MannKind Corporation™

INNOVATION IN DRUG DELIVERY BY INHALATION

In this article, Andrea Leone-Bay, PhD, Vice-President, Pharmaceutical Development, Robert Baughman, PharmD, PhD, Vice-President, Clinical Pharmacology & Bioanalytics, Chad Smutney, Senior Director, Device Technology, and Joseph Kocinsky, Senior Vice-President, Pharmaceutical Technology Development, all of MannKind Corporation, describe the powder fomulation technologies and delivery devices the company is developing for drug, including insulin, delivery to the systemic circulation via the lungs.

Historically, the lung has been viewed as a filtering organ not amenable for drug delivery. However, the lung provides a large absorptive surface area, a thin alveo-capillary membrane, and a large vascular bed through which the entire cardiac output flows with every heart beat. Additionally drugs administered by the pulmonary route avoid the challenges associated with transiting the gastro-intestinal tract.

Given these characteristics and the desire for rapidly absorbed drug products provided in patient-friendly formats, MannKind Corporation has developed an inhaled drug delivery technology based on dry-powder formulations delivered through discrete, breath-powered inhalers. Additionally, MannKind's proprietary inert excipient, FDKP (fumaryl diketopiperazine), the primary component of these Technosphere® dry-powder formulations, has the ability to deliver drugs in a cost-effective manner that is well-tolerated by patients.

MannKind has utilised this drug delivery technology during the development of Technosphere Insulin (Afrezza®), an innovative and patient-friendly orally inhaled insulin, to establish a formulation/device/development system with the potential to change the paradigm for inhaled drug delivery.

Going forward, systemic delivery by inhalation will have a dramatic impact on the market as more active agents are shown to benefit from this route of administration. However, the real impact will be realised when patients are given the opportunity to self-administer therapies in easy-to-use, patient-friendly delivery systems. MannKind's technology system meets all these requirements and offers the additional advantage of providing unique pharmacokinetics characterised by ultra-rapid drug absorption.

FORMULATION TECHNOLOGY

MannKind's dry-powder formulations are based on the novel excipient, fumaryl diketopiperazine (FDKP), shown in Figure 1.

FDKP is a substituted diketopiperazine that forms the Technosphere particle matrix and is the primary component of Technosphere dry-powder formulations. The particles can be either crystalline or amorphous (Figure 2). Crystalline particles are prepared by a controlled, pH-induced crystallisation process in which FDKP nanocrystals self-assemble into microparticles.[1-6]

A crystalline Technosphere particle can be envisioned as a three-dimensional sphere constructed from a deck of playing cards. Each card represents an FDKP nanocrystal and the sphere constructed from the cards represents a Technosphere particle. The back and front faces of the cards provide the sphere with a large surface area. The spaces between the cards provide the sphere with a high internal porosity resulting in low density and suitable aerodynamic properties for deposition in the distal airways.

These crystals provide a large surface area onto which drugs can be adsorbed to make an inhalation powder.[7] Amorphous particles can be formed from a salt of FDKP and the drug. Such particles are a homogenous composite of the FDKP salt and drug. Once the crystalline or amorphous Technosphere particles are formed, they are not processed further. Particle size is fixed during particle formation (either

Andrea Leone-Bay
Vice-President, Pharmaceutical Development
T: +1 203 796 3421
F: +1 203 798 7740
E: aleone-bay@mannkindcorp.com

Dr Robert Baughman
Vice-President, Clinical Pharmacology & Bioanalytics

Mr Chad Smutney
Senior Director, Device Technology

Mr Joseph Kocinsky
Senior Vice-President, Pharmaceutical Technology Development

MannKind Corporation
One Casper Street
Danbury, CT 06810
United States

www.mannkindcorp.com

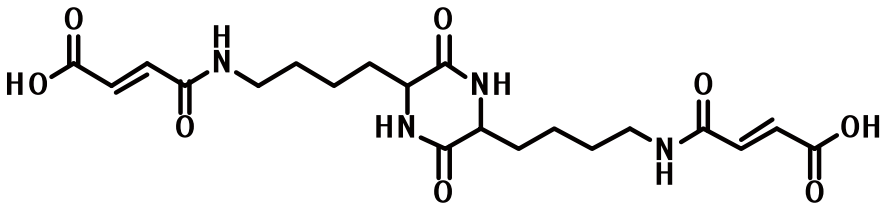

Figure 1: Chemical structure of FDKP.

crystallisation or spray drying) eliminating the need for milling, sizing, or blending.

Upon inhalation, Technosphere particles carry the drug to the lungs, dissolving immediately at the prevailing physiological pH in the lungs due to FDKP's high solubility at pH ≥ 6. Here, the drug is absorbed into the systemic circulation.

Drugs inhaled as Technosphere powders are often characterised by pharmacokinetic profiles that mimic intravenous injection. Absorption begins almost immediately after inhalation and circulating drug concentrations peak within minutes of administration. Duration of drug exposure is determined by the inherent circulating half-life of the drug itself. Drugs ranging in molecular weight from 300 to 100,000 Da are absorbed readily. Drugs having molecular weights >100,000 Da can be formulated for local lung delivery, but their systemic absorption is limited by their large molecular size.

The fumaryl diketopiperazine (FDKP) is absorbed but not metabolised, and is excreted intact, primarily in urine. FDKP does not directly facilitate drug absorption, but functions solely as the particle matrix.[8] Taken together, these unique features contribute to the distinctive pharmacokinetic profiles of drugs administered as Technosphere powders.

DELIVERY BY INHALATION

Technosphere powders are inhaled using small, high-resistance, breath-powered inhalers (see Figure 3). The Dreamboat™ inhaler is a re-usable device designed for 15 days of use. To take a dose of medication, the patient simply opens the device, inserts a unit-dose plastic cartridge containing the Technosphere powder formulation, closes the device, and inhales the powder through the mouthpiece in a single breath. The powder is expelled from the device by the patient's inhalation; no other activation is required. After dosing, the patient opens the device and then removes and discards the emptied cartridge.

Alternatively, the Cricket inhaler is a single-use disposable device comprising two components. To take a dose of medication, the patient simply removes the pre-loaded, single-use device from the package, activates by depressing the purple button, and inhales the powder through the mouthpiece in a single breath. The powder is expelled from the device by the patient's inhalation, no other activation is required. After dosing, the patient discards the used device. It is intended for indications that are short in duration or time of need.

COMBINATION PRODUCT DEVELOPMENT, DEVICE DESIGN

Successful delivery of dry-powder formulations requires careful consideration of many factors. Human anatomy dictates that particles with aerodynamic diameters of 1-10 µm have the highest probability of reaching and depositing in the deep lung.[9] Larger particles may be filtered by the tortuous path from mouth to alveoli and smaller ones may not settle or impact and can be exhaled.

As a result of the need for micrometer-sized particles, the normally insignificant static and van der Waals forces cannot be ignored and can begin to affect the "dispersability" of the powder leading to cohesion and agglomeration. Therefore, for a breath-powered inhaler to work effectively it must maximally harness the energy contained in an inhalation to lift and separate individual particles, but not impart too great a velocity onto any one. Particles with high momentum cannot change direction quickly enough to avoid inertial impaction in the conducting airways and may never reach the distal lung tissue.

An effective inhalation system must also consistently deliver the same mass of powder and adequately protect it from deleterious environmental factors prior to use. Moisture, for example, can quickly change a particle's morphology or permanently link it to neighboring particles to form large agglomerates.

Finally, users of inhalation systems vary in age, dexterity and cognitive ability. The most limited of users must still be able to co-ordinate the steps required for operation, or else the device is rendered useless.

These aspects of device design were evaluated in developing the Dreamboat inhalation system to deliver Technosphere powders (see Figure 4). A breath-powered mode of delivery offers advantages because patients are not required to synchronise an activation step with a sequential inhalation step. Instead, activation occurs by the patient's inhalation alone. In addition, several key features including re-usability and high resistance were incorporated. While the device itself is re-usable, the cartridge containing the powder formulation is single-use and is prefilled with a discreet quantity of powder. Other

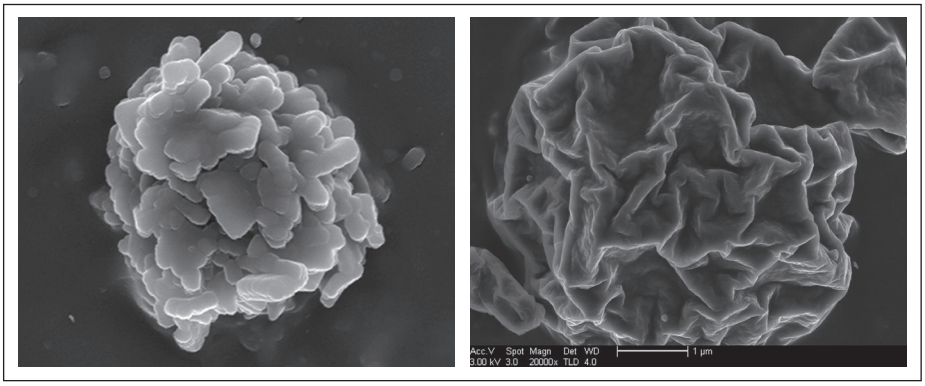

Figure 2: Crystalline particle (left) and amorphous particle (right).

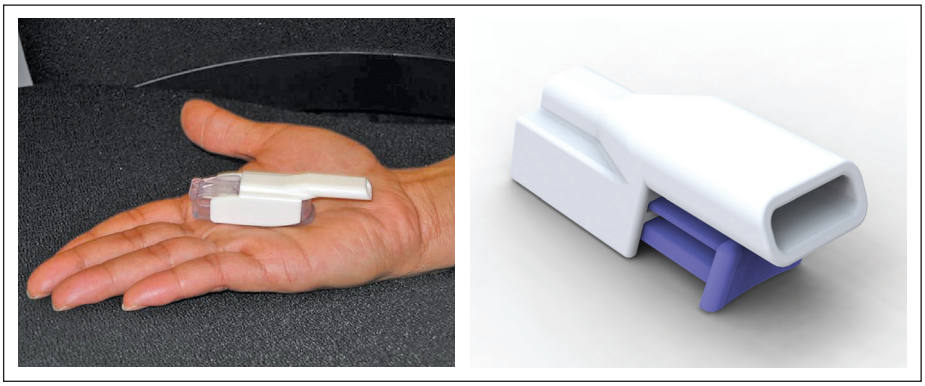

Figure 3: Dreamboat (left) and Cricket (right) inhalers.

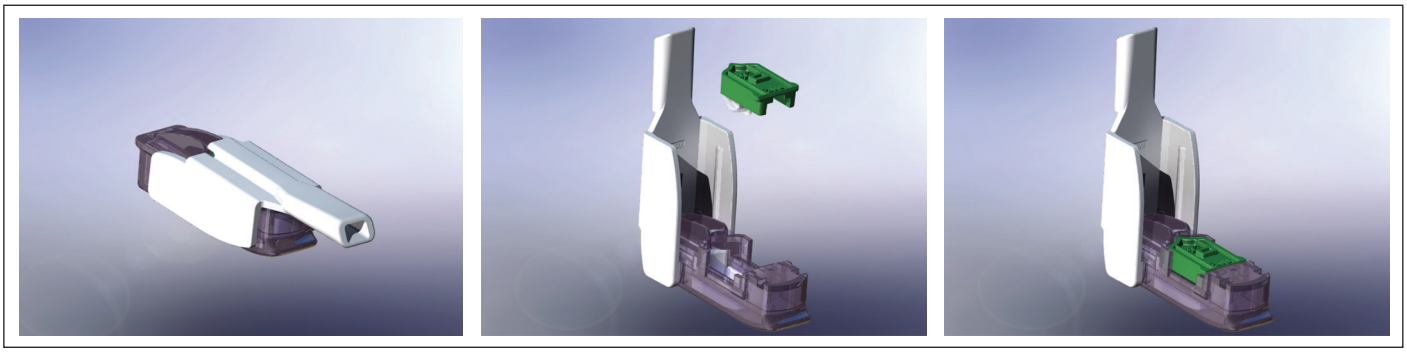

Figure 4: Technosphere powder inhalation system showing device (left panel), device with single-use, pre-metered cartridge containing drug powder (centre panel), and device with cartridge installed (right panel).

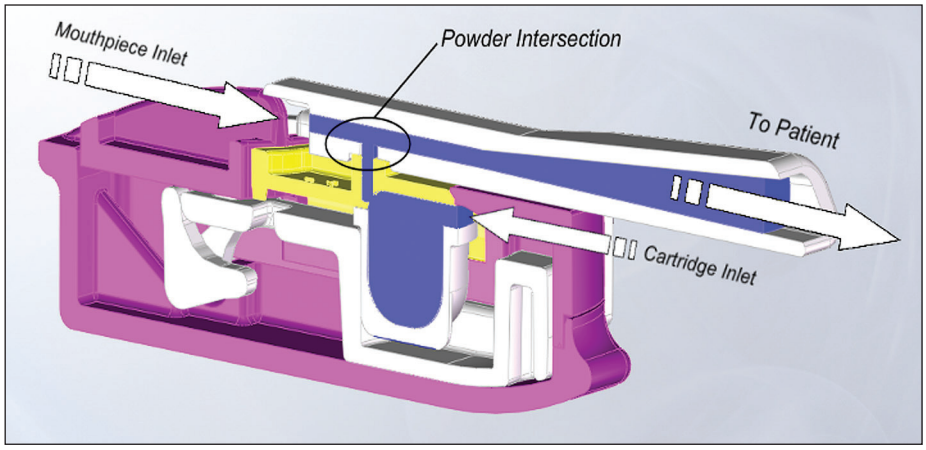

Figure 5: Inhalation system flow path.

desirable characteristics included in the design were small size for portability and discreetness, and simple, intuitive operation.

A concept called "flow balance" was employed in the design to provide effective dispersion and de-agglomeration of the powder. Air flow moving through the cartridge initiates de-agglomeration and lifts the powder from the bottom of the cartridge to the top exit port. By-pass air flow moving down the mouthpiece intersects air flow moving from the cartridge exit. Here it is sheared to complete the de-agglomeration process before exiting the mouthpiece (Figure 5). This air-flow balance allows complete discharge of the cartridge contents as well as providing forces that are sufficient to de-agglomerate the powder into particles sized within the respirable range.

The contributors to the flow balance including inlet/outlet areas, feature geometries, and proximities define the principle characteristic of the system called flow resistance. Based on the inhalation pressure supplied by the patient, the resistance determines the available air flow that drives powder delivery/performance. Importantly, pressure differentials across the inhalation system produce flow rates that are consistent with the Bernoulli principle, shown by the equation:

$$\Delta P^{1/2} = \Phi R$$

where ΔP is pressure drop, Φ is flow rate, and R is resistance. [10,11]

According to the equation, device system resistance is defined as the slope of the line produced by the relationship between the square root of pressure and flow (Figure 6). A high resistance was established to help increase flow turbulence at critical de-agglomeration points within the device system while simultaneously effecting slow average plume velocities to minimise throat deposition. Other researchers have found similar benefits from high resistance in delivery via dry-powder inhalers.[12-14]

Figure 7 shows the cumulative geometric particle size distributions for a range of fill masses and pressure drops (air-flow rates) in the device system. The inhalation system demonstrated consistent performance across the range of fill masses and applied flow rates. This consistent performance across a diverse range of pressure drops shows that this inhalation system is suitable for broad patient populations including pediatric, geriatric and populations with compromised pulmonary function.

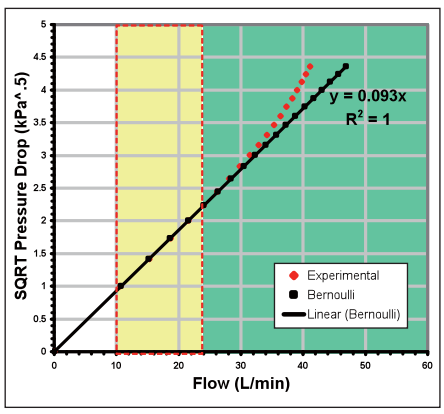

Figure 6: Experimental (measured) and predicted (Bernoulli) behavior of inhalation system resistance: Square Root of Pressure Drop vs Flow Rate.

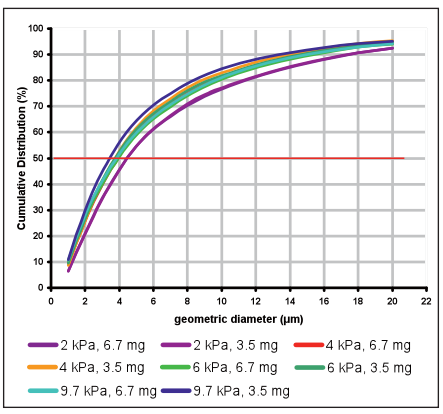

Figure 7: Cumulative geometric particle-size distributions over a range of cartridge-fill masses and pressure drops in the device system.

ADVANCING COMBINATION PRODUCT DEVELOPMENT THROUGH PATIENT PROFILING

The breath-powered mode of delivery and the high resistance within the Dreamboat design were carefully considered and selected. However, it was vital to understand how these attributes interfaced with patient abilities.

During use, pressure applied to the delivery system is the driving force imparting energy to the system (inhaler plus cartridge plus powder) and the product of pressure and time is a measure of the impact of this force

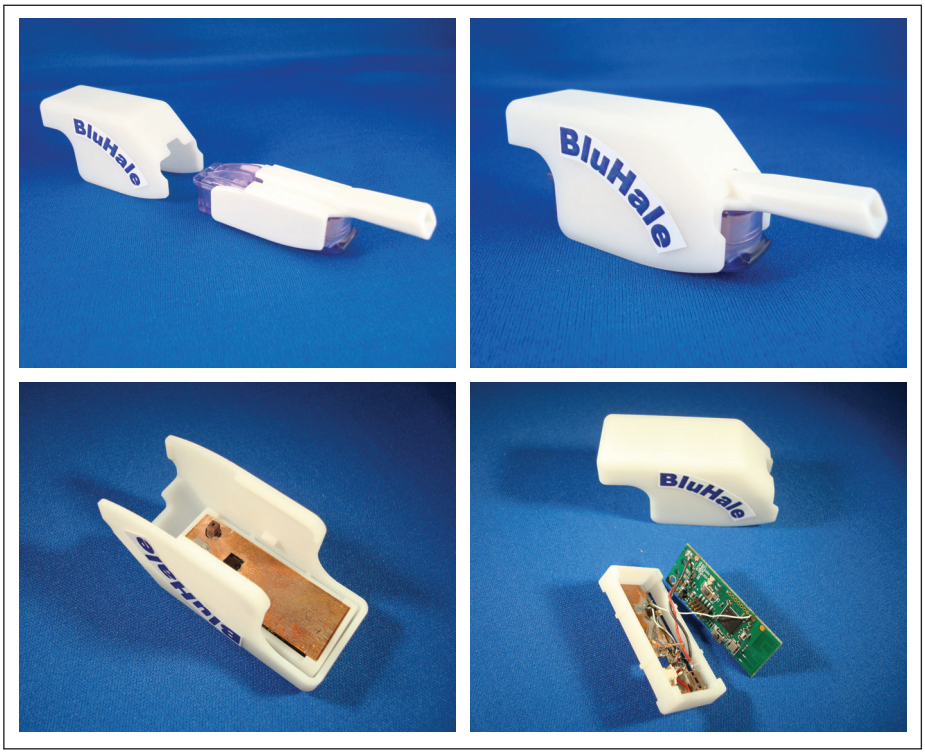

Figure 8: BluHale Jacket Technology

on the powder. These two parameters, peak inspiratory pressure (PIP) and area under the pressure-time curve (AUC), indicate utility of an inhalation effort.

Sensitivity of delivery performance to inhalation effort can be assessed by probing PIP and AUC values during the powder discharge. Since this generally occurs early in the development of the inhalation effort, PIP in the first two seconds ($PIP_{0\text{-}2\ sec}$) and AUC in the first second ($AUC_{0\text{-}1\ sec}$) are more specific and useful measures.

Recognising the criticality of these parameters, MannKind developed a compact and wireless pressure profiling technology, called BluHale®, to rapidly advance and understand the patient/delivery system interaction.

A small, discreet electro-acoustic sensor was used to measure the sound emitted by air flow through the system. Since higher flows (and greater sounds) result from higher pressures, the sensor output was calibrated to applied pressure.

Sound is a unique characteristic for inhalation devices because it generally emanates from the system in all directions. This allows it to be measured remotely unlike traditional pressure/flow sensors that must be located within the flow path. Data can be easily collected during dose administration without affecting sensor integrity or changing airflow dynamics through the device. Additionally, the inhaler interface with the subject is unchanged because of the compact nature of the electro-acoustic sensing technology and its simple adaption onto the device. The sensor, along with circuitry, is housed within a jacket-like frame that is easily affixed onto a dry-powder inhaler (see Figure 8).

Pressure-time profiles are captured and transmitted in real time to a graphical user interface. This enables subjects to achieve prescribed inhalation effort parameters successfully by watching the user interface during the inhalation.

During clinical use, BluHale pressure-time curves were collected and parameterised for $PIP_{0\text{-}2sec}$ and $AUC_{0\text{-}1sec}$ (shown in Figure 9). In various clinical trials during which Technosphere formulations were administered to healthy subjects, $PIP_{0\text{-}2sec}$ values of ~4 kPa and $AUC_{0\text{-}1sec}$ values of ~3 kPa.sec were demonstrated.

An inhalation profile exhibiting these nominal values was then reproduced in the lab with an inhalation simulator to test delivery device performance attributes such as geometric particle-size distribution and mass percent emitted from the device. Based on this testing, design iterations were made to optimise the median geometric particle size of the emitted aerosol and maximise mass percent emitted.

Median geometric particle sizes of 3-4 µm with 97% emitted masses were realised in the final design. Variants of this nominal inhalation effort were then explored with the goal of establishing an effort threshold for performance as defined by minimum $PIP_{0\text{-}2sec}$ and $AUC_{0\text{-}1sec}$ values. In other words, it was desired to understand which inhalation efforts caused performance deterioration.

To this end, deterioration was defined by median geometric particle sizes above 4.9 µm (33% greater than the smallest achieved median size) or cartridge emptying below 87% (10% less than the nominal 97%), either condition resulting in failure. The threshold $PIP_{0\text{-}2sec}$ was found to be 2.0 kPa and the threshold $AUC_{0\text{-}1sec}$ was found to be 1.2 kPa.sec (see graphical depiction in Figure 10).

Thus, by recording subject inhalation profiles with a novel sound sensing system, MannKind was able to advance the development of its device delivery system rapidly. The design was accelerated and the difficult tasks of device characterisation and specification development were simplified. The end result was a high resistance, breath-powered delivery device system with robust performance across a large spectrum of patient inhalation efforts.

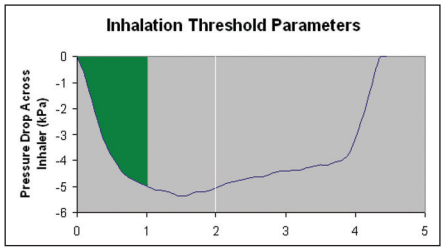

Figure 9: Parameterised BluHale pressure time profile

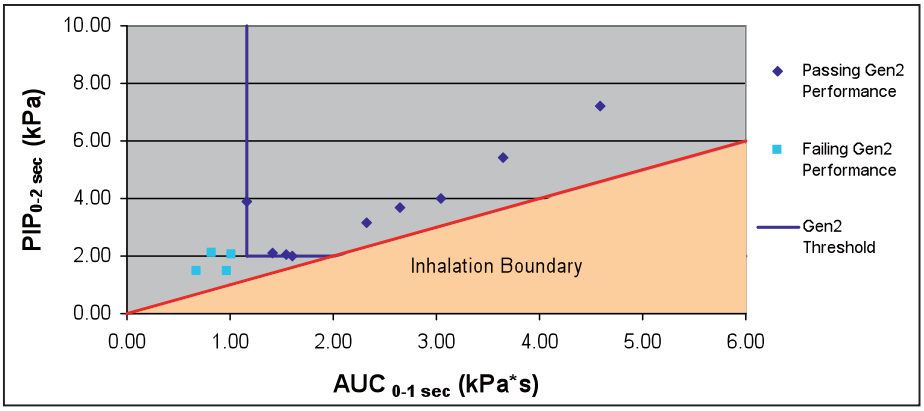

Figure 10: Threshold limits for the MannKind Gen2 Inhalation System

TECHNOLOGY EXEMPLIFIED IN AFREZZA™ (TECHNOSPHERE® INSULIN)

Insulin delivery by inhalation appears to be advantageous when compared against the other non-injected routes (oral, dermal, nasal).[15] Pulmonary insulin dosing was first reported in 1925 when Gänsslen described his investigation using a nebuliser.[16] While an effect on blood glucose was noted, the low bioavailability and constraints of the dosing apparatus made this route impractical.

However, the development more than 20 years ago of handheld inhalers and the accompanying technology for generating an aerosol with the requisite particle size distribution for lung deposition reignited the experimentation and development of pulmonary insulin administration. A number of inhalers (differing in the number of components, size, weight, and ease of use) that utilise solution or dry-powder formulations (with varying excipients) that entered clinical testing have been previously reviewed.[17,18]

Afrezza insulin is different from all other inhaled insulin products because it provides ultra-rapid insulin absorption with corresponding clinical benefits, as well as a number of novel formulation and device characteristics (described above) that appear to mitigate problems identified with earlier technologies.

CLINICAL TRIAL RESULTS

In a 12-week randomised, controlled trial in 110 patients with Type 1 diabetes, Afrezza insulin was administered at mealtime. The Afrezza-treated subjects demonstrated significantly reduced HbA1c concentrations from baseline (-0.83%), without experiencing weight gain. The control group, that received prandial treatment with injected insulin showed a similar statistically significant glycaemic improvement from baseline (-0.99%). However, the injected group experienced a weight change of +0.89 kg compared with -0.41 kg for the Afrezza group.[19]

Another study enrolled adult patients with Type 2 diabetes mellitus and poor glycaemic control in ten countries. Patients were randomly allocated to receive 52 weeks of treatment with prandial Afrezza plus bedtime insulin glargine (n=334) or twice daily premixed biaspart insulin (n=343) (70% insulin aspart protamine suspension and 30% insulin aspart injection [rDNA origin]). Over the 52-weeks, 107 patients on inhaled insulin plus insulin glargine and 85 on biaspart insulin discontinued the trial. The per-protocol analyses included 211 patients on inhaled insulin plus insulin glargine and 237 on biaspart insulin. Change in HbA1c with inhaled insulin plus insulin glargine (–0·68%, SE 0·077, 95% CI –0·83 to –0·53) was similar and non-inferior to that with biaspart insulin (–0·76%, 0·071, –0·90 to –0·62). The between-group difference was 0·07% (SE 0·102, 95% CI –0·13 to 0·27). As reported in previous studies, patients had significantly lower weight gain and fewer mild-to-moderate and severe hypoglycaemic events on inhaled insulin plus insulin glargine than on biaspart insulin. The safety and tolerability profile was similar for both treatments, apart from increased occurrence of cough. No statistically significant differences were noted between groups in the mean change from baseline in FEV1, FVC or lung diffusion capacity at week 52.[20]

Overall, these clinical data show that inhaled Afrezza insulin offers glycaemic control comparable to current injected insulin with less weight gain, reduced risk of hypoglycaemia, and reduced postprandial glucose excursion. These clinical data are correlated with the unique pharmacokinetics of Afrezza. Application of this technology to several other peptide and small-molecule drugs has the potential to deliver similar advantages.

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