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Novel routes of insulin delivery, with a special emphasizes on inhaled insulin: Expanding the scope of Insulin Administration

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Abstract
Diabetes is a long-term illness associated with insufficient insulin production and corresponding hyperglycemia. The best blood glucose-lowering medication is still insulin, which is a crucial component of diabetes therapy. Due to a variety of factors, including apprehension over repeated injections, many diabetics are, nevertheless, unwilling to begin or not adhere to their insulin therapy. The United States FDA has approved Afreeza, a brand-new inhaled insulin powder, for the treatment of diabetes. Both trials show that afreeza is generally well tolerated, with hypoglycemia and cough being the most frequent side effects. Additional research is required since concerns about long-term pulmonary safety have not been addressed. Overall, afreeza looks to be a viable noninvasive option to frequent injections for people with diabetes who are at risk of not taking their medications. This article provides a review of the development of afreeza, pharmacokinetics and pharmacodynamics, administration, its clinical trial data and some adverse effects.

Keywords: Diabetes Mellitus, Insulin Delivery, Afrezza, technosphere, inhaled insulin.

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by an inability to produce enough insulin, the emergence of insulin resistance, or occasionally both. According to the 2016 WHO Global Diabetes Report, the predicted number of adults with the illness increased dramatically from 108 million in 1980 to 422 million in 2014 [1]. In 2030, 366 million individuals worldwide were expected to have diabetes, according to Wild et al., however the International Diabetes Federation (IDF) estimates that figure was already achieved in 2011 and that by 2030, there might be as many as 552 million adults worldwide [2][3]. According to the IDF's most recent estimate, which was published in 2018 and is displayed in Table 1, there were 451 million individuals (aged 18 to 99) who had diabetes in 2017. The prediction for 2045 shows a significant increase to 693 million [4].

Table 1. Estimated number and prevalence of diabetic adults

Year	Number (Millions)	Adult prevalence (%)
2017	451	8.4%
2045	693	9.9%

The parenteral route of administration is currently the primary method of administering insulin to diabetes patients who are insulin-dependent. In many circumstances, people must receive repeated subcutaneous injections of either long-acting, intermediate-acting, short-acting, or fast acting insulin on a daily basis in order to maintain the proper level of blood glucose. Numerous researchers are working to create novel carrier systems for the secure and efficient delivery of insulin via non-invasive routes, principally buccal, oral, pulmonary, nasal, and transdermal systems, in an effort to improve patient compliance and reduce the inconvenience of daily painful insulin administration [5][6]. This article provides a narrative review of inhaled insulin preparations, to talk about the pharmacokinetics of inhaled insulin, and specifically to evaluate the outcomes of inhaled insulin clinical trials and some adverse effects.

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Diabetes Mellitus

Diabetes is a significant contributor to the development of cardiovascular disease and is linked to a two- to three-fold increased risk of myocardial infarction and stroke [5]. According to the WHO, diabetes mellitus can be divided into four types: type 1, type 2, gestational diabetes, and intermediate disorders such impaired glucose tolerance and impaired fasting glycaemia [1].

Two major forms of diabetes are typically recognized: Type 1 diabetes (DM1), which is characterized by the death of pancreatic beta cells that produce insulin as a result of an autoimmune response, and type 2 diabetes (DM2), which is characterized by irregularities in insulin secretion and action. Gestational diabetes is a third form, less frequent transient manifestation of diabetes that affects some pregnant women [5].

Structure and biosynthesis of insulin

The monomeric human insulin has a molecular weight of 5.8 kDa and is composed of 51 amino acids, 21 in the A chain and 30 in the B chain. One disulphide linkage exists in the A chain and two disulphide bonds connect the A and B chains [6][7][8][9]. The gene for this protein synthesis (insulin) is found on chromosome 11, and is triggered by cells of the pancreatic islets of Langerhans.

The first step in the biosynthesis of insulin is the translation of mRNA into preproinsulin, a 110 amino acid polypeptide containing an N-terminal signal peptide. Afterward come the B chain, the connecting peptide (C-peptide), and the C-terminal A chain. When preproinsulin enters the endoplasmic reticulum (ER), it converts into proinsulin and disulfide bridges form between the B and A chains. Proinsulin exits the ER, travels through the Golgi complex, and then enters the TGN, where it is sorted into organelles that are enclosed by membranes known as secretory granules [10]. When the C-peptide in this space is cleaved, proinsulin becomes develop insulin, which only consists of the B and A chains. Secretory granules containing mature insulin are either degraded intracellularly by autophagy or transported directly to lysosomes by crinophagy until they fuse with the plasma membrane to let out insulin [11][12][13]. Hyperglycemia boosts de novo insulin generation at the same time, allowing beta cells to replace their insulin granule store while also maintaining secretory competence since newly synthesized insulin is preferentially secreted [14][15].

II. NOVEL ROUTES OF INSULIN DELIVERY

Novel approaches of insulin delivery includes:

Intravenous Infusion

Insulin is injected directly into the patient's bloodstream as part of intravenous (IV) insulin therapy. It might be used by medical experts to treat patients with high blood sugar levels. IV insulin therapy is a rapid and reliable method of giving insulin intravenously. IV insulin therapy is a successful treatment for hyperglycemic episodes due to its quick-acting nature. A catheter, a small tube, is placed into the arm to deliver IV insulin therapy. The catheter will be inserted into a vein by the doctor using a needle. Saline, insulin, and other fluids are kept in a bag that the catheter is linked to. A person's blood sugar levels dictate how long they will need IV insulin. According to a trusted source, IV insulin therapy can last for three to twelve hours [16].

Subcutaneous Infusion

Insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII), has been used for more than five decades and is growing increasingly popular. The first insulin pump that has been approved by the FDA can conform to detector data, suspend on low or impending low, and provide automatic corrective gelcap boluses when glucose levels are near predetermined objects. CGM devices have lately been put onto the pump screen. Automated insulin administration technologies are revolutionizing the way that people regulate their blood sugar [17][18]. According to current estimates, approximately 1 million diabetics utilize insulin pump therapy worldwide [19].

Oral insulin Delivery

The maximum patient compliance is achieved when insulin is administered orally via the gastrointestinal tract (GIT), which also eliminates the discomfort and inconveniences associated with subcutaneous insulin administration. Moreover, oral insulin delivery is easy to use, eliminates the discomfort of needles, lowers infection risk, improves absorption, and closely mirrors the normal process of insulin secretion [20]. In order to create systems that can protect insulin and improve its absorption, oral delivery of insulin is the most practical and appealing method [21]. Similar to endogenously produced insulin, oral insulin is delivered directly to the liver through portal circulation [22].

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Transdermal insulin delivery

Insulin cannot be delivered using passive transdermal delivery systems; however, proteins and other large molecule formulations can be delivered using active transdermal delivery systems through the skin and into the bloodstream. Although the major function of skin is to guard against physical harm and infection, it also blocks the absorption of significant amounts of insulin and many medicinal chemicals from entering the bloodstream. Drug delivery across the skin (transdermal) barrier, both passive and active, is currently being explored to overcome this barrier. The transdermal insulin medication delivery system has the following characteristics: It delivers insulin passively; comes in patch, cream, and spray forms; and takes a day to diffuse through skin and take effect systemically [23][24]. Several methods have been investigated to improve insulin transdermal distribution, including the use of chemical enhancers, iontophoresis, liposomes, ultrasound, thermal ablation, and microneedles. Due to the protein drug's high molecular weight, passive insulin absorption via the skin is inefficient, which presents a problem for transdermal insulin delivery [25][26].

Buccal insulin delivery

Insulin is administered buccally through aerosol, where it is absorbed through the inner walls of the oral cavity and travels to the systemic circulation after being placed inside the mouth. Buccal and sublingual insulin administration produces better results due to low proteolytic enzyme activity levels, high tissue vascularization, a large surface area for absorption, and ease of administration [27][28].

Nasal route delivery

Intranasal insulin delivery has several advantages over oral, subcutaneous (noninvasive and painless), and inhaling methods (no difficulty with lung function), making it appealing for insulin delivery and perhaps improving patient compliance [29]. Due to the easy access to the nose, the high level of vascularization, and the relatively large surface area (150 cm^2) of absorption, nasal injection is a viable delivery method for insulin. However, a highly active mucociliary clearance mechanism that prevents the medication from staying in contact with the mucosa for an extended period of time and the presence of proteolytic enzymes work against a high biodisponibility [30].

Pulmonary insulin delivery

The most promising alternate delivery method for insulin now appears to be pulmonary inhalation. The justification for pulmonary administration is supported by a number of facts: With bronchioles, alveoli ducts, and alveoli making about 95% of the overall absorption area, the lungs have a sizable, highly vascularized potential absorption area (100-150 m^2). Alveoles are covered by a very thin (0.1-0.2 mm) monolayer of epithelial cells. The transport of molecules is not completely understood, however for small molecules like insulin, the major method is junctional paracellular transport, whereas transcytoses is favored for larger molecules [31]. For administering insulin to the alveolar space, numerous devices have been designed and are being clinically tested. For each of the devices, the bioavailability of inhaled insulin differs [32]. To obtain the best glycemic control, the ideal gadget should deliver insulin in the proper way. Also, patients should find it convenient. Devices are often metered-dose inhalers or drug-powder inhalers called nebulizers [33]. Presently, the most popular methods for delivering pulmonary insulin involve dry-powder inhalers [34].

Sublingual insulin delivery

Under the tongue is where the product is inserted in this method. Using the right permeation enhancers has improved insulin's ability to be absorbed under the tongue.[35] [36]. The East Gate Biotech produced EGP-1214, a compressed tablet contains human recombinant insulin for sublingual delivery. Initial EGP-1214 trials showed the ease of use of the created sublingual insulin tablet. It exhibits a rapid steady onset of glucose reduction activity (within 30 minutes) and does not cause irritation to the sublingual mucosa. More research on this product is needed to establish proper pharmacokinetic data. Sublingual insulin tablets may become a popular option for diabetic patients [37].

Intra-peritoneal insulin delivery

A promising alternative to the conventional subcutaneous insulin delivery method is intraperitoneal (IP) insulin administration. IP insulin administration results in faster pharmacokinetics or pharmacodynamics, allowing an artificial pancreas controller to react to glycemic disturbances more quickly. In contrast to the disadvantages of intra-peritoneal insulin administration, which include a high insulin requirement dependent on the dilution effect and, in particular, insulin binding to the

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surface of the dialysis fluid reservoir, intra-peritoneal insulin administration has been shown to improve the physiological effects of insulin in patients with diabetic nephropathy during CAPD or IPD treatment [38].

III. INHALED INSULIN

Inhaled route of administration for insulin are essentially recombinant insulin in the powdered form that is administered with the aid of an inhaler directly to the lungs. This method can be used in place of subcutaneous insulin delivery and appears to be efficient, well-tolerated, and well-liked by patients [39]. Exubera, which was introduced in 2006, and Afrezza, which was introduced in 2014, were examples of inhaled insulin that had an advantage over oral insulin due to their enormous capacity for solute exchange, thin diffusion barrier, and lack of certain GIT peptides that are responsible for the destruction of oral insulin. However, insulin that is breathed tends to raise the risk of respiratory infections, pharyngitis, etc [40][41].

Physiology of inhaling insulin

A novel way for diabetics to receive their insulin medication is by inhaling it into their lungs. The same characteristics that make the lung an excellent organ for exchange of gases additionally make it an excellent organ for absorbing tiny molecules into the circulation. At 115 m^2, the pulmonary capillary region is nearly as large as the respiratory alveolar surface area.or the size of a tennis court. With each breath, air enters about 300 million alveoli. Additionally, the alveolar lining cell is just 1-2 cm^2 away from the pulmonary capillary lumen, favoring rapid absorption into the bloodstream [42]. The ratio of a molecule's molecular mass to its absorption through the alveolar-capillary interface is inverse. The extremely thin, vesiculated, permeable membrane easily absorbs small peptides like insulin (around 6000 Da). Because the mucociliary procedures are so lower at the alveolar level, molecules that reach there devote considerable time there [43]. A number of factors influences the lower pulmonary accumulation of an aerosol or powdered composition. The particle size is one of them. Large airways and the pharynx receive deposits of particles larger than 5 cm^2 in diameter. Typically, particles 1-3 cm^2 access the alveoli and lower airways. Deposition is also impacted by particle velocity. While lower airway deposition calls for flow rates of 15 to 25 L/min, upper airway impaction benefits from flow rates of >35 L/min or 10 L/min. A little portion of an aerosol or dry powder typically does not penetrate the lungs profoundly, even under perfect circumstances [44].

The first inhaled insulin: Exubera

The first inhaled insulin for individuals with T1DM or T2DM, Exubera (Nektar Therapeutics/Pfizer), received FDA approval in 2006 [45]. Exubera's low commercial success led to its withdrawal from the market some months after its launch. The failure was attributed to factors: (1) a bulky, large and complex inhaler; (2) the time-consuming administration technique; (3) Exubera doses were labeled in milligrams rather than units, making conversion difficult; and (4) the need for complete pulmonary function tests due to minor pulmonary function abnormalities linked with the medicine. Exubera was regarded as a "convenience" medication after patients overcame these obstacles because its pharmacokinetics (PK) and pharmacodynamics (PD) were so close to SC injection of rapid-acting insulin analogs. Last but not least, in formerly heavy smokers, a minor possible lung cancer signal was observed [46][47].

Second wind of inhaled insulin: Afrezza

Notwithstanding the drawbacks associated with Exubera, pulmonary insulin delivery is still a reliable method of administration [48]. The FDA authorized MannKind's Afrezza (rapid-acting oral inhalation insulin) in 2014 to help adults with T1DM or T2DM improve their glycemic control [49]. Afrezza Insulin, a dry powder formulation, contains human insulin that has been adsorbed onto Technosphere (fumary diketopiperazine) microparticles. Those with type 2 diabetes who inhaled the drug saw a fast spike in levels of serum insulin within 5 minutes, which reached at 15 minutes [50].

Technosphere® insulin inhalation powder, a dry powder formulation with human recombinant insulin adsorbed onto carrier Technosphere microparticles with a median diameter of 2.0 to 2.5 m, is what makes up the Afrezza device. These microparticles are the perfect size for deep lung delivery [51] [49] and are found in the formulation of the Afrezza device. To distribute inhaled Afrezza, cartridges are put into a thumb-sized delivery device. The MedTone delivery device, which was used in clinical studies until 2010, is smaller and less effective than the current Afrezza inhaler [51][46]. Despite being smaller than the Exubera inhaler, the original TI inhaler device was called the MedTone and was roughly the size of one's palm.[52].

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A comparison between Exubera and Afrezza

The particle sizes of Afrezza and Exubera are comparable and within the respirable range, despite the fact that their excipients differ [53]. One of the many obvious distinctions between these two things is their distribution techniques. MannKind's Dreamboat is a user-friendly device. In contrast to Exubera, which requires inhalation after "standing cloud formation," Afrezza's inhaler is easier to use, takes less time, and is smaller, allowing it to be used privately [54]. To facilitate the transition from injectable to inhaled insulin, the insulin dosages in Afrezza cartridges are marked in international units corresponding to doses of subcutaneously administered insulin. Because Exubera dosages were specified in milligrams, determining the equivalent insulin units necessitated a separate dose conversion step.

Pharmacokinetics/Pharmacodynamics of Afrezza (TI)

Inhaled Afrezza has a rapid onset and a short half-life [51][55]. When Afrezza particles are inhaled, they dissolve in the neutral pH of the lungs, and insulin is rapidly absorbed into the bloodstream. Afrezza observes a linear, dose-related response. [51][45]. Comparatively to insulin lispro or regular human insulin, Afrezza takes shorter time (10–15 minutes) to reach its maximum plasma drug concentration and more time (about 45 minutes) to reach its peak effect on decreasing blood sugar. [51][55][56].

This has been consistently demonstrated in crossover, hyperinsulinemic, euglycemic glucose clamp research. The most recent study, which involved 30 T1DM patients, found that Afrezza's action on the metabolism began 2–3 hours earlier than equivalent doses of insulin lispro (15–19 minutes vs. 45–52 minutes) and lasted 2–3 hours less (1.8–6.4 hours vs. 5.0–9.8 hours) [57]. Afrezza's impact on glucose elimination takes place earlier than SC insulins. Because Afrezza is given orally, the effects of an acute respiratory tract infection on the PK/PD profiles have been investigated [58]. Patients with T1DM or T2DM who developed a URTI while taking Afrezza experienced no significant side effects. Similar to this, there is no statistically significant difference between the PK profile of people with mild to moderate chronic obstructive pulmonary disease (COPD) and healthy controls [59].

Administration and dosing considerations
Administration

Afrezza is administered using a small, thumb-sized inhaler and single-use cartridges containing 4 units, 8 units, or 12 units of Afrezza. There is only one inhalation required for each cartridge. If the indicated dose exceeds 12 units, a cartridge is required. To accomplish this, the first cartridge is loaded, used, then removed; the procedure is then repeated with a second cartridge. Store Afrezza cartridges in the refrigerator until ready to use. Blister cards must be used within 10 days if they have not been opened or refrigerated; blister cards that have been opened must be used within 3 days. The inhaler is replaced with a new one every 15 days, eliminating the necessity for the user to clean it.[49].

Dosing

Patients who are insulin-naive should start with 4 units of Afrezza at each meal. People who are currently using SC mealtime insulin should switch to TI, according to a conversion table on the product packaging. One-third of the daily prescribed dose of basal insulin is given at bedtime to persons who use SC premixed insulin, and the remaining two-thirds is given as TI prandial insulin at each meal. The same conversion is used to determine the dose of insulin taken during meals. The individual's metabolic requirements, blood glucose monitoring results (from self-monitoring of blood glucose, continuous glucose monitoring, or flash glucose monitoring), and goal glycemic control should all be taken into account when modifying subsequent doses [49].

Table 2. Afrezza Mealtime-Dose Conversion [60]

Injected Insulin Dose	Inhaled Afrezza Dose
Up to 4 units	4 units
5 to 8 units	8 units
9 to 12 units	12 units
13 to 16 units	16 units
17 to 20 units	20 units
21 to 24 units	24 units

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Clinical Trials

Afrezza safety and efficacy studies involved over 6500 individuals who were healthy as well as those with type 1 and type 2 diabetes. These people were exposed to Afrezza for a minimum of two weeks. Four Phase III clinical trials were conducted to evaluate the effectiveness of Afrezza. A total of 971 type 2 diabetics and 883 type 1 diabetics who were either insulin naive, had inadequate glycemic control on oral anti-diabetic medications, or had previously received insulin therapy were enrolled. These were all randomized controlled multicenter trials with treatment periods of 24 or 52 weeks. In each of the four studies, Afrezza was compared to either placebos or standard-of-care comparator drugs. The comparison studies were all open-label, but the placebo-controlled research had a double-blind design.

Afrezza's pharmacokinetic properties were carefully studied in 31 trials including healthy participants and individuals with type I or type II diabetes [61]. In this investigation, the time to maximum concentration (t max) of inhaled insulin was 12–15 minutes, while that of subcutaneous injection of recombinant human insulin was 120 minutes. Insulin levels returned to baseline after inhalation in a period of three hours as contrast to almost six hours after human insulin recombinant was infused subcutaneously. The dose administered had no impact on the measured t max, which remained consistent throughout the research.

The relative absorption of insulin administered subcutaneously versus inhalation was also investigated in this pharmacokinetic study. Insulin inhaled had a median relative bioavailability of 24%, with a range of 20-27%. In comparison to subcutaneous insulin administration, inhaled insulin caused a faster rise in serum levels of insulin (within just fifteen minutes of administration) and a faster start to action (within roughly 25-30 minutes), which more closely resembled the usual physiological reaction to the absorption of glucose following meals [61][62]. Indeed, inhaled insulin has a similar quick start of action to intravenous insulin, resulting in the first version with effects that closely resemble early physiological release of insulin [63]. Afrezza's relative bioavailability was examined again in a second trial; after administering 20 units of the inhaled drug, the observed bioavailability compared to 8 units of a subcutaneously given fast-acting insulin analogue was 33%. Overall, pharmacokinetic investigations revealed that Afrezza has a bioavailability of roughly 30% when compared to rapid-acting insulin analogues and subcutaneously injected ordinary human insulin (recombinant human insulin) [61].

Type 1 diabetes

Afrezza was examined in two Phase III clinical trials (each lasting 24 and 52 weeks) to determine its safety and efficacy in the treatment of type 1 diabetes.

In both studies, participants median ages ranged from 18 to 76 years, while their median body mass indices (BMIs) ranged from 1 to 64 years. The study individuals in the 24-week and 52-week trials had pretreatment fasting plasma glucose (FPG) concentrations of less than 180 mg/dL and pretreatment glycosylated hemoglobin (HbA1c) values of 7.5-10.0% and 7-11%, respectively. Afrezza's noninferiority to alternative insulin treatments was the primary objective of these two active-control trials, which were both carried out. For the 24-week trial and the 52-week trial, basal insulin dosages of insulin glargine, insulin detemir, or isophane insulin human were employed. During the 24-week trial, patients in each treatment group received basal insulin and were allocated at random to either prandial Afrezza therapy or prandial subcutaneous administration of the rapid-acting analog insulin aspart; during the 52-week trial, patients in each treatment group was given insulin glargine and were unintentionally allocated to either prandial Afrezza or prandial insulin aspart. In both trials, the primary efficacy goal was the mean change in HbA1c concentration from baseline, while the secondary efficacy endpoint was the mean variation in FPG concentrations from baseline to the conclusion of the trial period. The efficacy results were statistically examined in the 24-week study using mixed-model repeated measurements and in the 52-week trial using analysis of covariance (ANCOVA). In all trials, the prespecified noninferiority margin was 0.4%; consequently, for noninferiority to be established, the upper limit of the 95% confidence interval (CI)for the among-group variance had to be less than that amount. During the 24-week trial, the HbA1c reductions from the mean baseline value of 7.9% were comparable between the Afrezza group and the comparator group, with a mean variation of -0.21% (i.e., -0.21 percentage point) (95% confidence interval [CI], -0.33% to -0.09%) vs a mean change of -0.40% (95% CI, -0.52% to -0.28%). During the 52-week trial, the average HbA1c reductions in the Afrezza and comparator groups from the mean baseline of 8.4% were identical (mean change, -0.13% [95% CI, -0.24% to -0.01%] versus -0.37% [95% CI, -0.49% to -0.25%]). The Afrezza group experienced a mean decrease in FPG

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levels from baseline of 25.27 mg/dL during the 24-week trial, while the comparison group experienced a decrease of 10.15 mg/mL. The average FPG rises from beginning in the Afrezza and comparison groups in the 52-week trial were -35.5 and -20.6 mg/mL, respectively [61].

Type 2 diabetes

The safety and efficacy of Afrezza in controlling of type 2 diabetes were studied in two Phase III clinical studies lasting 24 and 52 weeks, respectively [61]. The 24-week research was a placebo-controlled equivalency trial, as opposed to the longer study, which was a comparison experiment. Ages 26 to 75 and diabetes durations of 2 to 12 years were among the patients in the 24-week trial [64]. In this experiment, 328 individuals were enrolled; all were insulin-naive, had previously received either metformin monotherapy or a combination of two or more oral antidiabetic medications, and had been on a stable regimen for at least three months prior to participation. Each participant had a BMI below 45 kg/m2 and a HbA1c score ranging from 7.5 to 10.0%.

For delivery during meals, Patients were randomly assigned to take in cartridges having either 10 units of inhaled insulin (considering bioavailability, 26%) or a placebo of non-insulin Technosphere powder. The change in HbA_{1c} between baseline and trial end served as the primary efficacy objective (24 weeks). The HbA_{1c} target was reached, while FPG and weight changes from baseline were the secondary efficacy outcomes. In the statistical examinations of the primary as well as secondary efficacy outcomes, a one-sided, one-sample t test for within-group differences and a one-sided, two-sample t test for among-group differences were employed. At randomization, the adjusted average baseline HbA1c levels in both of the groups were comparable (8.25% in the Afrezza group and 8.27% in the placebo group). The primary efficacy comparison demonstrated that Afrezza beat placebo in terms of lowering mean HbA1c concentration by -0.40% (95% CI, -0.57% to -0.23%; p 0.001). According to comparative data on the secondary effectiveness endpoints, patients using Afrezza had a higher chance than those taking a placebo of achieving either one or both of the predetermined HbA1c targets. Afrezza users had a HbA1c score of less than 6.5% at the end of the 24-week trial, which was four times greater than placebo users. Over 38% of Afrezza patients had a HbA1c of less than 7%. 15 During the 24-week study, the Afrezza group experienced a small increase in weight (0.49 kg), while the placebo group experienced a mean weight change of -1.13 kg (95% CI, -2.34 to -0.90 kg). By the conclusion of the trial, the Afrezza group had a greater mean FPG diminution (-11.20 mg/dL) than the placebo group (-3.78 mg/dL).

Afrezza's second Phase III trial in the treatment of type 2 diabetic patients was a 52-week comparison experiment that included participants who had previously been treated with insulin. 15 The effects of Afrezza with basal subcutaneous insulin were compared to those of twice-daily subcutaneous administration of an already mixed biphasic rapid-acting (BPR) insulin equivalent composed of 70% insulin aspart protamine solution and 30% insulin aspart protamine (referred to as "BPR 70/30"). Participants' ages ranged from 19 to 79, and their diabetes had been present for 1 to 52 years on average. This experiment included 618 individuals in all. Volunteers were enrolled if their BMI was above 45 kg/m2 and their HbA1c was 7.0-11.0%, as in the 24-week experiment. Treatment group participants were administered either prandial BPR 70/30 or prandial Afrezza plus subcutaneous basal insulin (insulin glargine). The major efficacy goal was an alteration in HbA1c from baseline through the investigation's end (52 weeks). The secondary efficacy objectives included weight change, FPG change, and HbA1c goal achievement. Statistical assessments of the primary as well as secondary efficacy objectives were performed using ANCOVA (analysis of covariance). At the time of randomization, the corrected mean HbA1c readings of the two groups were comparable. According to an examination of the data on the primary efficacy endpoints after 52 weeks, Afrezza and BPR 70/30 were equivalent in terms of the mean HbA1c decrease from baseline, with an among-group difference of 0.12% (95% CI, -0.05% to 0.29%). HbA1c values were 8.69% at baseline in the Afrezza group and changed on average by -0.59%; 8.68% at baseline in the BPR 70/30 group and changed on average by -0.71%. According to statistics on secondary efficacy endpoints, the HbA1c objective of 7% was achieved by nearly the same proportions of patients in both groups (22.1% in the Afrezza group and 26.8% in the BPR 70/30 group). The Afrezza group had a larger mean FPG change at the end of the 52-week trial (-26.7 mg/dL versus -12.9 mg/dL in the BPR 70/30 group). In comparison to the BPR 70/30 group, which gained 2.5 kg (95% confidence interval: 1.9-3.0 kg), the Afrezza group gained just 0.9 kg (95% CI: 0.3-1.5 kg).

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Adverse effects

Cough

Within a 52-week Afrezza trial enrolling patients with type 2 diabetes, cough was the most common medication-emergent adverse effect [65]. A mild, dry cough, which occurred in around 32% of those who received Afrezza, gradually decreased in frequency over time. Coughing issues were rarely the cause of trial termination. Cough is a common side effect of any inhaled drypowder formulation [66][67].

Hypoglycemia

While using insulin as part of an anti-diabetic drug therapy, managing hypoglycemia is a constant concern [68]. Afrezza patients with type 2 diabetes saw significantly fewer occurrences of hypoglycemia than those on an insulin analogue. The Phase III study outcomes reveal a reduction in serious hypoglycemia with Afrezza administration compared to insulin aspart treatment (31% against 49%) [69]. Patients with type 1 diabetes who were given Afrezza instead of lispro insulin reported a similar observation. When compared to the control group, Afrezza substantially decreased the possibility of mild-to-moderate hypoglycemia. [70].

Diabetic ketoacidosis.

Ketoacidosis associated with diabetes A potentially fatal disease known as diabetic ketoacidosis (DKA) can arise in diabetic patients who do not receive adequate insulin. In the 52-week diabetes type-1 experiment, DKA events occurred at a slightly higher rate in patients receiving Afrezza therapy than in patients receiving placebo. The bulk of DKA occurrences, on the other hand, were connected to infections, treatment interruptions, or lower dosages; these incidents were later discovered to be controllable through teaching initiatives at the investigational locations. In the Afrezza group, the total DKA rate was 0.46%, while the overall DKA rate in the comparison group was 0.23% [62].

IV. Conclusion

Inhaled route of administration for insulin are essentially recombinant insulin in the powdered form that is administered with the aid of an inhaler directly to the lungs. This method can be used in place of subcutaneous insulin delivery and appears to be efficient, well-tolerated, and well-liked by patients. Afrezza is a medicine that is reliable and efficient for persons with both 1 and 2 type of diabetes, and it may be a replacement to giving insulin injections for postprandial control of blood glucose management. Afrezza is a promising non-injectable insulin delivery solution for type 1 and type 2 diabetes mellitus treatment. Afrezza looks to be as effective as and equivalent to currently existing prandial insulin solutions, and it appears to be a safe alternative to injectable insulin based on available research. As with any new agent, more long-term data will be useful in determining Afrezza's full potential in the treatment of diabetes and the product's success. More research is needed to determine the long-term safety of afrezza in terms of pulmonary concerns.

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