



## Clinical trial results:

**An exploratory, blinded, randomized, placebo-controlled study in subjects with depressive disorder to investigate the effect of minocycline on relapse after successful intravenous ketamine/minocycline-induced (partial) symptoms response**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002954-21 |
| Trial protocol           | BE NL ES       |
| Global end of trial date | 10 July 2014   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 23 June 2016 |
| First version publication date | 23 June 2016 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | KETIVEDI2001 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01809340 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Janssen-Cilag International N.V.  |
| Sponsor organisation address | Archimedesweg 29, Leiden, Netherlands, 2333CM   |
| Public contact               | Clinical Registry Group, Janssen-Cilag International NV, 3171 524 21 66, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen-Cilag International NV, 3171 524 21 66, 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**

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 10 July 2014 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 10 July 2014 |
| Was the trial ended prematurely? | Yes          |

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of this study was to assess whether the antidepressant response to intravenous (IV) ketamine can be maintained by minocycline compared to placebo.

Protection of trial subjects:

Safety and tolerability of the participants and assessment of suicidal ideation and behavior using the CSSRS, were evaluated by monitoring of adverse events (AEs), physical examination, body weight, supine vital signs, digital pulse oximetry, 12-lead electrocardiogram (ECG), and continuous ECG monitoring.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 19 June 2013 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Belgium: 14    |
| Country: Number of subjects enrolled | France: 7      |
| Country: Number of subjects enrolled | Netherlands: 8 |
| Worldwide total number of subjects   | 29             |
| EEA total number of subjects         | 29             |

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)                      | 25 |
| From 65 to 84 years                       | 4  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 29 participants were enrolled with Major Depressive Disorder (MDD) or Bipolar Depression Disorder (BPD) of Type II were randomized and treated.

### Period 1

|                              |                        |
|------------------------------|------------------------|
| Period 1 title               | 12-Day Treatment Phase |
| Is this the baseline period? | Yes                    |
| Allocation method            | Not applicable         |
| Blinding used                | Not blinded            |

### Arms

|           |   |
|-----------|---|
| Arm title | Open Label: Ketamine/ Minocycline (12 Days) |
|-----------|---|

Arm description:

Participants received intravenous infusion of 0.5 milligram/kilogram (mg/kg) of body weight ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Ketamine               |
| Investigational medicinal product code |                        |
| Other name                             | Ketamine Hydrochloride |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Participants were administered ketamine hydrochloride Intravenous (IV) injection at a dose of 50 milligram(s)/ 5 millilitre (mg/ml) over 40 minutes on Days 1, 3, 5, 8, 10, and 12.

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Minocycline Hydrochloride       |
| Investigational medicinal product code |                                 |
| Other name                             | Minocin - hard capsule - 100 mg |
| Pharmaceutical forms                   | Capsule, hard                   |
| Routes of administration               | Oral use                        |

Dosage and administration details:

Participants were administered with Minocycline 200 mg (milligrams) capsule (2\*100mg=200mg) on day 1, and 100 mg twice daily on days 2 to 11 and 100 mg on the morning of day 12 orally.

|                                       |  |
|---------------------------------------|--|
| <b>Number of subjects in period 1</b> | Open Label:<br>Ketamine/<br>Minocycline (12<br>Days) |
| Started                               | 29   |
| Completed                             | 29   |

|   |                                      |
|---|--------------------------------------|
| <b>Period 2</b>   |                                      |
| Period 2 title  | 6-Week Treatment Phase               |
| Is this the baseline period?  | No                                   |
| Allocation method   | Randomised - controlled              |
| Blinding used   | Double blind                         |
| Roles blinded   | Subject, Investigator                |
| <b>Arms</b>   |                                      |
| Are arms mutually exclusive?  | Yes                                  |
| <b>Arm title</b>  | Ketamine non-responders: Minocycline |
| Arm description:  |                                      |
| Participants without ketamine response (ketamine non-responders) in 12-day open label treatment phase self-administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54. |                                      |
| Arm type  | Experimental                         |
| Investigational medicinal product name  | Minocycline Hydrochloride            |
| Investigational medicinal product code  |                                      |
| Other name  | Minocin - hard capsule - 100 mg      |
| Pharmaceutical forms  | Capsule, hard                        |
| Routes of administration  | Oral use                             |
| Dosage and administration details:  |                                      |
| Participants were administered with Minocycline 100 mg capsule twice daily from Day 12 to Day 54, orally.   |                                      |
| <b>Arm title</b>  | Ketamine responders: Minocycline     |
| Arm description:  |                                      |
| Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.        |                                      |
| Arm type  | Experimental                         |
| Investigational medicinal product name  | Minocycline Hydrochloride            |
| Investigational medicinal product code  |                                      |
| Other name  |                                      |
| Pharmaceutical forms  | Capsule, hard                        |
| Routes of administration  | Oral use                             |
| Dosage and administration details:  |                                      |
| Participants were administered with Minocycline 100 mg capsule twice daily from Day 12 to Day 54, orally.   |                                      |
| <b>Arm title</b>  | Ketamine responders: Placebo         |
| Arm description:  |                                      |
| Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered placebo matching with minocycline orally twice daily from Day 12 to Day 54.      |                                      |
| Arm type  | Placebo                              |
| Investigational medicinal product name  | Placebo                              |
| Investigational medicinal product code  |                                      |
| Other name  |                                      |
| Pharmaceutical forms  | Capsule, hard                        |
| Routes of administration  | Oral use                             |
| Dosage and administration details:  |                                      |
| Participants were administered with placebo during treatment period.  |                                      |

| Number of subjects in period<br>2 <sup>[1]</sup> | Ketamine non-<br>responders:<br>Minocycline | Ketamine<br>responders:<br>Minocycline | Ketamine<br>responders: Placebo |
|--|---|--|---------------------------------|
|  |   |  |                                 |
| Started  | 5   | 7                                      | 7                               |
| Completed  | 4   | 7                                      | 5                               |
| Not completed                                    | 1   | 0                                      | 2                               |
| Other  | 1   | -                                      | -                               |
| Randomised but not treated                       | -   | -                                      | 1                               |
| Lost to follow-up                                | -   | -                                      | 1                               |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 10 participants who were ketamine non-responders from the 12-day Open Label Treatment Phase did not enter the optional 6-week Open label treatment phase.

## Baseline characteristics

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Open Label: Ketamine/ Minocycline (12 Days) |
|-----------------------|---|

Reporting group description:

Participants received intravenous infusion of 0.5 milligram/kilogram (mg/kg) of body weight ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.

| Reporting group values                      | Open Label:<br>Ketamine/<br>Minocycline (12<br>Days) | Total |  |
|---|--|-------|--|
| Number of subjects                          | 29   | 29    |  |
| Title for AgeCategorical<br>Units: subjects |  |       |  |
| Children (2-11 years)                       | 0  | 0     |  |
| Adolescents (12-17 years)                   | 0  | 0     |  |
| Adults (18-64 years)                        | 25   | 25    |  |
| From 65 to 84 years                         | 4  | 4     |  |
| 85 years and over                           | 0  | 0     |  |
| Title for AgeContinuous<br>Units: years     |  |       |  |
| arithmetic mean                             | 50.5   |       |  |
| standard deviation                          | ± 12.53  | -     |  |
| Title for Gender<br>Units: subjects         |  |       |  |
| Female                                      | 16   | 16    |  |
| Male  | 13   | 13    |  |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Open Label: Ketamine/ Minocycline (12 Days) |
| Reporting group description:<br>Participants received intravenous infusion of 0.5 milligram/kilogram (mg/kg) of body weight ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily. |   |
| Reporting group title  | Ketamine non-responders: Minocycline        |
| Reporting group description:<br>Participants without ketamine response (ketamine non-responders) in 12-day open label treatment phase self-administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.                            |   |
| Reporting group title  | Ketamine responders: Minocycline            |
| Reporting group description:<br>Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self-administered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.                                   |   |
| Reporting group title  | Ketamine responders: Placebo                |
| Reporting group description:<br>Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self-administered placebo matching with minocycline orally twice daily from Day 12 to Day 54.                                 |   |

### Primary: Percentage of subjects who were relapse-free (among responders) on Day54 (Week 6)

|   |  |
|---|--|
| End point title   | Percentage of subjects who were relapse-free (among responders) on Day54 (Week 6) <sup>[1]</sup> |
| End point description:<br>A participants was defined as "relapsed" if Montgomery-Asberg Depression Rating Scale (MADRS) total score had returned to greater than or equal to 30 after at least the first dose administration of minocycline or placebo in the 6-week blinded, treatment phase. The Montgomery-Asberg Depression Rating Scale (MADRS) measures depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60. Higher scores represent a more severe condition by Treatment. Intent to treat (ITT) analysis set included all subjects who received at least 1 dose of study drug and had both baseline and at least 1 post-baseline MADRS total score. Data for this endpoint was collected from only who were ketamine responders. |  |
| End point type  | Primary  |
| End point timeframe:<br>Day 54 (Week 6)   |  |

#### 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: Statistical analysis was not reported as inferential analysis was not performed as planned.

| End point values            | Ketamine responders: Minocycline | Ketamine responders: Placebo |  |  |
|-----------------------------|----------------------------------|------------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group              |  |  |
| Number of subjects analysed | 7                                | 7                            |  |  |
| Units: Percentage           |                                  |                              |  |  |
| number (not applicable)     | 85.7                             | 57.1                         |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in MADRS total score from Day 12 to end-of-study (Day 54)

|                 |  |
|-----------------|--|
| End point title | Change in MADRS total score from Day 12 to end-of-study (Day 54) |
|-----------------|--|

End point description:

The Montgomery-Asberg Depression Rating Scale (MADRS) measures depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60. Higher scores represent a more severe condition. ITT population. Here "n" signifies number of subjects who were analysed for this outcome measure at specific time points.

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

End point timeframe:

Day 12 and Day 54

| End point values                     | Ketamine responders: Minocycline | Ketamine responders: Placebo |  |  |
|--------------------------------------|----------------------------------|------------------------------|--|--|
| Subject group type                   | Reporting group                  | Reporting group              |  |  |
| Number of subjects analysed          | 7                                | 6                            |  |  |
| Units: units on a scale              |                                  |                              |  |  |
| arithmetic mean (standard deviation) |                                  |                              |  |  |
| Day 12 (n=7, 6)                      | 9.6 (± 6.65)                     | 8.2 (± 4.26)                 |  |  |
| Change at Day 54 (n= 6, 2)           | 1 (± 2.53)                       | 4.5 (± 2.12)                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the MADRS total score from baseline during ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

|                 |  |
|-----------------|--|
| End point title | Change in the MADRS total score from baseline during ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12) |
|-----------------|--|

End point description:

The Montgomery-Asberg Depression Rating Scale (MADRS) measures depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60. Higher scores represent a more severe condition. ITT population. Here "n" signifies number of subjects who were analysed for this outcome measure at specific time points.

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

End point timeframe:

Day 1 Predose and Days 1, 3, 5, 8, 10 and 12

| End point values                     | Open Label:<br>Ketamine/<br>Minocycline (12<br>Days) |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                                      |  |  |  |
| Number of subjects analysed          | 29   |  |  |  |
| Units: Unit on a scale               |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Predose Day 1                        | 33 (± 5)   |  |  |  |
| Change at Day 1 (n=29)               | -8.7 (± 8.57)  |  |  |  |
| Change at Day 3 (n=29)               | -11.9 (± 7.66)                                       |  |  |  |
| Change at Day 5 (n=29)               | -14.2 (± 8.35)                                       |  |  |  |
| Change at Day 8 (n=29)               | -15.7 (± 9.17)                                       |  |  |  |
| Change at Day 10 (n=28)              | -17 (± 9.2)  |  |  |  |
| Change at Day 12 (n=26)              | -15.6 (± 10.62)                                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the MADRS total score from baseline after the IV ketamine treatment phase (Days 20, 27, 34, 41, 48, and 54)

|                 |   |
|-----------------|---|
| End point title | Change in the MADRS total score from baseline after the IV ketamine treatment phase (Days 20, 27, 34, 41, 48, and 54) |
|-----------------|---|

End point description:

The Montgomery-Asberg Depression Rating Scale (MADRS) measures depression severity and detects changes due to antidepressant treatment. The test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60. Higher scores represent a more severe condition. ITT population. Here "n" signifies number of subjects who were analysed for this outcome measure at specific time points.

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

End point timeframe:

Day 1 and days 20, 27, 34, 41, 48, and 54.

| End point values                     | Ketamine<br>responders:<br>Minocycline | Ketamine<br>responders:<br>Placebo |  |  |
|--------------------------------------|--|------------------------------------|--|--|
| Subject group type                   | Reporting group                        | Reporting group                    |  |  |
| Number of subjects analysed          | 7                                      | 7                                  |  |  |
| Units: unit on a scale               |  |                                    |  |  |
| arithmetic mean (standard deviation) |  |                                    |  |  |
| Day 1 Predose (n=7, 6)               | 33 (± 7.46)                            | 33 (± 3.27)                        |  |  |
| Change at Day 20 (n= 7, 6)           | -19.9 (± 10.88)                        | -20 (± 7.97)                       |  |  |
| Change at Day 27 (n= 6, 6)           | -22 (± 8.37)                           | -17.3 (± 16.74)                    |  |  |
| Change at Day 34 (n= 6, 5)           | -20 (± 8.94)                           | -25.4 (± 5.59)                     |  |  |
| Change at Day 41 (n= 6, 4)           | -18.2 (± 9.6)                          | -17.3 (± 12.2)                     |  |  |
| Change at Day 48 (n= 6, 3)           | -20.3 (± 9.95)                         | -25 (± 6.08)                       |  |  |

|                            |                |              |  |  |
|----------------------------|----------------|--------------|--|--|
| Change at Day 54 (n= 6, 3) | -21.8 (± 8.42) | -23 (± 5.29) |  |  |
|----------------------------|----------------|--------------|--|--|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Response during the IV ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Response during the IV ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12) |
|-----------------|--|

End point description:

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

End point timeframe:

Days 1, 3, 5, 8, 10 and 12

|                                   |  |  |  |  |
|-----------------------------------|--|--|--|--|
| <b>End point values</b>           | Open Label:<br>Ketamine/<br>Minocycline (12<br>Days) |  |  |  |
| Subject group type                | Reporting group                                      |  |  |  |
| Number of subjects analysed       | 29   |  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 48   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median Time to Relapse

|                 |                        |
|-----------------|------------------------|
| End point title | Median Time to Relapse |
|-----------------|------------------------|

End point description:

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

End point timeframe:

Day 12 up to End of Study (Day 54)

| End point values              | Ketamine responders:<br>Minocycline | Ketamine responders:<br>Placebo |  |  |
|-------------------------------|-------------------------------------|---------------------------------|--|--|
| Subject group type            | Reporting group                     | Reporting group                 |  |  |
| Number of subjects analysed   | 0 <sup>[2]</sup>                    | 0 <sup>[3]</sup>                |  |  |
| Units: Days                   |                                     |                                 |  |  |
| median (full range (min-max)) | ( to )                              | ( to )                          |  |  |

Notes:

[2] - Median levels were not reached due to the early stopping / small sample size.

[3] - Median levels were not reached due to the early stopping / small sample size.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia Suicide Severity Rating Scale (C-SSRS) Score

|                 |   |
|-----------------|---|
| End point title | Columbia Suicide Severity Rating Scale (C-SSRS) Score |
|-----------------|---|

End point description:

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

End point timeframe:

From Screening up to follow-up (Day 54)

| End point values            | Ketamine non-responders:<br>Minocycline | Ketamine responders:<br>Minocycline | Ketamine responders:<br>Placebo |  |
|-----------------------------|---|-------------------------------------|---------------------------------|--|
| Subject group type          | Reporting group                         | Reporting group                     | Reporting group                 |  |
| Number of subjects analysed | 0 <sup>[4]</sup>                        | 0 <sup>[5]</sup>                    | 0 <sup>[6]</sup>                |  |
| Units: unit on a scale      |   |                                     |                                 |  |
| number (not applicable)     |   |                                     |                                 |  |

Notes:

[4] - Data for this endpoint was not summarized and individual data were listed.

[5] - Data for this endpoint was not summarized and individual data were listed.

[6] - Data for this endpoint was not summarized and individual data were listed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Screening up to follow-up (Day 54)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Open Label: Ketamine/ Minocycline (12 Days) |
|-----------------------|---|

Reporting group description:

Participants received intravenous infusion of 0.5 milligram/kilogram of body weight (mg/kg) ketamine over 40 minutes on Days 1, 3, 5, 8, 10, and 12 in combination with minocycline 100 mg, orally administered twice daily.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Ketamine responders: Placebo |
|-----------------------|------------------------------|

Reporting group description:

Participants with ketamine response (ketamine responders) in 12-day open label treatment phase selfadministered placebo matching with minocycline orally twice daily from Day 12 to Day 54.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Ketamine responders: Minocycline |
|-----------------------|----------------------------------|

Reporting group description:

Participants with ketamine response (ketamine responders) in 12-day open label treatment phase selfadministered minocycline 100 milligram (mg), orally twice daily from Day 12 to Day 54.

|                       |   |
|-----------------------|---|
| Reporting group title | Minocycline 100 mg BID Open Label 6 Weeks |
|-----------------------|---|

Reporting group description:

Participants with ketamine response (ketamine responders) in 12-day open label treatment phase self administered placebo matching with minocycline orally twice daily from Day 12 to Day 54.

| Serious adverse events                             | Open Label:<br>Ketamine/<br>Minocycline (12<br>Days) | Ketamine<br>responders: Placebo | Ketamine<br>responders:<br>Minocycline |
|--|--|---------------------------------|--|
| Total subjects affected by serious adverse events  |  |                                 |  |
| subjects affected / exposed                        | 0 / 29 (0.00%)                                       | 1 / 6 (16.67%)                  | 0 / 7 (0.00%)                          |
| number of deaths (all causes)                      | 0  | 0                               | 0                                      |
| number of deaths resulting from adverse events     |  |                                 |  |
| Psychiatric disorders                              |  |                                 |  |
| Anxiety  |  |                                 |  |
| alternative assessment type:<br>Systematic         |  |                                 |  |
| subjects affected / exposed                        | 0 / 29 (0.00%)                                       | 1 / 6 (16.67%)                  | 0 / 7 (0.00%)                          |
| occurrences causally related to<br>treatment / all | 0 / 0  | 0 / 1                           | 0 / 0                                  |
| deaths causally related to<br>treatment / all      | 0 / 0  | 0 / 0                           | 0 / 0                                  |
| Serious adverse events                             | Minocycline 100 mg<br>BID Open Label 6<br>Weeks      |                                 |  |

|   |                |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 1 / 5 (20.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    |                |  |  |
| Psychiatric disorders                             |                |  |  |
| Anxiety   |                |  |  |
| alternative assessment type: Systematic           |                |  |  |
| subjects affected / exposed                       | 1 / 5 (20.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Open Label:<br>Ketamine/<br>Minocycline (12<br>Days) | Ketamine<br>responders: Placebo | Ketamine<br>responders:<br>Minocycline |
|---|--|---------------------------------|--|
| Total subjects affected by non-serious adverse events |  |                                 |  |
| subjects affected / exposed                           | 25 / 29 (86.21%)                                     | 3 / 6 (50.00%)                  | 6 / 7 (85.71%)                         |
| Vascular disorders                                    |  |                                 |  |
| Hypertension  |  |                                 |  |
| alternative assessment type: Systematic               |  |                                 |  |
| subjects affected / exposed                           | 1 / 29 (3.45%)                                       | 1 / 6 (16.67%)                  | 0 / 7 (0.00%)                          |
| occurrences (all)                                     | 1  | 1                               | 0                                      |
| Hot flush   |  |                                 |  |
| subjects affected / exposed                           | 0 / 29 (0.00%)                                       | 0 / 6 (0.00%)                   | 1 / 7 (14.29%)                         |
| occurrences (all)                                     | 0  | 0                               | 1                                      |
| General disorders and administration site conditions  |  |                                 |  |
| Fatigue   |  |                                 |  |
| alternative assessment type: Systematic               |  |                                 |  |
| subjects affected / exposed                           | 3 / 29 (10.34%)                                      | 0 / 6 (0.00%)                   | 0 / 7 (0.00%)                          |
| occurrences (all)                                     | 4  | 0                               | 0                                      |
| Feeling Abnormal                                      |  |                                 |  |
| alternative assessment type: Systematic               |  |                                 |  |
| subjects affected / exposed                           | 2 / 29 (6.90%)                                       | 0 / 6 (0.00%)                   | 1 / 7 (14.29%)                         |
| occurrences (all)                                     | 6  | 0                               | 1                                      |
| Feeling of Relaxation                                 |  |                                 |  |
| alternative assessment type:                          |  |                                 |  |

|  |  |  |   |
|--|--|--|---|
| Systematic<br>subjects affected / exposed<br>occurrences (all)   | 4 / 29 (13.79%)<br>8   | 0 / 6 (0.00%)<br>0   | 0 / 7 (0.00%)<br>0  |
| Reproductive system and breast disorders<br>Breast Tenderness<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0   | 1 / 7 (14.29%)<br>1   |
| Psychiatric disorders<br>Affect Lability<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Anxiety<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Bradyphrenia<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Depressed Mood<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dissociation<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Elevated Mood<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>alternative assessment type:<br>Systematic | 2 / 29 (6.90%)<br>4<br><br>4 / 29 (13.79%)<br>9<br><br>2 / 29 (6.90%)<br>2<br><br>1 / 29 (3.45%)<br>4<br><br>12 / 29 (41.38%)<br>48<br><br>1 / 29 (3.45%)<br>2 | 0 / 6 (0.00%)<br>0<br><br>0 / 6 (0.00%)<br>0<br><br>0 / 6 (0.00%)<br>0<br><br>1 / 6 (16.67%)<br>2<br><br>2 / 6 (33.33%)<br>2<br><br>0 / 6 (0.00%)<br>0 | 1 / 7 (14.29%)<br>2<br><br>1 / 7 (14.29%)<br>1<br><br>0 / 7 (0.00%)<br>0<br><br>1 / 7 (14.29%)<br>1<br><br>2 / 7 (28.57%)<br>2<br><br>1 / 7 (14.29%)<br>1 |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| subjects affected / exposed                    | 2 / 29 (6.90%)  | 0 / 6 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                              | 2               | 0              | 0              |
| Negative Thoughts                              |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |
| subjects affected / exposed                    | 0 / 29 (0.00%)  | 1 / 6 (16.67%) | 0 / 7 (0.00%)  |
| occurrences (all)                              | 0               | 1              | 0              |
| Suicidal Ideation                              |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |
| subjects affected / exposed                    | 0 / 29 (0.00%)  | 1 / 6 (16.67%) | 0 / 7 (0.00%)  |
| occurrences (all)                              | 0               | 1              | 0              |
| Tension  |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |
| subjects affected / exposed                    | 1 / 29 (3.45%)  | 1 / 6 (16.67%) | 0 / 7 (0.00%)  |
| occurrences (all)                              | 2               | 2              | 0              |
| Dissociative disorder                          |                 |                |                |
| subjects affected / exposed                    | 1 / 29 (3.45%)  | 0 / 6 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                              | 5               | 0              | 0              |
| Investigations                                 |                 |                |                |
| Blood Pressure Increased                       |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |
| subjects affected / exposed                    | 1 / 29 (3.45%)  | 0 / 6 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                              | 5               | 0              | 1              |
| Injury, poisoning and procedural complications |                 |                |                |
| Contusion                                      |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |
| subjects affected / exposed                    | 0 / 29 (0.00%)  | 0 / 6 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                              | 0               | 0              | 1              |
| Nervous system disorders                       |                 |                |                |
| Dizziness                                      |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |
| subjects affected / exposed                    | 8 / 29 (27.59%) | 1 / 6 (16.67%) | 1 / 7 (14.29%) |
| occurrences (all)                              | 26              | 1              | 1              |
| Dysarthria                                     |                 |                |                |
| alternative assessment type:<br>Systematic     |                 |                |                |



|  |                  |                |                |
|--|------------------|----------------|----------------|
| subjects affected / exposed                | 3 / 29 (10.34%)  | 0 / 6 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                          | 4                | 0              | 0              |
| Headache                                   |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 11 / 29 (37.93%) | 1 / 6 (16.67%) | 2 / 7 (28.57%) |
| occurrences (all)                          | 18               | 2              | 4              |
| Hyperaesthesia                             |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 0 / 29 (0.00%)   | 1 / 6 (16.67%) | 0 / 7 (0.00%)  |
| occurrences (all)                          | 0                | 1              | 0              |
| Hypoaesthesia                              |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 1 / 29 (3.45%)   | 0 / 6 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                          | 3                | 0              | 1              |
| Migraine                                   |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 1 / 29 (3.45%)   | 0 / 6 (0.00%)  | 2 / 7 (28.57%) |
| occurrences (all)                          | 1                | 0              | 2              |
| Somnolence                                 |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 4 / 29 (13.79%)  | 0 / 6 (0.00%)  | 0 / 7 (0.00%)  |
| occurrences (all)                          | 9                | 0              | 0              |
| Sciatica                                   |                  |                |                |
| subjects affected / exposed                | 0 / 29 (0.00%)   | 0 / 6 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                          | 0                | 0              | 1              |
| Eye disorders                              |                  |                |                |
| Diplopia                                   |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 4 / 29 (13.79%)  | 0 / 6 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                          | 7                | 0              | 1              |
| Vision Blurred                             |                  |                |                |
| alternative assessment type:<br>Systematic |                  |                |                |
| subjects affected / exposed                | 4 / 29 (13.79%)  | 0 / 6 (0.00%)  | 1 / 7 (14.29%) |
| occurrences (all)                          | 8                | 0              | 1              |
| Gastrointestinal disorders                 |                  |                |                |

|   |                      |                     |                     |
|---|----------------------|---------------------|---------------------|
| Abdominal Discomfort<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 2 / 29 (6.90%)<br>2  | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Diarrhoea<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 29 (0.00%)<br>1  | 0 / 6 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| Dry Mouth<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 2 / 29 (6.90%)<br>2  | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Hypoaesthesia Oral<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 2 / 29 (6.90%)<br>3  | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Nausea<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 5 / 29 (17.24%)<br>9 | 1 / 6 (16.67%)<br>1 | 1 / 7 (14.29%)<br>1 |
| Skin and subcutaneous tissue disorders<br>Hyperhidrosis<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)             | 2 / 29 (6.90%)<br>2  | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Muscle Tightness<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 29 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Myalgia<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 29 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| Infections and infestations   |                      |                     |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Gastroenteritis<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Rash Pustular<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |
| Tinea Pedis<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 29 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |
| Metabolism and nutrition disorders<br>Increased Appetite<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 29 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 | 0 / 7 (0.00%)<br>0  |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>   | Minocycline 100 mg<br>BID Open Label 6<br>Weeks |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 4 / 5 (80.00%)                                  |  |  |
| Vascular disorders<br>Hypertension<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Hot flush<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0    |  |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Feeling Abnormal              | 0 / 5 (0.00%)<br>0                              |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  |  |  |
| Feeling of Relaxation<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  |  |  |
| Reproductive system and breast disorders<br>Breast Tenderness<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  |  |  |
| Psychiatric disorders<br>Affect Lability<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 5 (0.00%)<br>0  |  |  |
| Anxiety<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  |  |  |
| Bradyphrenia<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  |  |  |
| Depressed Mood<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  |  |  |
| Dissociation<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 2 / 5 (40.00%)<br>2 |  |  |
| Elevated Mood<br>alternative assessment type:   |                     |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Systematic                                     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Insomnia                                       |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Negative Thoughts                              |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Suicidal Ideation                              |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Tension  |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Dissociative disorder                          |                |  |  |
| subjects affected / exposed                    | 1 / 5 (20.00%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Investigations                                 |                |  |  |
| Blood Pressure Increased                       |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Injury, poisoning and procedural complications |                |  |  |
| Contusion                                      |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |
| subjects affected / exposed                    | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                              | 0              |  |  |
| Nervous system disorders                       |                |  |  |
| Dizziness                                      |                |  |  |
| alternative assessment type:<br>Systematic     |                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                | 1 / 5 (20.00%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Dysarthria                                 |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                          | 0              |  |  |
| Headache                                   |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 1 / 5 (20.00%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Hyperaesthesia                             |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                          | 0              |  |  |
| Hypoaesthesia                              |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                          | 0              |  |  |
| Migraine                                   |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                          | 0              |  |  |
| Somnolence                                 |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 1 / 5 (20.00%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Sciatica                                   |                |  |  |
| subjects affected / exposed                | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                          | 0              |  |  |
| Eye disorders                              |                |  |  |
| Diplopia                                   |                |  |  |
| alternative assessment type:<br>Systematic |                |  |  |
| subjects affected / exposed                | 0 / 5 (0.00%)  |  |  |
| occurrences (all)                          | 0              |  |  |
| Vision Blurred                             |                |  |  |

|  |   |  |  |
|--|---|--|--|
| alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  |  |  |
| Gastrointestinal disorders<br>Abdominal Discomfort<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry Mouth<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypoaesthesia Oral<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>1 / 5 (20.00%)<br>1 |  |  |
| Skin and subcutaneous tissue disorders<br>Hyperhidrosis<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  |  |  |
| Musculoskeletal and connective tissue disorders<br>Muscle Tightness<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia   | 1 / 5 (20.00%)<br>1   |  |  |

|  |  |  |  |
|--|--|--|--|
| alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0   |  |  |
| Infections and infestations<br>Gastroenteritis<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash Pustular<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Tinea Pedis<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1<br><br>0 / 5 (0.00%)<br>0<br><br>1 / 5 (20.00%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Increased Appetite<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0   |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 07 August 2013 | The first amendment was released to revise to facilitate participant recruitment (without changing the aims of the protocol) and provide further clarification regarding participant eligibility requirements.  |
| 18 March 2014  | The second amendment was released to amend the criteria for Ketamine responder criteria were amended to reflect normal variation in response. Additionally the maximum number of concomitant psychotropic drugs were increased to better reflect clinical practice. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was terminated prematurely due to slow recruitment resulting in expiration of trial supplies  
Inability to secure new trial supplies due to availability issues.

Notes: