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: - 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.	

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 Units: Subjects			
Adults (18-64 years)	10	11	11
From 65-84 years	2	1	1
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	10	42	
From 65-84 years	2	6	
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	9	11	11
From 65-84 years	2	1	1
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	10	9	11
From 65-84 years	2	2	1
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	11	10	
From 65-84 years	1	2	
Gender categorical 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 Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Gender categorical 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 Units: Subjects			
Adults (18-64 years)			
From 65-84 years			

Gender categorical Units: Subjects			
Female Male			

Reporting group values	ITF2984 2000 mcg - ITT - EoT		
Number of subjects	42		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Gender categorical Units: Subjects			
Female 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 Normalization of IGF-1/Summary of Normalization of IGF-1 at 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 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 occurrences (all)	0 / 42 (0.00%) 0		
Flatulence subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Proctalgia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 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). The nonclinical results, clinical results, and study rationale sections in the introduction were updated with information from recently completed studies. A minimum baseline GH value was added to the inclusion criteria (GH at baseline > 2.5 µg/L). The following exclusion criteria were added: - 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); - 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; - Subjects with abnormal coagulation, prothrombin time, or activated partial thromboplastin time increased by 30% above normal limits; - Subjects who had a history or presence of pancreatitis at the moment of the screening visit; - Subjects with severely decreased renal function (serum creatinine > 2.0 mg/dL or 176 µmol/L). 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. 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. The summary of risk management was updated with the most recent information. The PK Analysis Set was added to the statistical methods section. 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. 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." 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. 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: