First approved inhaled insulin therapy for diabetes mellitus

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The long-term benefits of tight glycemic control in preventing microvascular and macrovascular complications are well established in both Type 1 diabetes mellitus (Type 1 DM) and Type 2 diabetes mellitus (Type 2 DM). Nonetheless, achievement of recommended haemoglobin A_{1c} (HbA_{1c}) goals (≤ 6.5 – 7.0%) has remained elusive, especially in patients with diabetes who require insulin therapy. Delayed/suboptimal titration of insulin is partly related to poor acceptance of multiple injection regimen by both physicians and patients. EXUBERA® (human insulin [rDNA origin]; Pfizer), the first approved inhaled insulin for the treatment of diabetic patients, has been shown to be safe and as effective as regular/rapidly acting insulin in improving glycemic control. In addition to controlling postprandial glucose excursions, EXUBERA exerts a major action to reduce fasting plasma glucose (FPG) concentration. Thus, it has the potential to be used as a monotherapy in Type 2 DM, as well as in combination with an insulin sensitizer in Type 2 DM or in combination with long-acting insulin in both Type 2 DM and Type 1 DM.

Keywords: diabetes mellitus, EXUBERA, glycemic control, inhaled insulin

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1. Background

1.1 Overview of glucose homeostasis

In the postabsorptive state, the fasting plasma glucose (FPG) concentration in healthy adults is maintained within a very narrow range: 65 – 105 mg/dl (3.6 – 5.8 mmol/l) [1,2]. Under basal conditions, insulin-independent tissues, the brain and the splanchnic organs, account for the majority of total body glucose use (50 – 60% and 20 – 25%, respectively). Muscle, an insulin-dependent tissue, is responsible for most of the remaining 20 – 25% of glucose disposal in the fasting state [1,2]. The basal rate of tissue glucose uptake is precisely equaled by an equivalent rate of glucose output by the liver. After the ingestion of glucose, this delicate balance between hepatic glucose production (HGP) and tissue glucose use is disrupted, and the maintenance of normal glucose homeostasis in the fed state is dependent on four processes that occur simultaneously and in a coordinated, tightly integrated fashion [1,2]: i) in response to hyperglycemia, insulin secretion is stimulated; ii) the combination of hyperinsulinemia plus hyperglycemia augments glucose uptake by splanchnic (liver and gut) and peripheral (primarily muscle) tissues; iii) both insulin and hyperglycemia suppress HGP; iv) insulin inhibits lipolysis in adipocytes and the reduction in plasma free fatty acid (FFA) concentration enhances muscle glucose uptake and facilitates the suppression of HGP.

1.2 Existing treatment

In Type 1 diabetes mellitus (Type 1 DM), autoimmune destruction of the β cells in the pancreas, with resultant hypoinsulinemia, represents the primary pathogenic disturbance, and treatment requires basal insulin replacement (to suppress HGP and maintain normal FPG levels) in combination with a rapidly acting insulin with each

meal (to control postprandial glucose excursions). In Type 2 diabetes mellitus (Type 2 DM), insulin resistance in the liver (resulting in excess HGP and elevated FPG concentrations) and in muscle (leading to postprandial hyperglycemia), in combination with progressive β-cell failure, all contribute to the disturbance in glucose homeostasis [2]. Thus, a rational approach to therapy in Type 2 DM patients requires the use of an insulin sensitizer in combination with agents that enhance/preserve β-cell function and/or in combination with insulin-replacement therapy.

1.3 Medical need

The long-term benefits of tight glycemic control in the prevention of both microvascular and macrovascular complications have been well established in Type 1 DM and Type 2 DM patients [3-8]. Whether the improvement in glycemic control is achieved with insulin or oral agents, a 1% reduction in HbA_{1c} has been consistently associated with a 25 – 35% decrease in microvascular complications [3-6]. Improved glycemic control with insulin [6,7] and insulin sensitizers [5,8] has also been shown to reduce macrovascular complications. The early use of insulin may also slow the loss of endogenous insulin secretion in Type 2 DM patients [9].

Recently, EXUBERA® (human insulin [rDNA origin]; Pfizer), a dry powder, that is an inhaled form of fast-acting insulin developed by Pfizer and the sanofi-aventis group in conjunction with Nektar Therapeutics, has been approved by the FDA as the first inhaled insulin system. This review examines the rationale, efficacy and safety of EXUBERA in the treatment of both Type 1 DM and Type 2 DM patients.

2. Scientific rationale

2.1 Lung anatomy

Lung airways contain thick-walled bronchial tubes that divide > 20 times before branching into thin-walled alveoli. Bronchial tubes are impermeable to insulin, whereas insulin can easily cross the alveoli. Inhaled medications for asthma and chronic obstructive pulmonary disease (COPD) act on the bronchial tubes without having to reach the alveoli and circulation. The doses of these medications do not need to be accurately predetermined, as they can be titrated based on symptoms (e.g., bronchodilators) and because excessive doses cause few side effects (e.g., corticosteroids and membrane stabilizers). In contrast, insulin must reach the alveolar capillary circulation in precise amounts to control the blood glucose without causing hypoglycemia.

For insulin to reach the alveoli, particle size must be closely controlled between 1 and 3 µm [10]; larger particles deposit in the bronchial tubes and smaller particles are exhaled. Insulin particles between 1 and 3 µm can be produced as a dry powder or as a liquid [10,11]. A mechanical release system is used to create a standing cloud of dry powdered insulin, whereas a mechanical/electronic release system is used to generate a fine mist of solubilized insulin. Rapid and turbulent airflow must be avoided with both systems, as this promotes deposition of insulin particles in the throat and bronchial tubes. Therefore, alveolar delivery of insulin requires slow and even inhalations.

The adult lung contains ~ 500 million alveoli with a total surface area (143 m^2) that is 70-times greater than the entire body [12]. Inhaled insulin molecules are transported across the alveolar cell membrane into the capillary blood by a process termed transcytosis [13]. Alveolar epithelial cells engulf insulin in small membrane bubbles called caveolae, which shuttle insulin across the cell membrane into the bloodstream.

Peak activity of inhaled insulin occurs ~ 60 min after inhalation [14] making it satisfactory for prandial use. Approximately 30% of the inhaled dose is absorbed into the alveolar capillary circulation [14], 20% is deposited in the throat and bronchial tree. Between 20 and 40% of the insulin that reaches the alveoli is actually taken up into the bloodstream.

2.2 Pulmonary function in diabetes

Studies show that the forced vital capacity (FVC) and the forced expiratory volume in the first second (FEV_1) are lower in diabetic patients than non-diabetic individuals [15-18]. In the Copenhagen City Heart Study [19], the difference between the diabetic and non-diabetic groups was ~ 8%, which is similar to the difference between a smoker and someone who has never smoked. The cause of the decrease in pulmonary function is unclear. Patients with diabetes are commonly overweight and have a high body mass index (BMI) that is associated with a reduced ventilatory capacity. In the Framingham Heart Study, a lower than predicted lung function was associated with elevated fasting glucose levels [20].

2.3 Competitive environment

2.3.1 EXUBERA: indications

EXUBERA has been approved for the treatment of adult patients with diabetes mellitus [21]. In patients with Type 1 DM, EXUBERA should be used to control post-meal glucose excursions in combination with a long-acting insulin preparation to provide basal insulin replacement. In patients with Type 2 DM, EXUBERA can be used as a monotherapy, as a combination therapy with oral agents or in combination with a long-acting insulin [21]. Because insulin resistance is a hallmark feature of Type 2 DM [22,23], the authors believe that when EXUBERA is used with an oral agent, combination with an insulin sensitizer (thiazolidinedione or metformin) provides the most rational approach. It is noteworthy that in many studies of Type 2 DM, the use of EXUBERA as a monotherapy or in combination with an oral agent effectively reduced the FPG concentration, even though its pharmacodynamic effect has been largely shown to wane by 6 h (see Section 9.1). Although it has not been approved for use in children (6 – 11 years) and adolescents (12 – 17 years) with Type 1 DM, EXUBERA has been shown to effectively reduce plasma glucose levels in both groups [21]. The absorption of EXUBERA is independent of the patient's BMI. This is in

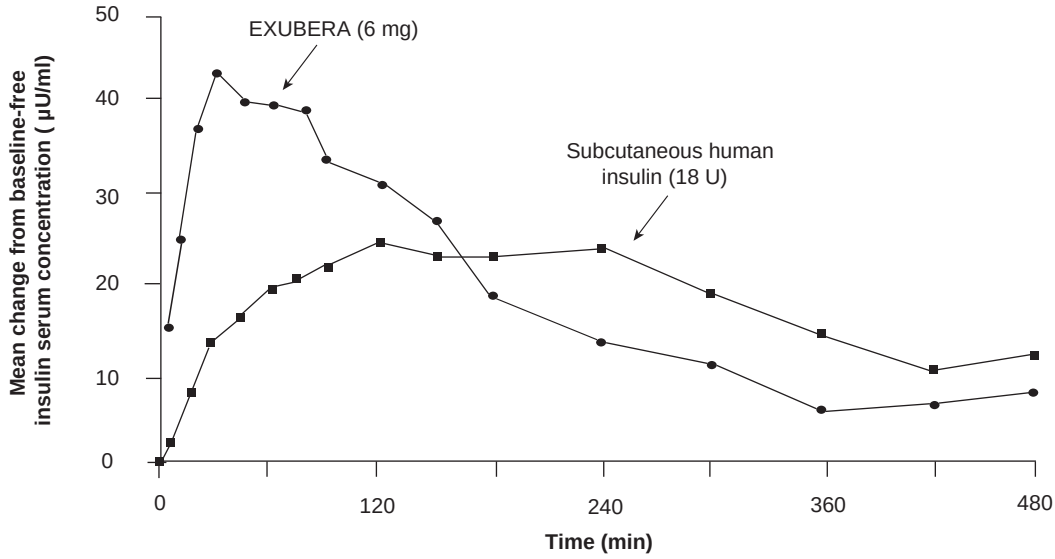

Figure 1. Time course of change from baseline in serum-free insulin concentration in healthy, nondiabetic subjects who received a single dose of EXUBERA (6 mg) and a single dose of subcutaneously injected human regular insulin (18 U) on separate days. The doses of EXUBERA and subcutaneous insulin have been shown to produce an equivalent stimulation of whole body glucose disposal.

contrast to the absorption of subcutaneous insulin, during which the absorption of this formulation decreases with increasing BMI. The effect of renal and hepatic impairment on the pharmacokinetics of EXUBERA has not been studied and the drug should be used carefully in patients with these disorders.

2.3.2 *EXUBERA: pharmacodynamics/pharmacokinetics*

EXUBERA consists of blister packets containing 1 or 3 mg of human insulin inhalation powder (HIIP), which are administered using the EXUBERA inhaler. After an EXUBERA blister is inserted into the inhaler, the patient pumps the handle of the inhaler and presses a button, causing the blister to be pierced. The insulin inhalation powder is then dispersed into the chamber, allowing the patient to inhale the aerosolized powder. Up to 45% of the 1-mg blister contents and up to 25% of the 3-mg blister contents may be retained in the blister. The 1-mg blister packet is equal to ~ 3 units of subcutaneously injected insulin and the 3-mg blister packet is equal to ~ 8 units. In a study comparing the administration of three 1-mg blister packets, the C_{max} and AUC for plasma insulin concentration were ~ 30 – 40% greater than that after one 3-mg blister packet [21].

In patients with Type 1 DM and Type 2 DM, the serum insulin concentration reaches its peak faster after inhalation of EXUBERA (49 min; range = 30 – 90 min) than after subcutaneous injection of human regular insulin (105 min; range = 60 – 240 min) (Figure 1) [21]. This pharmacokinetic profile is consistent with the pharmacodynamic time course of action of the two insulin preparations. The onset of glucose-lowering activity in healthy volunteers occurs within 31 min, the maximum glucose-lowering effect is observed at ~ 108 min and the duration of action lasts for about 6 h: longer than that of subcutaneous lispro insulin, but comparable to regular insulin [24]. In a more recent study [25], EXUBERA was compared with subcutaneous lispro and regular insulin in 17 healthy subjects using the euglycemic glucose clamp technique (Figure 2). EXUBERA had a faster onset of action (32 min) compared with subcutaneous regular insulin (48 min; $p = 0.001$) and subcutaneous lispro insulin (41 min; $p < 0.05$). The time of maximal metabolic action of EXUBERA and lispro insulin was comparable (143 versus 137 min; p = nonsignificant), but significantly shorter than regular insulin (193 min; $p < 0.01$). The duration of metabolic activity with EXUBERA (387 min) was similar to that of regular insulin (415 min; p = nonsignificant) and longer than lispro insulin (313 min; $p < 0.01$).

The reproducibility of the insulin pharmacokinetics and glucose profile has been examined in two studies with similar results [26,27]. Gelfand *et al.* administered EXUBERA (two separate inhalations) and subcutaneous regular insulin (two separate injections) in a four-way, randomized-sequence crossover study in 16 Type 2 DM patients, who ingested a standardized Sustacal meal [26]. The intrasubject differences between the two same-dose routes of administration were small, and the reproducibility for EXUBERA was similar to that of subcutaneous regular insulin.

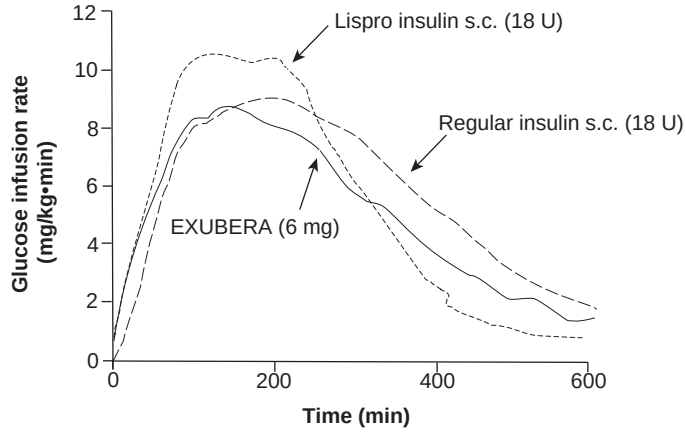

Figure 2. Time course of change in the glucose infusion rate required to maintain euglycemia in healthy non-diabetic subjects following a single dose of EXUBERA® (6 mg), subcutaneous lispro insulin (18 U), and subcutaneous regular insulin (18 U) on separate days.

The pharmacokinetics of EXUBERA have not been studied in diabetic patients with asthma and other chronic pulmonary conditions. Therefore, the use of EXUBERA in these groups is not recommended. However, when administered to non-diabetic subjects with COPD, the plasma insulin levels were approximately double than that found in subjects without COPD [21]. The use of EXUBERA in smokers or in individuals who have discontinued smoking within 6 months is not recommended [21]. In one study [28], the plasma insulin levels were greater than two fold in smokers compared with non-smokers. In contrast, exposure of nondiabetic individuals to passive cigarette smoke for 2 h reduced systemic insulin levels by 20 – 30%. In patients with diabetes who experienced an intercurrent respiratory illness, there were no differences in glycemic control or incidence of hypoglycemia in EXUBERA-treated versus subcutaneous insulin-treated patients.

3. Clinical studies

The efficacy and safety of EXUBERA has been evaluated in > 2500 individuals with Type 1 DM (three studies) and Type 2 DM (six studies) (see Sections 3.1, 3.2 and Figures 3 and 4).

3.1 Type 1 diabetes mellitus

Quattrin *et al.* randomized 335 Type 1 DM subjects (baseline HbA_{1c} = 8.1%) to receive either premeal EXUBERA plus bedtime Ultralente or 2 or 3 injections of subcutaneous regular insulin plus Neutral Protamine Hagedorn (NPH) insulin for 24 weeks (Figure 3) [29]. After 24 weeks, the HbA_{1c} was 7.9 ± 1.1% in the EXUBERA group and 7.7 ± 0.9% in the subcutaneous insulin group, indicating equivalency of inhaled and subcutaneous regular insulin. Skyler *et al.* randomized 328 patients with Type 1 DM (HbA_{1c} = 8.1 ± 1.0%) to receive either premeal EXUBERA or regular subcutaneous insulin in combination with NPH insulin before breakfast and at night (Figure 3) [30]. After 24 weeks, the HbA_{1c} was 7.7 ± 0.1% in the EXUBERA group and 7.8 ± 1.2% in the subcutaneous insulin group. The two treatment regimens were statistically comparable with respect to the reduction in HbA_{1c} and the percentage of patients achieving HbA_{1c} were < 7 and < 8%. In a preliminary proof-of-concept study in 72 Type 1 DM patients, Skyler *et al.* also demonstrated a similar reduction in HbA_{1c} in individuals randomized to twice-daily isophane insulin plus EXUBERA before meals versus once-daily ultralente insulin plus subcutaneous regular insulin before each meal (Figure 3) [31].

In summary, trials in Type 1 DM demonstrate that treatment regimens comparing a long-acting insulin plus EXUBERA versus long-acting insulin plus subcutaneous regular human insulin, yield comparable results with respect to the reduction in HbA_{1c}.

3.2 Type 2 diabetes mellitus

Rosenstock *et al.* [32] conducted an open-label, multi-center study in 309 Type 2 DM patients who were randomized to one of three groups: continued current oral hypoglycemic agents (OHA); premeal EXUBERA as a monotherapy (with discontinuation of all oral agents); and present oral agent

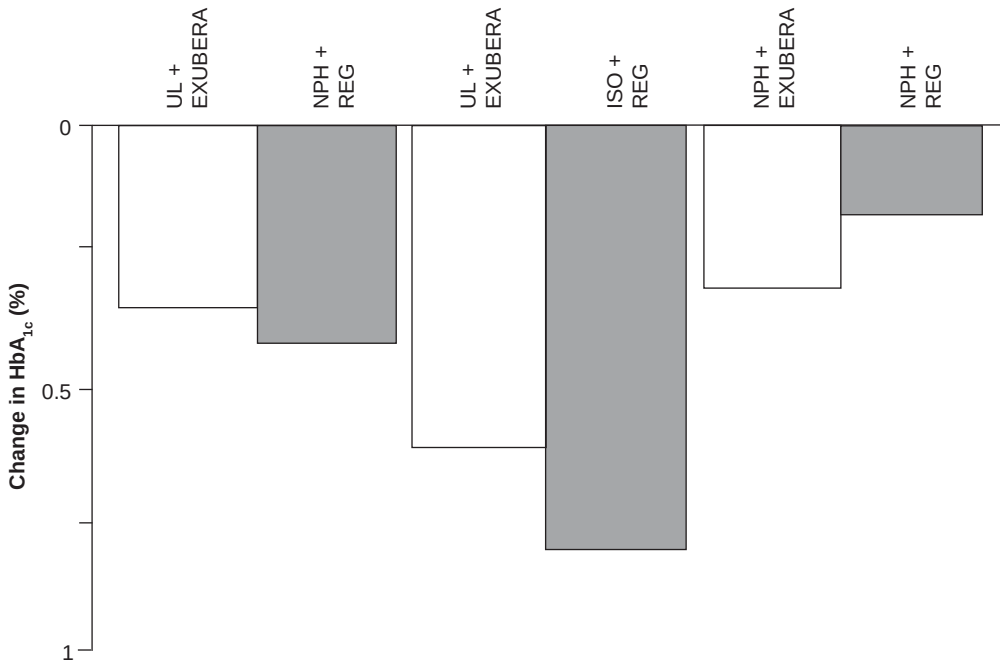

Figure 3. Decrease in HbA_{1c} levels in Type 1 diabetic subjects who were treated with EXUBERA® plus a long-acting insulin versus subcutaneous injected human regular (REG) insulin plus a long-acting insulin. EXUBERA and regular insulin produced similar reductions in HbA_{1c} levels in all three studies.
Information from [29-31].
ISO: Isophane; NPH: Neutral Protamine Hagedorn; UL: ultralente.

therapy plus EXUBERA (Figure 4). After 12 weeks there was a significant improvement from baseline in HbA_{1c} (-1.4 and -1.9%, respectively), FPG, and 2-h plasma glucose (PG) in both the EXUBERA monotherapy and EXUBERA plus OHA groups, compared with the OHA only group. Weiss *et al.* evaluated the effect of EXUBERA on glycemic control in 68 Type 2 DM patients who were poorly controlled near maximal/maximal therapeutic doses of an OHA (sulfonylurea and/or metformin) (Figure 4) [33]. In patients randomized to receive EXUBERA three-times daily before meals plus OHA therapy, the HbA_{1c} decreased by 2.3% versus a decline of 0.1% in subjects who continued oral agent therapy. In an open-label, parallel-group, 24-week, multi-center trial, Barnett *et al.* randomized 423 Type 2 DM patients (who were poorly controlled with sulfonylurea monotherapy) to receive either adjunctive treatment with metformin or premeal EXUBERA (Figure 4) [34]. The addition of EXUBERA produced a slightly greater reduction in HbA_{1c} compared with the addition of metformin (2.1 versus 1.8%; p = 0.01). DeFronzo *et al.* randomized 145 Type 2 DM patients who had a suboptimal control on diet and exercise (baseline HbA_{1c} = 9.4 – 9.5%) to receive premeal EXUBERA or rosiglitazone (4 mg b.i.d.) (Figure 4) [35]. After 3 months, the HbA_{1c} reduction was greater in the EXUBERA versus the rosiglitazone group (-2.3% versus -1.4%; p < 0.0001). Hollander *et al.* randomized 298 Type 2 DM patients, poorly controlled on at least two daily injections of insulin, to receive premeal EXUBERA plus bedtime ultralente or at least two subcutaneous injections of mixed regular/NPH insulin for 6 months (Figure 4) [36]. The reduction in HbA_{1c} was similar in the EXUBERA (-0.7%) and subcutaneous regular insulin (-0.8%) groups. In a small study, Cefalu *et al.* randomized 26 insulin-treated Type 2 DM patients, who were not taking oral agents, to continue their conventional stable insulin regimen or to start premeal EXUBERA with a single bedtime injection of ultralente insulin (Figure 4) [37]. In the EXUBERA group, HbA_{1c} declined by 0.7% and remained unchanged in the stable insulin regimen group.

4. Safety of EXUBERA

4.1 Pulmonary changes

Cough was reported more frequently in the EXUBERA group versus the comparison group (~ 20 – 30 versus 10%) in most published studies. However, the cough was usually mild-to-moderate and waned over time. There was a statistically significant decrease in FEV_1 and carbon monoxide diffusion capacity (DLCO) in Type 1 DM patients who were treated with EXUBERA for 6 months [29,30]. In Type 2 DM individuals treated with EXUBERA for a similar time period, changes in pulmonary function were small and no significant differences between groups (EXUBERA versus

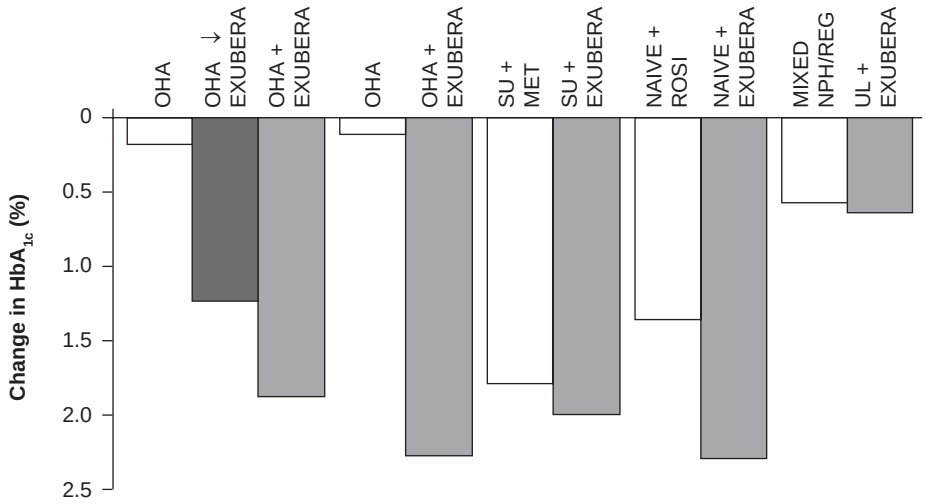

Figure 4. Decrease in HbA_{1c} levels in Type 2 diabetic subjects in whom EXUBERA® was added to/substituted for (OHA → EXUBERA) the patient's usual OHA or insulin therapeutic regimen.

Information from [32-36].

MET: Metformin; NAIVE: Drug naive; NPH: Neutral Protamine Hagedorn; OHA: Oral hypoglycemic agent; REG: Regular insulin; ROSI: Rosiglitazone; SU: Sulfonylurea; UL: Ultralente.

regular/long-acting insulin) for FEV_1, FVC, total lung capacity or DLCO were observed [32-35]. Recent long-term (2-year) safety data indicate that in both Type 1 DM and Type 2 DM patients, changes in FEV_1 and DLCO are small (< 1 – 2% from baseline), occur within the first 3 months of initiation of EXUBERA therapy and remain stable with no progression for 2 years [48,49]. There have been two cases of pulmonary fibrosis (0.4 per 10,000 subject months exposure) in patients treated with EXUBERA and one case of pulmonary fibrosis (0.5 per 10,000 subject months exposure) in the comparator (oral agent) group. The FDA recommends pulmonary function testing at baseline, after 6 months of initiation of EXUBERA therapy and annually thereafter, even if no symptoms are present. The use of EXUBERA in diabetic patients with COPD and asthma is not recommended because of insufficient studies in patients with these pulmonary diseases. If the FEV declines by ≥ 20% on follow-up testing, the FEV_1 measurement should be repeated. If the repeat value remains ≥ 20%, EXUBERA should be discontinued.

4.2 Hypoglycemia

Hypoglycemia is a potential complication with all forms of insulin therapy. In both Type 1 DM and Type 2 DM, the incidence of hypoglycemia was similar in patients treated with EXUBERA versus subcutaneous insulin injection. In the study conducted by Skyler *et al.* [30]; however, the rate of serious hypoglycemia was higher in the EXUBERA group. As expected, the incidence of hypoglycemia in Type 2 DM patients treated with EXUBERA was higher than in the group receiving oral agents.

4.3 Insulin antibodies

In most trials, the prevalence of insulin antibodies was higher in the EXUBERA versus subcutaneous insulin injection group, but the increased level of insulin antibodies was not associated with adverse glycemic consequences, as measured by the difference in HbA_{1c} levels, need for titration of insulin dosages, or frequency of hypoglycemia [29,30,32,34,35,50].

4.4 Body weight

Small and similar increases in body weight were observed in EXUBERA and subcutaneous insulin comparison groups.

4.5 Patient satisfaction

Rosenstock *et al.* [51] performed a 12-week study in subjects with Type 1 DM and Type 2 DM who were randomized to receive either EXUBERA with ultralente or 2 – 3 shots of subcutaneous insulin with ultralente or to a mixed/split insulin regimen, followed by a 1-year open-label extension. 85% of the patients who were treated with EXUBERA during the 12-week period chose to continue EXUBERA treatment, whereas only 21% treated with subcutaneous insulin during the 12-week study chose to remain on the regimen. There was greater patient satisfaction and compliance in the EXUBERA group, with durable effects on HbA_{1c} levels. In a study of theoretical treatment choices in inadequately controlled Type 2 DM individuals, diabetic patients were three times more likely to choose insulin therapy when inhaled insulin was provided as an option [52].

Table 1. Approximate guidelines for initial, premeal EXUBERA® dose.

Patient weight (kg)	Patient weight (lbs)	Initial dose per meal (mg)	Number of 1-mg blisters per dose	Number of 3-mg blisters per dose
30 – 39.9	68 – 87	1	1	–
40 – 59.9	88 – 132	2	2	–
60 – 79.9	133 – 176	3	–	1
80 – 99.9	177 – 220	4	1	1
100 – 119.9	221 – 264	5	2	1
120 – 139.9	265 – 308	6	–	2

5. Cost of EXUBERA

The Wholesale Acquisition Cost (also know as the list or catalog price) in the US ranges $3.73 – 5.00 per day. The retail pharmacy charge to the customer will vary from location to location. At present, Pfizer is negotiating with insurance companies for coverage.

6. Initial premeal EXUBERA dose

Guidelines for initial premeal EXUBERA dose, based on the patient's body weight, are provided in Table 1. These initial pre-meal doses are based on clinical trials in which patients consumed three meals per day and are calculated as follows: (body weight in kg) × (0.05 mg/kg), where tenths of a milligram are rounded down to the nearest whole milligram. This initial EXUBERA dose must then be individualized, based on the results of home blood glucose monitoring. As Type 2 DM patients are resistant to the action of insulin, higher doses of EXUBERA are likely to be required in patients with Type 2 DM versus those with Type 1 DM.

7. Other pulmonary insulin delivery systems in development

Each pulmonary insulin delivery system in development consists of three components: an insulin formulation, a unique insulin packaging and a unique delivery device.

7.1 AERx® Insulin Diabetes Management System

The AERx® Insulin Diabetes Management System (iDMS; Aradigm Corp., Novo Nordisk) device creates a fine aerosol mist of liquid insulin, which is then inhaled [55]. The battery-powered device is slightly larger than a paperback book and has a slot for placement of the insulin strip, a user input button, an information screen for the patient and a breath-control guidance light. To minimize variability in inhalation technique, the device contains a microprocessor that analyses the patient's inhalation and automatically activates when optimal inspiratory conditions are met. The breath control guidance light instructs the patient to continue to inhale until an optimal air volume is reached [56]. The liquid insulin for inhalation is contained in a small bubble on a strip, which is placed into the device. The strip itself has a one-use only nozzle, with hundreds of 1 µm holes, which release the insulin uniformly [55,57]. The insulin bubble is mechanically compressed to extrude the aqueous insulin through the nozzle and subsequently mixed with air to form an aerosol with a particle size diameter 1 – 3 µm.

AERx iDMS dosing is in units and each AERx unit has ~ 260 µg of insulin, which provides the same glucose-lowering effect as 1 unit of subcutaneously injected insulin [58]. By using the user input button, each strip can be selected to deliver 2 – 10 units of insulin [57].

The insulin pharmacokinetic and glucose-lowering pharmacodynamic profiles of AERx iDMS are linear over an inhaled dose range of 0.3 – 1.8 units/kg, when studied in a glucose clamp study in subjects with Type 1 DM. The onset of insulin action is ~ 10 min, with peak insulin levels occurring 50 – 60 min after inhalation. The duration of action is dependent on the dose, with a duration of 5 h at a dose of 0.3 units/kg and ~ 8 h at a dose of 1.8 units/kg [59]. Intrasubject variability is similar in Type 1 DM subjects administered with equivalent doses of either subcutaneous human regular insulin or inhaled insulin [58,59]. Peak serum insulin levels are affected by inhalation volume and depth. Thus, subjects with low air volume intake and/or shallow inspiration had significantly lower and delayed peak serum insulin levels [56]. In non-diabetic subjects, an upper respiratory tract infection had little effect on insulin pharmacokinetics or pharmacodynamics [60]. In patients with mild-to-moderate asthma, inhaled insulin absorption was decreased compared with healthy controls and intrasubject variability was increased [61]. In smokers, insulin $AUC_{(0\text{-}6\ h)}$ was 60% higher, C_{max} was 3-times higher and absorption was more rapid compared with non-smokers [62]. Similar observations have been made with EXUBERA.

In a 12-week study of patients with Type 2 DM, three AERx iDMS insulin inhalations in conjunction with bedtime NPH produced a similar reduction in HbA_{1c} as compared with fast-acting human insulin (Actrapid®; Novo Nordisk) given subcutaneously prior to each meal [55]. There were three major hypoglycemic episodes (requiring assistance) that were reported in two subjects treated with AERx, compared with none in the subcutaneous insulin group. The relative risk of overall hypoglycemia with AERx iDMSinsulin was slightly, although not significantly increased compared with subcutaneous insulin. The insulin antibody level increased only in the AERx group, but no correlation with side effects or efficacy was noted. No significant changes in pulmonary function tests (PFTs) were reported with AERx iDMS versus subcutaneous insulin [55].

At present, AERx iDMS is in Phase III trials. Advantages of the system include the ability to change the aqueous

Table 2. Inhaled insulin formulations, pharmacokinetics and issues.

Insulin	Pharmacokinetics			Formulation	Advantages/disadvantages
	Onset (min)	Peak (min)	Duration (h)		
EXUBERA®	30	30 – 90	6	Dry powder	Available only as 1- or 3-mg blister packs Slight ↓ FEV_1 and DLCO levels
AERx® iDMS	10	50 – 60	5 – 8	Liquid	Microprocessor in delivery device that minimizes inhalation variability Device durability is a concern Duration of action is dose dependent Similar lung cautions as EXUBERA
AIR®	15	45	6 – 8	Dry powder	Device is simple to use Dosing limited to 2- and 6-unit capsules Similar lung cautions as EXUBERA
Technosphere /Insulin®	Minutes	13	2 – 3	Dry powder	Microencapsulation delivery most likely gives insulin unique kinetics No PFT changes in published reports
Alveair™	–	–	–	Liquid	Unmodified human insulin; most likely to have the same kinetics/concerns as other inhaled insulins, but no kinetic/PFT data in humans as yet
Kos	15 – 30	90	6 – 8	Liquid	Meter-dose style inhalation device

PFT: Pulmonary function test.

insulin by 1 unit increments and the flexibility of one strip, which can deliver a dose from 2 – 10 units. Inhalation technique, as with EXUBERA, will be important as absorption kinetics can be affected by changing the inhalation pattern. The delivery system mechanics are complex, but the patient-friendly features for maximization of inhalation technique are unique. Disadvantages are the lack of long-term data on the device. In a 12-week study, 3% of study devices suffered non-recoverable malfunctions and patients required more instruction time and phone follow-up than with subcutaneous insulin [55].

7.2 AIR® inhaled insulin system

In the AIR® inhaled insulin system (HIIP; Alkermes/Eli Lilly), insulin is formulated from an insulin solution that is subsequently spray-dried to form low-density porous particles with low cohesive forces [63]. The insulin is then packaged into a capsule for use in the inhalation device. At present, 2-unit (0.9 mg/capsule) and 6-unit (2.6 mg/capsule) insulin capsules are in development. Each capsule is formulated to provide approximately the same glucose-lowering effect as an equivalent dose of subcutaneous insulin [64]. To insert a capsule, the mouthpiece of the device is removed and the capsule is inserted. On reattachment of the mouthpiece, the capsule is punctured. The energy provided by inhalation of air through the device is sufficient to make the capsule spin, forming an aerosol for inhalation [64].

Several pharmacokinetic and pharmacodynamic studies have been performed in healthy control subjects with the AIR inhaled insulin system. Following doses of 2.6, 5.2 and 7.8 mg (equivalent to 1, 2 and 3 inhalations of a 6-unit capsule), the onset of action (euglycemic glucose clamp) was 15 min, with peak serum insulin concentrations reached by 45 min. The duration of action was 6 – 7 h, but at the 7.8-mg dose, the duration of action was extended to ~ 8 h [65]. When HIIP was compared with lispro insulin, the onset and time to peak insulin concentration were similar, but the duration of action was longer with HIIP [65]. The pharmacokinetics and pharmacodynamics of 1 inhalation of 6 units or 3 inhalations of 2 units is equivalent, as measured by a 10-h euglycemic glucose clamp [64].

In a 12-week study in Type 1 DM subjects who were randomized to receive prandial coverage with subcutaneous insulin or HIIP in conjunction with glargine insulin, the reduction in HbA_{1c} levels with HIIP was equivalent to subcutaneous injected insulin. Total and severe hypoglycemic events did not differ between groups, but nocturnal hypoglycemia occurred more frequently with HIIP [66]. In a 4-week study in metformin-treated Type 2 DM, HIIP significantly lowered HbA_{1c} and 2-h postprandial glucose excursions based on seven-point self-monitoring of blood glucose. Pulmonary function tests (PFTs) showed small, but statistically significant, reductions in total lung capacity, FEV_1, FVC and DLCO [67]. In Type 1 DM patients, a small, but significant, reduction in DLCO was also noted [66]. HIIP is now in Phase III studies and long-term outcomes will help to further elucidate the side effect profile.

7.3 Inhaled Technosphere/Insulin®

Technosphere/Insulin® (T/I; Mannkind Corporation) is a drug delivery system that is based on a small organic molecule that self-assembles into small microspheres when placed in a mildly acidic setting, thus capturing and stabilizing insulin within it. The diameter of the spheres, ~ 2 – 3 µm, is appropriate for deep lung penetration [68]. When dried, the microspheres can be administered as an inhalation powder, as the technospheres dissolve in the neutral pH of the lungs. The dissolved organic compound is quickly excreted as ammonium salts [68]. The inhalation powder is placed in single-use, disposable plastic cartridges, which fit into the MedTone inhaler. The MedTone inhaler, which is smaller than the palm of the hand, has a mouthpiece that swings open, allowing the cartridge to be placed into the inhaler [68].

The pharmacokinetic onset and peak effect seem to be faster and the duration of action shorter than other inhaled insulin preparations. In non-diabetic healthy controls, the pharmacokinetic and pharmacodynamic parameters of 100 units of T/I have been compared with 10 units of regular human insulin, administered either by the intravenous or subcutaneous route during a 6-h euglycemic glucose clamp. The median time to maximal insulin concentration after T/I inhalation was ~ 13 min, compared with 9 min for intravenous regular human insulin, but much faster than the 121 min for subcutaneous human insulin. Insulin levels with T/I returned to baseline by 3 h [69]. Using the MedTone inhaler, a linear dose-dependent effect was observed with 25, 50 or 100 units of T/I [70]. A 12-week study compared prandial T/I with placebo in poorly controlled Type 2 DM subjects (HbA_{1c} = 7.8%) who were treated with diet or oral agent therapy. T/I reduced the HbA_{1c} by 0.7%, compared with 0.3% in placebo [48]. In poorly controlled Type 2 DM subjects administered with prandial T/I at doses of 28, 42 and 56 units for 12 weeks in conjunction with Lantus insulin, HbA_{1c} declined by 0.67, 0.70 and 0.78%, respectively. No reductions in FEV_1 or DLCO were reported over the 12-week study period [71]. In Type 1 DM subjects who were randomized to Lantus plus prandial T/I or aspart insulin for 3 months, the HbA_{1c} reduction for T/I and aspart insulin was similar: 0.83% and 0.99%, respectively. FEV_1 and DLCO with T/I therapy did not differ significantly from aspart insulin [72].

Overall, T/I seems to have a much different onset, peak and duration of action profile compared with other inhaled insulins. The short duration of action, 3 h, could potentially result in rebound hyperglycemia late in the dosing period in some patients, but could be advantageous in patients who require only additional prandial coverage. The short-term safety profile of T/I seems to be good, with no changes in FEV_1 and DLCO noted over 3 months. Phase III trials are presently ongoing.

7.4 Others

7.4.1 *Aerodose Insulin Inhaler®*

In 2005, Nektar Therapeutics, manufacturer of the inhaler for EXUBERA, acquired Aerogen, Inc. The merger makes it unlikely that the Aerodose Insulin Inhaler® system will be placed on the market independently, but it may be incorporated into future devices. Aerodose is a liquid-based inhaler that depends on vibrations to form an inhaled aerosol. Several articles have been published on its pharmacokinetics and pharmacodynamics [73-75].

7.4.2 *Alveair™*

The Alveair™ inhaled insulin delivery system (Coremed, Inc.) uses a polymer/bioadhesive platform to formulate insulin into micron-sized particles (median mass diameter = 1.9 µm) that are suitable for deep lung inhalation. Several pharmacokinetic/pharmacodynamic abstracts in animals have been reported [76,77]. Of note, insulin bioavailability was reported to be close to 100% in normal rats [77]. In four healthy, non-diabetic human subjects, Alveair had glucose-lowering effects within 1 h and a duration of action of ~ 8 h [78].

7.4.3 *Kos inhaled insulin*

Kos Pharmaceuticals is presently working on a metered-dose inhaler style insulin inhalation system. In 12 healthy, nondiabetic subjects, pharmacokinetic/pharmacodynamic effects seemed to be linear at three tested doses, with onset of the glucose-lowering effect within 30 min, peak effect at ~ 2 h and a duration of action similar to regular subcutaneous insulin [79]. In 24 poorly controlled Type 2 DM subjects (baseline HbA_{1c} = 8.4%) who were treated prandially with the Kos inhaler for 28 days, FPG, postprandial blood glucose and HbA_{1c} (-1.2%) decreased significantly [80].

It is well documented that diabetic patients prefer an alternative to injected insulin and many companies are presently developing inhaled insulin delivery systems. Each system is unique in formulation, dosage and delivery device, and should be considered individually based on these three components. No definitive advantage of dry powder versus liquid formulation is evident. EXUBERA and AIR (HIIP) use dry powders and AERx iDMS uses a liquid formulation. Both powder and liquid formulations seem to have a small effect on lung function. Technosphere, most probably due to the microencapsulation of insulin, has a different kinetic profile but as it is still in the early stage of development, the potential lack of effect on PFTs is still quite speculative. Packaging the insulin in increments of only two doses, as with EXUBERA and AIR inhaled insulin system, potentially limits individualization of doses. Therefore, insulin delivery packaging that allows similar incremental changes as subcutaneously injected insulin is advantageous. Delivery devices range from quite simple, (e.g., AIR [HIIP], to quite complex (e.g., AERx iDMS). As with glucose monitors, device choice may be individualized based on the patient's

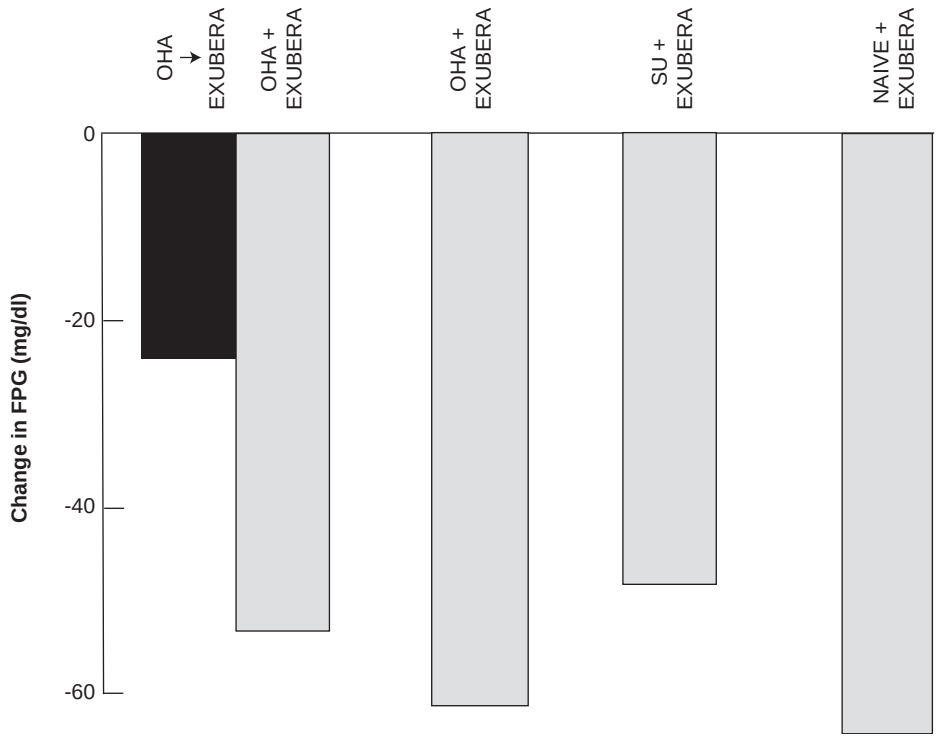

Figure 5. Decrease in FPG concentration in Type 2 diabetic subjects in whom EXUBERA was added to/substituted for (OHA → EXUBERA®) the patient's usual OHA regimen.
FPG: Fasting plasma glucose; NAÏVE: Drug naive; OHA: Oral hypoglycemic agent; SU: Sulfonylurea.

needs/abilities. Durability of these devices is important, but no data exist to compare these devices. Therefore, each device should be considered individually for its safety and efficacy. This therapeutic area promises to be quite competitive, with each system likely to have strong supporters and opposers.

8. Potential development issues

One negative aspect of EXUBERA therapy relates to the size of the blister packets (1 mg and 3 mg, which are equivalent to 3 units and 8 units, respectively, of insulin). These dosing packets are inconvenient for precise insulin dose adjustments. Long-term (beyond 2 years) safety data with respect to pulmonary function will be required to definitively establish the safety of EXUBERA, although the 2-year safety data do not indicate any evidence of pulmonary dysfunction and are very encouraging.

9. Expert opinion

Inhaled insulin is effective, well tolerated, accepted in both Type 1 DM and Type 2 DM diabetic patients, and provides a level of improved glycemic control that is equivalent to subcutaneous insulin regimens. Despite the proven long-term benefits of tight glycemic control, insulin therapy is often delayed or suboptimally implemented despite elevated HbA_{1c} levels. Inconvenience and poor patient acceptability of a multiple, daily insulin injection regimen contribute to the delay of insulin therapy and, in ~ 25% of patients with Type 2 DM, these limitations of insulin injection therapy contribute to poor glycemic control [53,54]. In such individuals, EXUBERA is likely to be especially beneficial. In summary, in all of the studies in Type 1 DM and Type 2 DM, EXUBERA has proven to be as effective as regular and rapidly acting insulin in improving glycemic control. In both Type 1 DM and Type 2 DM, the incidence of hypoglycemia is similar in patients treated with EXUBERA and subcutaneous insulin injection. Hypoglycemia is a potential complication of any form of insulin therapy and can be minimized by increasing patient awareness and frequent blood glucose monitoring. It is particularly noteworthy that the FPG concentration declined consistently and quite markedly in all of the studies in which EXUBERA was added to the regimen of drug-naive Type 2 DM patients [35] or Type 2 DM individuals who were poorly controlled on OHA [32-34] (Figure 5). In Type 2 DM, the elevated FPG concentration is primarily determined by the accelerated rate of HGP that occurs during the sleeping hours [38]. As the last dose of EXUBERA was administered with the evening meal (i.e., ~ 1800 h) and as the stimulatory effect of EXUBERA on glucose metabolism has largely waned by 6 h [24,25]

(Figure 2), the consistent reduction in FPG is somewhat surprising. This observation suggests that EXUBERA may be useful as a monotherapy in Type 2 DM patients. However, EXUBERA monotherapy will not address the basic underlying insulin resistance that is characteristic of essentially all of the Type 2 DM individuals [2,22,23].

9.1 Speculation

Potential mechanisms that could explain the effect of EXUBERA in reducing the FPG concentration include: amelioration of glucose toxicity; decreased Cori cycle activity; improvement in lipotoxicity; difference in the time course of action of EXUBERA to stimulate peripheral tissue (muscle) glucose disposal; and to inhibit HGP.

By reducing the mean day-long blood glucose levels, premeal EXUBERA may achieve sufficient glycemic control to decrease glucose toxicity [39], thus reducing the activity of glucose-6-phosphatase, which is the rate-limiting enzyme in HGP [40]. Decreased HGP would be expected to lead to a decline in FPG concentration. Reduction of postprandial glucose peaks by EXUBERA would also be expected to diminish the excessive rates of muscle lactate production [41,42], by directing glucose use to glycogenic and oxidative pathways. The resultant reduction in plasma levels of gluconeogenic substrates, especially lactate, would lead to a decline in basal and postprandial hepatic glucose output [43]. Furthermore, the improvement in postprandial glucose control, by ameliorating glucose toxicity, could lead to enhanced insulin secretion [44,45]. Improved glycemic control following three-times daily premeal EXUBERA could also result from amelioration of lipotoxicity [46]. Elevated plasma FFA levels cause insulin resistance in the liver and muscle. Thus, the resultant decrease in plasma FFA levels that occurs secondary to inhibition of lipolysis by hyperinsulinemia and that persists for 5 – 6 h after each meal [47], would be expected to inhibit the elevated basal/postprandial rates of HGP, to augment muscle insulin sensitivity and to improve beta-cell function [46]. Lastly, although the time course of action of EXUBERA to augment muscle glucose uptake is well defined [24,25], no studies have examined the time course of action of EXUBERA to inhibit HGP in either nondiabetic or diabetic subjects. It is possible that the inhibitory effect of EXUBERA on HGP persists longer than its stimulatory effect on muscle glucose uptake.

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