



## Clinical trial results:

**RCT comparing the analgesic efficacy of 4 therapeutic strategies based on 4 different major opioids (fentanyl, oxycodone, buprenorphine vs morphine) in cancer patients with moderate/severe pain, at the moment of starting 3rd step of WHO analgesic ladder.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-021017-23 |
| Trial protocol           | IT             |
| Global end of trial date | 31 July 2014   |

### Results information

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| Result version number             | v1 (current)                                  |
| This version publication date     | 28 March 2019                                 |
| First version publication date    | 28 March 2019                                 |
| Summary attachment (see zip file) | Study results (study results CT.GOV_CERP.pdf) |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | STUDIO CERP |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01809106 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Mario Negri Institute for Pharmacological Research                                         |
| Sponsor organisation address | Via G. La Masa 19, Milan, Italy, 20156                                                     |
| Public contact               | Oscar Corli, Mario Negri Institute for Pharmacological Research, oscar.corli@marionegri.it |
| Scientific contact           | Oscar Corli, Mario Negri Institute for Pharmacological Research, oscar.corli@marionegri.it |

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                       | 20 November 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 31 July 2014     |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

- The comparison of the analgesic efficacy of 4 treatment strategies based on 4 different strong opioids (oral morphine and oxycodone, transdermal fentanyl and buprenorphine) administered by randomization during a 4 weeks follow-up period, in patients with moderate to severe pain due to the cancer, measured at each visit by means of a NRS 0 to 10, and related to the average pain of the previous 24 hours.

Protection of trial subjects:

It was run according to the Declaration of Helsinki of Good Clinical Practice. Regulatory agencies and local ethics committees approved the study protocol. All patients gave written informed consent.

Background therapy:

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Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 31 May 2011 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 518 |
| Worldwide total number of subjects   | 518        |
| EEA total number of subjects         | 518        |

Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| 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)                      | 350 |
| From 65 to 84 years                       | 168 |

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

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted in 44 sites in Italy from May 2011 to July 2014.

### Pre-assignment

Screening details:

520 patients were randomized and 498 were included in ITT analysis

### Period 1

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

### Arms

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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Active comparator |
|------------------|-------------------|

Arm description:

Morphine

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

Dosage and administration details:

60 mg/day

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Experimental |
|------------------|--------------|

Arm description:

Oxycodone

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

Dosage and administration details:

40 mg/day

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Experimental |
|------------------|--------------|

Arm description:

Buprenorphine

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | Buprenorphine     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Transdermal patch |
| Routes of administration               | Transdermal use   |

Dosage and administration details:

35 µg/h

|                                        |                   |
|----------------------------------------|-------------------|
| <b>Arm title</b>                       | Experimental      |
| Arm description:                       |                   |
| Fentanyl                               |                   |
| Arm type                               | Experimental      |
| Investigational medicinal product name | Fentanyl          |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Transdermal patch |
| Routes of administration               | Transdermal use   |
| Dosage and administration details:     |                   |
| 25 µg/h                                |                   |

| <b>Number of subjects in period 1</b> | Active comparator | Experimental | Experimental |
|---------------------------------------|-------------------|--------------|--------------|
| Started                               | 130               | 130          | 130          |
| Completed                             | 122               | 125          | 127          |
| Not completed                         | 8                 | 5            | 3            |
| Never received treatment              | 1                 | 1            | -            |
| Lack of efficacy                      | 7                 | 4            | 3            |

| <b>Number of subjects in period 1</b> | Experimental |
|---------------------------------------|--------------|
| Started                               | 128          |
| Completed                             | 124          |
| Not completed                         | 4            |
| Never received treatment              | 4            |
| Lack of efficacy                      | -            |

## Baseline characteristics

### Reporting groups

|                                               |                   |
|-----------------------------------------------|-------------------|
| Reporting group title                         | Active comparator |
| Reporting group description:<br>Morphine      |                   |
| Reporting group title                         | Experimental      |
| Reporting group description:<br>Oxycodone     |                   |
| Reporting group title                         | Experimental      |
| Reporting group description:<br>Buprenorphine |                   |
| Reporting group title                         | Experimental      |
| Reporting group description:<br>Fentanyl      |                   |

| Reporting group values                                                                                                                                                                                                                                          | Active comparator | Experimental | Experimental |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------|--------------|
| Number of subjects                                                                                                                                                                                                                                              | 130               | 130          | 130          |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                              |                   |              |              |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                   |              |              |
| Age continuous<br>Units: years                                                                                                                                                                                                                                  |                   |              |              |
| arithmetic mean                                                                                                                                                                                                                                                 | 67.5              | 66.9         | 65.2         |
| standard deviation                                                                                                                                                                                                                                              | ± 11.7            | ± 11.1       | ± 13.5       |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                           |                   |              |              |
| Female                                                                                                                                                                                                                                                          | 59                | 56           | 60           |
| Male                                                                                                                                                                                                                                                            | 71                | 74           | 70           |

| Reporting group values                                                                                                                   | Experimental | Total            |  |
|------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------------|--|
| Number of subjects                                                                                                                       | 128          | 518              |  |
| Age categorical<br>Units: Subjects                                                                                                       |              |                  |  |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>months) |              | 0<br>0<br>0<br>0 |  |

|                           |        |     |  |
|---------------------------|--------|-----|--|
| Children (2-11 years)     |        | 0   |  |
| Adolescents (12-17 years) |        | 0   |  |
| Adults (18-64 years)      |        | 0   |  |
| From 65-84 years          |        | 0   |  |
| 85 years and over         |        | 0   |  |
| Age continuous            |        |     |  |
| Units: years              |        |     |  |
| arithmetic mean           | 68     |     |  |
| standard deviation        | ± 10.6 | -   |  |
| Gender categorical        |        |     |  |
| Units: Subjects           |        |     |  |
| Female                    | 56     | 231 |  |
| Male                      | 72     | 287 |  |

### Subject analysis sets

|                                                                                                                                                                                                                                                                                                        |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Subject analysis set title                                                                                                                                                                                                                                                                             | ITT analysis set   |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Intention-to-treat |
| Subject analysis set description:                                                                                                                                                                                                                                                                      |                    |
| the intention-to-treat (ITT) population, which included all randomized patients without major violations of the eligibility criteria and with at least one pain evaluation after baseline.                                                                                                             |                    |
| Subject analysis set title                                                                                                                                                                                                                                                                             | Safety             |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Safety analysis    |
| Subject analysis set description:                                                                                                                                                                                                                                                                      |                    |
| Only patients who started on opioid were included in the safety analysis, which considered patients in the arm of the treatment they actually received. Each patient was considered until the end of the 28-day follow-up, or until a switch or premature discontinuation of the study for any reason. |                    |

| Reporting group values                             | ITT analysis set | Safety |  |
|----------------------------------------------------|------------------|--------|--|
| Number of subjects                                 | 498              | 515    |  |
| Age categorical                                    |                  |        |  |
| Units: Subjects                                    |                  |        |  |
| In utero                                           |                  |        |  |
| Preterm newborn infants (gestational age < 37 wks) |                  |        |  |
| Newborns (0-27 days)                               |                  |        |  |
| Infants and toddlers (28 days-23 months)           |                  |        |  |
| Children (2-11 years)                              |                  |        |  |
| Adolescents (12-17 years)                          |                  |        |  |
| Adults (18-64 years)                               |                  |        |  |
| From 65-84 years                                   |                  |        |  |
| 85 years and over                                  |                  |        |  |
| Age continuous                                     |                  |        |  |
| Units: years                                       |                  |        |  |
| arithmetic mean                                    | 66.9             |        |  |
| standard deviation                                 | ± 11.8           | ±      |  |
| Gender categorical                                 |                  |        |  |
| Units: Subjects                                    |                  |        |  |
| Female                                             | 221              | 229    |  |
| Male                                               | 277              | 286    |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                             |                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                       | Active comparator  |
| Reporting group description:<br>Morphine                                                                                                                                                                                                                                                                                                    |                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                       | Experimental       |
| Reporting group description:<br>Oxycodone                                                                                                                                                                                                                                                                                                   |                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                       | Experimental       |
| Reporting group description:<br>Buprenorphine                                                                                                                                                                                                                                                                                               |                    |
| Reporting group title                                                                                                                                                                                                                                                                                                                       | Experimental       |
| Reporting group description:<br>Fentanyl                                                                                                                                                                                                                                                                                                    |                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                  | ITT analysis set   |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                   | Intention-to-treat |
| Subject analysis set description:<br>the intention-to-treat (ITT) population, which included all randomized patients without major violations of the eligibility criteria and with at least one pain evaluation after baseline.                                                                                                             |                    |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                  | Safety             |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                   | Safety analysis    |
| Subject analysis set description:<br>Only patients who started on opioid were included in the safety analysis, which considered patients in the arm of the treatment they actually received. Each patient was considered until the end of the 28-day follow-up, or until a switch or premature discontinuation of the study for any reason. |                    |

### Primary: Proportion of Non-Responder (NR) Participants

|                                                                                                                                                                                                                                                                                                                                                                                             |                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                             | Proportion of Non-Responder (NR) Participants |
| End point description:<br>Evaluation of the proportion of Non-Responder (NR) participants. NR correspond to the subjects who do not report any analgesic effects, with a P.I.D. (pain intensity difference) from visit 6 and visit 1 $\neq$ < 0%, (using a 0-10 NRS ). It includes the situations of average pain intensity "stable" or "worsened" at day 28 compared with baseline values. |                                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                              | Primary                                       |
| End point timeframe:<br>28 days                                                                                                                                                                                                                                                                                                                                                             |                                               |

| End point values            | Active comparator | Experimental    | Experimental    | Experimental    |
|-----------------------------|-------------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group   | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 122               | 125             | 127             | 124             |
| Units: Number of patients   | 14                | 18              | 14              | 11              |

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| End point values            | ITT analysis set     |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 498                  |  |  |  |

|                           |    |  |  |  |
|---------------------------|----|--|--|--|
| Units: Number of patients | 57 |  |  |  |
|---------------------------|----|--|--|--|

## Statistical analyses

|                                                                                                                                                                                                                         |                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                       | Primary analysis                                               |
| Statistical analysis description:<br>The $\chi^2$ test (or Fisher's exact test, where appropriate) was used to assess differences between oral oxycodone, TD buprenorphine or TD fentanyl, compared with oral morphine. |                                                                |
| Comparison groups                                                                                                                                                                                                       | Experimental v Experimental v Experimental v Active comparator |
| Number of subjects included in analysis                                                                                                                                                                                 | 498                                                            |
| Analysis specification                                                                                                                                                                                                  | Pre-specified                                                  |
| Analysis type                                                                                                                                                                                                           | superiority                                                    |
| P-value                                                                                                                                                                                                                 | < 0.05                                                         |
| Method                                                                                                                                                                                                                  | Chi-squared                                                    |
| Parameter estimate                                                                                                                                                                                                      | Proportion                                                     |
| Variability estimate                                                                                                                                                                                                    | Standard deviation                                             |

## Secondary: Proportion of Full-responder

|                                                                                                                                                                                                                               |                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| End point title                                                                                                                                                                                                               | Proportion of Full-responder |
| End point description:<br>Evaluation of the proportion of subjects who report full analgesia (full responders: FR). FR is operationally defined as a patient with a P.I.D. $\geq$ 30% from visit 6 and visit 1 (NRS 0 to 10). |                              |
| End point type                                                                                                                                                                                                                | Secondary                    |
| End point timeframe:<br>28 days                                                                                                                                                                                               |                              |

| End point values            | Active comparator | Experimental    | Experimental    | Experimental    |
|-----------------------------|-------------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group   | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 122               | 125             | 127             | 124             |
| Units: Number of patients   | 89                | 90              | 95              | 88              |

| End point values            | ITT analysis set     |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 498                  |  |  |  |
| Units: Number of patients   | 362                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: The Opioid Escalation Index

|                 |                             |
|-----------------|-----------------------------|
| End point title | The Opioid Escalation Index |
|-----------------|-----------------------------|

End point description:

The proportion of subjects with an increase of opioid daily dose > 5% compared with the basal dosage (OEI%).

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

End point timeframe:

28 days

| End point values              | Active comparator | Experimental    | Experimental    | Experimental    |
|-------------------------------|-------------------|-----------------|-----------------|-----------------|
| Subject group type            | Reporting group   | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed   | 122               | 125             | 127             | 124             |
| Units: Number of participants | 13                | 24              | 18              | 45              |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

4 weeks

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

### Dictionary used

|                 |    |
|-----------------|----|
| Dictionary name | NA |
|-----------------|----|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Adverse events |
|-----------------------|----------------|

Reporting group description: -

| Serious adverse events                               | Adverse events   |  |  |
|------------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events    |                  |  |  |
| subjects affected / exposed                          | 12 / 515 (2.33%) |  |  |
| number of deaths (all causes)                        | 0                |  |  |
| number of deaths resulting from adverse events       |                  |  |  |
| Nervous system disorders                             |                  |  |  |
| Hyperalgesia                                         |                  |  |  |
| subjects affected / exposed                          | 1 / 515 (0.19%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| General disorders and administration site conditions |                  |  |  |
| Exitus                                               |                  |  |  |
| subjects affected / exposed                          | 1 / 515 (0.19%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 1 / 1            |  |  |
| Decline general condition                            |                  |  |  |
| subjects affected / exposed                          | 2 / 515 (0.39%)  |  |  |
| occurrences causally related to treatment / all      | 2 / 2            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Hyperpirexia                                         |                  |  |  |
| subjects affected / exposed                          | 2 / 515 (0.39%)  |  |  |
| occurrences causally related to treatment / all      | 2 / 2            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Gastrointestinal disorders                      |                 |  |  |
| Bowel occlusion                                 |                 |  |  |
| subjects affected / exposed                     | 2 / 515 (0.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oral cavity bleeding                            |                 |  |  |
| subjects affected / exposed                     | 1 / 515 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Asthenia                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 515 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Hepatic disorder                                |                 |  |  |
| subjects affected / exposed                     | 1 / 515 (0.19%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Dyspnea                                         |                 |  |  |
| subjects affected / exposed                     | 2 / 515 (0.39%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atelectasis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 515 (0.19%) |  |  |
| 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>                     | Adverse events     |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 404 / 515 (78.45%) |  |  |
| General disorders and administration site conditions  |                    |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| Drowsiness                  |                    |  |  |
| subjects affected / exposed | 304 / 515 (59.03%) |  |  |
| occurrences (all)           | 1                  |  |  |
| Confusional state           |                    |  |  |
| subjects affected / exposed | 221 / 515 (42.91%) |  |  |
| occurrences (all)           | 1                  |  |  |

## 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? Yes

| Date         | Interruption                                                                                                                                                                                                              | Restart date |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 31 July 2014 | In September 2014, in view of the disappointing recruitment, the Steering Committee decided to early stop enrollment, fully aware that the study could lose the power to test the planned differences between treatments. | -            |

Notes:

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26940689>

<http://www.ncbi.nlm.nih.gov/pubmed/29220110>