



## Clinical trial results:

### A Phase 3, Randomized, Active Comparator, Double-Blind, Multi-Center Study to Compare the Efficacy, Safety and Tolerability of ITCA 650 to Sitagliptin as Add-on Therapy to Metformin in Patients with Type 2 Diabetes

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002117-19 |
| Trial protocol           | LV DK DE       |
| Global end of trial date | 07 July 2015   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 14 August 2016 |
| First version publication date | 14 August 2016 |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | ITCA 650-CLP-105 |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01455870 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Intarcia Therapeutics, Inc   |
| Sponsor organisation address | 24650 Industrial Blvd, Hayward, CA, United States, 94545                                 |
| Public contact               | Chief Medical Officer, Intarcia Therapeutics, Inc, +1 617.936.2500, medinfo@intarcia.com |
| Scientific contact           | Chief Medical Officer, Intarcia Therapeutics, Inc, +1 617.936.2500, medinfo@intarcia.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                       | 07 July 2015 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 07 July 2015 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 07 July 2015 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

Demonstrate that ITCA 650 is non-inferior to sitagliptin in reducing HbA1c in patients with type 2 diabetes following 52 weeks of treatment. The noninferiority margin was 0.3%. If non-inferiority is demonstrated, then ITCA 650 will be tested for superiority in reducing HbA1c.

Protection of trial subjects:

The study protocol, all study protocol amendments, written study patient information, informed consent form (ICF), and any other appropriate study-related information were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) at each study site. All subjects were free to withdraw from the clinical trial at any time for any reason given. Protocol pre-defined reasons for discontinuation were the following: (1) Patient withdraws consent or requests discontinuation from the study for any reason; (2) Sponsor discontinues the study; (3) Pregnancy; (4) Occurrence of a clinical or laboratory AE, either serious or non serious, at the discretion of the Investigator; (5) Need to initiate therapy with an excluded concomitant medication; (6) Permanent discontinuation of study medication; (7) Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol; (8) Loss of glucose control. Close medical monitoring of all subjects was adhered to throughout the trial duration. An independent safety monitor evaluated safety information on a continuous basis in a blinded fashion. Patients who experienced hyperglycemia were prescribed rescue therapy as described in the protocol.

Background therapy:

Metformin, at least  $\geq 1500$  mg/day oral.

Evidence for comparator:

The choice of a control group with an active comparator (sitagliptin) was justified because it allowed all participants to receive active treatment. Sitagliptin is an approved pharmacotherapy for the treatment of type 2 diabetes worldwide and has a well characterized safety and efficacy profile.

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 13 May 2013 |
| 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 | Denmark: 18        |
| Country: Number of subjects enrolled | Germany: 18        |
| Country: Number of subjects enrolled | Latvia: 19         |
| Country: Number of subjects enrolled | United States: 321 |
| Country: Number of subjects enrolled | Israel: 9          |

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | South Africa: 37 |
| Country: Number of subjects enrolled | Croatia: 18      |
| Country: Number of subjects enrolled | Mexico: 45       |
| Country: Number of subjects enrolled | Canada: 34       |
| Country: Number of subjects enrolled | Malaysia: 15     |
| Country: Number of subjects enrolled | Saudi Arabia: 1  |
| Worldwide total number of subjects   | 535              |
| EEA total number of subjects         | 73               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 448 |
| From 65 to 84 years                       | 87  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

One hundred and twenty four global investigational sites were involved in the recruitment and treatment of 535 and patients.

### Pre-assignment

Screening details:

Eligible subjects were males and females age 18 to 80 years inclusive with a diagnosis of type 2 diabetes for  $\geq 3$  months. Subjects also had HbA1c  $\geq 7.5\%$  and  $\leq 10.5\%$  and a body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> and  $\leq 45$  kg/m<sup>2</sup>.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall study (D0 - Week 52) (overall period) |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                       |
| Blinding used                | Double blind                                  |
| Roles blinded                | Subject, Investigator, Monitor                |

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | Group 1: ITCA 650 |

Arm description:

Group 1: ITCA 650 osmotic mini-pump placed sub-dermally. ITCA 650 was combined with an oral placebo to maintain the blind.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | ITCA 650 20 mcg/day |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Implant             |
| Routes of administration               | Subcutaneous use    |

Dosage and administration details:

From randomization to Week 13, subjects receive 20 mcg/day of ITCA 650. From week 13 to week 52, subjects receive 60 mcg/day of ITCA 650. Subjects also take oral placebo for treatment period duration to maintain the blind between treatment groups.

|  |                     |
|--|---------------------|
| Investigational medicinal product name | ITCA 650 60 mcg/day |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Implant             |
| Routes of administration               | Subcutaneous use    |

Dosage and administration details:

From randomization to Week 13, subjects receive 20 mcg/day of ITCA 650. From week 13 to week 52, subjects receive 60 mcg/day of ITCA 650. Subjects also take oral placebo for treatment period duration to maintain the blind between treatment groups.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Group 2: Sitagliptin |
|------------------|----------------------|

Arm description:

Sitagliptin 100 mg/day, oral administration. Group 2 subjects received an ITCA placebo device to maintain the blind.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |               |
|--|---------------|
| Investigational medicinal product name | Sitagliptin   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Sitagliptin 100 mg/day plus ITCA placebo.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Group 1: ITCA 650 | Group 2: Sitagliptin |
|---|-------------------|----------------------|
| Started   | 265               | 265                  |
| Completed   | 204               | 217                  |
| Not completed                                       | 61                | 48                   |
| Patients who did not complete treatment             | 61                | 48                   |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Five of the enrolled subjects (all enrolled in the UNITED STATES) were never treated so although 535 subjects were randomized, only 530 actually received treatment and entered the treatment period.

## Baseline characteristics

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Group 1: ITCA 650 |
|-----------------------|-------------------|

Reporting group description:

Group 1: ITCA 650 osmotic mini-pump placed sub-dermally. ITCA 650 was combined with an oral placebo to maintain the blind.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Group 2: Sitagliptin |
|-----------------------|----------------------|

Reporting group description:

Sitagliptin 100 mg/day, oral administration. Group 2 subjects received an ITCA placebo device to maintain the blind.

| Reporting group values | Group 1: ITCA 650 | Group 2: Sitagliptin | Total |
|------------------------|-------------------|----------------------|-------|
| Number of subjects     | 265               | 265                  | 530   |
| Age categorical        |                   |                      |       |
| Units: Subjects        |                   |                      |       |
| Adults (18-64 years)   | 220               | 223                  | 443   |
| From 65-84 years       | 45                | 42                   | 87    |
| Age continuous         |                   |                      |       |
| Units: years           |                   |                      |       |
| arithmetic mean        | 55.4              | 54.6                 |       |
| standard deviation     | ± 9.84            | ± 10.32              | -     |
| Gender categorical     |                   |                      |       |
| Units: Subjects        |                   |                      |       |
| Female                 | 120               | 107                  | 227   |
| Male                   | 145               | 158                  | 303   |

## End points

### End points reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | Group 1: ITCA 650    |
| Reporting group description:<br>Group 1: ITCA 650 osmotic mini-pump placed sub-dermally. ITCA 650 was combined with an oral placebo to maintain the blind. |                      |
| Reporting group title  | Group 2: Sitagliptin |
| Reporting group description:<br>Sitagliptin 100 mg/day, oral administration. Group 2 subjects received an ITCA placebo device to maintain the blind.       |                      |

### Primary: Change in HbA1c (%) between Week 52 and Day 0

|   |   |
|---|---|
| End point title   | Change in HbA1c (%) between Week 52 and Day 0 |
| End point description:<br>Calculated as: Value of HbA1c (%) at Week 52 - Hba1c at baseline (%) (mITT population).                       |   |
| End point type  | Primary                                       |
| End point timeframe:<br>The primary efficacy variable is the change in HbA1c (%) between baseline and Week 52 from the mITT population. |   |

| End point values                      | Group 1: ITCA 650 | Group 2: Sitagliptin |  |  |
|---------------------------------------|-------------------|----------------------|--|--|
| Subject group type                    | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed           | 263               | 257                  |  |  |
| Units: Change from Baseline HbA1c (%) |                   |                      |  |  |
| least squares mean (standard error)   | -1.47 (± 0.08)    | -0.76 (± 0.08)       |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Change in HbA1c (%) between Week 52 and Day 0 |
| Statistical analysis description:<br>Mixed Model Repeated Measures (MMRM) was used to compare the ITCA 650 treatment group to the sitagliptin treatment group. In the model, change from baseline HbA1c through Week 52 was the outcome variable. Treatment group, visit, and the interaction between treatment and visit were fixed effects. Baseline HbA1c was the covariate. |   |
| Comparison groups   | Group 1: ITCA 650 v Group 2: Sitagliptin      |
| Number of subjects included in analysis   | 520   |
| Analysis specification  | Pre-specified                                 |
| Analysis type   | non-inferiority <sup>[1]</sup>                |
| P-value   | < 0.001                                       |
| Method  | Mixed models analysis                         |
| Parameter estimate  | LS Mean Difference (final values)             |
| Point estimate  | -0.71   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.93   |
| upper limit         | -0.49   |

Notes:

[1] - 0.3 % inferiority margin.

## Secondary: Composite HbA1c/Weight Reduction

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Composite HbA1c/Weight Reduction |
|-----------------|----------------------------------|

End point description:

Proportion of patients with decrease in HbA1c >0.5% and weight loss ≥2 kg between Week 52 and Day 0.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Proportion of patients who achieved Composite HbA1c/Weight Reduction at Week 52.

| End point values            | Group 1: ITCA 650  | Group 2: Sitagliptin |  |  |
|-----------------------------|--------------------|----------------------|--|--|
| Subject group type          | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed | 171 <sup>[2]</sup> | 126 <sup>[3]</sup>   |  |  |
| Units: Not Applicable       |                    |                      |  |  |
| Achieved                    | 104                | 35                   |  |  |
| Not Achieved                | 67                 | 91                   |  |  |

Notes:

[2] - 171 evaluable subjects from ITCA 650 group, mITT population

[3] - 126 evaluable subjects from sitagliptin group, mITT population

## Statistical analyses

|                            |                                  |
|----------------------------|----------------------------------|
| Statistical analysis title | Composite HbA1c/Weight Reduction |
|----------------------------|----------------------------------|

Statistical analysis description:

The ITCA 650 treatment group was compared to the sitagliptin treatment group using a logistic regression model with proportion of patients with HbA1c reduction > 0.5% and weight loss ≥ 2kg from baseline at Week 52 as the outcome variable, and treatment as a factor and baseline HbA1c (%) and baseline body weight as covariates.

|   |  |
|---|--|
| Comparison groups                       | Group 1: ITCA 650 v Group 2: Sitagliptin |
| Number of subjects included in analysis | 297                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other                                    |
| P-value                                 | < 0.001                                  |
| Method                                  | Regression, Logistic                     |
| Parameter estimate                      | Odds ratio (OR)                          |
| Point estimate                          | 3.6                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 2.3                                      |
| upper limit                             | 5.6                                      |



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**Secondary: Change in body weight between Week 52 and Day 0**

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|                 |   |
|-----------------|---|
| End point title | Change in body weight between Week 52 and Day 0 |
|-----------------|---|

End point description:

Change in weight (kg) from baseline - 52 week time point.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change in weight (kg) from baseline - 52 week time point.

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|                                     |                     |                      |  |  |
|-------------------------------------|---------------------|----------------------|--|--|
| <b>End point values</b>             | Group 1: ITCA 650   | Group 2: Sitagliptin |  |  |
| Subject group type                  | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed         | 263                 | 257                  |  |  |
| Units: kilogram(s)                  |                     |                      |  |  |
| least squares mean (standard error) | -3.97 ( $\pm$ 0.33) | -1.25 ( $\pm$ 0.35)  |  |  |

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change in body weight between Week 52 and Day 0 |
| Comparison groups                       | Group 2: Sitagliptin v Group 1: ITCA 650        |
| Number of subjects included in analysis | 520   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | other   |
| P-value                                 | < 0.001   |
| Method                                  | Mixed models analysis                           |
| Parameter estimate                      | LS Mean Difference (final values)               |
| Point estimate                          | -2.71   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -3.66   |
| upper limit                             | -1.77   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (Day 0 - End of study).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Group 1: ITCA 650 |
|-----------------------|-------------------|

Reporting group description:

Group 1: ITCA 650 osmotic mini-pump placed sub-dermally. ITCA 650 plus oral placebo (to maintain blind between treatment groups).

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Group 2: Sitagliptin |
|-----------------------|----------------------|

Reporting group description:

Group 2: Sitagliptin 100 mg/day plus ITCA placebo.

| Serious adverse events  | Group 1: ITCA 650 | Group 2: Sitagliptin |  |
|---|-------------------|----------------------|--|
| Total subjects affected by serious adverse events                   |                   |                      |  |
| subjects affected / exposed   | 15 / 265 (5.66%)  | 20 / 265 (7.55%)     |  |
| number of deaths (all causes)                                       | 0                 | 0                    |  |
| number of deaths resulting from adverse events                      | 0                 | 0                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                      |  |
| Malignant neoplasm of unknown primary site                          |                   |                      |  |
| subjects affected / exposed   | 1 / 265 (0.38%)   | 0 / 265 (0.00%)      |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0                |  |
| deaths causally related to treatment / all                          | 0 / 1             | 0 / 0                |  |
| Uterine leiomyoma   |                   |                      |  |
| subjects affected / exposed   | 1 / 265 (0.38%)   | 0 / 265 (0.00%)      |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0                |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                |  |
| Mucinous cystadenocarcinoma ovary                                   |                   |                      |  |
| subjects affected / exposed   | 0 / 265 (0.00%)   | 1 / 265 (0.38%)      |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1                |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                |  |
| Vascular disorders  |                   |                      |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Deep Vein Thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Pneumothorax   |                 |                 |  |
| subjects affected / exposed                          | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                |                 |                 |  |
| Depression   |                 |                 |  |
| subjects affected / exposed                          | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Suicidal ideation                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Mental status changes                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications       |                 |                 |  |
| Incisional hernia                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Seroma   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Head injury                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Congestive Heart Failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 265 (0.75%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 265 (0.00%) | 2 / 265 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Migraine  |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal ulcer                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Rotator cuff syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis infective                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 265 (0.38%) | 0 / 265 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 265 (0.75%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 265 (0.00%) | 1 / 265 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Group 1: ITCA 650  | Group 2: Sitagliptin |  |
|---|--------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                    |                      |  |
| subjects affected / exposed                           | 146 / 265 (55.09%) | 112 / 265 (42.26%)   |  |
| Nervous system disorders                              |                    |                      |  |
| Dizziness   |                    |                      |  |
| subjects affected / exposed                           | 14 / 265 (5.28%)   | 7 / 265 (2.64%)      |  |
| occurrences (all)                                     | 14                 | 7                    |  |
| Headache  |                    |                      |  |
| subjects affected / exposed                           | 21 / 265 (7.92%)   | 21 / 265 (7.92%)     |  |
| occurrences (all)                                     | 24                 | 26                   |  |
| Gastrointestinal disorders                            |                    |                      |  |

|                                    |                   |                   |  |
|------------------------------------|-------------------|-------------------|--|
| Diarrhoea                          |                   |                   |  |
| subjects affected / exposed        | 30 / 265 (11.32%) | 19 / 265 (7.17%)  |  |
| occurrences (all)                  | 36                | 23                |  |
| Gastrooesophageal reflux disease   |                   |                   |  |
| subjects affected / exposed        | 15 / 265 (5.66%)  | 5 / 265 (1.89%)   |  |
| occurrences (all)                  | 16                | 6                 |  |
| Nausea                             |                   |                   |  |
| subjects affected / exposed        | 83 / 265 (31.32%) | 36 / 265 (13.58%) |  |
| occurrences (all)                  | 119               | 40                |  |
| Vomiting                           |                   |                   |  |
| subjects affected / exposed        | 51 / 265 (19.25%) | 14 / 265 (5.28%)  |  |
| occurrences (all)                  | 76                | 15                |  |
| Infections and infestations        |                   |                   |  |
| Nasopharyngitis                    |                   |                   |  |
| subjects affected / exposed        | 7 / 265 (2.64%)   | 16 / 265 (6.04%)  |  |
| occurrences (all)                  | 9                 | 20                |  |
| Upper respiratory tract infection  |                   |                   |  |
| subjects affected / exposed        | 18 / 265 (6.79%)  | 24 / 265 (9.06%)  |  |
| occurrences (all)                  | 21                | 30                |  |
| Urinary tract infection            |                   |                   |  |
| subjects affected / exposed        | 25 / 265 (9.43%)  | 17 / 265 (6.42%)  |  |
| occurrences (all)                  | 32                | 24                |  |
| Metabolism and nutrition disorders |                   |                   |  |
| Hyperglycaemia                     |                   |                   |  |
| subjects affected / exposed        | 5 / 265 (1.89%)   | 14 / 265 (5.28%)  |  |
| occurrences (all)                  | 6                 | 15                |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 14 November 2012  | Changes to study design, additional clarification to some study procedures. |
| 10 September 2013 | Updates to the I/E criteria and safety procedures.                          |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported