Clinical trial results:
An open label study to evaluate the safety and efficacy of 12 week treatment with CFZ533 in patients with Graves' disease

Summary

EudraCT number	2015-005564-41
Trial protocol	DE
Global end of trial date	24 April 2017

Results information

Result version number	v1 (current)
This version publication date	09 May 2018
First version publication date	09 May 2018

Trial information

Trial identification

Sponsor protocol code	CCFZ533X2205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02713256
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	24 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of CFZ533 on thyroid function in Graves' disease after 12 week treatment

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2016
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	Germany: 13
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	15
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 15 patients were enrolled and all of them completed the study.

Period 1

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

Arms

Arm title	CFZ533 10 mg/kg

Arm description:

CFZ533 intravenously over approximately one hour

Arm type	Experimental
Investigational medicinal product name	CFZ533
Investigational medicinal product code	CFZ533
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CFZ533 10mg/kg intravenous (iv) over approximately one hour on Study Days 1, 15, 29, 57 and 85.

Number of subjects in period 1	CFZ533 10 mg/kg
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	CFZ533 10 mg/kg
Reporting group description:	
CFZ533 intravenously over approximately one hour	

Reporting group values	CFZ533 10 mg/kg	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	44.3		
standard deviation	± 12.9	-	
Sex: Female, Male Units: Subjects			
Female	13	13	
Male	2	2	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	14	14	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	CFZ533 10 mg/kg
Reporting group description:	
CFZ533 intravenously over approximately one hour	

Primary: Percentage of participants whose thyroid stimulating hormone (TSH) levels normalize after 12 week treatment

End point title	Percentage of participants whose thyroid stimulating hormone (TSH) levels normalize after 12 week treatment[1]
End point description:	
Normalization of TSH is defined as TSH level greater than 0.35 mU/L after 12 week treatment (Day 85). No statistical analysis was planned for this primary outcome	
End point type	Primary
End point timeframe:	
12 week (DAY 85)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome

End point values	CFZ533 10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants whose total triiodothyronine (total T3) levels decrease after 12 week treatment

End point title	Percentage of participants whose total triiodothyronine (total T3) levels decrease after 12 week treatment[2]
End point description:	
Percentage of participants whose total triiodothyronine (total T3) levels decrease after 12 week treatment. A decrease is when total T3 level is below Upper limit of normal (ULN) ≤ 2.79 nmol/L No statistical analysis was planned for this primary outcome	
End point type	Primary
End point timeframe:	
12 week (DAY 85)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome

End point values	CFZ533 10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of participants				
number (not applicable)	38.5			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants whose free thyroxine (free T4) levels decrease after 12 week treatment

End point title	Percentage of participants whose free thyroxine (free T4) levels decrease after 12 week treatment[3]

End point description:

Percentage of participants whose free thyroxine (free T4) levels decrease after 12 weeks of treatment (DAY85). A decrease is when free T4 level is below Upper limit of normal (ULN) ≤ 22.7 pmol/L)
No statistical analysis was planned for this primary outcome

End point type	Primary

End point timeframe:

12 week (DAY 85)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome

End point values	CFZ533 10 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of participants				
number (not applicable)	30.8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	CFZ533 10 mg/kg

Reporting group description:

CFZ533 10 mg/kg

Serious adverse events	CFZ533 10 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	CFZ533 10 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)		
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
CARDIAC MURMUR			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
HEPATIC ENZYME INCREASED			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
DIARRHOEA			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
DRY MOUTH			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
NAUSEA			

subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2 1 / 15 (6.67%) 2		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		
Skin and subcutaneous tissue disorders ALOPECIA subjects affected / exposed occurrences (all) HYPERHIDROSIS subjects affected / exposed occurrences (all) PRURITUS subjects affected / exposed occurrences (all) URTICARIA subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all) SLEEP DISORDER subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 2 1 / 15 (6.67%) 1		
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all) OSTEOPENIA subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		

Infections and infestations			
CYSTITIS			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	5		
SKIN INFECTION			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2016	Amendment 1: The purpose of this amendment was to address comments received from the US Food and Drug Administration (FDA) in the advice/information request letter following submission of the investigational new drug (IND) application. Additional changes included, other administrative changes or clarifications.
18 May 2016	Amendment 2: The purpose of this amendment was to revise the inclusion criteria to be more reflective of the patient characteristics based on the feedback received from the study investigators. Due to the mechanistic nature of the study, newly diagnosed patients with GD were the target population for more homogeneity of the disease states. However, this treatment option could provide more benefit for patients relapsing from ATD treatments in the real world based on communication with the investigators, therefore, patients did not necessarily need to be newly diagnosed with GD (within 6 months of screening) to participate in the study. Few other changes and clarifications are also made in the enrollment criteria. Additionally, other administrative changes were made throughout the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported