



## Clinical trial results:

### An Open-label, Multicenter, Phase 1/2 Study of JNJ-40346527, an FMS Inhibitor, in Subjects with Relapsed or Refractory Hodgkin Lymphoma

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-005795-42 |
| Trial protocol           | DE             |
| Global end of trial date | 13 August 2013 |

## Results information

|                                |                                                 |
|--------------------------------|-------------------------------------------------|
| Result version number          | v2 (current)                                    |
| This version publication date  | 15 July 2016                                    |
| First version publication date | 03 August 2015                                  |
| Version creation reason        | • Correction of full data set<br>Review of data |

## Trial information

### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | 40346527HKL1001 |
|-----------------------|-----------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01572519 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Janssen Research & Development, LLC                                                        |
| Sponsor organisation address | Archimedesweg 29-2333CM, Leiden, Netherlands, B235-0                                       |
| Public contact               | Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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:

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**Results analysis stage**

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|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 13 August 2013 |
| Is this the analysis of the primary completion data? | No             |

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|                                  |                |
|----------------------------------|----------------|
| Global end of trial reached?     | Yes            |
| Global end of trial date         | 13 August 2013 |
| Was the trial ended prematurely? | No             |

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Notes:

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**General information about the trial**

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Main objective of the trial:

To determine the safety, pharmacokinetics, and preliminary efficacy information of JNJ-40346527 in participants with relapsed or refractory Hodgkin lymphoma.  
To establish the recommended Phase 2 dose for JNJ-40346527.

Protection of trial subjects:

Safety was evaluated based on the variables like adverse events, Clinical laboratory tests (hematology, serum chemistry, and urinalysis), Vital sign measurements, Physical examinations, Electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance status.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 06 July 2012 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | France: 11  |
| Worldwide total number of subjects   | 21          |
| EEA total number of subjects         | 21          |

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Notes:

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**Subjects enrolled per age group**

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 18 |
| From 65 to 84 years                       | 3  |
| 85 years and over                         | 0  |

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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 21 participants were enrolled and treated with JNJ 40346527.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|                              |                        |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes                    |
| <b>Arm title</b>             | 150 mg once daily (QD) |

Arm description:

Participants received JNJ-40346527, 150 milligram (mg) capsules once daily.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | JNJ-40346527     |
| Investigational medicinal product code | JNJ-40346527-AAC |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

JNJ-40346527 Capsules 150 mg once daily

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 300 mg QD |
|------------------|-----------|

Arm description:

Participants received JNJ-40346527, 300 mg capsules once daily.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | JNJ-40346527     |
| Investigational medicinal product code | JNJ-40346527-AAC |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

JNJ-40346527 Capsules 300 mg once daily

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 450 mg QD |
|------------------|-----------|

Arm description:

Participants received JNJ-40346527, 450 mg capsules once daily.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | JNJ-40346527     |
| Investigational medicinal product code | JNJ-40346527-AAC |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

JNJ-40346527 Capsules 450 mg once daily

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 600 mg QD |
|------------------|-----------|

Arm description:

Participants received JNJ-40346527, 600 mg capsules once daily.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | JNJ-40346527     |
| Investigational medicinal product code | JNJ-40346527-AAC |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

JNJ-40346527 Capsules 600 mg once daily

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | 150 mg twice daily (BID) |
|------------------|--------------------------|

Arm description:

Participants received JNJ-40346527, 150 mg capsules twice daily.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | JNJ-40346527     |
| Investigational medicinal product code | JNJ-40346527-AAC |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule          |
| Routes of administration               | Oral use         |

Dosage and administration details:

JNJ-40346527 Capsules 150 mg twice daily

| <b>Number of subjects in period 1</b> | 150 mg once daily (QD) | 300 mg QD | 450 mg QD |
|---------------------------------------|------------------------|-----------|-----------|
| Started                               | 3                      | 5         | 3         |
| Completed                             | 0                      | 0         | 0         |
| Not completed                         | 3                      | 5         | 3         |
| Physician decision                    | 1                      | -         | -         |
| Adverse event, non-fatal              | -                      | -         | -         |
| Other                                 | 1                      | -         | -         |
| Lack of efficacy                      | 1                      | 5         | 3         |

| <b>Number of subjects in period 1</b> | 600 mg QD | 150 mg twice daily (BID) |
|---------------------------------------|-----------|--------------------------|
| Started                               | 3         | 7                        |
| Completed                             | 0         | 0                        |
| Not completed                         | 3         | 7                        |
| Physician decision                    | -         | -                        |
| Adverse event, non-fatal              | -         | 1                        |
| Other                                 | -         | -                        |
| Lack of efficacy                      | 3         | 6                        |

## Baseline characteristics

### Reporting groups

|                                                                             |                          |
|-----------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                       | 150 mg once daily (QD)   |
| Reporting group description:                                                |                          |
| Participants received JNJ-40346527, 150 milligram (mg) capsules once daily. |                          |
| Reporting group title                                                       | 300 mg QD                |
| Reporting group description:                                                |                          |
| Participants received JNJ-40346527, 300 mg capsules once daily.             |                          |
| Reporting group title                                                       | 450 mg QD                |
| Reporting group description:                                                |                          |
| Participants received JNJ-40346527, 450 mg capsules once daily.             |                          |
| Reporting group title                                                       | 600 mg QD                |
| Reporting group description:                                                |                          |
| Participants received JNJ-40346527, 600 mg capsules once daily.             |                          |
| Reporting group title                                                       | 150 mg twice daily (BID) |
| Reporting group description:                                                |                          |
| Participants received JNJ-40346527, 150 mg capsules twice daily.            |                          |

| Reporting group values                      | 150 mg once daily (QD) | 300 mg QD | 450 mg QD |
|---------------------------------------------|------------------------|-----------|-----------|
| Number of subjects                          | 3                      | 5         | 3         |
| Title for AgeCategorical<br>Units: subjects |                        |           |           |
| Children (2-11 years)                       | 0                      | 0         | 0         |
| Adolescents (12-17 years)                   | 0                      | 0         | 0         |
| Adults (18-64 years)                        | 2                      | 5         | 2         |
| From 65 to 84 years                         | 1                      | 0         | 1         |
| 85 years and over                           | 0                      | 0         | 0         |
| Title for AgeContinuous<br>Units: Years     |                        |           |           |
| arithmetic mean                             | 48                     | 33.4      | 49        |
| standard deviation                          | ± 24.88                | ± 9.99    | ± 18.52   |
| Title for Gender<br>Units: subjects         |                        |           |           |
| Female                                      | 0                      | 1         | 2         |
| Male                                        | 3                      | 4         | 1         |

| Reporting group values                      | 600 mg QD | 150 mg twice daily (BID) | Total |
|---------------------------------------------|-----------|--------------------------|-------|
| Number of subjects                          | 3         | 7                        | 21    |
| Title for AgeCategorical<br>Units: subjects |           |                          |       |
| Children (2-11 years)                       | 0         | 0                        | 0     |
| Adolescents (12-17 years)                   | 0         | 0                        | 0     |
| Adults (18-64 years)                        | 3         | 6                        | 18    |
| From 65 to 84 years                         | 0         | 1                        | 3     |
| 85 years and over                           | 0         | 0                        | 0     |

|                                                                                  |                |                 |    |
|----------------------------------------------------------------------------------|----------------|-----------------|----|
| Title for AgeContinuous<br>Units: Years<br>arithmetic mean<br>standard deviation | 29.3<br>± 10.5 | 38.6<br>± 18.57 | -  |
| Title for Gender<br>Units: subjects                                              |                |                 |    |
| Female                                                                           | 2              | 5               | 10 |
| Male                                                                             | 1              | 2               | 11 |

## End points

### End points reporting groups

|                                                                                                                                                                                                                      |                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title                                                                                                                                                                                                | 150 mg once daily (QD)                 |
| Reporting group description:<br>Participants received JNJ-40346527, 150 milligram (mg) capsules once daily.                                                                                                          |                                        |
| Reporting group title                                                                                                                                                                                                | 300 mg QD                              |
| Reporting group description:<br>Participants received JNJ-40346527, 300 mg capsules once daily.                                                                                                                      |                                        |
| Reporting group title                                                                                                                                                                                                | 450 mg QD                              |
| Reporting group description:<br>Participants received JNJ-40346527, 450 mg capsules once daily.                                                                                                                      |                                        |
| Reporting group title                                                                                                                                                                                                | 600 mg QD                              |
| Reporting group description:<br>Participants received JNJ-40346527, 600 mg capsules once daily.                                                                                                                      |                                        |
| Reporting group title                                                                                                                                                                                                | 150 mg twice daily (BID)               |
| Reporting group description:<br>Participants received JNJ-40346527, 150 mg capsules twice daily.                                                                                                                     |                                        |
| Subject analysis set title                                                                                                                                                                                           | JNJ-40346527                           |
| Subject analysis set type                                                                                                                                                                                            | Per protocol                           |
| Subject analysis set description:<br>Participants who received at least one dose of study medication.                                                                                                                |                                        |
| Subject analysis set title                                                                                                                                                                                           | Evaluable Participant Population (EPP) |
| Subject analysis set type                                                                                                                                                                                            | Full analysis                          |
| Subject analysis set description:<br>Evaluable Participant Population includes Participants who received at least 1 dose of the study treatment, and had baseline and at least one post- treatment tumor assessment. |                                        |
| Subject analysis set title                                                                                                                                                                                           | Safety Analysis Set (SAS)              |
| Subject analysis set type                                                                                                                                                                                            | Safety analysis                        |
| Subject analysis set description:<br>Participants who received at least one dose of study medication.                                                                                                                |                                        |

### Primary: Recommended Phase 2 dose (RP2D) for JNJ-40346527

|                                                                                                                                                                                            |                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| End point title                                                                                                                                                                            | Recommended Phase 2 dose (RP2D) for JNJ-40346527 <sup>[1]</sup> |
| End point description:<br>RP2D will be determined based on pharmacodynamics, biomarker response or clinical response, as well as the incidence rate and nature of the toxicities observed. |                                                                 |

|                                                                       |         |
|-----------------------------------------------------------------------|---------|
| End point type                                                        | Primary |
| End point timeframe:<br>Up to 24 hours after last dose administration |         |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis were performed for this endpoint.

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | JNJ-40346527         |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 21 <sup>[2]</sup>    |  |  |  |
| Units: milligram (mg)       |                      |  |  |  |
| number (not applicable)     | 150                  |  |  |  |

Notes:

[2] - EPP

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Overall Response Rate

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Number of Participants with Overall Response Rate <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------|

End point description:

Overall response rate is defined as the number of participants who achieve complete response or partial response, during or after study treatment. Here 'N' signifies number of subjects who were analysed for this outcome measure.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 6 months after the last subject is enrolled

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis were performed for this endpoint.

|                             |                        |                  |                  |                  |
|-----------------------------|------------------------|------------------|------------------|------------------|
| <b>End point values</b>     | 150 mg once daily (QD) | 300 mg QD        | 450 mg QD        | 600 mg QD        |
| Subject group type          | Reporting group        | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed | 3 <sup>[4]</sup>       | 5 <sup>[5]</sup> | 3 <sup>[6]</sup> | 3 <sup>[7]</sup> |
| Units: Participants         |                        |                  |                  |                  |
| number (not applicable)     |                        |                  |                  |                  |
| Complete Response (CR)      | 1                      | 0                | 0                | 0                |
| Partial Response (PR)       | 0                      | 0                | 0                | 0                |

Notes:

[4] - EPP

[5] - EPP

[6] - EPP

[7] - EPP

|                             |                          |  |  |  |
|-----------------------------|--------------------------|--|--|--|
| <b>End point values</b>     | 150 mg twice daily (BID) |  |  |  |
| Subject group type          | Reporting group          |  |  |  |
| Number of subjects analysed | 6 <sup>[8]</sup>         |  |  |  |
| Units: Participants         |                          |  |  |  |
| number (not applicable)     |                          |  |  |  |
| Complete Response (CR)      | 0                        |  |  |  |
| Partial Response (PR)       | 0                        |  |  |  |

Notes:

[8] - EPP



## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Treatment-Emergent Adverse Events

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Number of Participants With Treatment-Emergent Adverse Events |
|-----------------|---------------------------------------------------------------|

End point description:

A treatment-emergent adverse event (TEAE) was defined as an event that occurred up to 30 days after the last dose of study medication treatment period during which it emerged (i.e. started or worsened in severity, relation, or other attribute), and even if the event continued to be present.

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

End point timeframe:

Up to 30 days after the last dose of study medication

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | JNJ-40346527         |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 21 <sup>[9]</sup>    |  |  |  |
| Units: participants         |                      |  |  |  |
| number (not applicable)     | 19                   |  |  |  |

Notes:

[9] - SAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Plasma Concentration (C<sub>max</sub>) of JNJ-40346527

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Maximum Plasma Concentration (C <sub>max</sub> ) of JNJ-40346527 |
|-----------------|------------------------------------------------------------------|

End point description:

C<sub>max</sub> refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Here 'n' signifies number of subjects who were analysed for this outcome measure.

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

End point timeframe:

Day 1 and Day 21

|                                        |                        |                   |                   |                   |
|----------------------------------------|------------------------|-------------------|-------------------|-------------------|
| <b>End point values</b>                | 150 mg once daily (QD) | 300 mg QD         | 450 mg QD         | 600 mg QD         |
| Subject group type                     | Reporting group        | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed            | 3 <sup>[10]</sup>      | 5 <sup>[11]</sup> | 3 <sup>[12]</sup> | 3 <sup>[13]</sup> |
| Units: nanogram per milliliter (ng/mL) |                        |                   |                   |                   |
| arithmetic mean (standard deviation)   |                        |                   |                   |                   |
| Day 1 (n= 3, 5, 3, 3, 7)               | 278 (± 71.4)           | 552 (± 198)       | 552 (± 655)       | 358 (± 244)       |

|                           |             |             |              |             |
|---------------------------|-------------|-------------|--------------|-------------|
| Day 21 (n= 2, 3, 3, 3, 6) | 304 (± 321) | 598 (± 156) | 1157 (± 409) | 843 (± 394) |
|---------------------------|-------------|-------------|--------------|-------------|

Notes:

[10] - EPP

[11] - EPP

[12] - EPP

[13] - EPP

|                                        |                          |  |  |  |
|----------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>                | 150 mg twice daily (BID) |  |  |  |
| Subject group type                     | Reporting group          |  |  |  |
| Number of subjects analysed            | 7 <sup>[14]</sup>        |  |  |  |
| Units: nanogram per milliliter (ng/mL) |                          |  |  |  |
| arithmetic mean (standard deviation)   |                          |  |  |  |
| Day 1 (n= 3, 5, 3, 3, 7)               | 313 (± 86.9)             |  |  |  |
| Day 21 (n= 2, 3, 3, 3, 6)              | 483 (± 182)              |  |  |  |

Notes:

[14] - EPP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Minimum Plasma Concentration (Cmin) of JNJ-40346527

|                                                                                                                                                                                                                                                            |                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                                                            | Minimum Plasma Concentration (Cmin) of JNJ-40346527 |
| End point description:                                                                                                                                                                                                                                     |                                                     |
| Cmin refers to the lowest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Here 'N' signifies number of subjects who were analysed for this outcome measure. |                                                     |
| End point type                                                                                                                                                                                                                                             | Secondary                                           |
| End point timeframe:                                                                                                                                                                                                                                       |                                                     |
| Day 21                                                                                                                                                                                                                                                     |                                                     |

|                                        |                        |                   |                   |                   |
|----------------------------------------|------------------------|-------------------|-------------------|-------------------|
| <b>End point values</b>                | 150 mg once daily (QD) | 300 mg QD         | 450 mg QD         | 600 mg QD         |
| Subject group type                     | Reporting group        | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed            | 2 <sup>[15]</sup>      | 3 <sup>[16]</sup> | 3 <sup>[17]</sup> | 3 <sup>[18]</sup> |
| Units: nanogram per milliliter (ng/mL) |                        |                   |                   |                   |
| arithmetic mean (standard deviation)   | 100 (± 101)            | 160 (± 63.2)      | 277 (± 89)        | 129 (± 45.4)      |

Notes:

[15] - EPP

[16] - EPP

[17] - EPP

[18] - EPP

|                                        |                          |  |  |  |
|----------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>                | 150 mg twice daily (BID) |  |  |  |
| Subject group type                     | Reporting group          |  |  |  |
| Number of subjects analysed            | 6 <sup>[19]</sup>        |  |  |  |
| Units: nanogram per milliliter (ng/mL) |                          |  |  |  |
| arithmetic mean (standard deviation)   | 196 (± 41)               |  |  |  |

Notes:

[19] - EPP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Reach the Maximum Plasma Concentration (Tmax) of JNJ-40346527

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Time to Reach the Maximum Plasma Concentration (Tmax) of JNJ-40346527 |
|-----------------|-----------------------------------------------------------------------|

End point description:

The Tmax is defined as actual sampling time to reach maximum observed analyte concentration. Here 'n' signifies number of subjects who were analysed for this outcome measure

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

End point timeframe:

Day 1 and Day 21

| End point values              | 150 mg once daily (QD) | 300 mg QD         | 450 mg QD         | 600 mg QD         |
|-------------------------------|------------------------|-------------------|-------------------|-------------------|
| Subject group type            | Reporting group        | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed   | 3 <sup>[20]</sup>      | 5 <sup>[21]</sup> | 3 <sup>[22]</sup> | 3 <sup>[23]</sup> |
| Units: hours                  |                        |                   |                   |                   |
| median (full range (min-max)) |                        |                   |                   |                   |
| Day 1 (n= 3, 5, 3, 3, 7)      | 4.1 (1 to 4.5)         | 3 (2 to 4)        | 2.1 (2.1 to 2.1)  | 3 (2 to 4)        |
| Day 21 (n= 2, 3, 3, 3, 6)     | 1 (1 to 3.1)           | 4.1 (4 to 5.9)    | 3 (2 to 4.5)      | 3.9 (3 to 4)      |

Notes:

[20] - EPP

[21] - EPP

[22] - EPP

[23] - EPP

| End point values              | 150 mg twice daily (BID) |  |  |  |
|-------------------------------|--------------------------|--|--|--|
| Subject group type            | Reporting group          |  |  |  |
| Number of subjects analysed   | 7 <sup>[24]</sup>        |  |  |  |
| Units: hours                  |                          |  |  |  |
| median (full range (min-max)) |                          |  |  |  |
| Day 1 (n= 3, 5, 3, 3, 7)      | 1 (1 to 6)               |  |  |  |
| Day 21 (n= 2, 3, 3, 3, 6)     | 2.5 (1.9 to 8)           |  |  |  |

Notes:

[24] - EPP

## Statistical analyses

No statistical analyses for this end point

**Secondary: Area Under the Plasma Concentration-Time Curve From 0 to 24 Hours (AUC[0-24]) Post Dose of JNJ-40346527**

|                                                                                                                                                                                                                                                                                                              |                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                              | Area Under the Plasma Concentration-Time Curve From 0 to 24 Hours (AUC[0-24]) Post Dose of JNJ-40346527 |
| End point description:<br>The AUC (0-24) calculated by trapezoidal summation [time t is the time 24 hours after dose administration). Here 'n' signifies number of subjects who were analysed for this outcome measure. The value '99999' indicates that the data were not reported at specific time points. |                                                                                                         |
| End point type                                                                                                                                                                                                                                                                                               | Secondary                                                                                               |
| End point timeframe:<br>Day 1 and Day 21                                                                                                                                                                                                                                                                     |                                                                                                         |

| End point values                                | 150 mg once daily (QD) | 300 mg QD         | 450 mg QD         | 600 mg QD         |
|-------------------------------------------------|------------------------|-------------------|-------------------|-------------------|
| Subject group type                              | Reporting group        | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed                     | 3 <sup>[25]</sup>      | 5 <sup>[26]</sup> | 3 <sup>[27]</sup> | 3 <sup>[28]</sup> |
| Units: nanogram * hour per milliliter (ng*h/mL) |                        |                   |                   |                   |
| arithmetic mean (standard deviation)            |                        |                   |                   |                   |
| Day 1 (n= 3, 5, 3, 3, 7)                        | 1931 (± 404)           | 3935 (± 2001)     | 2536 (± 4135)     | 2657 (± 1255)     |
| Day 21 (n= 2, 3, 3, 3, 6)                       | 3417 (± 3436)          | 7588 (± 2248)     | 12804 (± 4875)    | 6961 (± 2656)     |

Notes:

[25] - EPP

[26] - EPP

[27] - EPP

[28] - EPP

| End point values                                | 150 mg twice daily (BID) |  |  |  |
|-------------------------------------------------|--------------------------|--|--|--|
| Subject group type                              | Reporting group          |  |  |  |
| Number of subjects analysed                     | 6 <sup>[29]</sup>        |  |  |  |
| Units: nanogram * hour per milliliter (ng*h/mL) |                          |  |  |  |
| arithmetic mean (standard deviation)            |                          |  |  |  |
| Day 1 (n= 3, 5, 3, 3, 7)                        | 99999 (± 99999)          |  |  |  |
| Day 21 (n= 2, 3, 3, 3, 6)                       | 7471 (± 2349)            |  |  |  |

Notes:

[29] - EPP

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Total drug Clearance of JNJ-40346527 (CL/F)**

|                                                                                                                                                                                                              |                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| End point title                                                                                                                                                                                              | Total drug Clearance of JNJ-40346527 (CL/F) |
| End point description:<br>The CL is a quantitative measure of the rate at which a drug substance is removed from the body. Here 'N' signifies number of subjects who were analysed for this outcome measure. |                                             |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Day 21               |           |

| End point values                     | 150 mg once daily (QD) | 300 mg QD         | 450 mg QD         | 600 mg QD         |
|--------------------------------------|------------------------|-------------------|-------------------|-------------------|
| Subject group type                   | Reporting group        | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed          | 2 <sup>[30]</sup>      | 3 <sup>[31]</sup> | 3 <sup>[32]</sup> | 3 <sup>[33]</sup> |
| Units: Litre per hour                |                        |                   |                   |                   |
| arithmetic mean (standard deviation) | 43.7 (± 43.9)          | 42.4 (± 14.5)     | 39.4 (± 17)       | 97.7 (± 45.6)     |

Notes:

[30] - EPP

[31] - EPP

[32] - EPP

[33] - EPP

| End point values                     | 150 mg twice daily (BID) |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 6 <sup>[34]</sup>        |  |  |  |
| Units: Litre per hour                |                          |  |  |  |
| arithmetic mean (standard deviation) | 49.3 (± 16.8)            |  |  |  |

Notes:

[34] - EPP

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after the last dose of study medication

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | 300 mg QD |
|-----------------------|-----------|

Reporting group description:

Participants received JNJ-40346527, 300 mg capsules once daily.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | 150 mg once daily (QD) |
|-----------------------|------------------------|

Reporting group description:

Participants received JNJ-40346527, 150 milligram (mg) capsules once daily.

|                       |           |
|-----------------------|-----------|
| Reporting group title | 600 mg QD |
|-----------------------|-----------|

Reporting group description:

Participants received JNJ-40346527, 600 mg capsules once daily.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | 150 mg twice daily (BID) |
|-----------------------|--------------------------|

Reporting group description:

Participants received JNJ-40346527, 150 mg capsules twice daily.

|                       |           |
|-----------------------|-----------|
| Reporting group title | 450 mg QD |
|-----------------------|-----------|

Reporting group description:

Participants received JNJ-40346527, 450 mg capsules once daily.

| Serious adverse events                               | 300 mg QD      | 150 mg once daily (QD) | 600 mg QD     |
|------------------------------------------------------|----------------|------------------------|---------------|
| Total subjects affected by serious adverse events    |                |                        |               |
| subjects affected / exposed                          | 2 / 5 (40.00%) | 0 / 3 (0.00%)          | 0 / 3 (0.00%) |
| number of deaths (all causes)                        | 1              | 0                      | 0             |
| number of deaths resulting from adverse events       |                |                        |               |
| General disorders and administration site conditions |                |                        |               |
| Acute Phase Reaction                                 |                |                        |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 3 (0.00%)          | 0 / 3 (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         |
| Gastrointestinal disorders                           |                |                        |               |
| Obstruction Gastric                                  |                |                        |               |
| subjects affected / exposed                          | 0 / 5 (0.00%)  | 0 / 3 (0.00%)          | 0 / 3 (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         |

|                                                 |                |               |               |
|-------------------------------------------------|----------------|---------------|---------------|
| Respiratory, thoracic and mediastinal disorders |                |               |               |
| Dyspnoea                                        |                |               |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (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         |
| Lung Disorder                                   |                |               |               |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0         | 0 / 0         |

| <b>Serious adverse events</b>                        | 150 mg twice daily (BID) | 450 mg QD      |  |
|------------------------------------------------------|--------------------------|----------------|--|
| Total subjects affected by serious adverse events    |                          |                |  |
| subjects affected / exposed                          | 1 / 7 (14.29%)           | 1 / 3 (33.33%) |  |
| number of deaths (all causes)                        | 0                        | 0              |  |
| number of deaths resulting from adverse events       |                          |                |  |
| General disorders and administration site conditions |                          |                |  |
| Acute Phase Reaction                                 |                          |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)            | 1 / 3 (33.33%) |  |
| occurrences causally related to treatment / all      | 0 / 0                    | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0          |  |
| Gastrointestinal disorders                           |                          |                |  |
| Obstruction Gastric                                  |                          |                |  |
| subjects affected / exposed                          | 1 / 7 (14.29%)           | 0 / 3 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1                    | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders      |                          |                |  |
| Dyspnoea                                             |                          |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)            | 1 / 3 (33.33%) |  |
| occurrences causally related to treatment / all      | 0 / 0                    | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0          |  |
| Lung Disorder                                        |                          |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)            | 0 / 3 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 0                    | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                                                    | 300 mg QD      | 150 mg once daily (QD) | 600 mg QD       |
|--------------------------------------------------------------------------------------|----------------|------------------------|-----------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 4 / 5 (80.00%) | 3 / 3 (100.00%)        | 3 / 3 (100.00%) |
| Vascular disorders                                                                   |                |                        |                 |
| Haematoma                                                                            |                |                        |                 |
| subjects affected / exposed                                                          | 0 / 5 (0.00%)  | 0 / 3 (0.00%)          | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 0              | 0                      | 0               |
| General disorders and administration site conditions                                 |                |                        |                 |
| Asthenia                                                                             |                |                        |                 |
| subjects affected / exposed                                                          | 0 / 5 (0.00%)  | 1 / 3 (33.33%)         | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 0              | 1                      | 0               |
| Chills                                                                               |                |                        |                 |
| subjects affected / exposed                                                          | 0 / 5 (0.00%)  | 1 / 3 (33.33%)         | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 0              | 1                      | 0               |
| Fatigue                                                                              |                |                        |                 |
| subjects affected / exposed                                                          | 1 / 5 (20.00%) | 0 / 3 (0.00%)          | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 1              | 0                      | 0               |
| Oedema Peripheral                                                                    |                |                        |                 |
| subjects affected / exposed                                                          | 0 / 5 (0.00%)  | 0 / 3 (0.00%)          | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 0              | 0                      | 0               |
| Pyrexia                                                                              |                |                        |                 |
| subjects affected / exposed                                                          | 4 / 5 (80.00%) | 3 / 3 (100.00%)        | 1 / 3 (33.33%)  |
| occurrences (all)                                                                    | 5              | 6                      | 1               |
| Respiratory, thoracic and mediastinal disorders                                      |                |                        |                 |
| Cough                                                                                |                |                        |                 |
| subjects affected / exposed                                                          | 1 / 5 (20.00%) | 0 / 3 (0.00%)          | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 1              | 0                      | 0               |
| Dyspnoea                                                                             |                |                        |                 |
| subjects affected / exposed                                                          | 0 / 5 (0.00%)  | 0 / 3 (0.00%)          | 0 / 3 (0.00%)   |
| occurrences (all)                                                                    | 0              | 0                      | 0               |



|                                                                                                                      |                    |                     |                    |
|----------------------------------------------------------------------------------------------------------------------|--------------------|---------------------|--------------------|
| Laryngeal Inflammation<br>subjects affected / exposed<br>occurrences (all)                                           | 0 / 5 (0.00%)<br>0 | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0 |
| Oropharyngeal Pain<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 5 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 |
| Pleural Effusion<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 5 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 5 (0.00%)<br>0 | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0 |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 5 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 |
| Investigations<br>Blood Creatine Phosphokinase Increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 5 (0.00%)<br>0 | 1 / 3 (33.33%)<br>6 | 0 / 3 (0.00%)<br>0 |
| Eosinophil Count Increased<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 5 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 |
| Weight Decreased<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 5 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 |
| Injury, poisoning and procedural complications<br>Ankle Fracture<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0 |
| Procedural Pain<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 5 (0.00%)<br>0 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0 |
| Cardiac disorders<br>Tachycardia                                                                                     |                    |                     |                    |

|                                                                                                        |                     |                     |                     |
|--------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                       | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)               | 2 / 5 (40.00%)<br>3 | 2 / 3 (66.67%)<br>5 | 1 / 3 (33.33%)<br>1 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Lymph Node Pain<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 2 / 3 (66.67%)<br>2 |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)             | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Eye disorders<br>Eczema Eyelids<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 1 / 3 (33.33%)<br>1 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 1 / 3 (33.33%)<br>1 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |

|                                                                                                             |                     |                     |                     |
|-------------------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                  | 3 / 5 (60.00%)<br>3 | 1 / 3 (33.33%)<br>1 | 1 / 3 (33.33%)<br>1 |
| Oral Pain<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>2 |
| Tongue Ulceration<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                | 2 / 5 (40.00%)<br>3 | 1 / 3 (33.33%)<br>1 | 2 / 3 (66.67%)<br>4 |
| Hepatobiliary disorders<br>Hepatic Function Abnormal<br>subjects affected / exposed<br>occurrences (all)    | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>2 | 0 / 3 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                                                | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Night Sweats<br>subjects affected / exposed<br>occurrences (all)                                            | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                    | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Renal and urinary disorders<br>Renal Failure<br>subjects affected / exposed<br>occurrences (all)            | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal and connective tissue                                                                       |                     |                     |                     |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| disorders                   |                |                |                |
| Arthralgia                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 3 (33.33%) | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Back Pain                   |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Musculoskeletal Pain        |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Torticollis                 |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Infections and infestations |                |                |                |
| Bronchitis                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Fungal Skin Infection       |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Furuncle                    |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Herpes Virus Infection      |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Nasopharyngitis             |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 1              | 1              |
| Oral Candidiasis            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Oral Herpes                 |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Otitis Media                |                |                |                |

|                                    |               |                |               |
|------------------------------------|---------------|----------------|---------------|
| subjects affected / exposed        | 0 / 5 (0.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 0              | 0             |
| Scrotal Infection                  |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 1              | 0             |
| Upper Respiratory Tract Infection  |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 2              | 0             |
| Urinary Tract Infection            |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 1              | 0             |
| Metabolism and nutrition disorders |               |                |               |
| Decreased Appetite                 |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 1              | 0             |
| Dehydration                        |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 0              | 0             |
| Enzyme Abnormality                 |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 0              | 0             |
| Hyperamylasaemia                   |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 2              | 0             |
| Hyperglycaemia                     |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 0              | 0             |
| Hyperkalaemia                      |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 0              | 0             |
| Hyperlipasaemia                    |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 3              | 0             |
| Hypoalbuminaemia                   |               |                |               |
| subjects affected / exposed        | 0 / 5 (0.00%) | 0 / 3 (0.00%)  | 0 / 3 (0.00%) |
| occurrences (all)                  | 0             | 0              | 0             |

|                             |                |               |               |
|-----------------------------|----------------|---------------|---------------|
| Hypokalaemia                |                |               |               |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 1              | 0             | 0             |
| Hypophosphataemia           |                |               |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Type 2 Diabetes Mellitus    |                |               |               |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |

| <b>Non-serious adverse events</b>                     | 150 mg twice daily (BID) | 450 mg QD      |  |
|-------------------------------------------------------|--------------------------|----------------|--|
| Total subjects affected by non-serious adverse events |                          |                |  |
| subjects affected / exposed                           | 6 / 7 (85.71%)           | 2 / 3 (66.67%) |  |
| Vascular disorders                                    |                          |                |  |
| Haematoma                                             |                          |                |  |
| subjects affected / exposed                           | 1 / 7 (14.29%)           | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1                        | 0              |  |
| General disorders and administration site conditions  |                          |                |  |
| Asthenia                                              |                          |                |  |
| subjects affected / exposed                           | 1 / 7 (14.29%)           | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1                        | 0              |  |
| Chills                                                |                          |                |  |
| subjects affected / exposed                           | 0 / 7 (0.00%)            | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 0                        | 0              |  |
| Fatigue                                               |                          |                |  |
| subjects affected / exposed                           | 1 / 7 (14.29%)           | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1                        | 0              |  |
| Oedema Peripheral                                     |                          |                |  |
| subjects affected / exposed                           | 1 / 7 (14.29%)           | 0 / 3 (0.00%)  |  |
| occurrences (all)                                     | 1                        | 0              |  |
| Pyrexia                                               |                          |                |  |
| subjects affected / exposed                           | 2 / 7 (28.57%)           | 1 / 3 (33.33%) |  |
| occurrences (all)                                     | 3                        | 1              |  |
| Respiratory, thoracic and mediastinal disorders       |                          |                |  |
| Cough                                                 |                          |                |  |

|                                                |                |                |  |
|------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                    | 2 / 7 (28.57%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 2              | 0              |  |
| Dyspnoea                                       |                |                |  |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 2              | 0              |  |
| Laryngeal Inflammation                         |                |                |  |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 0              | 0              |  |
| Oropharyngeal Pain                             |                |                |  |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 1              | 0              |  |
| Pleural Effusion                               |                |                |  |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Rhinorrhoea                                    |                |                |  |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 0              | 0              |  |
| Psychiatric disorders                          |                |                |  |
| Insomnia                                       |                |                |  |
| subjects affected / exposed                    | 3 / 7 (42.86%) | 1 / 3 (33.33%) |  |
| occurrences (all)                              | 3              | 1              |  |
| Investigations                                 |                |                |  |
| Blood Creatine Phosphokinase Increased         |                |                |  |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 1 / 3 (33.33%) |  |
| occurrences (all)                              | 1              | 1              |  |
| Eosinophil Count Increased                     |                |                |  |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 1              | 0              |  |
| Weight Decreased                               |                |                |  |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 1              | 0              |  |
| Injury, poisoning and procedural complications |                |                |  |
| Ankle Fracture                                 |                |                |  |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                              | 0              | 0              |  |
| Procedural Pain                                |                |                |  |

|                                                                                                                                                                                                                                                       |                                                                          |                                                                         |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                      | 0 / 7 (0.00%)<br>0                                                       | 1 / 3 (33.33%)<br>1                                                     |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                  | 1 / 7 (14.29%)<br>1                                                      | 0 / 3 (0.00%)<br>0                                                      |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                              | 2 / 7 (28.57%)<br>2                                                      | 0 / 3 (0.00%)<br>0                                                      |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Lymph Node Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Lymphopenia<br>subjects affected / exposed<br>occurrences (all) | 2 / 7 (28.57%)<br>5<br><br>0 / 7 (0.00%)<br>0<br><br>1 / 7 (14.29%)<br>1 | 1 / 3 (33.33%)<br>2<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0 |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                            | 0 / 7 (0.00%)<br>0                                                       | 0 / 3 (0.00%)<br>0                                                      |  |
| Eye disorders<br>Eczema Eyelids<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                   | 1 / 7 (14.29%)<br>1                                                      | 0 / 3 (0.00%)<br>0                                                      |  |
| Gastrointestinal disorders<br>Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea                                                       | 1 / 7 (14.29%)<br>3<br><br>2 / 7 (28.57%)<br>2                           | 0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0                            |  |



|                                        |                |                |  |
|----------------------------------------|----------------|----------------|--|
| subjects affected / exposed            | 2 / 7 (28.57%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 4              | 0              |  |
| Dyspepsia                              |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Nausea                                 |                |                |  |
| subjects affected / exposed            | 2 / 7 (28.57%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 3              | 0              |  |
| Oral Pain                              |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Stomatitis                             |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Tongue Ulceration                      |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Vomiting                               |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 2              | 0              |  |
| Hepatobiliary disorders                |                |                |  |
| Hepatic Function Abnormal              |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Skin and subcutaneous tissue disorders |                |                |  |
| Hyperhidrosis                          |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Pruritus                               |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Night Sweats                           |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                      | 0              | 0              |  |
| Rash                                   |                |                |  |

|                                                                                                                   |                     |                     |  |
|-------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                  | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Renal and urinary disorders<br>Renal Failure<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Back Pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 7 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |  |
| Musculoskeletal Pain<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Torticollis<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Fungal Skin Infection<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 7 (14.29%)<br>1 | 0 / 3 (0.00%)<br>0  |  |
| Furuncle<br>subjects affected / exposed<br>occurrences (all)                                                      | 1 / 7 (14.29%)<br>1 | 0 / 3 (0.00%)<br>0  |  |
| Herpes Virus Infection<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 7 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 7 (14.29%)<br>1 | 1 / 3 (33.33%)<br>1 |  |
| Oral Candidiasis                                                                                                  |                     |                     |  |

|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Oral Herpes                        |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Otitis Media                       |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Scrotal Infection                  |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Upper Respiratory Tract Infection  |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Urinary Tract Infection            |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Metabolism and nutrition disorders |                |                |  |
| Decreased Appetite                 |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Dehydration                        |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Enzyme Abnormality                 |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 1 / 3 (33.33%) |  |
| occurrences (all)                  | 1              | 2              |  |
| Hyperamylasaemia                   |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Hyperglycaemia                     |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Hyperkalaemia                      |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |

|                             |                |               |  |
|-----------------------------|----------------|---------------|--|
| Hyperlipasaemia             |                |               |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 3 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Hypoalbuminaemia            |                |               |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 3 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Hypokalaemia                |                |               |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 3 (0.00%) |  |
| occurrences (all)           | 0              | 0             |  |
| Hypophosphataemia           |                |               |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 3 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |
| Type 2 Diabetes Mellitus    |                |               |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 3 (0.00%) |  |
| occurrences (all)           | 1              | 0             |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported