# 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 |
| Public contact | Dr Richard Philipson, Calliditas Therapeutics Suisse SA, +46 556659-9766, richard.philipson@calliditas.com |
| Scientific contact | Philippe Wiesel, Genkyotex SA, +33 (0) 4 56 44 81 12, philippe.wiesel@genkyotex.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 | 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<br>(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<br>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<br>Units: years | | | |
| arithmetic mean | 62.1 | 62.2 | |
| standard deviation | ± 8.64 | ± 9.9 | - |
| Gender categorical<br>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<br>(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).<br>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.<br>• 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.<br>• Additional blood sampling points for PK and PD, and urinary PD were added.<br>• 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.<br>- 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.<br>• 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: