements speak only as of the date of this press release and the company undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

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