# Clinical trial results:
# A Randomized, Multicenter, Phase II study to Investigate Efficacy and Safety of ITF2984 in Acromegalic patients.

## Summary

| | |
|---|---|
| EudraCT number | 2013-003183-31 |
| Trial protocol | CZ IT NL HU ES RO PL FR |
| Global end of trial date | 08 February 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 May 2020 |
| First version publication date | 10 May 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | DSC/13/2984/05 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02111044 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | ITALFARMACO S.p.A. |
| Sponsor organisation address | Via dei Lavoratori, 54, Cinisello Balsamo (MI), Italy, 20092 |
| Public contact | Clinical Scientist, ITALFARMACO S.p.A., +39 0264431, s.manzoni@italfarmaco.com |
| Scientific contact | Clinical Scientist, ITALFARMACO S.p.A., +39 0264431, s.manzoni@italfarmaco.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 | 08 February 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 February 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the effect of treatment on GH and IGF-1 concentrations.

Protection of trial subjects:

This study was carried out in accordance with the principles enunciated in the International Council on Harmonisation (ICH) harmonised tripartite guideline regarding Good Clinical Practice (GCP) (E6 Consolidated Guidance) the Declaration of Helsinki, the European and local regulations, and the Italfarmaco/contract research organisation (CRO) standard operating procedures (SOPs).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 January 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Serbia: 8 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Poland: 11 |
| Country: Number of subjects enrolled | Romania: 2 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | Hungary: 14 |
| Country: Number of subjects enrolled | Italy: 10 |
| Worldwide total number of subjects | 48 |
| EEA total number of subjects | 40 |

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) | 43 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study enrolled patients with active acromegaly, de novo or partial responder to previous treatment with somatostatin analogs. Due to the small number of de novo patients, the recruitment of these patients should be at least 1/3 of the total enrolment.

### Pre-assignment

Screening details:

For patients who had previously received medical therapy for acromegaly a washout period, before study entry, of 3 months for long-acting formulation of somatostatin analogs, 2 weeks for octreotide sc, 2 months for pegvisomant and/or cabergoline was foreseen.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial by sequence (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable, this was a randomised open-label study.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Octreotide 100- ITF2984 2000 - ITF2984 500 - ITF2984 1000 |

Arm description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
- Octreotide 100 mcg tid
- ITF2984 2000 mcg bid
- ITF2984 500 mcg bid
- ITF2984 1000 mcg bid

Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Octreotide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Octreotide 100 mcg/ml, solution for injection in prefilled syringe: Each prefilled syringe with l ml of solution for
injection contains 100 mcg of octreotide as octreotide acetate.
Octreotide 100 mcg sc was administered three times daily (t.i.d) for 4 weeks

| | |
|---|---|
| Investigational medicinal product name | ITF2984 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Glass pre-filled syringes containing 1 ml of ready to use s.c. solution of ITF2984 diacetate:
ITF2984 500 mcg sc b.i.d for 4 weeks,
ITF2984 1000 mcg sc b.i.d for 4 weeks,
ITF2984 2000 mcg sc b.i.d for 4 weeks.

| | |
|---|---|
| **Arm title** | ITF2984 500 - Octreotide 100 - ITF2984 1000 - ITF2984 2000 |

Arm description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
ITF2984 500 mcg bid
Octreotide 100 mcg tid
ITF2984 1000 mcg bid
ITF2984 2000 mcg bid.
Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Octreotide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Octreotide 100 mcg/ml, solution for injection in prefilled syringe: Each prefilled syringe with l ml of solution for
injection contains 100 mcg of octreotide as octreotide acetate.
Octreotide 100 mcg sc was administered three times daily (t.i.d) for 4 weeks,

| | |
|---|---|
| Investigational medicinal product name | IFT2984 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Glass pre-filled syringes containing 1 ml of ready to use s.c. solution of ITF2984 diacetate:
ITF2984 500 mcg sc b.i.d for 4 weeks,
ITF2984 1000 mcg sc b.i.d for 4 weeks
ITF2984 2000 mcg sc b.i.d for 4 weeks.

| | |
|---|---|
| **Arm title** | ITF2984 1000 - ITF2984 500 - ITF2984 2000 - Octreotide 100 |

Arm description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
- ITF2984 1000 mcg bid
- ITF2984 500 mcg bid
- ITF2984 2000 mcg bid
- Octreotide 100 mcg tid -
Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Octreotide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Octreotide 100 mcg/ml, solution for injection in prefilled syringe: Each prefilled syringe with l ml of solution for
injection contains 100 mcg of octreotide as octreotide acetate.
Octreotide 100 mcg sc was administered three times daily (t.i.d) for 4 weeks,

| | |
|---|---|
| Investigational medicinal product name | ITF2984 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Glass pre-filled syringes containing 1 ml of ready to use s.c. solution of ITF2984 diacetate:

ITF2984 500 mcg sc b.i.d for 4 weeks,
ITF2984 1000 mcg sc b.i.d for 4 weeks,
ITF2984 2000 mcg sc b.i.d for 4 weeks.

| **Arm title** | ITF2984 2000 - ITF2984 1000 - Octreotide 100 - ITF2984 500 |
|---|---|

Arm description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
- ITF2984 2000 mcg bid
- ITF2984 1000 mcg bid
- Octreotide 100 mcg tid
- ITF2984 500 mcg bid.

Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Octreotide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Octreotide 100 mcg/ml, solution for injection in prefilled syringe: Each prefilled syringe with l ml of solution for
injection contains 100 mcg of octreotide as octreotide acetate.
Octreotide 100 mcg sc was administered three times daily (t.i.d) for 4 weeks,

| Investigational medicinal product name | ITF2984 |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Glass pre-filled syringes containing 1 ml of ready to use s.c. solution of ITF2984 diacetate:
ITF2984 500 mcg sc b.i.d for 4 weeks,
ITF2984 1000 mcg sc b.i.d for 4 weeks,
ITF2984 2000 mcg sc b.i.d for 4 weeks.

| **Number of subjects in period 1** | Octreotide 100-ITF2984 2000 - ITF2984 500 - ITF2984 1000 | ITF2984 500 - Octreotide 100 - ITF2984 1000 - ITF2984 2000 | ITF2984 1000 - ITF2984 500 - ITF2984 2000 - Octreotide 100 |
|---|---|---|---|
| Started | 12 | 12 | 12 |
| Completed | 11 | 11 | 7 |
| Not completed | 1 | 1 | 5 |
| Consent withdrawn by subject | - | 1 | 1 |
| Adverse event, non-fatal | - | - | 3 |
| Lost to follow-up | 1 | - | 1 |

| **Number of subjects in period 1** | ITF2984 2000 - ITF2984 1000 - Octreotide 100 - ITF2984 500 |
|---|---|

| | |
|---|---|
| Started | 12 |
| Completed | 11 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | - |
| Lost to follow-up | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Octreotide 100- ITF2984 2000 - ITF2984 500 - ITF2984 1000 |
| Reporting group description: | |
| Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:<br>- Octreotide 100 mcg tid<br>- ITF2984 2000 mcg bid<br>- ITF2984 500 mcg bid<br>- ITF2984 1000 mcg bid<br>Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks. | |
| Reporting group title | ITF2984 500 - Octreotide 100 - ITF2984 1000 - ITF2984 2000 |
| Reporting group description: | |
| Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:<br>ITF2984 500 mcg bid<br>Octreotide 100 mcg tid<br>ITF2984 1000 mcg bid<br>ITF2984 2000 mcg bid.<br>Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks. | |
| Reporting group title | ITF2984 1000 - ITF2984 500 - ITF2984 2000 - Octreotide 100 |
| Reporting group description: | |
| Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:<br>- ITF2984 1000 mcg bid<br>- ITF2984 500 mcg bid<br>- ITF2984 2000 mcg bid<br>- Octreotide 100 mcg tid -<br>Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks. | |
| Reporting group title | ITF2984 2000 - ITF2984 1000 - Octreotide 100 - ITF2984 500 |
| Reporting group description: | |
| Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:<br>- ITF2984 2000 mcg bid<br>- ITF2984 1000 mcg bid<br>- Octreotide 100 mcg tid<br>- ITF2984 500 mcg bid.<br>Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks. | |

| Reporting group values | Octreotide 100- ITF2984 2000 - ITF2984 500 - ITF2984 1000 | ITF2984 500 - Octreotide 100 - ITF2984 1000 - ITF2984 2000 | ITF2984 1000 - ITF2984 500 - ITF2984 2000 - Octreotide 100 |
|---|---|---|---|
| Number of subjects | 12 | 12 | 12 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 10 | 11 | 11 |
| From 65-84 years | 2 | 1 | 1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 8 | 7 | 8 |
| Male | 4 | 5 | 4 |

| Reporting group values | ITF2984 2000 - ITF2984 1000 - Octreotide 100 - ITF2984 500 | Total | |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Number of subjects | 12 | 48 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 10 | 42 | |
| From 65-84 years | 2 | 6 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 29 | |
| Male | 6 | 19 | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Octreotide 100 - ITF2984 2000-500-1000 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | ITF2984 500 - Octreotide 100 - ITF2984 1000-2000 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | ITF2984 1000 - 500 - 2000 - Octreotide 100 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | ITF2984 2000 - 1000 - Octreotide 100 - ITF2984 500 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | Octreotide 100 mcg - ITT - CfB |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| | |
|---|---|
| Subject analysis set title | ITF2984 500 mcg - ITT - CfB |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| | |
|---|---|
| Subject analysis set title | ITF2984 1000 mcg - ITT - CfB |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| | |
|---|---|
| Subject analysis set title | ITF2984 2000 mcg - ITT - CfB |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| | |
|---|---|
| Subject analysis set title | Octreotide 100 mcg - ITT - Baseline |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 500 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 1000 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 2000 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | Octreotide 100 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 500 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 1000 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 2000 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| **Reporting group values** | Octreotide 100 - ITF2984 2000-500-1000 - safety | ITF2984 500 - Octreotide 100 - ITF2984 1000-2000 - safety | ITF2984 1000 - 500 - 2000 - Octreotide 100 - safety |
|---|---|---|---|
| Number of subjects | 11 | 12 | 12 |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 9 | 11 | 11 |
| From 65-84 years | 2 | 1 | 1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 7 | 7 | 8 |
| Male | 4 | 5 | 4 |

| **Reporting group values** | ITF2984 2000 - 1000 - Octreotide 100 - ITF2984 500 - safety | Octreotide 100 mcg - ITT - CfB | ITF2984 500 mcg - ITT - CfB |
|---|---|---|---|
| Number of subjects | 12 | 41 | 43 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 10 | 9 | 11 |
| From 65-84 years | 2 | 2 | 1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | | |
| Male | 6 | | |

| **Reporting group values** | ITF2984 1000 mcg - ITT - CfB | ITF2984 2000 mcg - ITT - CfB | Octreotide 100 mcg - ITT - Baseline |
|---|---|---|---|
| Number of subjects | 47 | 42 | 41 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 11 | 10 | |
| From 65-84 years | 1 | 2 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | | | |
| Male | | | |

| **Reporting group values** | ITF2984 500 mcg - ITT - Baseline | ITF2984 1000 mcg - ITT - Baseline | ITF2984 2000 mcg - ITT - Baseline |
|---|---|---|---|
| Number of subjects | 43 | 46 | 42 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | | | |
| Male | | | |

| **Reporting group values** | Octreotide 100 mcg - ITT - EoT | ITF2984 500 mcg - ITT - EoT | ITF2984 1000 mcg - ITT - EoT |
|---|---|---|---|
| Number of subjects | 41 | 42 | 43 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | | | |

| **Reporting group values** | ITF2984 2000 mcg - ITT - EoT | | |
|---|---|---|---|
| Number of subjects | 42 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years)<br>From 65-84 years | | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Octreotide 100- ITF2984 2000 - ITF2984 500 - ITF2984 1000 |

Reporting group description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
- Octreotide 100 mcg tid
- ITF2984 2000 mcg bid
- ITF2984 500 mcg bid
- ITF2984 1000 mcg bid

Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Reporting group title | ITF2984 500 - Octreotide 100 - ITF2984 1000 - ITF2984 2000 |

Reporting group description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
ITF2984 500 mcg bid
Octreotide 100 mcg tid
ITF2984 1000 mcg bid
ITF2984 2000 mcg bid.

Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Reporting group title | ITF2984 1000 - ITF2984 500 - ITF2984 2000 - Octreotide 100 |

Reporting group description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
- ITF2984 1000 mcg bid
- ITF2984 500 mcg bid
- ITF2984 2000 mcg bid
- Octreotide 100 mcg tid -

Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Reporting group title | ITF2984 2000 - ITF2984 1000 - Octreotide 100 - ITF2984 500 |

Reporting group description:

Patients were randomised in a 1:1:1:1 ratio, through Interactive Voice Response System (IVRS) to receive the following sequence of study treatments:
- ITF2984 2000 mcg bid
- ITF2984 1000 mcg bid
- Octreotide 100 mcg tid
- ITF2984 500 mcg bid.

Each period of treatment lasted 4 weeks, and was followed by a washout period of 2 weeks.

| | |
|---|---|
| Subject analysis set title | Octreotide 100 - ITF2984 2000-500-1000 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | ITF2984 500 - Octreotide 100 - ITF2984 1000-2000 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | ITF2984 1000 - 500 - 2000 - Octreotide 100 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | ITF2984 2000 - 1000 - Octreotide 100 - ITF2984 500 - safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set includes all subjects who received at least one dose of at least one study drug.

| | |
|---|---|
| Subject analysis set title | Octreotide 100 mcg - ITT - CfB |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 500 mcg - ITT - CfB |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 1000 mcg - ITT - CfB |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 2000 mcg - ITT - CfB |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | Octreotide 100 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 500 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 1000 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 2000 mcg - ITT - Baseline |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | Octreotide 100 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 500 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug

intake.

| Subject analysis set title | ITF2984 1000 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

| Subject analysis set title | ITF2984 2000 mcg - ITT - EoT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The Intent-To-Treat (ITT) Analysis Set was defined as all randomised subjects that received the study drug with at least 1 evaluation of the primary endpoint (GH and IGF-1 value) after the study drug intake.

## Primary: Change from baseline in GH level at the end of each month of treatment

| End point title | Change from baseline in GH level at the end of each month of treatment |
|---|---|

End point description:

The primary analysis of the primary variables assessed whether the reduction from baseline in GH and IGF-1 levels was > 0 separately for each treatment.
The secondary analysis of the primary variables assessed evidence of a dose-response for ITF2984; the effect of each of the ITF2984 doses was compared with octreotide. In addition, the lowest ITF dose (ITF2984 500 µg) was compared with each of the other doses

| End point type | Primary |
|---|---|

End point timeframe:

EoT in Period 1, 2, 3 and 4. Each Period is represented by one-month treatment. "overall" data are reported in the system. Complete data for the 4 treatment periods are attached.

| End point values | Octreotide 100 mcg - ITT - CfB | ITF2984 500 mcg - ITT - CfB | ITF2984 1000 mcg - ITT - CfB | ITF2984 2000 mcg - ITT - CfB |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 42 | 43 | 42 |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | -1.28 (± 7.884) | -1.01 (± 4.224) | -3.47 (± 9.535) | -5.57 (± 11.354) |

| End point values | Octreotide 100 mcg - ITT - Baseline | ITF2984 500 mcg - ITT - Baseline | ITF2984 1000 mcg - ITT - Baseline | ITF2984 2000 mcg - ITT - Baseline |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 43 | 46 | 42 |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 9.16 (± 8.797) | 9.10 (± 9.970) | 9.45 (± 11.079) | 10.40 (± 12.734) |

| End point values | Octreotide 100 mcg - ITT - EoT | ITF2984 500 mcg - ITT - EoT | ITF2984 1000 mcg - ITT - EoT | ITF2984 2000 mcg - ITT - EoT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 42 | 43 | 42 |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 7.88 (± 9.722) | 8.15 (± 7.888) | 6.24 (± 6.081) | 4.82 (± 5.307) |

| Attachments (see zip file) | Summary of GH Levels/Summary of GH Level (µg:L) at |
|---|---|

## Statistical analyses

| Statistical analysis title | ITF2984 500 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - CfB v Octreotide 100 mcg - ITT - CfB |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.1955 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of geometric means |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.4 |

Notes:

[1] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| Statistical analysis title | ITF2984 1000 mcg vs ITF2984 500 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - CfB v ITF2984 1000 mcg - ITT - CfB |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | = 0.0048 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of geometric means |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 0.91 |

Notes:

[2] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 2000 mcg vs ITF2984 500 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of geometric means |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.43 |
| upper limit | 0.64 |

Notes:

[3] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 1000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 1000 mcg - ITT - CfB v Octreotide 100 mcg - ITT - CfB |

| | |
|---|---|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.1226 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of geometric means |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.04 |

Notes:

[4] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 2000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v Octreotide 100 mcg - ITT - CfB |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of geometric means |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.73 |

Notes:

[5] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | Octreotide 100 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model.
A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - EoT v Octreotide 100 mcg - ITT - Baseline |

| | |
|---|---|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| P-value | = 0.0165 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 0.96 |

Notes:

[6] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

| **Statistical analysis title** | ITF2984 500 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model. A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - Baseline v ITF2984 500 mcg - ITT - EoT |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | = 0.3134 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.09 |

Notes:

[7] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

| **Statistical analysis title** | ITF2984 1000 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model. A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | ITF2984 1000 mcg - ITT - Baseline v ITF2984 1000 mcg - ITT - |

| | EoT |
|---|---|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | other[8] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 0.82 |

Notes:

[8] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

| **Statistical analysis title** | ITF2984 2000 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model.
A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| Comparison groups | ITF2984 2000 mcg - ITT - Baseline v ITF2984 2000 mcg - ITT - EoT |
|---|---|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other[9] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 0.57 |

Notes:

[9] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

## Primary: Change from baseline in IGF-1 level at the end of each month of treatment

| End point title | Change from baseline in IGF-1 level at the end of each month of treatment |
|---|---|

End point description:

The primary analysis of the primary variables assessed whether the reduction from baseline in GH and IGF-1 levels was > 0 separately for each treatment.
The secondary analysis of the primary variables assessed evidence of a dose-response for ITF2984; the effect of each of the ITF2984 doses was compared with octreotide. In addition, the lowest ITF dose (ITF2984 500 µg) was compared with each of the other doses

| End point type | Primary |
|---|---|

End point timeframe:

EoT in Period 1, 2, 3 and 4. Each Period is represented by one-month treatment. "overall" data are reported in the system. Complete data for the 4 treatment periods are attached.

| **End point values** | Octreotide 100 mcg - ITT - CfB | ITF2984 500 mcg - ITT - CfB | ITF2984 1000 mcg - ITT - CfB | ITF2984 2000 mcg - ITT - CfB |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 41 | 43 | 42 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | -27.948 (± 24.6531) | -9.572 (± 17.1436) | -22.983 (± 20.4323) | -36.253 (± 20.6453) |

| **End point values** | Octreotide 100 mcg - ITT - Baseline | ITF2984 500 mcg - ITT - Baseline | ITF2984 1000 mcg - ITT - Baseline | ITF2984 2000 mcg - ITT - Baseline |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 42 | 47 | 42 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 81.524 (± 26.3922) | 80.653 (± 25.7428) | 81.962 (± 31.3650) | 84.368 (± 26.8854) |

| **End point values** | Octreotide 100 mcg - ITT - EoT | ITF2984 500 mcg - ITT - EoT | ITF2984 1000 mcg - ITT - EoT | ITF2984 2000 mcg - ITT - EoT |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 42 | 43 | 42 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 53.576 (± 25.7877) | 71.175 (± 26.8510) | 57.282 (± 26.0949) | 48.115 (± 25.8697) |

| **Attachments (see zip file)** | Summary of IGF-1 level/Summary of IGF-1 level at baseline, |
|---|---|

## Statistical analyses

| **Statistical analysis title** | ITF2984 500 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of the geometric means |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.25 |
| upper limit | 1.55 |

Notes:

[10] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 1000 mcg vs ITF2984 500 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - CfB v ITF2984 1000 mcg - ITT - CfB |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of the geometric means |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 0.88 |

Notes:

[11] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 2000 mcg vs ITF2984 500 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |

| | |
|---|---|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of the geometric means |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.7 |

Notes:

[12] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 1000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 1000 mcg - ITT - CfB v Octreotide 100 mcg - ITT - CfB |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.092 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of the geometric means |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.23 |

Notes:

[13] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF2984 2000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Secondary analysis: Treatment and dose comparisons using linear mixed effects model.
Treatment comparisons are presented as treatment ratios of the above geometric means, adjusted for the effects described in the linear mixed model (see Primary analysis).
The system inappropriately adds up the number of patients in each arm. Since it is a crossover study, the subjects in the two groups are the same and therefore the comparison is intra-group.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v Octreotide 100 mcg - ITT - CfB |

| | |
|---|---|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[14] |
| P-value | = 0.0144 |
| Method | Mixed models analysis |
| Parameter estimate | adjusted ratio of the geometric means |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 0.97 |

Notes:

[14] - A linear mixed model was fitted to the change in log transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | Octreotide 100 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model. A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - Baseline v Octreotide 100 mcg - ITT - EoT |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other[15] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.7 |

Notes:

[15] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

| **Statistical analysis title** | ITF 500 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model. A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - Baseline v ITF2984 500 mcg - ITT - EoT |

| | |
|---|---|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other[16] |
| P-value | = 0.0188 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 0.97 |

Notes:

[16] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

| **Statistical analysis title** | ITF 1000 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model. A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | ITF2984 1000 mcg - ITT - Baseline v ITF2984 1000 mcg - ITT - EoT |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | other[17] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.77 |

Notes:

[17] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

| **Statistical analysis title** | ITF 2000 mcg - EoT vs Baseline |
|---|---|

Statistical analysis description:

Primary analysis: Mean change from Baseline to End of Treatment using linear mixed-effects model. A linear mixed model was fitted to the change in log-transformed GH level from Baseline to the end of each month of treatment. Explanatory variables fitted were: treatment, the log-transformed baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - Baseline v ITF2984 2000 mcg - ITT - EoT |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | other[18] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Adjusted geometric mean |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 0.61 |

Notes:

[18] - The mean change from baseline to the end of treatment for each treatment was presented as the geometric mean for the ratio End of treatment concentration: Baseline concentration, adjusted for the effects described in the linear mixed model.

The system inappropriately adds up the number of patients at Baseline and EoT.

## Secondary: Number of patients with reduction of GH < 1.0 mcg/l and/or normalization of IGF-1 at the end of each month of treatment

| | |
|---|---|
| End point title | Number of patients with reduction of GH < 1.0 mcg/l and/or normalization of IGF-1 at the end of each month of treatment |

End point description:

The number and percentage of subjects with reduction of GH < 1.0 µg/L and normalisation of IGF-1, the number and percentage of subjects with reduction of GH < 1.0 µg/L and the number and percentage of subjects with normalisation of IGF-1 at the end of each treatment period were presented for each treatment/period combination (16 combinations) and by treatment (combining periods)

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

End point timeframe:

EoT in Period 1, 2, 3 and 4. Each Period is represented by one-month treatment. "overall" data are reported in the system. Complete data for the 4 treatment periods are attached.

| End point values | Octreotide 100 mcg - ITT - CfB | ITF2984 500 mcg - ITT - CfB | ITF2984 1000 mcg - ITT - CfB | ITF2984 2000 mcg - ITT - CfB |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 43 | 47 | 42 |
| Units: number | | | | |
| number (not applicable) | | | | |
| Overall - GH <0.1 mcg/L - YES | 1 | 0 | 1 | 2 |
| Overall - GH <0.1 mcg/L - NO | 40 | 42 | 42 | 40 |
| Overall - IGF-1 normalization - YES | 14 | 5 | 11 | 21 |
| Overall - IGF-1 normalization - NO | 27 | 37 | 32 | 21 |
| Overall - GH <0.1 mcg/L and IGF-1 norm - YES | 1 | 0 | 1 | 2 |
| Overall - GH <0.1 mcg/L and IGF-1 norm - NO | 40 | 42 | 42 | 40 |

| | |
|---|---|
| **Attachments (see zip file)** | Reduction of GH/Summary of Reduction of GH Level to less<br>Normalization of IGF-1/Summary of Normalization of IGF-1 at<br>Reduction of GH and Norm of IGF-1/Summary of Reduction of |

## Statistical analyses

| **Statistical analysis title** | ITF 2985 500 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, adjusted for the effects described above in the generalised linear mixed logistic regression model.

Analytical statistics are presented uniquely for Normalization of IGF-1 levels at the end of treatment period because the models for Reduction of GH levels to <1.0 mgc/L at the end of treatment period and Reduction of GH levels to <1.0 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.0234 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 0.79 |

Notes:

[19] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a normalization of IGF-1 (nmol/ml) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 1000 mcg vs ITF 2985 500 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Normalization of IGF-1 levels at the end of treatment period because the models for Reduction of GH levels to <1.0 mgc/L at the end of treatment period and Reduction of GH levels to <1.0 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - CfB v ITF2984 1000 mcg - ITT - CfB |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[20] |
| P-value | = 0.2259 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.62 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 12.55 |

Notes:

[20] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a normalization of IGF-1 (nmol/ml) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period. Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 2000 mcg vs ITF 2985 500 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Normalization of IGF-1 levels at the end of treatment period because the models for Reduction of GH levels to <1.0 mgc/L at the end of treatment period and Reduction of GH levels to <1.0 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.0003 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 15.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.61 |
| upper limit | 68.41 |

Notes:

[21] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a normalization of IGF-1 (nmol/ml) at
the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period. Subject was
included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 1000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Normalization of IGF-1 levels at the end of treatment period because the models for Reduction of GH levels to <1.0 mgc/L at the end of treatment period and Reduction of GH levels to <1.0 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - CfB v ITF2984 1000 mcg - ITT - CfB |

| | |
|---|---|
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[22] |
| P-value | = 0.2311 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 1.65 |

Notes:

[22] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a normalization of IGF-1 (nmol/ml) at
the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period. Subject was
included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 2000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Normalization of IGF-1 levels at the end of treatment period because the models for Reduction of GH levels to <1.0 mgc/L at the end of treatment period and Reduction of GH levels to <1.0 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - CfB v ITF2984 2000 mcg - ITT - CfB |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | = 0.079 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 8.53 |

Notes:

[23] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a normalization of IGF-1 (nmol/ml) at
the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period. Subject was
included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

## Secondary: Number of patients with reduction of GH <2.5 mcg/L and/or normalizatin of IGF-1 at the end of each month of treatment

| End point title | Number of patients with reduction of GH <2.5 mcg/L and/or normalizatin of IGF-1 at the end of each month of treatment |
|---|---|

End point description:

The number and percentage of subjects with reduction of GH < 2.5 µg/L and/or normalisation of IGF-1 at the end of each treatment period was presented for each treatment/period combination (16

combinations) and by treatment (combining periods).

Data on the normalization of IGF-1 alone are reported among those on the endpoint "Number of patients with reduction of GH <1.0 mcg/L and/or normalization of IGF-1 at the end of each month of treatment".

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

End point timeframe:

EoT in Period 1, 2, 3 and 4. Each Period is represented by one-month treatment. "overall" data are reported in the system. Complete data for the 4 treatment periods are attached.

| **End point values** | Octreotide 100 mcg - ITT - CfB | ITF2984 500 mcg - ITT - CfB | ITF2984 1000 mcg - ITT - CfB | ITF2984 2000 mcg - ITT - CfB |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 43 | 47 | 42 |
| Units: number | | | | |
| number (not applicable) | | | | |
| Overall - GH <2.5 mcg/L - YES | 7 | 3 | 8 | 19 |
| Overall - GH <2.5 mcg/L - NO | 34 | 39 | 35 | 23 |
| Overall - GH <2.5 mcg/L and IGF-1 norm - YES | 4 | 2 | 4 | 14 |
| Overall - GH <2.5 mcg/L and IGF-1 norm - NO | 37 | 40 | 39 | 28 |

| **Attachments (see zip file)** | Reduction of GH/Summary of Reduction of GH Level to less<br>Reduction of GH and norm of IGF-1/Summary of Reduction of |
|---|---|

## Statistical analyses

| **Statistical analysis title** | ITF 2985 500 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, again adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Reduction of GH levels to <2.5 mgc/L at the end of treatment period because the model for Reduction of GH levels to <2.5 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| Comparison groups | Octreotide 100 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |
|---|---|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[24] |
| P-value | = 0.1878 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 1.86 |

Notes:

[24] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a reduction of GH level to < 2.5
(mcg/litre) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period.
Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 1000 mcg vs ITF 2985 500 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, again adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Reduction of GH levels to <2.5 mgc/L at the end of treatment period because the model for Reduction of GH levels to <2.5 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | ITF2984 500 mcg - ITT - CfB v ITF2984 1000 mcg - ITT - CfB |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[25] |
| P-value | = 0.2135 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 22.71 |

Notes:

[25] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a reduction of GH level to < 2.5
(mcg/litre) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period.
Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 2000 mcg vs ITF 2985 500 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, again adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Reduction of GH levels to <2.5 mgc/L at the end of treatment period because the model for Reduction of GH levels to <2.5 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v ITF2984 500 mcg - ITT - CfB |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[26] |
| P-value | = 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 43.77 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.43 |
| upper limit | 298.09 |

Notes:

[26] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a reduction of GH level to < 2.5
(mcg/litre) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period.
Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 1000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, again adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Reduction of GH levels to <2.5 mgc/L at the end of treatment period because the model for Reduction of GH levels to <2.5 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | Octreotide 100 mcg - ITT - CfB v ITF2984 1000 mcg - ITT - CfB |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[27] |
| P-value | = 0.9509 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.21 |
| upper limit | 4.39 |

Notes:

[27] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a reduction of GH level to < 2.5
(mcg/litre) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period.
Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

| **Statistical analysis title** | ITF 2985 2000 mcg vs Octreotide 100 mcg |
|---|---|

Statistical analysis description:

Treatment comparisons are presented as odds ratio, again adjusted for the effects described above in the generalised linear mixed
logistic regression model.

Analytical statistics are presented uniquely for Reduction of GH levels to <2.5 mgc/L at the end of treatment period because the model for Reduction of GH levels to <2.5 mgc/L and Normalization of IGF-1 at the end of treatment failed to converge.

| | |
|---|---|
| Comparison groups | ITF2984 2000 mcg - ITT - CfB v Octreotide 100 mcg - ITT - CfB |

| | |
|---|---|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | = 0.0011 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 12.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.79 |
| upper limit | 55.46 |

Notes:

[28] - A generalised linear mixed logistic regression model was fitted to the response to treatment based on a reduction of GH level to < 2.5
(mcg/litre) at the end of the Treatment Period. Explanatory variables fitted were: treatment, the baseline value for each period, and period.
Subject was included as a random effect. If any data were missing, the Kenward-Roger adjusted degrees of freedom were used.

## Secondary: Number of patients with improvement of signs and symptoms of acromegaly at the end of each month of treatment

| | |
|---|---|
| End point title | Number of patients with improvement of signs and symptoms of acromegaly at the end of each month of treatment |

End point description:

The number of subjects showing an improvement in signs and symptoms of acromegaly was presented for each treatment/period combination (16 combinations), and by treatment (combining periods).
For each of the signs and symptoms a subject was deemed to have improved within a treatment period for a particular sign and symptom if during the period there was a reduction in that sign and symptom.
Improvement was summarised for each signs and symptom by treatment period.

Overall data are reported. For single periods and single signs and symptoms, see the attached table.

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

End point timeframe:

EoT in Period 1, 2, 3 and 4. Each Period is represented by one-month treatment. "overall" data are reported in the system. Complete data for the 4 treatment periods are attached.

| End point values | Octreotide 100 mcg - ITT - CfB | ITF2984 500 mcg - ITT - CfB | ITF2984 1000 mcg - ITT - CfB | ITF2984 2000 mcg - ITT - CfB |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 43 | 47 | 42 |
| Units: number | | | | |
| number (not applicable) | | | | |
| Overall - Headache - YES | 8 | 14 | 17 | 12 |
| Overall - Headache - NO | 33 | 28 | 27 | 30 |
| Overall - Excessive sweating - YES | 9 | 13 | 16 | 19 |
| Overall - Excessive sweating - NO | 32 | 29 | 28 | 22 |
| Overall - Joint pain - YES | 15 | 16 | 16 | 19 |
| Overall - Joint pain - NO | 26 | 26 | 28 | 22 |
| Overall - Fatigue - YES | 16 | 17 | 14 | 15 |
| Overall - Fatigue - NO | 25 | 25 | 30 | 27 |
| Overall - Soft tissue swelling - YES | 14 | 12 | 17 | 14 |
| Overall - Soft tissue swelling - NO | 27 | 30 | 27 | 28 |

| | | | | |
|---|---|---|---|---|
| Overall - Numbness/tingling of extremities - YES | 13 | 8 | 13 | 8 |
| Overall - Numbness/tingling of extremities - NO | 28 | 34 | 31 | 34 |
| Overall - Health status - YES | 10 | 16 | 24 | 18 |
| Overall - Health status - NO | 31 | 26 | 20 | 24 |
| Overall - Across all signs and symptoms - YES | 32 | 31 | 38 | 39 |
| Overall - Across all signs and symptoms - NO | 9 | 11 | 6 | 3 |

| | |
|---|---|
| **Attachments (see zip file)** | Sign and symptoms/Improvement of signs and symptoms of |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE were assessed at Randomization /crossover (day O; visits 2, 5, 8, 11); during the 4 periods of treatment of 4 weeks each (V3, V6, V9, V12); during follow-up /EW (V4, V7, V10, V13, V14)

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | OCR100µg |
| Reporting group description: - | |
| Reporting group title | ITF2984 500µg |
| Reporting group description: - | |
| Reporting group title | ITF2984 1000µg |
| Reporting group description: - | |
| Reporting group title | ITF2984 2000µg |
| Reporting group description: - | |

| Serious adverse events | OCR100µg | ITF2984 500µg | ITF2984 1000µg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Hyperhydrosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Severe ketoacidosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | ITF2984 2000µg | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| number of deaths (all causes) | 0 | | |

| | | | |
|---|---|---|---|
| number of deaths resulting from adverse events | 0 | | |
| General disorders and administration site conditions | | | |
| Hyperhydrosis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Severe ketoacidosis | | | |
| subjects affected / exposed | 0 / 42 (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: 5 %

| **Non-serious adverse events** | OCR100µg | ITF2984 500µg | ITF2984 1000µg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 41 (60.98%) | 22 / 43 (51.16%) | 27 / 47 (57.45%) |
| Investigations | | | |
| GGT increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences (all) | 2 | 1 | 1 |
| ALT increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| AST increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood ALP increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 43 (4.65%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 2 | 2 |
| Injection site pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 0 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 1 | 2 |
| Injection site pain | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 4 | 0 | 1 |
| Injection site nodule | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Discomfort | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site inflammation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site mass | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site urticaria | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site vescicles | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 2 / 43 (4.65%) | 8 / 47 (17.02%) |
| occurrences (all) | 12 | 3 | 8 |
| Constipation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 0 | 4 |
| abdominal pain | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 2 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 1 | 2 |
| Abdominal distention | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences (all) | 4 | 1 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Periodontal inflammation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Saliva altered | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Toothache | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| **Non-serious adverse events** | ITF2984 2000µg | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 42 (59.52%) | | |
| Investigations | | | |
| GGT increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| ALT increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| AST increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood ALP increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | | |
| occurrences (all) | 4 | | |
| Injection site pruritus | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | | |
| occurrences (all) | 4 | | |

| | | | | |
|---|---|---|---|---|
| Fatigue | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Injection site pain | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences (all) | 1 | | | |
| Injection site nodule | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Chest discomfort | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Discomfort | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences (all) | 1 | | | |
| Injection site inflammation | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Injection site mass | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences (all) | 1 | | | |
| Injection site urticaria | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences (all) | 1 | | | |
| Injection site vescicles | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Injection site reaction | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| Oedema peripheral | | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | | |
| occurrences (all) | 0 | | | |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | | |
| occurrences (all) | 8 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| abdominal pain | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 2 | | |
| Abdominal distention | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Periodontal inflammation | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Saliva altered | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toothache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0 | | |
| Flatulence<br>subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0 | | |
| Proctalgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0 | | |
| Metabolism and nutrition disorders<br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 42 (4.76%)<br>2 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 July 2014 | An update was made to the emergency safety procedures. In particular, it was clarified that any SAE had to be reported within 24 hours using the SAE form available in the eCRF. Faxing an SAE form could be done in case of technical issues (backup procedure).<br>The nonclinical results, clinical results, and study rationale sections in the introduction were updated with information from recently completed studies.<br>A minimum baseline GH value was added to the inclusion criteria (GH at baseline > 2.5 µg/L).<br>The following exclusion criteria were added:<br>- Subjects with additional active malignant disease within the last 5 years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix);<br>- Subjects with a marked baseline prolongation of QT/QTc interval, i.e., a mean QT/QTc > 450 ms after 3 consecutive measurements at least 5 minutes apart;<br>- Subjects with abnormal coagulation, prothrombin time, or activated partial thromboplastin time increased by 30% above normal limits;<br>- Subjects who had a history or presence of pancreatitis at the moment of the screening visit;<br>- Subjects with severely decreased renal function (serum creatinine > 2.0 mg/dL or 176 µmol/L).<br>It was clarified in the section on study procedures that at screening, if it was necessary to confirm the active acromegaly by 2-hour 5 –point mean GH and oral glucose test that the instructions provided in the laboratory manual needed to be followed.<br>was clarified that a subject diary would be used in the study and specified throughout the section on study procedures when this diary needed to be collected.<br>The summary of risk management was updated with the most recent information.<br>The PK Analysis Set was added to the statistical methods section.<br>It was corrected in the statistical section that the interim analysis was not blinded. |
| 11 November 2014 | Serbia was added to the list of participating countries.<br>The criterion excluding subjects with significant cardiovascular morbidity within the 3 months preceding enrolment was updated to "subjects who had had a significant cardiovascular disease in the 3 months prior to inclusion such as congestive heart failure (New York Heart Association class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, sustained clinically significant bradycardia, advanced heart block, or with a history of acute myocardial infarction."<br>A recommendation on dose adjustment of beta-blockers, calcium channel blockers, or medicinal products to control the electrolyte balance and insulin and antidiabetic agents was added to the section on concomitant medication. In addition, a recommendation on clinical monitoring for HR in case bradycardic agents were used was added.<br>HcAb1 was added to the list of clinical chemistry parameters to be evaluated. |

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.

| |
|---|
| No limitations or caveats are applicable to this summary of the results. |

Notes: