UNIVERSITY OF BIRMINGHAM

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Human insulin inhalation system (Technosphere Insulin Inhalation System) for type 1 diabetes

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Human insulin inhalation system (Technosphere Insulin Inhalation System) for type 1 diabetes

Target group

- Type 1 diabetes mellitus – adults, in combination with intermediate or long-acting insulin.

Technology description

Human insulin inhalation system (Technosphere Insulin System, Technosphere Insulin) is an insulin inhalation system consisting of dry powder short-acting insulin and a breath-activated inhalation device that delivers the insulin into the respiratory tract. Technosphere Insulin is absorbed more quickly than subcutaneously injected rapid acting insulin analogues and other short-acting human insulin formulations, and has a faster onset and shorter duration of action.

Technosphere Insulin is intended for use as a prandial (with meals) insulin therapy and is expected to be available in two dosages; doses to be confirmed[a].

Innovation and/or advantages

If successful in licensing, Technosphere Insulin would offer a very rapid acting insulin that mimics the normal prandial insulin release, with similar glycaemic control and a potentially lower risk of hypoglycaemia compared to other short-acting insulins, with minimal or no weight gain.

Developer

Mannkind Corporation.

Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

NHS or Government priority area

This topic is relevant to The National Service Framework for Children, Young People and Maternity Services (2004) and The National Service Framework for Diabetes (2007).

Relevant guidance

NICE Technology Appraisals

- In development. Buccal insulin for the management of type 1 diabetes. Expected date of issue to be confirmed[1].
- Continuous subcutaneous insulin for the treatment of diabetes mellitus. 2008[2].
- Inhaled insulin for the treatment of diabetes (types 1 and 2). 2006 (obsolete appraisal; product withdrawn from market)[3].
- Guidance on the use of patient education models for diabetes. 2003[4].
- Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. 2002[5].

NICE Clinical Guidelines

- NICE clinical guideline. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. 2008[6].
- NICE clinical guideline. Diagnosis and management of type 1 diabetes in children, young people and adults. 2004[7].

[a] Current clinical trials use 15U and 30U doses.

- NICE intervention procedure guidance. Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. 2008[8].
- SIGN. Management of diabetes. 2010[9].

Clinical need and burden of disease

In England and Wales there were an estimated 2,227,323 people with diabetes in 2008[10], with type 1 diabetes accounting for around 15%[11], an estimated 334,100 people. Diabetes is the most common metabolic disease in the young[12]. In 2008-9, there were 15,627 children and young people (aged 0-24 years) registered with diabetes in England and Wales, of which 98.6% had type 1 diabetes[13].

Type 1 diabetes has significant short-term impacts on health and lifestyle and is associated with major long-term complications and reduced life expectancy[13]. The cumulative prevalence of end-stage renal failure resulting from diabetic nephropathy in people with type 1 diabetes, has been reported as 2.2% at 20 years, and 7.7% at 30 years[14]. The prevalence of diabetic retinopathy, which is a common cause of acquired blindness, is 20-25% in people with type 1 diabetes[15]. The relative risk of cardiovascular disease in people with type 1 diabetes can be as much as 10-fold greater than that in non-diabetic individuals[16].

Existing comparators and treatments

People with type 1 diabetes require insulin replacement therapy from diagnosis and one aim of treatment of type 1 diabetes is to obtain near-normal blood glucose control. The choice of insulin regimen depends on factors such as age, duration of diabetes, lifestyle, and individual patient/family preferences.

NICE guidance states that while the insulin regimen should be individualised for each patient, three basic types of insulin regimen can be considered[2,7]:

- One, two or three insulin injections per day of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin.
- Multiple daily injection regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue.
- Continuous subcutaneous (SC) insulin infusion (insulin pump therapy).

Efficacy and safety

Trial	MKC-TI-117, NCT00700622; insulin glargine with Technosphere Insulin or insulin lispro; phase III.	MCK-TI-101, NCT00539396; Technosphere Insulin or SC rapid acting insulin (insulin aspart); phase II.
Sponsor	Mannkind Corporation.	Mannkind Corporation.
Status	Trial complete but unpublished.	Published in abstract.
Source of information	Company press release[17], trial registry[18], manufacturer.	Published[19,20,21], trial registry[22], manufacturer.
Location	USA, Brazil.	Russia.
Design	Randomised, active-controlled, open-label.	Randomised, active-controlled, open-label.
Participants and schedule	n=130; adults; type 1 diabetes; body mass index (BMI)≤30kg/m^2; HbA1c 7%-9%; FEV1[b] ≥70% of predicted, DLCO[c] ≥70%; insulin ≤1.5 units/kg/day.	n=110; adults; type 1 diabetes; BMI<40kg/m^2; HbA1c 7%-11.5%; SC insulin for ≥ 90 days. Randomised to insulin glargine with

[b] FEV1: forced expiratory volume in 1 second

	Randomised to insulin glargine with either Technosphere Insulin or insulin lispro.	either Technosphere Insulin or insulin aspart.
Follow-up	Active treatment 16 weeks, then 4 week follow up.	Active treatment 12 weeks, then 2 week follow up.
Primary outcome	Noninferiority; mean change in HbA1c.	Change in blood glucose following standard meal.
Secondary outcome	Proportion achieving HbA1c ≤6.5%, ≤7.0%, or ≤7.0% with no episodes of severe hypoglycaemia; 2-hour post-prandial glucose (PPG)<180 mg/dL (10.0 mmol/L) and <140 mg/dL (7.8 mmol/L) following meal challenge; body weight.	Mean change in HbA1c.
Key results	Technosphere Insulin (both doses) vs insulin lispro respectively (intention-to-treat population): mean reduction in HbA1c: -0.10% vs -0.03%, difference (0.07%); HbA1c≤6.5%: 9.6% vs 6.5% (p=0.0277). Mean reduction in fasting blood glucose (FBG): 41.53 vs 9.16mg/dL (p=0.0107); mean PPG at 30 mins: 130 vs 195.09mg/dL, 60 mins: 136 vs 214.49mg/dL, 90 mins: 163.94 vs 228.45mg/dL, 120 mins: 199.53 vs 241.39mg/dL. Total hypoglycaemia (events per subject month): 6.2 vs 8.2 (p=0.0345), and mild/moderate hypoglycaemia 6.0 vs 8.0 (p=0.0269).	For Technosphere Insulin vs insulin aspart respectively: PPG 0.92 mmol/L vs 3.0 mmol/L; mean reduction in HbA1c (SD): 0.83 (1.11), p<0.001 vs 0.99 (1.07), p<0.001, no statistically significant difference between groups (p=0.458).
Adverse effects (AEs)	Most common AEs: cough, hypoglycaemia and upper respiratory tract infection (URTI). For Technosphere Insulin and insulin lispro respectively (incidence): hypoglycaemia: both 97%; cough: 44.6% vs 0%; URTI: 7.7% vs 9.2%.	For Technosphere Insulin vs insulin aspart respectively (incidence): hypoglycaemia: 89% vs 93%; cough: 26% vs 4%.

Trial	MKC-TI-030, NCT00308737; type 1 or 2 diabetes, or without diabetes; Technosphere Insulin, usual or no anti diabetic care; phase III	MKC-TI-009, NCT00308308; SC insulin vs Technosphere Insulin, both with SC basal insulin; phase III.	MKC-TI-134, NCT00642616; type 1 or 2 diabetes, asthma or COPD, usual care with or without Technosphere Insulin; phase III.
Sponsor	Mannkind Corporation.	Mannkind Corporation.	Mannkind Corporation.
Status	Trial complete but unpublished.	Trial complete but unpublished.	Ongoing.
Source of information	Company press release[23], trial registry[24], manufacturer.	Trial registry[25], manufacturer.	Trial registry[26], manufacturer.
Location	EU (inc UK), USA, Canada and other countries.	EU (inc UK), USA, Canada and other countries.	USA.

[c] DLCO: diffusing capacity of the lung for carbon monoxide

Design	Randomised, open-label.	Randomised, active-controlled, open-label.	Randomised, active-controlled, open-label.
Participants and schedule	n=2,343; adults; type 1 (n=538) or type 2 diabetes and non-diabetics; BMI ≤42kg/m^2; HbA1c 6.6%-12%; FEV1≥70% of predicted, DLCO ≥80%. Randomised to Technosphere Insulin, usual anti-diabetic care or no intervention (controls).	n=587; adults; type 1 diabetes; BMI≤35kg/m^2; HbA1c 7%-11%; FEV1≥70% of predicted, DLCO≥70%; insulin≤1.4 units/kg/day. Randomised to Technosphere Insulin or SC insulin.	n=510; adults; type 1 or type 2 diabetes, asthma or chronic obstructive pulmonary disease (COPD); BMI≤35kg/m^2; HbA1c 7%-11%; no change in anti-diabetic regimen for ≥90 days. Randomised to usual anti-diabetic therapy with the addition of Technosphere Insulin or the substitution of Technosphere Insulin for short-acting prandial insulin.
Follow-up	Active treatment 2 years, then 4 weeks follow up.	Active treatment 52 weeks then 4 weeks follow-up.	Active treatment 12 months then 2 month follow-up.
Primary outcome	Pulmonary function: FEV1.	Mean change in HbA1c.	Lung function & pulmonary safety: post-bronchodilator FEV1.
Secondary outcome	Pulmonary endpoints: FVC, DLCO, TLC[d]; glycaemic control, change in HbA1c, change in body weight and frequency of defined mild, moderate and severe hypoglycaemia.	Safety.	Asthma and COPD exacerbations; acute changes in FEV1 after Technosphere Insulin; health-related quality of life (St. George's Respiratory Questionnaire; Asthma Control Questionnaire; change in HbA1c; incidence and frequency of hypoglycaemia events.
Key results	Participants with type 1 diabetes: Technosphere Insulin vs usual care respectively: mean reduction in HbA1c 0.29% vs 0.31%; hypoglycemic events 61.8% vs 66.1%; weight change: -0.59 vs +1.38kg (p=0.0007).	-	-
Expected reporting date	Q1/Q2 2011.	Q1/Q2 2011.	Q1/Q2 2011.
Adverse events (AEs)	Technosphere Insulin vs usual care respectively: severe hypoglycaemia events per 100 subject-months: 2.36 vs 3.76.	-	-

[d] TLC: Total lung capacity.

Trial	MKC-TI-126, NCT00741429; adults; 2 month safety follow-up trial.
Sponsor	Mannkind Corporation.
Status	Trial complete but unpublished.
Source of information	Trial registry[27], manufacturer.
Location	EU (inc UK), USA, Canada and other countries.
Design	Observational, open label.
Participants and schedule	n=672; adults; type 1 or type 2 diabetes; completed trials: MKC-T1-009, MKC-TI-102, MKC-TI-103 or MKC-TI-030. Previously received Technosphere Insulin or previously received comparator antidiabetic medication from participation in parent trial (MKC-T1-009, MKC-TI-102, MKC-TI-103 or MKC-TI-030).
Follow-up	-
Primary outcome	Safety.
Expected reporting date	Q1/Q2 2011.

Estimated cost and cost impact

The cost of Technosphere Insulin is not yet known. The costs of other short-acting SC insulins are[28]:

Drug	**Dose**	**Cost for units stated**
Actrapid	1,000 units	£7.48
Humulin S	1,000 units 5 x 300 unit cartridges	£15.68 £26.71
Insuman rapid	5 x 300 unit cartridges	£22.52
Insulin aspart	1000 units 5 x 300 unit cartridges	£16.60 £29.14
Insulin lispro	1000 units 5 x 300 unit cartridges	£16.61 £28.31

Claimed or potential impact – speculative

Patients

- ☐ Reduced mortality or increased length of survival
- ☐ Reduction in associated morbidity or Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☑ Other: alternative route of administration
- ☐ None identified

Services

- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use: if shorter length of stay, reduced referrals.
- ☐ Other:
- ☑ None identified

Costs

- ☐ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☐ New costs:
- ☐ Savings:
- ☑ Other: Unknown comparative cost

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