Clinical trial results:
A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study Evaluating the Safety and Efficacy of Oral GKT137831 in Patients with Type 2 Diabetes and Albuminuria

Summary

EudraCT number	2013-002507-34
Trial protocol	DE CZ PL
Global end of trial date	30 March 2015

Results information

Result version number	v1 (current)
This version publication date	20 May 2022
First version publication date	20 May 2022

Trial information

Trial identification

Sponsor protocol code	GSN000200

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02010242
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genkyotex SA
Sponsor organisation address	16 ch des Aulx, Plan les Ouates, Switzerland, 1228
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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	28 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2015
Global end of trial reached?	Yes
Global end of trial date	30 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of oral GKT137831 in comparison with placebo, in patients with type 2 diabetes and albuminuria.

Protection of trial subjects:

In order to ensure patient safety, a SMB will conduct periodic, scheduled reviews of patient data while the study is in progress. The role and responsibilities of the SMB will be outlined in detail in a separate SMB charter. The SMB will receive unblinded eCRF and laboratory data in the form of tables and listings, and adjudicate on patient status changes and dosing decisions (where appropriate). The data will include, but is not limited to, demographics, patient enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data including PK, dose adjustments, protocol adherence, and patient withdrawals. The SMB will evaluate the progress of the study, assess data quality and timeliness, participant recruitment, accrual and retention, and participant risk versus benefit. In addition the SMB will monitor external factors relevant to the study, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects,
the SMB will make recommendations to the Sponsor concerning continuation, termination or modifications of the study. In case an absolute reticulocyte count decreases to <50% of the baseline value (defined as the average of the 3 values measured during Visits 3, 4 and 5), the Investigator will instruct the patient to interrupt treatment and to return to the study center within 7 days to perfom a retest. If the retest value is also below 50% of baseline, treatment will not be resumed. Treatment can be resumed only if the retest value for the reticulocyte count is 50% of the baseline value.

Background therapy:

Patients are required to take the following concomitant medications:
Patients must be taking an ACEI or an ARB for at least 6 weeks prior to the first screening visit (Visit 1) and during the screening period in order to enter the run-in period. The dose must have been stable for at least 4 weeks prior to the first screening visit (Visit 1). Combination therapy associating an ACEI and an ARB is not permitted. During the run-in period, the dose of ACEI or ARB must be adjusted to the maximal tolerated dose. The dose of ACEI, ARB, and other antihypertensive therapy should remain stable following the second visit of the run-in period, Week -2 (Visit 4), and during the double-blind treatment period.

Evidence for comparator:

N.A

Actual start date of recruitment	16 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Poland: 13

Country: Number of subjects enrolled	Czechia: 21
Country: Number of subjects enrolled	United States: 56
Country: Number of subjects enrolled	Canada: 21
Worldwide total number of subjects	136
EEA total number of subjects	43

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)	81
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Subject enrolled: 18 MARCH 2014
Last subject completed: 19 MARCH 2015

Pre-assignment

Screening details:

Male or female aged 18 to 80 years, complied with the requirements of the study; history of type 2 diabetes, stratified by presence or absence of impaired renal function, receiving a stable dose of ACEI or ARB, who met all the inclusion criteria and none of the exclusion
criteria.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

This is a double-blind study: the Sponsor, subjects, investigator staff, persons performing the assessments and data reviewers and statisticians will remain blinded to the identity of the study treatments. The identity of the study treatments will be concealed by the use of IMPs which are all identical in packaging, labelling, schedule of administration, appearance and odour. Randomization data will be kept strictly confidential, and will be accessible only to authorized personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	A 12-week period of treatment with oral GKT137831

Arm description:

Patients will self-administer orally, 100 mg GKT137831 twice daily for the first 6 weeks (Days 1 to 41), and 200 mg GKT137831 twice daily for the remaining 6 weeks (Days 42 to 84).

Arm type	Experimental
Investigational medicinal product name	GKT137831
Investigational medicinal product code	
Other name	setanaxib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During the first 6-week period patients will self-administer 1 capsule of 100 mg GKT137831 in the morning, and 1 capsule of 100 mg GKT137831 in the evening, and during the second 6-week period patients will self-administer 2 capsules of 100 mg GKT137831 in the morning, and 2 capsules of 100 mg GKT137831 in the evening.

Arm title	Placebo

Arm description:

Placebo twice daily administration. Patients will self-administer orally, 100 mg matching placebo twice daily for the first 6 weeks
(Days 1 to 41), and 200 mg matching placebo twice daily for the remaining 6 weeks (Days 42 to 84).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	Placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During the first 6-week period patients will self-administer 1 capsule of 100 mg matching placebo in the morning, and 1 capsule of 100 mg matching placebo in the evening, and during the second 6-week period patients will self-administer 2 capsules of 100 mg matching placebo in the morning, and 2 capsules of 100 mg matching placebo in the evening.

Number of subjects in period 1	A 12-week period of treatment with oral GKT137831	Placebo
Started	68	68
Completed	64	61
Not completed	4	7
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	2
non-compliance with study drug	1	1
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	A 12-week period of treatment with oral GKT137831
Reporting group description:	
Patients will self-administer orally, 100 mg GKT137831 twice daily for the first 6 weeks (Days 1 to 41), and 200 mg GKT137831 twice daily for the remaining 6 weeks (Days 42 to 84).	
Reporting group title	Placebo
Reporting group description:	
Placebo twice daily administration. Patients will self-administer orally, 100 mg matching placebo twice daily for the first 6 weeks (Days 1 to 41), and 200 mg matching placebo twice daily for the remaining 6 weeks (Days 42 to 84).	

Reporting group values	A 12-week period of treatment with oral GKT137831	Placebo	Total
Number of subjects	68	68	136
Age categorical Units: Subjects			
Adults (18-64 years)	38	43	81
From 65-84 years	30	25	55
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.1	62.2	
standard deviation	± 8.64	± 9.9	-
Gender categorical Units: Subjects			
Female	16	16	32
Male	52	52	104

End points

End points reporting groups

Reporting group title	A 12-week period of treatment with oral GKT137831
Reporting group description:	
Patients will self-administer orally, 100 mg GKT137831 twice daily for the first 6 weeks (Days 1 to 41), and 200 mg GKT137831 twice daily for the remaining 6 weeks (Days 42 to 84).	
Reporting group title	Placebo
Reporting group description:	
Placebo twice daily administration. Patients will self-administer orally, 100 mg matching placebo twice daily for the first 6 weeks (Days 1 to 41), and 200 mg matching placebo twice daily for the remaining 6 weeks (Days 42 to 84).	

Primary: UACR Absolute value and ratio to baseline by study visit and Treatment group

End point title	UACR Absolute value and ratio to baseline by study visit and Treatment group
End point description:	
UACR from baseline to Visits 9, 10, and 11 (i.e. weeks 8, 10 and 12 of the treatment period, respectively). Baseline for UACR is defined as the geometric mean of the geometric means of the UACR values measured on Day-14 (visit 4) and Day 1 (visit 5). End of treatment is defined as the geometric mean of the geometric means of the UACR values measured at week 8 (visit 9), week 10 (visit 10) and week 12 (visit 11). Number of subjects in the ITT population who have evaluable results	
End point type	Primary
End point timeframe:	
Visit 4 (week -2) to visit 11 (week 12)	

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	59		
Units: mg/g				
geometric mean (confidence interval 90%)				
Baseline Geometric Mean	705.72 (637.07 to 774.36)	696.30 (611.98 to 780.61)		
Adjusted End of treatment Geom. Mean	758.22 (695.61 to 826.46)	705.29 (646.19 to 769.80)		
Mean for ratio of end of Ttmt v.s baseline	1.10 (1.01 to 1.20)	1.02 (0.94 to 1.11)		

Statistical analyses

Statistical analysis title	Analysis in UACR from baseline by Visit/Treatment

Statistical analysis description:

Primary efficacy endpoint was analyzed using ANCOVA comparing GKT137831 vs placebo after controlling for the baseline UACR level. The UACR were log-transformed prior to analysis. The model included treatment group and log-transformed baseline UACR value as predicted variables. The results were back-transformed exponentially to calculate geo. mean values and associated 90% CIs and 1-sided p-values. The null hypothesis was that the difference in the adjusted mean logarithm of UACR was equal to 0.

Comparison groups	Placebo v A 12-week period of treatment with oral GKT137831
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 1 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	90 %
sides	1-sided
Variability estimate	Standard deviation

Notes:

[1] - All statistical analyses were performed on a comparison-wise basis without adjustment for multiple comparisons.
[2] - No difference observed between arms from baseline

Secondary: Glucose metabolism HOMA

End point title	Glucose metabolism HOMA

End point description:

Change in HOMA-B, HOMA-IR from baseline. Number of subjects in the ITT population who have evaluable results

End point type	Secondary

End point timeframe:

Visits 5 (week 0), 8 (week 6) and 11 (week 12)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mg/dL				
arithmetic mean (standard deviation)				
HOMA-IR W6 change from baseline	0.916 (± 2.84)	2.013 (± 1.943)		
HOMA-IR W12 change from baseline	0.344 (± 2.32)	-1.833 (± 3.95)		
HOMA-B W6 change from baseline	12.94 (± 24.06)	50.10 (± 75.81)		
HOMA-B W12 change from baseline	-12.41 (± 38.72)	47.63 (± 120.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Glucose metabolism HbA1c

End point title	Glucose metabolism HbA1c

End point description:

Change in HbA1c from baseline. Number of subjects in the ITT population who have evaluable results

End point type	Secondary

End point timeframe:

Visits 5 (week0), 8 (week 6) and 11 (week 12)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	68		
Units: percentage of glycated haemoglobin				
arithmetic mean (standard deviation)				
W6 change from baseline	0.02 (± 0.538)	-0.03 (± 0.618)		
W12 change from baseline	0.12 (± 0.659)	0.03 (± 0.722)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 24h Albumin excretion

End point title	Change in 24h Albumin excretion

End point description:

Change in 24hours Albumin excretion from baseline. Number of subjects analyzed in the ITT population who have evaluable results

End point type	Secondary

End point timeframe:

Visits 5 (week 0) and 11 (week 12)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: mg/24hrs				

arithmetic mean (standard deviation)	389.82 (± 1540.30)	-56.15 (± 1569.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 24h urine UACR from baseline

End point title	Change in 24h urine UACR from baseline

End point description:

Change in 24 hours Urine UACR from baseline. Number of subjects analyzed in the IIT population who have evaluable results

End point type	Secondary

End point timeframe:

Visits 5 (week 0) and 11 (week 12)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: mg/g				
arithmetic mean (standard deviation)	220.15 (± 592.995)	169.98 (± 706.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: eGFR change by study visit

End point title	eGFR change by study visit

End point description:

Change in eGFR from baseline by study visit. Number of subjects analyzed in the ITT population who have evaluable results

End point type	Secondary

End point timeframe:

Visits 5 (week 0), 6 (week 2), 7 (week 4), 8 (week 6), 9 (week 8), 10 (week 10), 11 (week 12) , follow up (week 16)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	68		
Units: mL/min/SSA				
arithmetic mean (standard deviation)				
Change in week2 (V6) eGFR from baseline	-0.5 (± 6.07)	-0.4 (± 7.27)		
Change in week 4 (V7) eGFR from baseline	-0.6 (± 8.25)	-1.5 (± 6.55)		
Change in week 6 (V8) eGFR from baseline	-0.1 (± 8.13)	-0.3 (± 6.8)		
Change in week 8 (V9) eGFR from baseline	-1.1 (± 8.7)	-1.7 (± 7.31)		
Change in week 10 (V10) eGFR from baseline	-0.7 (± 8.21)	-1.9 (± 7.89)		
Change in week 12 (V11) eGFR from baseline	-1.5 (± 8.28)	-1.2 (± 8.08)		
Change in week 16 (follow up) eGFR from baseline	-1.3 (± 8.21)	-1.9 (± 10.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Erectile dysfunction

End point title	Erectile dysfunction

End point description:

Changes at week 12 in IEFF questionnaire assessing erectile dysfunction in patients presenting with these diabetic complications at baseline (Baseline <=25 in the erectile function domain)- Score from 1 to 30. Score 1 to 10: severe erectile dysfunction, Score 11-16: moderate erectile dysfunction, Score 17-25: light erectile dysfunction, Score 26-30:normal erectile function
Number of subjects analyzed in the ITT population who have evaluable results.

End point type	Secondary

End point timeframe:

Visits 5 (week 0), and 11 (week 12)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: score on a scale				
arithmetic mean (standard deviation)	0.8 (± 5.86)	-0.5 (± 5.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Neuropathic pain

End point title	Neuropathic pain

End point description:

Changes in Visual Analog Scale (VAS) assessing neuropathic leg pain in patients presenting with these diabetic complications at baseline (subjects with a baseline VAS>=20mm are included) - 100mm VAS scale was used- Presence of neuropathic pain for a score of at least 20mm. Number of subjects analyzed in the ITT population who have evaluable results.

End point type	Secondary

End point timeframe:

Visits 5 (week 0), and 11 (week 12)

End point values	A 12-week period of treatment with oral GKT137831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: score on a scale				
arithmetic mean (standard deviation)	-15.3 (± 21.79)	-10.5 (± 22.18)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 9-10 months

Adverse event reporting additional description:

Adverse events were collected after signing the informed consent form (ICF) and up to completion of the 30-day follow up period after the last administration of IMP

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	A 12-week period of treatment with oral GKT137831

Reporting group description:

Patients will self-administer orally, 100 mg GKT137831 twice daily for the first 6 weeks (Days 1 to 41), and 200 mg GKT137831 twice daily for the remaining 6 weeks (Days 42 to 84).

Reporting group title	Placebo

Reporting group description:

Placebo twice daily administration. Patients will self-administer orally, 100 mg matching placebo twice daily for the first 6 weeks
(Days 1 to 41), and 200 mg matching placebo twice daily for the remaining 6 weeks (Days 42 to 84).

Serious adverse events	A 12-week period of treatment with oral GKT137831	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 68 (4.41%)	5 / 68 (7.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycemic encephalopathy			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non cardiac chest pain			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lobular Pneumonia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract inifection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycemia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	A 12-week period of treatment with oral GKT137831	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 68 (48.53%)	42 / 68 (61.76%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Edema peripheral			
subjects affected / exposed	2 / 68 (2.94%)	6 / 68 (8.82%)	
occurrences (all)	2	6	
Fatigue			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Non cardiac chest pain			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Respiratory, Thoracic disorders			
subjects affected / exposed	2 / 68 (2.94%)	3 / 68 (4.41%)	
occurrences (all)	2	5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 68 (0.00%)	3 / 68 (4.41%)	
occurrences (all)	0	3	
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Cardiac disorders			

Cardiac disorders			
subjects affected / exposed	1 / 68 (1.47%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	1	3	
Headache			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Diarrhea			
subjects affected / exposed	3 / 68 (4.41%)	4 / 68 (5.88%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Anthralgia			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	1	4	
Myalgia			

subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	0 / 68 (0.00%)	3 / 68 (4.41%)	
occurrences (all)	0	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Tooth abscess			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	4 / 68 (5.88%)	2 / 68 (2.94%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	1	4	
Hypoglycemia			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2013	• Eligibility criteria were modified in order to define inadequately controlled SBP as an exclusion criterion. Consequently, Inclusion Criterion 7 was removed and a new Exclusion Criterion 9 was added. • Eligibility criteria were modified in order to exclude subjects with marked anemia. Consequently, Exclusion Criterion 18 was amended to specify that subjects with marked anemia defined as hemoglobin <10.0 g/dL (or 4.9 mmol/L) during screening were ineligible to enter the study. • Additional blood sampling points for PK and PD, and urinary PD were added. • Other changes were text clarifications and corrections with minimal impact on the study conduct or analysis.
25 March 2014	- Eligibility criteria were modified in order to allow the enrolment of subjects with stable thyroid disorder requiring hormone replacement therapy. Consequently, Exclusion Criterion 11 was amended to allow subject with stable doses of thyroid hormone(s) for at least 4 weeks prior to the first screening visit (Visit 1) and TSH values not greater than the upper limit of the normal range at Visit 1. - Eligibility criteria were modified in order to exclude subjects with a history of EPO use within the 4 weeks prior to Visit 1. Consequently Exclusion Criterion 21 was amended. • Other changes were text clarifications and corrections with minimal impact on the study conduct or analysis.

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.

N.A

Notes: