



## Clinical trial results:

**A multi-centre, open-label, single therapy, dose ranging study to characterise the pharmacokinetics and tolerability of BTDS 5-20 g/h in children who require opioid analgesia for moderate to severe mouth pain secondary to chemotherapy induced mucositis**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2008-002428-27  |
| Trial protocol           | GB DK           |
| Global end of trial date | 21 October 2012 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 30 December 2016 |
| First version publication date | 30 December 2016 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BUP1501 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00947466 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Mundipharma Research Ltd.  |
| Sponsor organisation address | 194-198 Cambridge Science Park, Cambridge, United Kingdom, CB4 0GW                                       |
| Public contact               | Mundipharma Research Ltd., European Medical Operations, +44 1223424900, info@contact-clinical-trials.com |
| Scientific contact           | Mundipharma Research Ltd., European Medical Operations, +44 1223424900, info@contact-clinical-trials.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? | Yes |

Notes:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 21 October 2012 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 21 October 2012 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 21 October 2012 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

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**General information about the trial**

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Main objective of the trial:

To characterise the pharmacokinetics of BTDS 5-20 µg/h in children.

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Protection of trial subjects:

Approximately 15 subjects weighing  $\geq 25$ kg were to be recruited in the first phase of the study. The data obtained from these subjects were reviewed by an IDSMC. If the IDSMC was satisfied that there are no significant safety concerns then approximately 15 further subjects were to be recruited weighing  $\geq 25$ kg and approximately 30 further subjects were to be recruited weighing  $\geq 15$ kg and  $< 25$ kg.

Changed To: Approximately 15 subjects weighing  $\geq 10$ kg will be recruited in the first phase of the study. The data obtained from these subjects will be reviewed by an IDSMC. If the IDSMC is satisfied that there are no significant safety concerns then recruitment will continue. [Protocol amendment number 4, 12 Apr 2010, (UK) and number 2, 05 May 2010, (DK)].

Addition: The IDSMC will also review the data after approximately 15 further subjects weighing  $\geq 12$ kg have been recruited. [Protocol amendment number 5, 04 Jul 2011, (UK) and number 3, 27 Jul 2011, (DK)].

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Background therapy:

On Day 1 subjects were allowed rescue doses of morphine to treat any breakthrough pain. Each rescue dose should not have exceeded 1/6th of the total daily morphine dose.

On Days 2-3 it was recommended that any rescue dose was 1/12th of the total daily morphine dose. If this failed to control the pain and further rescue doses were required they could be increased to 1/6th of the total daily morphine dose.

From Day 4 onwards when the maximum effect of buprenorphine was likely to be established, a continuous infusion of morphine should have been commenced for any subjects who required more than 3 rescue doses in the previous 24 hours. The total continuous infusion over 24 hours should have been equivalent to the total dose of morphine received as rescue analgesia in the previous 24 hour period. For subsequent days (including post patch removal), the continuous infusion may have been adjusted according to the clinical impression of the mucositis, pain scores, opioid side effects and the requirements for additional rescue doses.

On Day 8 when the patch was removed, if required, a continuous morphine infusion could have been commenced at 0.01mg/kg/hour and reduced by 50% on Day 8. Rescue doses of PO or IV morphine could have been used throughout the follow up period to treat any breakthrough pain at 1/6th of the total daily morphine dose.

All doses of supplementary medication (date, time, and dose) were recorded in the CRF. Any changes in concomitant medication were recorded throughout the study.

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Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 06 February 2010 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Worldwide total number of subjects   | 25                 |
| EEA total number of subjects         | 25                 |

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)  | 1  |
| Children (2-11 years)                     | 15 |
| Adolescents (12-17 years)                 | 9  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

All 25 subjects were enrolled in one site in the UK between 25 Feb 2010 and 10 Oct 2012.

### Pre-assignment

Screening details:

A total of 28 subjects provided written informed consent and were screened. 3 subjects failed screening and so 25 subjects were entered the study. Of these, 18 subjects completed and 7 discontinued. The primary reasons for discontinuation were adverse events (1 subject), subject's choice (4 subjects) and lack of therapeutic effect (2 subjects).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (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>             | Weight <25kg |

Arm description:

Subjects weighing  $\geq 10$ kg and <25kg

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

Dosage and administration details:

The study used buprenorphine patches (BTDS) 5mg (5  $\mu$ g/h), 10mg (10  $\mu$ g/h) and 20mg (20  $\mu$ g/h). The dose was determined by subject weight. The nearest available patch size/combination of patches was used. The patch was applied to the upper back region (shoulder blade area) and subjects wore the same patch continuously for 7 days.

Subject weight:

$\geq 10$ kg to <20kg - 5  $\mu$ g/h

$\geq 20$ kg to <30kg - 10  $\mu$ g/h

$\geq 30$ kg to <40kg - 10  $\mu$ g/h + 5  $\mu$ g/h

$\geq 40$ kg - 20  $\mu$ g/h

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Weight $\geq 25$ kg |
|------------------|---------------------|

Arm description:

Subjects weighing  $\geq 25$ kg

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

Dosage and administration details:

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Subject weight:

$\geq 10$ kg to <20kg - 5  $\mu$ g/h

≥20kg to <30kg - 10 µg/h  
 ≥30kg to <40kg - 10 µg/h + 5 µg/h  
 ≥40kg - 20 µg/h

| <b>Number of subjects in period 1</b> | Weight <25kg | Weight ≥25kg |
|---------------------------------------|--------------|--------------|
| Started                               | 7            | 18           |
| Completed                             | 6            | 12           |
| Not completed                         | 1            | 6            |
| Consent withdrawn by subject          | 1            | 3            |
| Adverse event, non-fatal              | -            | 1            |
| Lack of efficacy                      | -            | 2            |

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Weight <25kg |
|-----------------------|--------------|

Reporting group description:

Subjects weighing ≥10kg and <25kg

|                       |              |
|-----------------------|--------------|
| Reporting group title | Weight ≥25kg |
|-----------------------|--------------|

Reporting group description:

Subjects weighing ≥25kg

| Reporting group values                             | Weight <25kg | Weight ≥25kg | Total |
|--|--------------|--------------|-------|
| Number of subjects                                 | 7            | 18           | 25    |
| Age categorical                                    |              |              |       |
| Units: Subjects                                    |              |              |       |
| In utero   | 0            | 0            | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0            | 0            | 0     |
| Newborns (0-27 days)                               | 0            | 0            | 0     |
| Infants and toddlers (28 days-23 months)           | 1            | 0            | 1     |
| Children (2-11 years)                              | 6            | 9            | 15    |
| Adolescents (12-17 years)                          | 0            | 9            | 9     |
| Adults (18-64 years)                               | 0            | 0            | 0     |
| From 65-84 years                                   | 0            | 0            | 0     |
| 85 years and over                                  | 0            | 0            | 0     |
| Age continuous                                     |              |              |       |
| Units: years                                       |              |              |       |
| arithmetic mean                                    | 4            | 11.1         |       |
| standard deviation                                 | ± 2          | ± 3.03       | -     |
| Gender categorical                                 |              |              |       |
| Units: Subjects                                    |              |              |       |
| Female   | 3            | 7            | 10    |
| Male   | 4            | 11           | 15    |
| Race   |              |              |       |
| Units: Subjects                                    |              |              |       |
| Caucasian  | 4            | 17           | 21    |
| Black  | 2            | 1            | 3     |
| Asian  | 1            | 0            | 1     |
| Weight   |              |              |       |
| Units: kg  |              |              |       |
| arithmetic mean                                    | 16.5         | 39.4         |       |
| standard deviation                                 | ± 4.79       | ± 11.19      | -     |
| Height   |              |              |       |
| Units: cm  |              |              |       |
| arithmetic mean                                    | 97.5         | 149.6        |       |
| standard deviation                                 | ± 14.39      | ± 15.62      | -     |

## End points

### End points reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Weight <25kg |
| Reporting group description:<br>Subjects weighing ≥10kg and <25kg |              |
| Reporting group title   | Weight ≥25kg |
| Reporting group description:<br>Subjects weighing ≥25kg           |              |

### Primary: Buprenorphine AUCt

|  |                    |
|--|--------------------|
| End point title  | Buprenorphine AUCt |
| End point description:<br>Buprenorphine AUCt values were determined from plasma buprenorphine concentrations measured from the time of dosing to the last measurable concentration.  |                    |
| End point type   | Primary            |
| End point timeframe:<br>Blood samples (2 mL each sample) for pharmacokinetic assessments were drawn at the following times 0h (before patch application), 24h, 48h, 72h, 96h, 120h, 144h, 168h (before patch removal), 192h, 216h, 240h, 264h. |                    |

| End point values                                    | Weight <25kg    | Weight ≥25kg    |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed                         | 7               | 18              |  |  |
| Units: pg.h/mL                                      |                 |                 |  |  |
| geometric mean (geometric coefficient of variation) | 21100.52 (± 95) | 34475.01 (± 56) |  |  |

### Statistical analyses

|   |                                   |
|---|-----------------------------------|
| Statistical analysis title  | Weight <25kg versus Weight ≥ 25kg |
| Statistical analysis description:<br>Dose adjusted area under the plasma concentration-time curve (AUCt/D) values were compared between weight groups (test versus reference, where the reference dose was Weight ≥ 25 kg) using an analysis of variance (ANOVA) with fixed terms for weight group (if applicable) on the logarithmic-transformed values. |                                   |
| Comparison groups   | Weight <25kg v Weight ≥25kg       |
| Number of subjects included in analysis   | 25                                |
| Analysis specification  | Pre-specified                     |
| Analysis type   | equivalence                       |
| Parameter estimate  | Ratio (%) (Test/Reference)        |
| Point estimate  | 172.7                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 103.69  |
| upper limit         | 287.65  |

### Primary: Buprenorphine Cmax

|  |                    |
|--|--------------------|
| End point title  | Buprenorphine Cmax |
| End point description:<br>Buprenorphine Cmax values were determined from plasma buprenorphine concentrations measured from the time of dosing to the last measurable concentration.  |                    |
| End point type   | Primary            |
| End point timeframe:<br>Blood samples (2 mL each sample) for pharmacokinetic assessments were drawn at the following times 0h (before patch application), 24h, 48h, 72h, 96h, 120h, 144h, 168h (before patch removal), 192h, 216h, 240h, 264h. |                    |

| End point values                                    | Weight <25kg    | Weight ≥25kg    |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed                         | 7               | 18              |  |  |
| Units: pg/mL  |                 |                 |  |  |
| geometric mean (geometric coefficient of variation) | 175.5 (± 70)    | 325.4 (± 40)    |  |  |

### Statistical analyses

|  |                                  |
|--|----------------------------------|
| Statistical analysis title   | Weight <25kg versus Weight ≥25kg |
| Statistical analysis description:<br>Dose adjusted maximum observed concentration (Cmax/D) values were compared between weight groups (test versus reference, where the reference dose was Weight ≥25 kg) using an analysis of variance (ANOVA) with fixed terms for weight group (if applicable) on the logarithmic-transformed values. |                                  |
| Comparison groups  | Weight <25kg v Weight ≥25kg      |
| Number of subjects included in analysis  | 25                               |
| Analysis specification   | Pre-specified                    |
| Analysis type  | equivalence                      |
| Parameter estimate   | Ratio (%) (Test/Reference)       |
| Point estimate   | 152.19                           |
| Confidence interval  |                                  |
| level  | 90 %                             |
| sides  | 2-sided                          |
| lower limit  | 104.24                           |
| upper limit  | 222.2                            |





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from the time a subject provided their informed consent at screening until 14 days after the subject's completion/discontinuation visit.

Adverse event reporting additional description:

Any AE that was still ongoing 14 days after the completion/discontinuation visit had an end date of 'ongoing' in the CRF, however the Investigator continued to follow up ongoing AEs and record information in the source documents.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Weight <25kg |
|-----------------------|--------------|

Reporting group description:

Subjects weighing ≥10kg and <25kg

|                       |              |
|-----------------------|--------------|
| Reporting group title | Weight ≥25kg |
|-----------------------|--------------|

Reporting group description:

Subjects weighing ≥25kg

| Serious adverse events                            | Weight <25kg   | Weight ≥25kg    |  |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events |                |                 |  |
| subjects affected / exposed                       | 2 / 7 (28.57%) | 4 / 18 (22.22%) |  |
| number of deaths (all causes)                     | 1              | 0               |  |
| number of deaths resulting from adverse events    | 0              | 0               |  |
| Investigations                                    |                |                 |  |
| Blood pressure increased                          |                |                 |  |
| subjects affected / exposed                       | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0           |  |
| Oxygen saturation decreased                       |                |                 |  |
| subjects affected / exposed                       | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences causally related to treatment / all   | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                          |                |                 |  |
| Encephalopathy                                    |                |                 |  |
| subjects affected / exposed                       | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0           |  |

|  |                |                |  |
|--|----------------|----------------|--|
| Blood and lymphatic system disorders                 |                |                |  |
| Neutrophenia   |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Therapeutic response decreased                       |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Eye disorders  |                |                |  |
| Miosis   |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                           |                |                |  |
| Pancreatitis   |                |                |  |
| subjects affected / exposed                          | 1 / 7 (14.29%) | 0 / 18 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Infections and infestations                          |                |                |  |
| Aspergillosis  |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Bacteraemia  |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Infection  |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Pneumonia influenzal                                 |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 18 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Viral infection                                 |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Weight <25kg    | Weight ≥25kg      |  |
|---|-----------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                 |                   |  |
| subjects affected / exposed                           | 7 / 7 (100.00%) | 18 / 18 (100.00%) |  |
| Vascular disorders                                    |                 |                   |  |
| Hypertension  |                 |                   |  |
| subjects affected / exposed                           | 0 / 7 (0.00%)   | 2 / 18 (11.11%)   |  |
| occurrences (all)                                     | 0               | 2                 |  |
| Hypotension   |                 |                   |  |
| subjects affected / exposed                           | 1 / 7 (14.29%)  | 5 / 18 (27.78%)   |  |
| occurrences (all)                                     | 1               | 8                 |  |
| Pallor  |                 |                   |  |
| subjects affected / exposed                           | 0 / 7 (0.00%)   | 2 / 18 (11.11%)   |  |
| occurrences (all)                                     | 0               | 2                 |  |
| General disorders and administration site conditions  |                 |                   |  |
| Application site discomfort                           |                 |                   |  |
| subjects affected / exposed                           | 0 / 7 (0.00%)   | 1 / 18 (5.56%)    |  |
| occurrences (all)                                     | 0               | 1                 |  |
| Application site erythema                             |                 |                   |  |
| subjects affected / exposed                           | 0 / 7 (0.00%)   | 2 / 18 (11.11%)   |  |
| occurrences (all)                                     | 0               | 2                 |  |
| Application site pain                                 |                 |                   |  |
| subjects affected / exposed                           | 0 / 7 (0.00%)   | 1 / 18 (5.56%)    |  |
| occurrences (all)                                     | 0               | 1                 |  |
| Application site pruritus                             |                 |                   |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 7 (0.00%)  | 2 / 18 (11.11%) |
| occurrences (all)           | 0              | 2               |
| Chest pain                  |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 1               |
| Chills                      |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 1               |
| Crepitations                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 1               |
| Device occlusion            |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 3               |
| Face oedema                 |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Fatigue                     |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Gait disturbance            |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 1               |
| Mucosal inflammation        |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Oedema                      |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)           | 0              | 1               |
| Oedema peripheral           |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Pain                        |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 18 (5.56%)  |
| occurrences (all)           | 1              | 1               |
| Pyrexia                     |                |                 |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 7 (14.29%)<br>2 | 3 / 18 (16.67%)<br>4 |  |
| Therapeutic response decreased<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Immune system disorders<br>Aspergillosis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>5  |  |
| Respiratory, thoracic and mediastinal disorders<br>Choking<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)  | 1 / 7 (14.29%)<br>1 | 2 / 18 (11.11%)<br>2 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 7 (42.86%)<br>4 | 1 / 18 (5.56%)<br>1  |  |
| Pulmonary oedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Respiratory distress<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 7 (14.29%)<br>1 | 0 / 18 (0.00%)<br>0  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Psychiatric disorders<br>Agitation<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 7 (14.29%)<br>1 | 0 / 18 (0.00%)<br>0  |  |
| Anxiety  |                     |                      |  |

|                                    |                |                 |  |
|------------------------------------|----------------|-----------------|--|
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Confusional state                  |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Personality Change                 |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Investigations                     |                |                 |  |
| Alanine aminotransferase increased |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Blood bilirubin increased          |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Blood magnesium decreased          |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 2 / 18 (11.11%) |  |
| occurrences (all)                  | 0              | 2               |  |
| Blood phosphorus increased         |                |                 |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                  | 1              | 0               |  |
| Blood potassium decreased          |                |                 |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 2 / 18 (11.11%) |  |
| occurrences (all)                  | 1              | 3               |  |
| Blood potassium increased          |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Blood pressure increased           |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Blood sodium decreased             |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |
| Blood triglycerides increased      |                |                 |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                  | 0              | 1               |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Drug level increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Fungal test positive<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 7 (14.29%)<br>2 | 4 / 18 (22.22%)<br>5 |  |
| International normalised ratio increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Oxygen saturation decreased<br>subjects affected / exposed<br>occurrences (all)              | 1 / 7 (14.29%)<br>3 | 3 / 18 (16.67%)<br>4 |  |
| PcO2 increased<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Ph urine decreased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Platelet Count decreased<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 7 (14.29%)<br>2 | 3 / 18 (16.67%)<br>3 |  |
| Stool analysis normal<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Weight increased   |                     |                      |  |



|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1 | 1 / 18 (5.56%)<br>1 |  |
| Injury, poisoning and procedural complications   |                     |                     |  |
| Contusion  |                     |                     |  |
| subjects affected / exposed                      | 1 / 7 (14.29%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Excoriation                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Fall   |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Limb injury                                      |                     |                     |  |
| subjects affected / exposed                      | 1 / 7 (14.29%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Cardiac disorders                                |                     |                     |  |
| Bradycardia                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Left ventricular dysfunction                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Nervous system disorders                         |                     |                     |  |
| Aphasia  |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Balance disorder                                 |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Dizziness  |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Dysarthria                                       |                     |                     |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Dyskinesia                                       |                     |                     |  |

|                                      |                |                 |  |
|--------------------------------------|----------------|-----------------|--|
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Encephalopathy                       |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Headache                             |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 2               |  |
| Hypoaesthesia                        |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Incoherent                           |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Neuropathy peripheral                |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Somnolence                           |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 2 / 18 (11.11%) |  |
| occurrences (all)                    | 0              | 2               |  |
| Tremor                               |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Blood and lymphatic system disorders |                |                 |  |
| Anaemia                              |                |                 |  |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                    | 0              | 1               |  |
| Coagulopathy                         |                |                 |  |
| subjects affected / exposed          | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                    | 1              | 0               |  |
| Febrile neutropenia                  |                |                 |  |
| subjects affected / exposed          | 4 / 7 (57.14%) | 3 / 18 (16.67%) |  |
| occurrences (all)                    | 4              | 3               |  |
| Neutropenia                          |                |                 |  |
| subjects affected / exposed          | 1 / 7 (14.29%) | 2 / 18 (11.11%) |  |
| occurrences (all)                    | 1              | 2               |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Ear and labyrinth disorders  |                     |                      |  |
| Cerumen impaction<br>subjects affected / exposed<br>occurrences (all)          | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Tympanic membrane disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Eye disorders  |                     |                      |  |
| Eye oedema<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Eye pruritus<br>subjects affected / exposed<br>occurrences (all)               | 1 / 7 (14.29%)<br>1 | 1 / 18 (5.56%)<br>2  |  |
| Miosis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 7 (14.29%)<br>1 | 2 / 18 (11.11%)<br>2 |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)             | 0 / 7 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Gastrointestinal disorders   |                     |                      |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)             | 2 / 7 (28.57%)<br>2 | 5 / 18 (27.78%)<br>6 |  |
| Abdominal pain upper   |                     |                      |  |

|                               |                |                 |
|-------------------------------|----------------|-----------------|
| subjects affected / exposed   | 1 / 7 (14.29%) | 1 / 18 (5.56%)  |
| occurrences (all)             | 1              | 2               |
| Constipation                  |                |                 |
| subjects affected / exposed   | 3 / 7 (42.86%) | 3 / 18 (16.67%) |
| occurrences (all)             | 4              | 3               |
| Diarrhoea                     |                |                 |
| subjects affected / exposed   | 4 / 7 (57.14%) | 5 / 18 (27.78%) |
| occurrences (all)             | 8              | 8               |
| Gastrointestinal inflammation |                |                 |
| subjects affected / exposed   | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |
| occurrences (all)             | 1              | 0               |
| Haematemesis                  |                |                 |
| subjects affected / exposed   | 1 / 7 (14.29%) | 2 / 18 (11.11%) |
| occurrences (all)             | 1              | 4               |
| Haematochezia                 |                |                 |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               |
| Ileus paralytic               |                |                 |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               |
| Lip dry                       |                |                 |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               |
| Lip swelling                  |                |                 |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               |
| Loose tooth                   |                |                 |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               |
| Mouth ulceration              |                |                 |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |
| occurrences (all)             | 0              | 1               |
| Nausea                        |                |                 |
| subjects affected / exposed   | 1 / 7 (14.29%) | 5 / 18 (27.78%) |
| occurrences (all)             | 1              | 5               |
| Oesophagitis                  |                |                 |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Pancreatitis                           |                |                 |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Proctalgia                             |                |                 |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Rectal haemorrhage                     |                |                 |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Retching                               |                |                 |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Tongue Coated                          |                |                 |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Vomiting                               |                |                 |  |
| subjects affected / exposed            | 3 / 7 (42.86%) | 6 / 18 (33.33%) |  |
| occurrences (all)                      | 5              | 7               |  |
| Hepatobiliary disorders                |                |                 |  |
| Hepatomegaly                           |                |                 |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Skin and subcutaneous tissue disorders |                |                 |  |
| Acne                                   |                |                 |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Decubitus ulcer                        |                |                 |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Dry skin                               |                |                 |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 2 / 18 (11.11%) |  |
| occurrences (all)                      | 0              | 3               |  |
| Excessive granulation tissue           |                |                 |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Livedo reticularis          |                |                 |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 1              | 1               |  |
| Pain of skin                |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Pruritus                    |                |                 |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 4 / 18 (22.22%) |  |
| occurrences (all)           | 1              | 5               |  |
| Rash                        |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Rash generalised            |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Rash macular                |                |                 |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Skin depigmentation         |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Skin discolouration         |                |                 |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Swelling face               |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Renal and urinary disorders |                |                 |  |
| Haematuria                  |                |                 |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 1              | 1               |  |
| Renal impairment            |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Endocrine disorders                             |                |                 |  |
| Precocious puberty                              |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Arthralgia                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Back pain                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Limb discomfort                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Muscular weakness                               |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Pain in extremity                               |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 2 / 18 (11.11%) |  |
| occurrences (all)                               | 0              | 4               |  |
| Upper extremity mass                            |                |                 |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                               | 1              | 0               |  |
| Infections and infestations                     |                |                 |  |
| Bacteraemia                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Catheter site infection                         |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Device related infection                        |                |                 |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Herpes zoster                                   |                |                 |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                               | 1              | 0               |  |

|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| Infection                          |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Oral Candidiasis                   |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Pneumonia                          |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Pneumonia influenzal               |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 18 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Rhinitis                           |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Stenotrophomonas infection         |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 18 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Streptococcal sepsis               |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 18 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Varicella                          |                |                |  |
| subjects affected / exposed        | 1 / 7 (14.29%) | 0 / 18 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Viral infection                    |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Vulvovaginal Candidiasis           |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Metabolism and nutrition disorders |                |                |  |
| Decreased appetite                 |                |                |  |
| subjects affected / exposed        | 0 / 7 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Dehydration                        |                |                |  |



|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Hypernatraemia              |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Hypokalaemia                |                |                 |  |
| subjects affected / exposed | 3 / 7 (42.86%) | 5 / 18 (27.78%) |  |
| occurrences (all)           | 4              | 7               |  |
| Hypophagia                  |                |                 |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 1              | 1               |  |
| Vitamin D deficiency        |                |                 |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)           | 0              | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 19 September 2008 | <p>Provides guidance with respect to the number of days the subjects need to remain as inpatients. All subjects need to remain as inpatients until patch removal (Day 8). From Day 8 to Day 12, subjects do not need to be inpatients as long as they return daily for assessments. PCO2 and oxygen saturation monitoring will be continuous up until Day 8.</p> <p>Provides further guidance that blood samples can now be taken from a central line as well as an indwelling cannula.</p> <p>Clarifies that hospitals can use their own internal protocol with respect to the use of Naloxone Hydrochloride.</p>  |
| 20 February 2009  | <p>Addresses the fact that after discussions with the Medicines for Children Research Network (MCRN), it was decided that recruitment would only be open to subjects weighing <math>\geq 15\text{kg}</math>. The study will now be conducted in two phases with subjects weighing <math>\geq 25\text{kg}</math> being recruited in the first phase of the study. The data obtained from these subjects will then be reviewed by an Independent Data and Safety Monitoring Committee (IDSMC). If the IDSMC is satisfied that there are no significant safety concerns, subjects weighing <math>\geq 15\text{kg}</math> and <math>&lt; 25\text{kg}</math> will then be included in the second phase of the study. This approach also leads to slight changes in dose being administered for safety purposes.</p> <p>As this study will now be only conducted in children weighing <math>\geq 15\text{kg}</math>, this leads to a change in study title. The study title now is:</p> <p>BUP1501: A multi-centre, open-label, single therapy, dose ranging study to characterise the pharmacokinetics and tolerability of BTDS 5-20 <math>\mu\text{g/h}</math> in children who require opioid analgesia for severe mouth pain secondary to chemotherapy induced mucositis</p> <p>Also addresses the fact that the original protocol was not clear that the capnography was mandatory and continuous for the whole time that the subject had the patch applied, so this has been re-worded.</p> <p>Recommends that the patch is positioned on/near the subject's shoulder blade and that the patch can be removed if it is felt the subject has achieved adequate pain control</p> |

|               |  |
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| 21 April 2009 | <p>Addresses the fact that 7-day buprenorphine transdermal system has a changed therapeutic indication in adults and is now indicated for the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia. After extensive discussions with Dr Richard Hain (Principal Investigator) and the Danish Regulatory Authorities (DKMA) who act as the reference Member State for BuTrans, it was felt that this study would benefit from assessing whether any children entering the study had moderate to severe pain. There would be no change in the study design; the FLACC or FPS (R) pain scales will be utilised in the same manner and the pain score on entry will be used as a baseline pain score. These pain scores would be reviewed to see if some children classified their pain as moderate rather than severe. Although we expect the majority of children suffering oral mucositis to experience severe pain we know that pain is very subjective and some may report moderate pain and this would give us the opportunity to characterise the pharmacokinetics in moderate to severe pain.</p> <p>As this study will now be conducted in children with moderate to severe pain, this leads to a change in study title. The study title now is:</p> <p>BUP1501: A multi-centre, open-label, single therapy, dose ranging study to characterise the pharmacokinetics and tolerability of BTDS 5-20 µg/h in children who require opioid analgesia for moderate to severe mouth pain secondary to chemotherapy induced mucositis</p> <p>Also addresses some omissions from amendment number 2. In amendment number 2, all references to "age group" should have been changed to "weight group", however some of these were omitted erroneously.</p> |
| 12 April 2010 | <p>Instigated after a meeting with Dr Richard Hain (Chief Investigator), Dr Richard Howard (Principal Investigator, Great Ormond Street Hospital, UK) and representatives from the Medicines for Children Research Network, UK.</p> <p>It was discussed and agreed that subjects weighing <math>\geq 10\text{kg}</math> could safely be recruited into the study (current weight limit <math>\geq 15\text{kg}</math>) and that subjects of any weight could be recruited initially (currently recruiting only subjects weighing <math>\geq 25\text{kg}</math>). It was felt by all of the clinicians present that neither of these two changes would compromise subject safety.</p> <p>It was also decided that the measurement of PCO<sub>2</sub> and oxygen saturation levels during the study would be discretionary as this intervention was not normally part of clinical practice in these subjects.</p>   |

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| 04 July 2011      | <p>Instigated following the meeting of the Independent Data Monitoring Committee (IDSMC) on 01 July 2011.</p> <p>Following an interim whole statistics analysis, 2 out of 15 patients were identified as having buprenorphine AUCt values of 87.5 and 85.3 ng.h/mL, which are above the guideline limits set out in the protocol. Guidelines for the IDMC are to recommend stopping the study if any subject has an AUCt measure of buprenorphine greater than 82 ng.h/mL.</p> <p>It was therefore decided by the sponsor on the 20 April 2011 to put recruitment on hold until the IDSMC had convened to review the interim safety data and pharmacokinetic exposure profile and make a recommendation on whether the study should continue in its current design.</p> <p>The IDSMC suggested the following modifications to the protocol, which form the basis of this amendment:</p> <ul style="list-style-type: none"> <li>• Increase the lower age limit to 2 years</li> <li>• Increase the lower weight limit to 12 kg</li> <li>• Increase the AUCt safety threshold recommendation for the IDMC, based on data from more recent healthy volunteer studies (increased to greater than 156 ng.h/mL).</li> <li>• Recommend that when a patient is immobile such as in a high dependency unit or PICU that an alternative patch site (above the abdomen) could be considered</li> <li>• If the Investigator feels it is appropriate to use a different strength of patch from the recommended dose, then this is allowable (especially if the subject has a weight close to the lower limits of the dose)</li> <li>• A further meeting of the IDSMC to be convened after the next 15 patients have been recruited with the revised protocol</li> </ul> <p>The risk benefit document has been updated with the above information and there is considered to be no change to the risk benefit profile for the IMP.</p> |
| 06 September 2011 | <p>Instigated following a recommendation from the UK Ethics Committee (letter dated 15 August 2011).</p> <p>Further guidance has been included in the protocol regarding how close to the lower weight limit a child should be in order to allow the clinician to exercise their discretion to change to a lower dose.</p>  |

Notes:

## 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.

This trial was prematurely discontinued after only 25 of the 60 planned subjects were enrolled due to recruitment issues. However, it was agreed that further recruitment into this study would not have added any meaningful information.

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