MannKind Launches Inhale-3 Study to Address the Most Important Unmet Need Today in Adults Living With Type 1 Diabetes (T1D)

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- *Large trial in adults comparing A1c and mealtime control when switching from injectable insulin or pumps to inhaled insulin (Afrezza® (insulin human) Inhalation Powder)*
- *Time-in-range during waking hours remains a challenge despite advances in diabetes technology*
- *Lack of mealtime control is the underlying issue preventing approximately 80%(1) of the T1D population from achieving A1c goal*

DANBURY, Conn. and WESTLAKE VILLAGE, Calif., June 22, 2023 (GLOBE NEWSWIRE) -- **MannKind Corporation (Nasdaq: MNKD)**, a company focused on the development and commercialization of inhaled therapeutic products and devices for patients with endocrine and orphan lung diseases, announced today that it is launching the INHALE-3 study to address the most important unmet need today in adults living with T1D.

“This large study is planned to assess improvement in mealtime glycemic control, which continues to be a serious challenge for the majority of people living with type 1 diabetes,” said Michael Castagna, PharmD, Chief Executive Officer of MannKind Corporation. “INHALE-3 will study the effect of Afrezza on mealtime control, which has a time-action profile that closely mimics that of physiologic insulin in the first 120 minutes after a meal.”

INHALE-3 is a 17-week randomized controlled trial with a 13-week extension. The study will randomly assign participants over 18 years of age with T1D who are using MDI, an automated insulin delivery (AID) system, or a pump without automation to either continue their usual care or adopt an insulin regimen of basal injections plus Afrezza. Both arms will utilize continuous glucose monitoring to assess mealtime control and A1c levels.

“People living with diabetes deserve options and innovation that can reduce burdens and provide impactful glucose control,” said Dr. Irl B. Hirsch, Professor of Medicine and Diabetes Treatment and Teaching Chair at the University of Washington. “As protocol chair for the INHALE-3 study, I am looking forward to working with leading clinical sites across the country to collect meaningful data regarding the use of inhaled insulin.”

Approximately 120 patients will be randomized in the study conducted in collaboration with the Jaeb Center for Health Research and 20 sites across the country, including the Joslin Diabetes Center, the Barbara Davis Center for Diabetes, the University of Washington Diabetes Institute, Northwestern University, Mayo Clinic, and University of North Carolina Diabetes Care Center.

For more information on INHALE-3 and the list of participating sites, please visit: https://clinicaltrials.gov/ct2/show/NCT05904743.

About MannKind
MannKind Corporation (Nasdaq: MNKD) focuses on the development and commercialization of innovative therapeutic products and devices to address serious unmet medical needs for those living with endocrine and orphan lung diseases.

We are committed to using our formulation capabilities and device engineering prowess to lessen the burden of diseases such as diabetes, pulmonary arterial hypertension (PAH) and nontuberculous mycobacterial (NTM) lung disease. Our signature technologies – dry-powder formulations and inhalation devices – offer rapid and convenient delivery of medicines to the deep lung where they can exert an effect locally or enter the systemic circulation.

With a passionate team of Mannitarians collaborating nationwide, we are on a mission to give people control of their health and the freedom to live life.

Please visit mannkindcorp.com to learn more, and follow us on LinkedIn, Facebook, Twitter or Instagram.

Forward-Looking Statements
This press release contains forward-looking statements about the planned scope and potential implications of a clinical study that involves risks and uncertainties. Words such as “believes”, “anticipates”, “plans”, “expects”, “intends”, “will”, “goal”, “potential” and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon MannKind’s current expectations. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, the risk that continued testing of a drug product may not yield successful results or results that are consistent with earlier testing, as well as other risks detailed in MannKind’s filings with the Securities and Exchange Commission, including its Annual Report on Form 10-K for the year ended December 31, 2022, and subsequent periodic reports on Form 10-Q and current reports on Form 8-K. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this press release. All forward-looking statements are qualified in their entirety by this cautionary statement, and MannKind undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this press release.

Important Safety Information

Indications and Usage:

Afrezza® (insulin human) Inhalation Powder is a rapid acting inhaled human insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Limitations of Use: Not recommended for the treatment of diabetic ketoacidosis, not recommended in patients who smoke or have recently stopped smoking.

WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- **Acute bronchospasm has been observed in AFREZZA-treated patients with asthma and COPD.**
- **AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD.**
- **Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease in all patients.**

Contraindications

AFREZZA is contraindicated: during episodes of hypoglycemia, in patients with chronic lung disease (such as asthma or chronic obstructive pulmonary disease [COPD]) because of the risk of acute bronchospasm, and in patients with hypersensitivity to regular human insulin or any of the excipients in AFREZZA.

Warnings and Precautions

Acute Bronchospasm: In a study of patients with asthma whose bronchodilators were temporarily withheld for assessment, bronchoconstriction and wheezing following AFREZZA dosing was reported. Before initiating therapy, evaluate all patients with a medical history, physical examination, and spirometry (FEV1) to identify potential underlying lung disease. Do not use in patients with chronic lung disease such as asthma or COPD.

Hypoglycemia or Hyperglycemia with Changes in Insulin Regimen: Glucose monitoring is essential for patients receiving insulin therapy. Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made under close medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage modifications of concomitant oral antidiabetic treatment may be needed.

Hypoglycemia: Hypoglycemia is the most common adverse reaction associated with insulins, including AFREZZA. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). Hypoglycemia can happen suddenly, and symptoms may differ across patients and change over time in the same patient. Patients and caregivers should be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.

Decline in Pulmonary Function: AFREZZA causes a decline in lung pulmonary function over time as measured by FEV1. In clinical trials excluding patients with chronic lung disease and lasting up to 2 years, AFREZZA-treated patients experienced a small (40 mL) but greater FEV1 decline than comparator-treated patients. Assess pulmonary function with spirometry at baseline, after the first 6 months of therapy and annually thereafter even in the absence of pulmonary symptoms. In patients who have a decline of ≥20% in FEV1 from baseline, consider discontinuing AFREZZA. Consider more frequent lung function assessment in patients with pulmonary symptoms, e.g., wheezing, bronchospasm, breathing difficulties, or persistent or recurring cough. If symptoms persist, discontinue AFREZZA.

Lung Cancer: In clinical trials, 2 cases of lung cancer were observed in patients exposed to AFREZZA while no cases were reported for the comparators. In both cases, a prior history of heavy tobacco use was identified as a risk factor for lung cancer. Two additional cases of lung cancer (squamous cell and lung blastoma) were reported in non-smokers exposed to AFREZZA after the trial completion. These data are insufficient to determine whether AFREZZA has an effect on lung or respiratory tract tumors. In patients with active lung cancer, a prior history of lung cancer, or in patients at risk of lung cancer, consider whether the benefits of AFREZZA use outweigh this potential risk.

Diabetic Ketoacidosis (DKA): In clinical trials enrolling patients with type 1 diabetes, diabetic ketoacidosis (DKA) was more common in AFREZZA-treated patients (0.43%; n=13) than in comparator-treated patients (0.14%; n=3). Patients with type 1 diabetes should always use AFREZZA in combination with basal insulin. In patients at risk for DKA, such as those with an acute illness or infection, increase the frequency of glucose monitoring and consider discontinuing AFREZZA and giving insulin using an alternate route of administration.

Hypersensitivity Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including AFREZZA. If hypersensitivity reactions occur, discontinue AFREZZA, treat per standard of care and monitor until symptoms and signs resolve.

Hypokalemia: All insulin products, including AFREZZA, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Closely monitor potassium levels in patients at risk of hypokalemia and treat if indicated.

Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Fluid retention, which may lead to or exacerbate heart failure, can occur with concomitant use of TZDs and insulin. Observe these patients for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the TZD should be considered.

Drug Interactions

Certain drugs may affect glucose metabolism, increasing the risk of hypoglycemia or deceasing or increasing the blood glucose lowering effect of AFREZZA. Dose adjustment and increased frequency of blood glucose monitoring may be required. Co-administration of beta-blockers, clonidine, guanethidine, and reserpine with AFREZZA may reduce the signs and symptoms of hypoglycemia. For full list, see Prescribing Information.

Adverse Reactions

The most common adverse reactions associated with AFREZZA are hypoglycemia, cough, and throat pain or irritation.

To report SUSPECTED ADVERSE REACTIONS, contact MannKind Corporation at 1-877-323-8505 or FDA at www.fda.gov/medwatch or call 1-800-FDA-1088 (1-800-332-1088).

Please See Full Prescribing Information, including BOXED WARNING, Medication Guide and Instructions for Use at Afrezza.com/safety.

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SOURCE: (1) Foster NC, Beck RW, Miller KM, et al.. State of type 1 diabetes management and outcomes from the T1D exchange in

2016–2018. *Diabetes Technol Ther*. 2019; 21:66–72.

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