Clinical trial results:
A Phase 3, Multicenter, Open-Label, Randomized Clinical Trial to Evaluate the Safety of Technosphere® Insulin Inhalation Powder in Type 1 or Type 2 Diabetic Subjects with Obstructive Pulmonary Disease (Asthma or Chronic Obstructive Pulmonary Disease) Over a 12-month Treatment Period with a 2-month Follow-up

Summary

EudraCT number	2008-000564-16
Trial protocol	DE SK HU
Global end of trial date	25 November 2014

Results information

Result version number	v1 (current)
This version publication date	16 April 2016
First version publication date	16 April 2016

Trial information

Trial identification

Sponsor protocol code	MKC-TI-134

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00642616
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MannKind Corporation
Sponsor organisation address	61 S Paramus Rd Paramus, New Jersey, United States, 07652
Public contact	Vice President, Nikhil Amin, MannKind Corporation, 001 201983-5166, namin@mannkindcorp.com
Scientific contact	Vice President, Nikhil Amin, MannKind Corporation, 001 201983-5166, namin@mannkindcorp.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To examine the effects of prandially inhaled Technosphere® Insulin (TI) Inhalation Powder in combination with an antidiabetic regimen of insulin and/or oral antidiabetic agents (TI Inhalation Powder group) versus antidiabetic treatment without TI Inhalation Powder (Usual Care [UC] group) on lung function and pulmonary safety in type 1 or type 2 diabetic, currently non smoking subjects with asthma or Chronic Obstructive Pulmonary disease (COPD).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and in consideration of the local culture. The nature of the trial in which the subject will be/is participating, contact details and any information needed in the event of a medical emergency was provided to the subject. Collected personal data and human biological samples were processed in compliance with ICH E6 4.8.10-11 ensuring that those involved with the conduct of this study abide by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Ukraine: 2
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	34
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 517 subjects were screened in 5 countries. First subject was screened in March 2009.

Pre-assignment

Screening details:

2 week screening period followed by a 2 week run-in period. After the screening period, 51 subjects were randomized and 34 subjects met eligibility criteria after the 2 week run-in period and were treated. Study was terminated based on data safety monitoring board recommendations.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Technosphere® Insulin (Asthma)

Arm description:

Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with Asthma

Arm type	Experimental
Investigational medicinal product name	Technosphere® Insulin
Investigational medicinal product code	
Other name	Afrezza®
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Technosphere® Insulin delivered with Gen 2 inhaler with doses individualized for each subject in combination with an antidiabetic regimen of insulin and/or oral antidiabetic agents.

Arm title	Usual Care (Asthma)

Arm description:

Usual antidiabetic care in diabetic subjects with Asthma

Arm type	Active comparator
Investigational medicinal product name	Usual Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

Type 1 diabetics: long-acting (basal) insulin plus rapid-acting insulin, or pre-mix insulin Type 2 diabetics: oral antidiabetic medications with or without long-acting (basal) insulin.

Arm title	Technosphere® Insulin (COPD)

Arm description:

Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with COPD

Arm type	Experimental

Investigational medicinal product name	Technosphere® Insulin
Investigational medicinal product code	
Other name	Afrezza®
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Technosphere® Insulin delivered with Gen 2 inhaler with doses individualized for each subject in combination with an antidiabetic regimen of insulin and/or oral antidiabetic agents.

Arm title	Usual Care (COPD)

Arm description:

Usual antidiabetic care in diabetic subjects with COPD

Arm type	Active comparator
Investigational medicinal product name	Usual Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Tablet
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

Type 1 diabetics: long-acting (basal) insulin plus rapid-acting insulin, or pre-mix insulin Type 2 diabetics: oral antidiabetic medications with or without long-acting (basal) insulin.

Number of subjects in period 1	Technosphere® Insulin (Asthma)	Usual Care (Asthma)	Technosphere® Insulin (COPD)
Started	9	8	9
Completed	0	1	0
Not completed	9	7	9
Physician decision	-	-	1
Adverse Event	2	-	1
Withdrawal by Subject	-	1	1
Protocol Violation	-	-	2
Study Terminated by Sponsor	7	6	4

Number of subjects in period 1	Usual Care (COPD)
Started	8
Completed	1
Not completed	7
Physician decision	1
Adverse Event	-
Withdrawal by Subject	1
Protocol Violation	-
Study Terminated by Sponsor	5

Baseline characteristics

Reporting groups	
Reporting group title	Technosphere® Insulin (Asthma)
Reporting group description:	
Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with Asthma	
Reporting group title	Usual Care (Asthma)
Reporting group description:	
Usual antidiabetic care in diabetic subjects with Asthma	
Reporting group title	Technosphere® Insulin (COPD)
Reporting group description:	
Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with COPD	
Reporting group title	Usual Care (COPD)
Reporting group description:	
Usual antidiabetic care in diabetic subjects with COPD	

Reporting group values	Technosphere® Insulin (Asthma)	Usual Care (Asthma)	Technosphere® Insulin (COPD)
Number of subjects	9	8	9
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	69	49.75	67.44
standard deviation	± 7.26	± 15.73	± 8.38
Gender categorical			
Units: Subjects			
Female	6	4	2
Male	3	4	7

Reporting group values	Usual Care (COPD)	Total	
Number of subjects	8	34	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	68.88		
standard deviation	± 8.2	-	
Gender categorical			
Units: Subjects			
Female	1	13	
Male	7	21	

End points

End points reporting groups

Reporting group title	Technosphere® Insulin (Asthma)
Reporting group description:	
Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with Asthma	
Reporting group title	Usual Care (Asthma)
Reporting group description:	
Usual antidiabetic care in diabetic subjects with Asthma	
Reporting group title	Technosphere® Insulin (COPD)
Reporting group description:	
Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with COPD	
Reporting group title	Usual Care (COPD)
Reporting group description:	
Usual antidiabetic care in diabetic subjects with COPD	

Primary: Change in Post-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) From Baseline to Week 52

End point title	Change in Post-bronchodilator Forced Expiratory Volume in 1 Second (FEV1) From Baseline to Week 52[1]
End point description:	
Post-bronchodilator FEV1 was measured at the pulmonary function laboratory. Only two subjects completed both time points [one in the Usual Care (Asthma) Arm and one in the Usual Care (COPD) Arm].	
End point type	Primary
End point timeframe:	
52 Weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses was not done as no subject was analyzed.

End point values	Technosphere ® Insulin (Asthma)	Usual Care (Asthma)	Technosphere ® Insulin (COPD)	Usual Care (COPD)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: Subjects				

Notes:

[2] - Data is not provided due to privacy concerns.

[3] - Data is not provided due to privacy concerns.

[4] - Data is not provided due to privacy concerns.

[5] - Data is not provided due to privacy concerns.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Asthma Exacerbation by Treatment Arm

End point title	Number of Subjects With Asthma Exacerbation by Treatment Arm[6]

End point description:

Number of subjects who experienced worsening of asthma symptoms. Safety population: subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint applies only to subjects with underlying Asthma.

End point values	Technosphere ® Insulin (Asthma)	Usual Care (Asthma)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: Subjects				
number (not applicable)				
Exacerbation of Asthma	1	1		
No Exacerbation of Asthma	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With COPD Exacerbation by Treatment Arm

End point title	Number of Subjects With COPD Exacerbation by Treatment Arm[7]

End point description:

Number of subjects who experienced worsening of COPD symptoms. Safety population: subjects who received at least one dose of study medication. The outcome applies only to subjects with underlying COPD.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint applies only to subjects with underlying COPD.

End point values	Technosphere ® Insulin (COPD)	Usual Care (COPD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: subjects				
number (not applicable)				
COPD Exacerbation	3	1		
No Exacerbation	6	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Glycated Hemoglobin (HbA1C) From Baseline to Week 52

End point title	Change in Glycated Hemoglobin (HbA1C) From Baseline to Week 52

End point description:

Only two subjects completed both time points [one in the Usual Care (Asthma) Arm and one in the Usual Care (COPD) Arm].

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Technosphere ® Insulin (Asthma)	Usual Care (Asthma)	Technosphere ® Insulin (COPD)	Usual Care (COPD)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[8]	0[9]	0[10]	0[11]
Units: Subjects				

Notes:

[8] - Data is not provided due to privacy concerns.

[9] - Data is not provided due to privacy concerns.

[10] - Data is not provided due to privacy concerns.

[11] - Data is not provided due to privacy concerns.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to 30 days after the last study visit or study related procedure was performed regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Analysis was done on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Technosphere® Insulin (Asthma)

Reporting group description:

Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with Asthma.

Reporting group title	Usual Care With Anti-diabetic Agents (Asthma)

Reporting group description:

Usual antidiabetic care in diabetic subjects with Asthma.

Reporting group title	Technosphere® Insulin (COPD)

Reporting group description:

Technosphere® Insulin Inhalation Powder in combination with an antidiabetic regimen in diabetic subjects with COPD.

Reporting group title	Usual Care With Anti-diabetic Agents (COPD)

Reporting group description:

Usual antidiabetic care in diabetic subjects with COPD.

Serious adverse events	Technosphere® Insulin (Asthma)	Usual Care With Anti-diabetic Agents (Asthma)	Technosphere® Insulin (COPD)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-Cell Lymphoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal Obstruction			

subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Usual Care With Anti-diabetic Agents (COPD)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-Cell Lymphoma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal Obstruction			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Technosphere® Insulin (Asthma)	Usual Care With Anti-diabetic Agents (Asthma)	Technosphere® Insulin (COPD)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	7 / 8 (87.50%)	4 / 9 (44.44%)
Investigations			
Monocyte Count Increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pulmonary Function Test Decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Venous Insufficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Chest Discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Influenza Like Illness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oedema Peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Bronchial Obstruction			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	3 / 9 (33.33%)
occurrences (all)	0	0	3
Cough			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypoventilation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal Spasm			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Productive Cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Rhinitis Allergic			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Herpes Zoster			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pyelonephritis Chronic			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Respiratory Tract Infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Staphylococcal Infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Urinary Tract Infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Viral Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dyslipidaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	20	0	2
Obesity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Type 1 Diabetes Mellitus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Usual Care With Anti-diabetic Agents (COPD)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		

Investigations			
Monocyte Count Increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pulmonary Function Test Decreased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Venous Insufficiency			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Chest Discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Influenza Like Illness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Oedema Peripheral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal Pain Upper			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Bronchial Obstruction			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hypoventilation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Oropharyngeal Spasm			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Productive Cough			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinitis Allergic			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Herpes Zoster			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pyelonephritis Chronic			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory Tract Infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory Tract Infection Viral			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Staphylococcal Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tracheitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Urinary Tract Infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Viral Infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dyslipidaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Hypoglycaemia subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 59		
Obesity subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Type 1 Diabetes Mellitus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2008	Following changes were made: • Schedules for visits throughout the study were clarified. • Assessments at early termination were same as those being done at visit 10. • Specifics of spirometry to be done in each treatment group were clarified.
14 January 2009	• Interdeterminate lung disease group was replaced to COPD and asthma as per the recommendations of Food and Drug Administration (FDA). • Sample size was increased to accommodate 2 treatment groups within each disease state due to projected drop-out of 35%. • Spirometry at the site would be done only to evaluate acute effects of TI inhalation powder, pre and post TI inhalation powder administration. • 30 minutes post TI inhalation powder administration time point and visit 3 assessment were added in FEV1 assessment. • HbA1c changed from visit 2 to visit 1. • Pulmonary AEs (other than cough and pulmonary exacerbations) were presented with all other AEs. • Eligibility criteria was modified as per the recommendations of FDA. • Changes in "Analysis of primary endpoint" was done to perform analysis separately within each disease state of COPD and asthma. • Analysis and endpoints were clarified. • Diabetic education would be performed by the site as part of routine care. • Addition of X-ray exclusion in exclusion criteria. • Clarification of exacerbation and use of corticosteroids and antibiotics for a respiratory Infection. • Elimination of urine cotinine test at Visits 2, 5, 6, 7, 8, 9, and 11. • Clarification of pulmonary function tests (PFT) testing and reporting procedures. • Hypoglycemia as Serious adverse event was clarified. • Imputation methods were clarified as LOCF.
03 September 2009	• 3-month follow-up period was changed to 2-month follow-up period. • 2-week period between the screening visit and the baseline visit was changed to 3-week to establish personal best peak expiratory flow over a 2-week period prior to initiation of the trial drugs. • Technosphere® Inhalation Powder was deleted as an IMP from the protocol. • Introduction section was updated to incorporate updated TI inhalation powder information. • Text of secondary objectives was modified to be more specific. • Trial diagram was modified to reflect new trial design. • Study population selection and other related information were modified to reflect new trial design. • Inclusion criteria and exclusion criteria were modified to reflect the correct inclusion criteria. • Trial stopping rules were added as per the recommendations of FDA. • Subjects received an electronic peak expiratory flow (PEF) meter and trained on proper usage at the clinic site. It was used to accurately measure daily morning and evening peak expiratory flow rates (PEFR). • PreprandiaL capillary plasma glucose was changed to 70-130 mg/dL (3.9-7.2 mmol/L) as per the 2009 American Diabetes Association (ADA) recommendations. • Dosing guidelines were updated as per the updated TI inhalation powder information.

07 September 2010	• Introduction section was updated as per the updated TI inhalation powder information. • Device description, study drug packaging, packaging and labeling etc. was revised to reflect the to-be-marketed inhaler. • TI inhalation powder cartridges in film/foil should be stored in refrigerated (at 2°C to 8°C or 36°F to 46°F for long term storage. • Definition of Serious adverse event, hypoglycemia and cough were updated. • Trial activities were revised for clarity. • Data collection, database quality assurance, recording of data etc. were revised to reflect that remote data capture would be used for the trail. • Schedule of PFTs were revised to reflect the actual sequence of testing done at the PFT laboratory.
15 July 2013	• 2-week screening period was amended to allow sufficient time to complete all screening procedures. • "PEF" was changed to "PEFR" for better clarity. • Time and events schedule were revised for better clarity. • Range of Body mass index (BMI) and HbA1c and other parameters in inclusion criteria and exclusion criteria were revised to study a broader study population and for clarification. • All primary and secondary analysis were planned to be conducted using mixed model repeated measure (MMRM) approach. • List of inhaled short-acting beta-agonists was updated based on more recently approved medications available for the treatment of asthma and COPD. • Definitions of pulmonary exacerbation, AEs, hypoglycemia, cough etc. were revised based on current CDISC definitions and clarifications. • Removal of subjects from the trial or study drug, rules for stopping the trial were revised to streamline reporting process. • Efficacy analysis would be done using MMRM analysis on full analysis set (FAS) population. • Dosing guidelines for study drug was revised for clarification on TI dose initiation and instructions for dose adjustments. • Schedule of lung diffusion testing was corrected.
13 August 2013	• Time and events schedule were revised to provide greater clarity. • Range of BMI and HbA1c and other parameters of inclusion criteria and some parameters in exclusion criteria were revised to study a broader study population and for clarification. • List of inhaled short-acting beta-agonists was updated based on more recently approved medications available for the treatment of asthma and COPD. • Definitions of pulmonary exacerbation, AEs, hypoglycemia, cough etc. were revised based on current CDISC definitions and clarifications. • Removal of subjects from the trial or study drug, rules for stopping the trial were revised to streamline reporting process. • Definition of intent-to-treat (ITT) population was replaced with FAS population that allowed the MMRM analysis to utilize all randomized subjects even when baseline or post baseline data was missing. • Efficacy analysis would be done using MMRM analysis on FAS population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of trial leading to small numbers of subjects analyzed

Notes: