



Clinical trial results:

Multi-center, double-blind, randomized, placebo-controlled, active reference, parallel-group, polysomnography dose response study to assess the efficacy and safety of ACT-541468 in adult subjects with insomnia disorder

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-000826-21 |
| Trial protocol | DE SE HU ES |
| Global end of trial date | 20 June 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 06 July 2018 |
| First version publication date | 06 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-078A201 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02839200 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Hegenheimermattweg 95, Allschwil, Switzerland, 4123 |
| Public contact | Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com |
| Scientific contact | Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.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 | 13 July 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 April 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 June 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the dose-response of ACT-541468 on the change of WASO [Wake After Sleep Onset] assessed by Polysomnography [PSG] after treatment on Days 1 and 2.

Protection of trial subjects:

The study was conducted in full compliance with ICH-GCP Guidelines, the principles of the 'Declaration of Helsinki', and with the laws and regulations of the countries in which the study was conducted. Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects involved. The protocol and any material provided to the subject (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC or IRB before the study was started. Prior to any study procedure, written informed consent was obtained from each participating subject. It was made clear to each subject that he or she was completely free to withdraw from it at any time for any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 29 September 2016 |
| 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 | Spain: 26 |
| Country: Number of subjects enrolled | Sweden: 11 |
| Country: Number of subjects enrolled | Germany: 199 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | United States: 101 |
| Worldwide total number of subjects | 360 |
| EEA total number of subjects | 256 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|-----|
| wk | |
| 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) | 360 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Conducted at 38 sites in 6 countries (Germany, Hungary, Israel, Spain, Sweden, and the USA)

Pre-assignment

Screening details:

Screening phase: screening period (screening visit followed by at least 7 days at home) and a run-in period (2 PSG nights on single-blind placebo, followed by 5–12 days with no treatment), and lasting a max. of 28 days. N = 360 subjects were randomized; N = 359 subjects were treated; N = 1 subject discontinued due to "randomization error."

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------------|
| Arm title | ACT-541468 5 mg |
|------------------|-----------------|

Arm description: -

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACT-541468 5 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

ACT-541468 5 mg orally once daily.

| | |
|------------------|------------------|
| Arm title | ACT-541468 10 mg |
|------------------|------------------|

Arm description: -

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACT-541468 10 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

ACT-541468 10 mg orally once daily.

| | |
|------------------|------------------|
| Arm title | ACT-541468 25 mg |
|------------------|------------------|

Arm description: -

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACT-541468 25 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

ACT-541468 25 mg orally once daily.

| | |
|--|------------------|
| Arm title | ACT-541468 50 mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | ACT-541468 50 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 2 x ACT-541468 25 mg orally once daily. | |
| Arm title | Zolpidem 10 mg |
| Arm description: - | |
| Arm type | Active reference |
| Investigational medicinal product name | Zolpidem 10 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Over-encapsulated tablets of commercially available Stilnox® for oral administration once daily. | |
| Arm title | Placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Placebo (2 types of placebo: one matching ACT-541468, one matching zolpidem) administered orally once daily during the treatment period. | |
| Placebo was also administered during the run-in period and during the run-out period. | |

| Number of subjects in period 1^[1] | ACT-541468 5 mg | ACT-541468 10 mg | ACT-541468 25 mg |
|---|-----------------|------------------|------------------|
| Started | 60 | 58 | 60 |
| Completed | 56 | 58 | 59 |
| Not completed | 4 | 0 | 1 |
| Consent withdrawn by subject | 2 | - | 1 |
| Adverse event, non-fatal | - | - | - |
| Lost to follow-up | 2 | - | - |

| Number of subjects in period 1^[1] | ACT-541468 50 mg | Zolpidem 10 mg | Placebo |
|---|------------------|----------------|---------|
| Started | 61 | 60 | 60 |
| Completed | 61 | 58 | 59 |
| Not completed | 0 | 2 | 1 |

| | | | |
|------------------------------|---|---|---|
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | - | 1 | - |
| Lost to follow-up | - | 1 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects number enrolled in the trial includes all subjects who were randomized (N= 360).

The number of subjects reported to be in the baseline period includes all subjects who were randomized and received at least 1 dose of treatment (N = 359). N = 1 discontinued due to randomization error.

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------------|
| Reporting group title | ACT-541468 5 mg |
| Reporting group description: - | |
| Reporting group title | ACT-541468 10 mg |
| Reporting group description: - | |
| Reporting group title | ACT-541468 25 mg |
| Reporting group description: - | |
| Reporting group title | ACT-541468 50 mg |
| Reporting group description: - | |
| Reporting group title | Zolpidem 10 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | ACT-541468 5 mg | ACT-541468 10 mg | ACT-541468 25 mg |
|---------------------------------------|-----------------|------------------|------------------|
| Number of subjects | 60 | 58 | 60 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 60 | 58 | 60 |
| Age continuous Units: years | | | |
| median | 41 | 48 | 48 |
| full range (min-max) | 22 to 64 | 21 to 63 | 18 to 64 |
| Gender categorical Units: Subjects | | | |
| Female | 38 | 38 | 39 |
| Male | 22 | 20 | 21 |

| Reporting group values | ACT-541468 50 mg | Zolpidem 10 mg | Placebo |
|---------------------------------------|------------------|----------------|----------|
| Number of subjects | 61 | 60 | 60 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 61 | 60 | 60 |
| Age continuous Units: years | | | |
| median | 46 | 43 | 48 |
| full range (min-max) | 18 to 63 | 23 to 61 | 23 to 64 |
| Gender categorical Units: Subjects | | | |
| Female | 39 | 38 | 38 |
| Male | 22 | 22 | 22 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 359 | | |

| | | | |
|----------------------|-----|--|--|
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 359 | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 230 | | |
| Male | 129 | | |

End points

End points reporting groups

| | |
|--------------------------------|------------------|
| Reporting group title | ACT-541468 5 mg |
| Reporting group description: - | |
| Reporting group title | ACT-541468 10 mg |
| Reporting group description: - | |
| Reporting group title | ACT-541468 25 mg |
| Reporting group description: - | |
| Reporting group title | ACT-541468 50 mg |
| Reporting group description: - | |
| Reporting group title | Zolpidem 10 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

Primary: Change in WASO from baseline to Days 1&2

| | |
|--|--|
| End point title | Change in WASO from baseline to Days 1&2 |
| End point description: | |
| WASO is the time (min) spent awake after onset of persistent sleep until lights on, as determined by PSG. | |
| The change from baseline to Days 1&2 in WASO (min) was analyzed with the MCP-Mod method (see attachment for dose-response relationship). | |
| Modified full analysis set. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline to Days 1&2 | |

| End point values | ACT-541468 5 mg | ACT-541468 10 mg | ACT-541468 25 mg | ACT-541468 50 mg |
|-------------------------------------|-----------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 60 | 61 |
| Units: minutes | | | | |
| least squares mean (standard error) | -28.4 (± 4.24) | -32.3 (± 4.32) | -37.7 (± 4.25) | -47.1 (± 4.21) |

| End point values | Zolpidem 10 mg | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 60 | | |
| Units: minutes | | | | |
| least squares mean (standard error) | -29.9 (± 4.30) | -21.4 (± 4.24) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Predicted mean (95% CL) dose-response profile/ACT-541468 - |
|-----------------------------------|--|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Between treatment - change in WASO - 5 mg |
| Comparison groups | Placebo v ACT-541468 5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.241 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.7 |
| upper limit | 4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.95 |

| | |
|---|--|
| Statistical analysis title | Between treatment - change in WASO - 10 mg |
| Comparison groups | ACT-541468 10 mg v Placebo |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.072 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -10.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.6 |
| upper limit | 1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Between treatment - change in WASO - 25 mg |
| Comparison groups | ACT-541468 25 mg v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.007 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -16.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.9 |
| upper limit | -4.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.95 |

| | |
|---|--|
| Statistical analysis title | Between treatment - change in WASO - 50 mg |
| Comparison groups | ACT-541468 50 mg v Placebo |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -25.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37.3 |
| upper limit | -13.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.92 |

| | |
|---|--|
| Statistical analysis title | Between treatment - change in WASO - Zolpidem 10mg |
| Comparison groups | Placebo v Zolpidem 10 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.155 |
| Method | ANCOVA |
| Parameter estimate | LS mean |
| Point estimate | -8.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.4 |
| upper limit | 3.3 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.97 |

Notes:

[1] - Separate ANCOVA model.

Secondary: Change in latency to persistent sleep (LPS) to Days 1&2

| | |
|--|---|
| End point title | Change in latency to persistent sleep (LPS) to Days 1&2 |
| End point description: | |
| LPS (min) is the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either sleep stage 1 (S1), sleep stage 2 (S2), sleep stage 3 (slow wave sleep) or REM, as determined by polysomnography (PSG). | |
| Full analysis set. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Days 1&2. | |

| End point values | ACT-541468 5 mg | ACT-541468 10 mg | ACT-541468 25 mg | ACT-541468 50 mg |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 60 | 61 |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | -26.88 (± 45.42) | -29.31 (± 26.79) | -36.14 (± 34.34) | -36.41 (± 26.71) |

| End point values | Zolpidem 10 mg | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 60 | | |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | -45.12 (± 32.82) | -22.02 (± 46.63) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subjective latency to sleep onset (sLSO) to Week 4

| | |
|--------------------------|--|
| End point title | Change in subjective latency to sleep onset (sLSO) to Week 4 |
| End point description: | |
| Full analysis set. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 4. | |

| End point values | ACT-541468 5 mg | ACT-541468 10 mg | ACT-541468 25 mg | ACT-541468 50 mg |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 52 | 56 | 57 |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | -13.38 (± 27.79) | -21.07 (± 24.26) | -15.5 (± 25.51) | -23.65 (± 24.12) |

| End point values | Zolpidem 10 mg | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 57 | | |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | -19.98 (± 19.28) | -16.32 (± 21.16) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in subjective WASO (sWASO) to Week 4

| | |
|--------------------------|---|
| End point title | Change in subjective WASO (sWASO) to Week 4 |
| End point description: | |
| Full analysis set. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to Week 4. | |

| End point values | ACT-541468 5 mg | ACT-541468 10 mg | ACT-541468 25 mg | ACT-541468 50 mg |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 | 45 | 53 | 49 |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | -31.32 (± 33.32) | -24.35 (± 33.4) | -29.8 (± 39.88) | -35.45 (± 37.53) |

| End point values | Zolpidem 10 mg | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 50 | | |

| | | | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | -29.08 (± 27.28) | -23.61 (± 32.62) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data on adverse events were collected from Screening to Safety Follow-up period.
Below, data are reported for treatment-emergent adverse events (TEAEs).

Adverse event reporting additional description:

Safety set.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description:

PLACEBO

| | |
|-----------------------|----------------|
| Reporting group title | ACT-541468 5mg |
|-----------------------|----------------|

Reporting group description:

ACT-541468 5mg

| | |
|-----------------------|-----------------|
| Reporting group title | ACT-541468 10mg |
|-----------------------|-----------------|

Reporting group description:

ACT-541468 10mg

| | |
|-----------------------|-----------------|
| Reporting group title | ACT-541468 25mg |
|-----------------------|-----------------|

Reporting group description:

ACT-541468 25mg

| | |
|-----------------------|-----------------|
| Reporting group title | ACT-541468 50mg |
|-----------------------|-----------------|

Reporting group description:

ACT-541468 50mg

| | |
|-----------------------|---------------|
| Reporting group title | ZOLPIDEM 10mg |
|-----------------------|---------------|

Reporting group description:

ZOLPIDEM 10mg

| Serious adverse events | PLACEBO | ACT-541468 5mg | ACT-541468 10mg |
|---|----------------|----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 2 / 58 (3.45%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Accident at work | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | ACT-541468 25mg | ACT-541468 50mg | ZOLPIDEM 10mg |
|---|-----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Accident at work | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | PLACEBO | ACT-541468 5mg | ACT-541468 10mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 60 (30.00%) | 21 / 60 (35.00%) | 21 / 58 (36.21%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Surgical and medical procedures | | | |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences (all) | 2 | 2 | 1 |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Medical device site erythema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Medical device site inflammation subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Medical device site irritation subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Medical device site pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Pharyngeal erythema subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Productive cough subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Psychiatric disorders | | | |
| Abnormal dreams subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Nervousness subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Nightmare subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Stress subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Bilirubin conjugated increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Blood calcium decreased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 2 / 60 (3.33%) | 1 / 58 (1.72%) |
| occurrences (all) | 1 | 2 | 2 |
| ECG signs of myocardial infarction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint injury | | | |

| | | | |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Defect conduction intraventricular | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cervicobrachial syndrome | | | |

| | | | |
|--------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 60 (1.67%) | 2 / 58 (3.45%) |
| occurrences (all) | 1 | 1 | 4 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 6 / 60 (10.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 1 | 7 | 5 |
| Hypersomnia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 3 / 60 (5.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 3 | 4 | 3 |
| Blood and lymphatic system disorders | | | |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia ear | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vertigo | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Chromatopsia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 1 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 3 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Faeces pale | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 2 / 60 (3.33%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Bladder discomfort subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Nocturia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Renal pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Muscle tightness subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 1 / 58 (1.72%) 2 |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 60 (0.00%) 0 | 0 / 58 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 1 / 58 (1.72%) 1 |
| Infections and infestations | | | |
| Acute sinusitis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 60 (1.67%) 1 | 0 / 58 (0.00%) 0 |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Helicobacter infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 2 / 60 (3.33%) | 2 / 58 (3.45%) |
| occurrences (all) | 4 | 2 | 2 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 58 (1.72%) |
| occurrences (all) | 0 | 0 | 1 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 60 (0.00%) | 0 / 58 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 0 / 58 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| Non-serious adverse events | ACT-541468 25mg | ACT-541468 50mg | ZOLPIDEM 10mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 60 (38.33%) | 21 / 61 (34.43%) | 24 / 60 (40.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 0 / 61 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 3 | 0 | 5 |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 2 / 60 (3.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Medical device site erythema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Medical device site inflammation subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Medical device site irritation subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Medical device site pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | 1 / 60 (1.67%) 2 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 2 | 1 / 61 (1.64%) 1 | 0 / 60 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Pharyngeal erythema subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Productive cough subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Psychiatric disorders | | | |
| Abnormal dreams subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | 1 / 60 (1.67%) 1 |
| Nervousness subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | 0 / 60 (0.00%) 0 |
| Nightmare subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Stress subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 1 / 61 (1.64%) 1 | 0 / 60 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Bilirubin conjugated increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 1 / 60 (1.67%) 1 |
| Blood calcium decreased | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| ECG signs of myocardial infarction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint injury | | | |

| | | | |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Defect conduction intraventricular | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cervicobrachial syndrome | | | |

| | | | |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 4 / 60 (6.67%) |
| occurrences (all) | 0 | 0 | 4 |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 5 / 61 (8.20%) | 6 / 60 (10.00%) |
| occurrences (all) | 5 | 6 | 8 |
| Hypersomnia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 4 / 61 (6.56%) | 3 / 60 (5.00%) |
| occurrences (all) | 5 | 5 | 3 |
| Blood and lymphatic system disorders | | | |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Paraesthesia ear | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Chromatopsia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 4 / 60 (6.67%) |
| occurrences (all) | 0 | 1 | 5 |
| Constipation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 3 | 0 | 1 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Faeces pale | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 61 (1.64%) | 4 / 60 (6.67%) |
| occurrences (all) | 2 | 1 | 5 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 2 / 61 (3.28%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Bladder discomfort subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Nocturia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Renal pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Muscle tightness subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Neck pain subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 1 / 61 (1.64%) 1 | 0 / 60 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Infections and infestations | | | |
| Acute sinusitis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 61 (0.00%) 0 | 0 / 60 (0.00%) 0 |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Helicobacter infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 2 / 61 (3.28%) | 5 / 60 (8.33%) |
| occurrences (all) | 0 | 2 | 5 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 61 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 03 August 2016 | Two global amendments were issued to the original AC-078A201 protocol (dated 3 May 2016). Global Amendment 1 was issued before enrolment of the first subject. Hence, all subjects were enrolled and treated under Global Protocol Versions 2 and 3. Some changes of Amendment 1: <ul style="list-style-type: none">• The list of forbidden concomitant medications was expanded (e.g. CYP3A4 substrates, inhibitors and inducers were added)• The list of inclusion/exclusion criteria was modified (e.g. subjects with severe renal impairment were not to be included)• The sleep diary questionnaire was amended by two additional questions |
| 16 December 2016 | Two global amendments were issued to the original AC-078A201 protocol (dated 3 May 2016). Global Amendment 1 was issued before enrolment of the first subject. Hence, all subjects were enrolled and treated under Global Protocol Versions 2 and 3. Some changes of Amendment 2: <ul style="list-style-type: none">• The list of forbidden concomitant medications was expanded (e.g., ethinylestradiol was removed)• The sleep diary questionnaire was improved |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported