



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Phase to Determine the Efficacy and Safety of Tozadenant as Adjunctive Therapy in Levodopa-Treated Patients with Parkinson's Disease Experiencing End-of-Dose "Wearing-Off" (TOZ-PD) Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2014-005630-60  |
| Trial protocol           | DE CZ ES AT IT  |
| Global end of trial date | 12 January 2018 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 23 February 2019 |
| First version publication date | 23 February 2019 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | TOZ-CL05 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02453386 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Acorda Therapeutics   |
| Sponsor organisation address | 420 Saw Mill River Road, Ardsley, United States, 10502  |
| Public contact               | Christopher Kenney, Senior Vice President - Medical Affairs, Acorda Therapeutics, +914 326-5775, ckenney@acorda.com |
| Scientific contact           | Christopher Kenney, Senior Vice President - Medical Affairs, Acorda Therapeutics, +914 326-5775, ckenney@acorda.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                       | 12 January 2018 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 12 January 2018 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 12 January 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary efficacy objective of this study is to demonstrate the efficacy of the A2a receptor antagonist tozadenant in the treatment of levodopa-treated PD patients experiencing end-of-dose "wearing-off", based on the change from Baseline to Week 24 in the number of hours per day spent in the OFF state.

Protection of trial subjects:

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms, patient information sheets, and advertising materials. For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The principal investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved informed consent form prior to the start of the study.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 20 July 2015 |
| 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: 37          |
| Country: Number of subjects enrolled | Austria: 8         |
| Country: Number of subjects enrolled | Czech Republic: 66 |
| Country: Number of subjects enrolled | Germany: 57        |
| Country: Number of subjects enrolled | Canada: 15         |
| Country: Number of subjects enrolled | Italy: 59          |
| Country: Number of subjects enrolled | United States: 207 |
| Worldwide total number of subjects   | 449                |
| EEA total number of subjects         | 227                |

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)                      | 200 |
| From 65 to 84 years                       | 249 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 80 sites in 7 countries (United States, Canada, Italy, Austria, Spain, Germany, Czech Republic). Planned patient enrollment numbers were achieved, but the study and the tozadenant development program were terminated prior to study completion by all patients, based on an unexpected emerging safety signal.

### Pre-assignment

Screening details:

Of the 616 patients screened in the study, a total of 449 were randomized: 149 to receive placebo, 151 to receive 60 mg BID tozadenant, and 149 to receive 120 mg BID tozadenant.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | 24 Weeks (overall period)                    |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description: -

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

Dosage and administration details:

The patients will take two tablets by mouth BID.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | 60 mg BID Tozadenant |
|------------------|----------------------|

Arm description: -

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Tozadenant   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

The patients take 60 mg BID.

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | 120 mg BID Tozadenant |
|------------------|-----------------------|

Arm description: -

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Tozadenant   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

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Dosage and administration details:

One or two doses of 60 mg or 120 mg BID.

| <b>Number of subjects in period 1</b> | Placebo | 60 mg BID<br>Tozadenant | 120 mg BID<br>Tozadenant |
|---------------------------------------|---------|-------------------------|--------------------------|
| Started                               | 149     | 151                     | 149                      |
| Completed                             | 108     | 102                     | 100                      |
| Not completed                         | 41      | 49                      | 49                       |
| Consent withdrawn by subject          | 9       | 10                      | 9                        |
| Other                                 | 1       | 1                       | -                        |
| Subject Terminated by Investigator    | 2       | -                       | 1                        |
| Sponsor Terminated the Study          | 11      | 14                      | 8                        |
| Adverse Events                        | 15      | 22                      | 30                       |
| Lost to follow-up                     | 1       | -                       | -                        |
| Subject Terminated by Sponsor         | 1       | 1                       | 1                        |
| Protocol deviation                    | 1       | 1                       | -                        |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | 24 Weeks |
|-----------------------|----------|

Reporting group description: -

| Reporting group values  | 24 Weeks | Total |  |
|---|----------|-------|--|
| Number of subjects  | 449      | 449   |  |
| Age categorical   |          |       |  |
| Overall, the majority of patients were male (67.0%) and Caucasian (97.6%), and the average age was 64.7 years (range: 35 to 81 years), characteristic of the general PD population. The treatment groups were well balanced with regard to these demographic variables. |          |       |  |
| Units: Subjects   |          |       |  |
| Adults (18-64 years)  | 200      | 200   |  |
| From 65-84 years  | 249      | 249   |  |
| 85 years and over   | 0        | 0     |  |
| Gender categorical  |          |       |  |
| Units: Subjects   |          |       |  |
| Female  | 148      | 148   |  |
| Male  | 301      | 301   |  |

## End points

### End points reporting groups

|                                |                       |
|--------------------------------|-----------------------|
| Reporting group title          | Placebo               |
| Reporting group description: - |                       |
| Reporting group title          | 60 mg BID Tozadenant  |
| Reporting group description: - |                       |
| Reporting group title          | 120 mg BID Tozadenant |
| Reporting group description: - |                       |

### Primary: Change from Baseline to Week 24 in the number of hours per day spent in OFF time

|  |  |
|--|--|
| End point title  | Change from Baseline to Week 24 in the number of hours per day spent in OFF time |
| End point description:<br>The primary efficacy endpoint was the change from baseline to Week 24 in OFF time, where OFF time in the Hauser Parkinson's Disease Home Diary (PD) was averaged over 3 days prior to the study visit. During Screening and through Part A of the study, the Hauser Parkinson's Disease Home Diary (PD) was completed on specified days directly preceding the scheduled study visits/assessments. Motor activity was recorded as OFF, ON (mobility improved), or asleep time. Patients were asked to record ON time according to dyskinesia categories "without dyskinesia", "with non troublesome dyskinesia" or "with troublesome dyskinesia". Patients (and/or caregivers) were trained to complete the PD diary to record their status at half hourly intervals as OFF, ON without dyskinesia, ON with non troublesome dyskinesia, ON with troublesome dyskinesia, or asleep. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline to 24 Weeks   |  |

| End point values                     | Placebo           | 60 mg BID Tozadenant | 120 mg BID Tozadenant |  |
|--------------------------------------|-------------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group   | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 108               | 104                  | 104                   |  |
| Units: Hours                         |                   |                      |                       |  |
| arithmetic mean (standard deviation) | -0.958 (± 2.2725) | -0.835 (± 2.9730)    | -1.789 (± 2.4802)     |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Change from Baseline to Week 24 in OFF time Hours |
| Statistical analysis description:<br>The change from baseline OFF hours was analyzed by a mixed model repeated measures ANCOVA that included country/region, treatment group, week, interaction between treatment group and week as fixed terms, baseline number of OFF hours as covariate and subject as random effect. |   |
| Comparison groups  | Placebo v 120 mg BID Tozadenant                   |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 212                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.026                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.724                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.362                         |
| upper limit                             | -0.087                         |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.3242                         |

### Secondary: Change in Good ON time from baseline to Week 24

|  |   |
|--|---|
| End point title  | Change in Good ON time from baseline to Week 24 |
| End point description:   |   |
| <p>The first key secondary efficacy endpoint was the change from baseline to Week 24 in good ON which was defined as ON without dyskinesia or ON with non-troublesome dyskinesia.</p> <p>Awake Time in Good ON State (hr) is the average of a maximum of 3 days diary. Patients were asked to record ON time according to dyskinesia categories "without dyskinesia", "with non troublesome dyskinesia" or "with troublesome dyskinesia". Patients (and/or caregivers) were trained to complete the PD diary to record their status at half hourly intervals as OFF, ON without dyskinesia, ON with non troublesome dyskinesia, ON with troublesome dyskinesia, or asleep. For patients with missing baseline or baseline was measured post-dose, screening was used as baseline in the calculation of change from baseline.</p> |   |
| End point type   | Secondary                                       |
| End point timeframe:   |   |
| Baseline to 24 Weeks   |   |

| End point values                     | Placebo          | 60 mg BID Tozadenant | 120 mg BID Tozadenant |  |
|--------------------------------------|------------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group  | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 108              | 104                  | 104                   |  |
| Units: Hours                         |                  |                      |                       |  |
| arithmetic mean (standard deviation) | 1.011 (± 2.5470) | 0.705 (± 3.1219)     | 1.689 (± 2.7335)      |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Activities of Daily Living (ADL) subscale + Part III Motor Function

|                 |   |
|-----------------|---|
| End point title | Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Activities of Daily Living (ADL) subscale + Part III Motor |
|-----------------|---|



## End point description:

The Unified Parkinson's Disease Rating Scale (UPDRS) is a scale to monitor Parkinson's Disease related disability and impairment. The scale itself has 4 components, (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor Examination; Part IV, Complications of Therapy). Points are assigned to every item based on the person's response, as well as observation and physical examination. Each part has multiple points that are individually scored, using zero for normal or no problems, 1 for minimal problems, 2 for mild problems, 3 for moderate problems, and 4 for severe problems. These scores are tallied to indicate the severity of the disease, with 199 points being the worst and total disability and 0 meaning no disability. For patients with missing baseline or baseline was measured post-dose, screening was used as baseline in the calculation of change from baseline. Total scores are calculated only when all Part II & III questions.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 24

| End point values                     | Placebo              | 60 mg BID Tozadenant | 120 mg BID Tozadenant |  |
|--------------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 108                  | 103                  | 106                   |  |
| Units: Score on a scale              |                      |                      |                       |  |
| arithmetic mean (standard deviation) | -2.80 ( $\pm$ 8.183) | -2.54 ( $\pm$ 8.584) | -3.68 ( $\pm$ 7.853)  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Change From Baseline to Week 24 in the ON state in Unified Parkinson's Disease Rating Scale (UPDRS) Part III**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline to Week 24 in the ON state in Unified Parkinson's Disease Rating Scale (UPDRS) Part III |
|-----------------|--|

## End point description:

Change from Baseline to Week 24 in the Unified Parkinson's Disease Rating Scale (UPDRS) Parts III Motor Function (motor subscale) total scores. Score Range of 0 - 108. Higher scores indicate greater impact of PD symptoms. Unified Parkinson's Disease Rating Scale (UPDRS) in the ON state was measured at a time representative of the ON state in that patient, not in "best" ON. Unified Parkinson's Disease Rating Scale Part III in OFF was not evaluated. For Patients with missing baseline or baseline was measured post-dose, screening was used as baseline in the calculation of change from baseline. Total scores are calculated only when all Part III questions are answered.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 24

| End point values                     | Placebo              | 60 mg BID Tozadenant | 120 mg BID Tozadenant |  |
|--------------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 108                  | 103                  | 106                   |  |
| Units: Score on a scale              |                      |                      |                       |  |
| arithmetic mean (standard deviation) | -2.15 ( $\pm$ 6.363) | -2.13 ( $\pm$ 6.822) | -2.93 ( $\pm$ 6.048)  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Global Assessments of Improvement: Clinical Global Impression of Improvement (CGI-I) Week 24

|                 |  |
|-----------------|--|
| End point title | Global Assessments of Improvement: Clinical Global Impression of Improvement (CGI-I) Week 24 |
|-----------------|--|

End point description:

For the Clinical Global Impression of Improvement (CGI-I), the investigator or rater is asked to rate the patient's total improvement, whether or not in his or her judgment it is due entirely to drug treatment, based on a 1-7 point weighted scale ranging from "very much improved" (1) to "very much worse" (7). A zero score is assigned if the score is not assessed. Scale: 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At Week 24

| End point values                     | Placebo           | 60 mg BID Tozadenant | 120 mg BID Tozadenant |  |
|--------------------------------------|-------------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group   | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 111               | 106                  | 107                   |  |
| Units: Score on a scale              |                   |                      |                       |  |
| arithmetic mean (standard deviation) | 3.5 ( $\pm$ 0.92) | 3.5 ( $\pm$ 1.07)    | 3.2 ( $\pm$ 0.98)     |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Patient Global Impression of Improvement (PGI-I) Week 24

|                 |  |
|-----------------|--|
| End point title | Patient Global Impression of Improvement (PGI-I) Week 24 |
|-----------------|--|

End point description:

For the Patient Global Impression of Improvement (PG-I), the patient is asked to rate the total improvement of their Parkinson's Disease, whether or not in the patient's judgment it is due entirely to drug treatment, based on a 1-7 point weighted scale. "very much improved" (1) to "very much worse" (7). A zero score is assigned if the score is not assessed. Scale: 1 = Normal, not at all ill, 2 = Borderline ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among the most extremely ill.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

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End point timeframe:

At Week24

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| <b>End point values</b>              | Placebo         | 60 mg BID<br>Tozadenant | 120 mg BID<br>Tozadenant |  |
|--------------------------------------|-----------------|-------------------------|--------------------------|--|
| Subject group type                   | Reporting group | Reporting group         | Reporting group          |  |
| Number of subjects analysed          | 111             | 106                     | 107                      |  |
| Units: Score on a scale              |                 |                         |                          |  |
| arithmetic mean (standard deviation) | 3.6 (± 1.14)    | 3.6 (± 1.21)            | 3.4 (± 1.14)             |  |

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 Weeks

Adverse event reporting additional description:

Safety evaluation was based on the Safety Set (SS) population who took at least 1 dose of IMP. In Part A, the SS included 447 of the total of 449 randomized patients.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | 60 mg BID Tozadenant |
|-----------------------|----------------------|

Reporting group description: -

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | 120 mg BID Tozadenant |
|-----------------------|-----------------------|

Reporting group description: -

| Serious adverse events  | Placebo           | 60 mg BID Tozadenant | 120 mg BID Tozadenant |
|---|-------------------|----------------------|-----------------------|
| Total subjects affected by serious adverse events                   |                   |                      |                       |
| subjects affected / exposed   | 15 / 148 (10.14%) | 13 / 150 (8.67%)     | 12 / 149 (8.05%)      |
| number of deaths (all causes)                                       | 1                 | 1                    | 1                     |
| number of deaths resulting from adverse events                      | 0                 |                      |                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                      |                       |
| Thyroid adenoma   |                   |                      |                       |
| subjects affected / exposed   | 0 / 148 (0.00%)   | 1 / 150 (0.67%)      | 0 / 149 (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                 |
| Vascular disorders  |                   |                      |                       |
| Accelerated hypertension  |                   |                      |                       |
| subjects affected / exposed   | 1 / 148 (0.68%)   | 0 / 150 (0.00%)      | 0 / 149 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0                | 0 / 0                 |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                | 0 / 0                 |
| Hypertension  |                   |                      |                       |
| subjects affected / exposed   | 0 / 148 (0.00%)   | 0 / 150 (0.00%)      | 1 / 149 (0.67%)       |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0                | 0 / 1                 |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                | 0 / 0                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Gait disturbance                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Reproductive system and breast disorders             |                 |                 |                 |
| Erectile dysfunction                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Psychiatric disorders                                |                 |                 |                 |
| Confusional state                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hallucination, visual                                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 2 / 149 (1.34%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications       |                 |                 |                 |
| Burns third degree                                   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Face injury  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Fractured sacrum                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Pubis fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory fume inhalation disorder            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| 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                               |                 |                 |                 |
| Angina pectoris                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Torsade de pointes                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Aphasia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carotid artery occlusion                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carpal tunnel syndrome                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyskinesia                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Intracranial aneurysm                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parkinson's disease                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 2 / 150 (1.33%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Iron deficiency anaemia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 0 / 150 (0.00%) | 1 / 149 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Anuria  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Calculus ureteric                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Cervical spinal stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 148 (1.35%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscle spasms                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Muscular weakness                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 148 (0.00%) | 1 / 150 (0.67%) | 0 / 149 (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           |
| Spinal column stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 148 (0.68%) | 0 / 150 (0.00%) | 0 / 149 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                                   |                                   |                                   |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| Infections and infestations<br>Appendicitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 150 (0.67%)<br>0 / 1<br>0 / 0 | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 150 (0.67%)<br>0 / 1<br>0 / 0 | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | 1 / 148 (0.68%)<br>0 / 1<br>0 / 0 | 0 / 150 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 |
| Septic shock<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 150 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 149 (0.67%)<br>0 / 1<br>0 / 0 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                     | 1 / 148 (0.68%)<br>0 / 1<br>0 / 0 | 0 / 150 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Placebo            | 60 mg BID Tozadenant | 120 mg BID Tozadenant |
|---|--------------------|----------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                    |                      |                       |
| subjects affected / exposed                           | 111 / 148 (75.00%) | 115 / 150 (76.67%)   | 111 / 149 (74.50%)    |
| Investigations  |                    |                      |                       |
| Blood creatine phosphokinase increased                |                    |                      |                       |
| subjects affected / exposed                           | 3 / 148 (2.03%)    | 4 / 150 (2.67%)      | 6 / 149 (4.03%)       |
| occurrences (all)                                     | 3                  | 4                    | 6                     |
| Weight decreased                                      |                    |                      |                       |
| subjects affected / exposed                           | 0 / 148 (0.00%)    | 4 / 150 (2.67%)      | 2 / 149 (1.34%)       |
| occurrences (all)                                     | 0                  | 4                    | 2                     |

|  |                        |                         |                         |
|--|------------------------|-------------------------|-------------------------|
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 4 / 148 (2.70%)<br>4   | 2 / 150 (1.33%)<br>2    | 0 / 149 (0.00%)<br>0    |
| Injury, poisoning and procedural complications                                       |                        |                         |                         |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 148 (0.68%)<br>1   | 0 / 150 (0.00%)<br>0    | 5 / 149 (3.36%)<br>5    |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 9 / 148 (6.08%)<br>9   | 22 / 150 (14.67%)<br>22 | 13 / 149 (8.72%)<br>13  |
| Vascular disorders   |                        |                         |                         |
| Flushing<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 148 (0.68%)<br>1   | 1 / 150 (0.67%)<br>1    | 4 / 149 (2.68%)<br>4    |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 148 (2.03%)<br>111 | 5 / 150 (3.33%)<br>115  | 3 / 149 (2.01%)<br>111  |
| Nervous system disorders   |                        |                         |                         |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                        | 9 / 148 (6.08%)<br>9   | 7 / 150 (4.67%)<br>7    | 7 / 149 (4.70%)<br>7    |
| Dyskinesia<br>subjects affected / exposed<br>occurrences (all)                       | 13 / 148 (8.78%)<br>13 | 22 / 150 (14.67%)<br>22 | 22 / 149 (14.77%)<br>22 |
| Parkinson's disease<br>subjects affected / exposed<br>occurrences (all)              | 7 / 148 (4.73%)<br>7   | 11 / 150 (7.33%)<br>11  | 3 / 149 (2.01%)<br>3    |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                       | 5 / 148 (3.38%)<br>5   | 5 / 150 (3.33%)<br>5    | 8 / 149 (5.37%)<br>8    |
| Sudden onset of sleep<br>subjects affected / exposed<br>occurrences (all)            | 4 / 148 (2.70%)<br>4   | 7 / 150 (4.67%)<br>7    | 7 / 149 (4.70%)<br>7    |
| Headache<br>subjects affected / exposed<br>occurrences (all)                         | 5 / 148 (3.38%)<br>5   | 3 / 150 (2.00%)<br>3    | 2 / 149 (1.34%)<br>2    |

|  |                 |                   |                  |
|--|-----------------|-------------------|------------------|
| General disorders and administration site conditions |                 |                   |                  |
| Fatigue  |                 |                   |                  |
| subjects affected / exposed                          | 2 / 148 (1.35%) | 7 / 150 (4.67%)   | 4 / 149 (2.68%)  |
| occurrences (all)                                    | 2               | 7                 | 4                |
| Gastrointestinal disorders                           |                 |                   |                  |
| Constipation   |                 |                   |                  |
| subjects affected / exposed                          | 2 / 148 (1.35%) | 15 / 150 (10.00%) | 8 / 149 (5.37%)  |
| occurrences (all)                                    | 2               | 15                | 8                |
| Dry mouth  |                 |                   |                  |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 2 / 150 (1.33%)   | 4 / 149 (2.68%)  |
| occurrences (all)                                    | 0               | 2                 | 4                |
| Nausea   |                 |                   |                  |
| subjects affected / exposed                          | 6 / 148 (4.05%) | 8 / 150 (5.33%)   | 13 / 149 (8.72%) |
| occurrences (all)                                    | 6               | 8                 | 13               |
| Respiratory, thoracic and mediastinal disorders      |                 |                   |                  |
| Cough  |                 |                   |                  |
| subjects affected / exposed                          | 2 / 148 (1.35%) | 1 / 150 (0.67%)   | 4 / 149 (2.68%)  |
| occurrences (all)                                    | 2               | 1                 | 4                |
| Psychiatric disorders                                |                 |                   |                  |
| Anxiety  |                 |                   |                  |
| subjects affected / exposed                          | 3 / 148 (2.03%) | 5 / 150 (3.33%)   | 2 / 149 (1.34%)  |
| occurrences (all)                                    | 3               | 5                 | 2                |
| Confusional state                                    |                 |                   |                  |
| subjects affected / exposed                          | 1 / 148 (0.68%) | 2 / 150 (1.33%)   | 4 / 149 (2.68%)  |
| occurrences (all)                                    | 1               | 2                 | 4                |
| Hallucination, visual                                |                 |                   |                  |
| subjects affected / exposed                          | 2 / 148 (1.35%) | 8 / 150 (5.33%)   | 8 / 149 (5.37%)  |
| occurrences (all)                                    | 2               | 8                 | 8                |
| Insomnia   |                 |                   |                  |
| subjects affected / exposed                          | 9 / 148 (6.08%) | 9 / 150 (6.00%)   | 9 / 149 (6.04%)  |
| occurrences (all)                                    | 9               | 9                 | 9                |
| Disorientation                                       |                 |                   |                  |
| subjects affected / exposed                          | 0 / 148 (0.00%) | 4 / 150 (2.67%)   | 0 / 149 (0.00%)  |
| occurrences (all)                                    | 0               | 4                 | 0                |
| Renal and urinary disorders                          |                 |                   |                  |

|   |                        |                      |                      |
|---|------------------------|----------------------|----------------------|
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)               | 0 / 148 (0.00%)<br>0   | 3 / 150 (2.00%)<br>3 | 4 / 149 (2.68%)<br>4 |
| Musculoskeletal and connective tissue disorders                                       |                        |                      |                      |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 148 (5.41%)<br>8   | 4 / 150 (2.67%)<br>4 | 7 / 149 (4.70%)<br>7 |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 148 (0.00%)<br>0   | 4 / 150 (2.67%)<br>4 | 2 / 149 (1.34%)<br>2 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 6 / 148 (4.05%)<br>6   | 5 / 150 (3.33%)<br>5 | 3 / 149 (2.01%)<br>3 |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 6 / 148 (4.05%)<br>6   | 3 / 150 (2.00%)<br>3 | 2 / 149 (1.34%)<br>2 |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 148 (0.68%)<br>1   | 4 / 150 (2.67%)<br>4 | 0 / 149 (0.00%)<br>0 |
| Infections and infestations   |                        |                      |                      |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 10 / 148 (6.76%)<br>10 | 7 / 150 (4.67%)<br>7 | 5 / 149 (3.36%)<br>5 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 148 (4.73%)<br>7   | 6 / 150 (4.00%)<br>6 | 1 / 149 (0.67%)<br>1 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 4 / 148 (2.70%)<br>4   | 4 / 150 (2.67%)<br>4 | 9 / 149 (6.04%)<br>9 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 19 May 2015  | <p>Amendment 1 Revisions:</p> <ol style="list-style-type: none"><li>1. Updated List of Abbreviations (p. 8-9).</li><li>2. Corrected typographical errors in Table 1: Part A - Schedule of Events/Evaluations (p. 30).</li><li>3. Revised Section 11.6, Unblinding Upon Completion of Part A (p. 131) to clarify that primary and secondary efficacy analyses will be conducted after the Part A data base is locked and will not be modified; and to clarify that exploratory analyses that do not involve the primary or secondary efficacy analyses are subject to modification.</li><li>4. Added the following exploratory endpoints to Parts A and B:</li></ol> <p>Part A</p> <ol style="list-style-type: none"><li>15. EuroQoL 5D-5L Health Questionnaire (EQ-5D-5L).</li><li>16. Treatment Satisfaction Questionnaire for Medication (TSQM 9) (evaluated at Weeks 6 and 24).</li></ol> <p>Part B</p> <ol style="list-style-type: none"><li>11. EQ-5D-5L.</li><li>12. TSQM 9 (evaluated at Week 76).</li></ol>   |
| 10 June 2015 | <p>Amendment 2 Revisions:</p> <ol style="list-style-type: none"><li>1. Revised Exclusion Criteria (EC) #24 to delete "including any history of hepatic or renal failure" (p. 22; p. 55).</li><li>2. Added EC #27: "Patients with moderate to severe hepatic or renal impairment." (p. 22; p. 55).</li><li>3. Added EC #28: "Patients who have taken strong CYP3A4 inhibitors or inducers within 4 weeks prior to Baseline (Visit 2) or who anticipate requiring the use of strong CYP3A4 inhibitors or inducers during the duration of the trial (see Section 5.9.2 and Appendix 15.15)" (p. 22; p. 55).</li><li>4. Added EC #29: "Patients with pacemakers or implantable cardioverter defibrillators" (p. 22; p. 55).</li><li>5. Added to Section 4.3.2, Definite Criteria for Withdrawal from Study: "9. Patients noted to have an elevated BP post-baseline, with a systolic BP <math>\geq</math> 160 mmHg and/or a diastolic BP <math>\geq</math> 100 mmHg that is present at 2 consecutive post-baseline study visits" (p. 57).</li><li>6. Added to Section 5.9.2, Prohibited Concomitant Medications/ Treatments, regarding medications prohibited throughout the study (Parts A and B): "Strong CYP3A4 inhibitors or inducers. Refer to Appendix 15.15" (p. 61).</li><li>7. Added paragraph at end of Section 9.5.1, Blood Pressure and Pulse Measurements: "Patients noted to have an elevated BP post-baseline, with a systolic BP <math>\geq</math> 160 mmHg and/or a diastolic BP <math>\geq</math> 100 mmHg that is present at 2 consecutive post-baseline study visits, will be discontinued from study (see Section 4.3.2)" (p. 118).</li><li>8. Added Appendix 15.15, Prohibited CYP3A4 Inhibitors and Inducers (p. 183).</li></ol> |

|                 |   |
|-----------------|---|
| 13 October 2017 | <p>Amendment 3 Revisions</p> <ol style="list-style-type: none"> <li>1. Updated company name, email addresses and telephone numbers of Study Director, and Chief Medical Officer in multiple places.</li> <li>2. Updated Study Contact Information</li> <li>3. Updated safety reporting fax number</li> <li>4. Added to Abbreviations ANC (absolute neutrophil count), WBC (white blood cells)</li> <li>5. Inserted into Parts A and B procedures additional blood draws for hematology.</li> <li>6. Added Tables 1.1 (Part A – Schedule of Events/ Evaluations for Hematology Monitoring) and 2.1 Part B – Schedule of Events/ Evaluations for Hematology Monitoring.</li> <li>7. Inserted into Criteria for Patient Discontinuation a lower limit for absolute neutrophils.</li> <li>8. Added the following as section 6.2.6 a Visit 3.5 (Week 4).</li> <li>9. Inserted section 6.2.9 a Visit 4.3 (Week 8).</li> <li>10. Inserted section 6.2.10 a Visit 4.8 (Week 10)</li> <li>11. Section 6.2.12: Clarified the next visit by number and differentiates next blood draw (visit 16) and telephone call (visit 18).</li> <li>12. Insert section 6.2.13 a Visit 5.5 (Week 16)</li> <li>13. Insert section 6.2.16 a Visit 6.5 (Week 22)</li> </ol> |
|-----------------|---|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported