MannKind Corporation is conducting a clinical development program with Technosphere Insulin (TI) Inhalation Powder (AFREZZA® insulin) for the treatment of patients with type 1 or type 2 diabetes mellitus. TI Inhalation Powder is a pulmonary delivered, dry powder formulation of insulin containing recombinant regular human insulin adsorbed onto Technosphere particles. Designed as prandial insulin, its action profile closely approximates the physiologic early phase insulin response with the duration of action similar to subcutaneously delivered insulin in serum glucose and short enough to reduce the potential risk of delayed postprandial hypoglycemia.

The clinical Phase 2/3 program utilized the first generation inhaler (MedTone Model C Inhaler). As a part of the MannKind Corporation next-generation device development program, a second-generation inhalation system, the Gen2B Inhaler, has been developed. Both the first- and second-generation devices are breath-powered, reusable, high resistance inhalers that use the same TI dry powder formulation. The Gen2B Inhaler is smaller, easier to load and handle, and requires 1 inhalation per cartridge as compared to 2 inhalations per cartridge with the first generation inhaler.

The primary objective of the study was to evaluate bioavailability of insulin delivered using the Gen2B and MedTone Model C inhalation systems. One of the secondary objectives was to study the effects on lung function immediately after inhalation of TI Inhalation Powder using the two inhalers shown in Figure 1.

Methods

Study Design: This was a Phase 1, single-center, open-label, randomized, three-part, crossover study in healthy normal volunteers to compare the bioavailability of TI Inhalation Powder when administered using the Gen2B and MedTone Model C inhalers. Parts I and II of the study were designed to ensure that the TI Inhalation Powder dose delivered by the Gen2B Inhaler was equivalent to that delivered by the MedTone Inhaler. Part III was designed to determine the variability associated with the two inhalers using an equivalent dose.

Part I: Twelve new TI Inhalation Powder naïve subjects participated in a 2-way, 2-period crossover phase of the study. TI Inhalation Powder dose used with the Gen2B Inhaler was increased from Pre- to Post-TI Inhalation Powder inhalation at 17, 33, 63, and 123 minutes after each administration of TI Inhalation Powder. TI Inhalation Powder dose used with the MedTone Inhaler was increased from Pre- to Post-TI Inhalation Powder inhalation at 17, 33, 63, and 123 minutes after each administration of TI Inhalation Powder to study the acute changes in the forced expiratory volume in one second (FEV1).

Results of the study demonstrate that the observed acute changes in FEV1 immediately post-inhalation in healthy volunteers are minimal and consistently smaller when TI Inhalation Powder is delivered using the Gen2B Inhaler compared to the MedTone Inhaler. This finding may simply be the function of the amount of the dry powder required to be inhaled by the subjects to achieve similar systemic insulin exposure with the two inhalation systems. The Gen2B inhalation system is developed to maintain all performance characteristics of the MedTone system. Both the MedTone and Gen2B devices are breath-powered, reusable, high resistance inhalers that rely on air flow balance to empty the cartridge and deagglomerate the powder. In vitro data demonstrate that the Gen2B Inhaler deagglomerates the powder more efficiently than the MedTone Inhaler. Compared to the MedTone Inhaler, the fraction of the emitted dose in the fine particle range is greater and the amount deposited in the oropharynx is smaller when TI Inhalation Powder is delivered with the Gen2B inhalation system. Thus, with the Gen2B Inhaler, 33% less powder per cartridge is required to provide comparable systemic insulin exposure. Overall, this efficiency reduces the total amount of powder required to be delivered to the patient with each dose.

Discussion

Forty-eight subjects were randomized to treatment; Table 1 summarizes baseline characteristics by treatment. Three subjects discontinued the trial and never received TI Inhalation Powder; Table 2 summarizes the acute changes after the administration of equivalent doses of TI Inhalation Powder using either the Gen2B or MedTone Model C inhalation system in healthy volunteers were small and clinically unlikely to be meaningful.

The observed changes in FEV1 immediately post-TI Inhalation Powder inhalation using the Gen2B Inhaler were minimal and consistently smaller compared with the MedTone Inhaler.

References