Clinical trial results:
First Line Pazopanib in Poor Risk Patients with Metastatic Renal Cell Carcinoma

Summary

EudraCT number	2011-001138-40
Trial protocol	DE
Global end of trial date	31 July 2017

Results information

Result version number	v1 (current)
This version publication date	31 March 2018
First version publication date	31 March 2018
Summary attachment (see zip file)	FLIPPER Synopsis (FLIPPER_Synopsis_Final-1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	IOM-605

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01521715
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	iOMEDICO AG
Sponsor organisation address	Hanferstr. 28, Freiburg, Germany, 79108
Public contact	iOMEDICO AG, iOMEDICO AG, 0049 761152420, info@iomedico.com
Scientific contact	iOMEDICO AG, iOMEDICO AG, 0049 761152420, info@iomedico.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	23 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2017
Global end of trial reached?	Yes
Global end of trial date	31 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary analysis will focus on the rate of poor risk patients as defined by the MSKCC criteria who are free of disease progression at 6 months after start of first line treatment with pazopanib.

Protection of trial subjects:

Informed consent of patient has been obtained in accordance with § 40 I 3 No. 3 Lit. b), II 1 AMG and § 40 I 3 No. 3 Lit. c). IIa 1&2 AMG by each investigator prior to inclusion of each patient to the study. The nature, objective and importance of the study, the possible benefits and disadvantages or risks, and the study procedures were explained to each patient orally and in writing. The patients were informed that their participation was voluntary, that they were free to withdraw from the study at any time, and that choosing not to participate would not impact on the patient's care or future treatment.
The patients were also informed that, by signing the ICF, they explicitly permitted authorized representatives of the sponsor and the regulatory authorities access to study-related personal data to the extent permitted by the applicable law(s) and/or regulations without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) and/or regulations. The patients were also informed that their consent to access their data might not be revoked.
Each patient was given sufficient time to read the ICF and to ask questions to the investigator prior to giving his/her written consent. Before entry to the study and prior to the conduct of any study-related procedure consent was recorded by means of the patient's dated signature. The patient was given a copy of the information sheet and his/her signed consent form. The consent form was retained by the investigator as part of the study records. The investigator did not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and the date when it was obtained were also documented in the electronic case report form (eCRF).

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	24 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	18
From 65 to 84 years	24
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The investigator enrolled patients based on previously defined inclusion (IC) and exclusion criteriea (EC). Patients who fulfilled all of the IC and non of the EC were eligible to FLIPPER trial. The recruitment of eligible patients was competitive among the centers participating in the trial.

Pre-assignment

Screening details:

In total n=60 patients were screened and according to the inclusion and exclusion criteria n=44 patients were enrolled into the study . One patient enrolled did not receive study treatment. Screening period was performed from day -30 to start of treatment. Tumor assessemnt was to be performed no later than 14 days prior to start of study treatment.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Arm title	Pazopanib Treatment

Arm description:

As recommended in the SmPC, 800 mg (2x400 mg) pazopanib per day were to be taken orally without food at least one hour before or two hours after a meal at approximately the same time of day. Administration should have been continued until progression or occurrence of intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	Votrient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administration of pazopanib: 2 tablets with a dose of 400 mg once daily (total daily dose 800 mg)

Number of subjects in period 1	Pazopanib Treatment
Started	44
Completed	27
Not completed	17
AE related to study drug	1
Consent withdrawn by subject	2
Other reason - End of Study	1
Non-compliance	1
More that 21 days withoutstudy medication	3
Patient wish (not toxicity)	6

AE not related to study drug	2
Enrolled but never treated	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
Age categorical			
Age at start of treatment			
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)	19	19	
From 65-84 years	23	23	
85 years and over	2	2	
Age continuous			
Units: years			
median	66		
full range (min-max)	40 to 87	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	35	35	
Ethic origin			
Units: Subjects			
Caucasian	44	44	
Karnofsky Performance Status			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only; therefore, one patient in Reporting group 1 was considered as missing.			
Units: Subjects			
>70	7	7	
<=70	35	35	
missing	2	2	
MSKCC at inclusion			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only; therefore, one patient in Reporting group 1 was considered as missing.			
Units: Subjects			
intermediate	11	11	
poor	29	29	
missing	4	4	
UICC stage at inclusion			

Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only; therefore, one patient in Reporting group 1 was considered as missing.			
Units: Subjects			
Stage IV	43	43	
missing	1	1	
Time from primary diagnosis to start of treatment Units: Subjects			
>=1 year	5	5	
< 1 year	36	36	
missing	3	3	
Prior nephrectomy Units: Subjects			
Nephrectomie	31	31	
No nephrectomie	9	9	
Partial nephrectomie	3	3	
missing	1	1	
Histology of the primary tumor Units: Subjects			
Predominatly cler cell	43	43	
missing	1	1	
Location of tumor at diagnosis			
Location of tumor at initial diagnosis (left/right kidney)			
Units: Subjects			
Left kidney	26	26	
Right Kidney	17	17	
missing	1	1	
Number of documented disease sites			
Most frequently documented lesions (>10% of patients affected in SAF) were [n (%)]: lung 28 (65.1%); lymph nodes 24 (55.8%); kidney 14 (32.6%); bone 11 (25.6%); liver 8 (18.6%); pleura 5 (11.6%).			
Units: Subjects			
<2	9	9	
>=2	32	32	
missing	3	3	
Weight			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only.			
Units: kg			
median	74.5		
full range (min-max)	53.0 to 167.2	-	
Body Mass Index (BMI)			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only.			
Units: kg/m2			
median	24.3		
full range (min-max)	16.7 to 45.4	-	

Subject analysis sets

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF set includes all patients who received at least one dose of pazopanib. This population is relevant for all safety parameters.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population includes all patients who received at least one dose of pazopanib and which fulfill one of the following points:

- have PD prior to 26 weeks +7 days after therapy start
- died because of tumor progression prior to 26 weeks +7 days after therapy start
- are assessable with regard to their disease status at 26 weeks ±7 days after therapy start (3rd tumor evaluation)
- experience SD, partial remission or complete remission after 26 weeks +7 days after therapy start

The mITT set is relevant for the analyses of the primary and secondary efficacy parameters.

Reporting group values	Safety Analysis Set (SAF)	mITT	
Number of subjects	43	34	
Age categorical			
Age at start of treatment			
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)	18	14	
From 65-84 years	23	20	
85 years and over	2	0	
Age continuous			
Units: years			
median	66	66	
full range (min-max)	40 to 87	40 to 83	
Gender categorical			
Units: Subjects			
Female	9	8	
Male	34	26	
Ethic origin			
Units: Subjects			
Caucasian	43	34	
Karnofsky Performance Status			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only; therefore, one patient in Reporting group 1 was considered as missing.			
Units: Subjects			
>70	7	5	
<=70	35	28	
missing	1	1	

MSKCC at inclusion			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only; therefore, one patient in Reporting group 1 was considered as missing.			
Units: Subjects			
intermediate	11	9	
poor	29	22	
missing	3	3	
UICC stage at inclusion			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only; therefore, one patient in Reporting group 1 was considered as missing.			
Units: Subjects			
Stage IV	43	34	
missing	0	0	
Time from primary diagnosis to start of treatment Units: Subjects			
>=1 year	5	4	
< 1 year	36	28	
missing	2	2	
Prior nephrectomy Units: Subjects			
Nephrectomie	31	26	
No nephrectomie	9	7	
Partial nephrectomie	3	1	
missing	0	0	
Histology of the primary tumor Units: Subjects			
Predominatly cler cell	43	34	
missing	0	0	
Location of tumor at diagnosis			
Location of tumor at initial diagnosis (left/right kidney)			
Units: Subjects			
Left kidney	26	23	
Right Kidney	17	11	
missing	0	0	
Number of documented disease sites			
Most frequently documented lesions (>10% of patients affected in SAF) were [n (%)]: lung 28 (65.1%); lymph nodes 24 (55.8%); kidney 14 (32.6%); bone 11 (25.6%); liver 8 (18.6%); pleura 5 (11.6%).			
Units: Subjects			
<2	9	7	
>=2	32	27	
missing	2	0	
Weight			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only.			
Units: kg			
median	74.5	74.0	
full range (min-max)	53.0 to 167.2	53. to 130	

Body Mass Index (BMI)			
Please note: Reporting group 1 (overall trial) values correspond to Reporting group 2 (SAF) since baseline characteristics were analysed for SAF and mITT population only.			
Units: kg/m2			
median	24.3	24	
full range (min-max)	16.7 to 45.4	16.7 to 40.6	

End points

End points reporting groups

Reporting group title	Pazopanib Treatment

Reporting group description:

As recommended in the SmPC, 800 mg (2x400 mg) pazopanib per day were to be taken orally without food at least one hour before or two hours after a meal at approximately the same time of day. Administration should have been continued until progression or occurrence of intolerable toxicity.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF set includes all patients who received at least one dose of pazopanib. This population is relevant for all safety parameters.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population includes all patients who received at least one dose of pazopanib and which fulfill one of the following points:

- have PD prior to 26 weeks +7 days after therapy start
- died because of tumor progression prior to 26 weeks +7 days after therapy start
- are assessable with regard to their disease status at 26 weeks ±7 days after therapy start (3rd tumor evaluation)
- experience SD, partial remission or complete remission after 26 weeks +7 days after therapy start

The mITT set is relevant for the analyses of the primary and secondary efficacy parameters.

Primary: 6-month PFS rate

End point title	6-month PFS rate[1]

End point description:

Proportion of patients free of progression at 6 months (26 weeks ±7 days) after start of first-line therapy with pazopanib. The analysis includes all patients that received at least one dose of pazopanib and which are assessable with regard to their disease status at 26 weeks ±7 days (or before in case of progressive disease (PD) prior to 26 weeks ±7 days after therapy start).
****
Final result: 6-months PFS rate [n (%, [95%-CI])]: 12 (35.29%, [19.7 - 53.5])
****

End point type	Primary

End point timeframe:

Time from first application of pazopanib to progression or death of any cause.

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: Planned patient number (n=80) could not be reached in a timely manner and patient number of the mITT population (n=34) was substantially lower than expected. Therefore, the statistical analysis for the primary endpoint is merely descriptive.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: Number	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression Free Survival (PFS) - Kaplan-Meier

End point title	Median Progression Free Survival (PFS) - Kaplan-Meier

End point description:

PFS is defined as time from first application of pazopanib to progression (PD according to RECIST 1.1) or death of any cause before start of new antineoplastic treatment. Patients without PD or death were censored at their last date of tumor evaluation.

End point type	Secondary

End point timeframe:

Time from first application of pazopanib to progression or death of any cause.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	4.5 (3.6 to 7.8)			

Attachments (see zip file)	PFS (mITT)/PFS_KM_Plot.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS defined as time from first application of pazopanib to death of any cause. Patients alive at the end of the study were censored with the date of the last contact to the patient

End point type	Secondary

End point timeframe:

OS is defined as time from first application of pazopanib to death of any cause.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	9.3 (6.6 to 22.2)			

Attachments (see zip file)	OS Kaplan-Meier Plot (mITT)/OS_KM_Plot.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as rate of patients with complete response (CR) or partial response (PR).

End point type	Secondary

End point timeframe:

Treatment period of pazopanib treatment [Time from first occurrence of a response (at least PR) to a documented PD or death due to PD (whichever came first)].

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: number	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was calculated as the time from first occurrence of a response (at least PR) to a documented PD. If a patient did not experience PD prior to onset of a subsequent therapy the time was censored at last date of tumor evaluation or start of new antineoplastic treatment, whatever came first. The analysis was only conducted for patients with response (at least PR).

End point type	Secondary

End point timeframe:

Time from first occurrence of a response (at least PR) to a documented PD or death due to PD (whichever came first).

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	11[2]			
Units: months				
median (confidence interval 95%)	9.7 (1.8 to 12.4)			

Notes:
[2] - The analysis was conducted only for patients with response (at least partial response)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAE were recorded from day of first dose of study medication to 30 days after last dose of study medication.

Adverse event reporting additional description:

The analysis of safety data will be based on SAF population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Pazopanib Treatment

Reporting group description:

The analysis of safety data is based on SAF population. AE were recorded from day of first dose of study medication to 30 days after last dose of study medication (TEAE).

Serious adverse events	Pazopanib Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 43 (44.19%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	7		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm of pleura			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant neoplasm progression			

subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Metastases to bone				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm progression				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cardiac disorders				
Bradycardia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac arrest				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pleural effusion			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haematuria			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteolysis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pazopanib Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 43 (83.72%)		
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	5		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	9		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	7		
Mucosal inflammation			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	12 / 43 (27.91%)		
occurrences (all)	12		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	7 / 43 (16.28%) 7 5 / 43 (11.63%) 5		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	 3 / 43 (6.98%) 3		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 7 / 43 (16.28%) 7		
Infections and infestations Folliculitis subjects affected / exposed occurrences (all)	 3 / 43 (6.98%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 6 / 43 (13.95%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2014	Amendment to study protocol (v2.0 dated 19-Nov-2013) and patient informed consent form.
09 May 2017	Amendment to study protocol (v4.0 dated 13-Apr-2017) and patient informed consent form (implementation of prematurely study end due to poor recruitment)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported