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:

Results analysis stage

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:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Approximately 15 subjects weighing ≥25kg 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 ≥25kg and approximately 30 further subjects were to be recruited weighing ≥15kg and <25kg.
Changed To: Approximately 15 subjects weighing ≥10kg 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 ≥12kg have been recruited. [Protocol amendment number 5, 04 Jul 2011, (UK) and number 3, 27 Jul 2011, (DK)].

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.

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:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	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
Arm title	Weight <25kg

Arm description:

Subjects weighing ≥10kg 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 µg/h), 10mg (10 µg/h) and 20mg (20 µg/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:
≥10kg to <20kg - 5 µg/h
≥20kg to <30kg - 10 µg/h
≥30kg to <40kg - 10 µg/h + 5 µg/h
≥40kg - 20 µg/h

Arm title	Weight ≥25kg

Arm description:

Subjects weighing ≥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:

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Subject weight:
≥10kg to <20kg - 5 µg/h

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

Number of subjects in period 1	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:	
Subjects weighing ≥10kg and <25kg	
Reporting group title	Weight ≥25kg
Reporting group description:	
Subjects weighing ≥25kg	

Primary: Buprenorphine AUCt	
End point title	Buprenorphine AUCt
End point description:	
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:	
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:	
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:

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:

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:

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 %

Non-serious adverse events	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	1 / 7 (14.29%)	3 / 18 (16.67%)	
occurrences (all)	2	4	
Therapeutic response decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Immune system disorders			
Aspergillosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 7 (14.29%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	3 / 7 (42.86%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Pulmonary oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory distress			
subjects affected / exposed	1 / 7 (14.29%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 18 (0.00%)	
occurrences (all)	1	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				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Drug level increased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Fungal test positive				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Haemoglobin decreased				
subjects affected / exposed	1 / 7 (14.29%)	4 / 18 (22.22%)		
occurrences (all)	2	5		
International normalised ratio increased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Oxygen saturation decreased				
subjects affected / exposed	1 / 7 (14.29%)	3 / 18 (16.67%)		
occurrences (all)	3	4		
PcO2 increased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Ph urine decreased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Platelet Count decreased				
subjects affected / exposed	1 / 7 (14.29%)	3 / 18 (16.67%)		
occurrences (all)	2	3		
Stool analysis normal				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Weight decreased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Weight increased				

subjects affected / exposed	1 / 7 (14.29%)	1 / 18 (5.56%)	
occurrences (all)	1	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			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Tympanic membrane disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eye disorders			
Eye oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	1 / 7 (14.29%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Miosis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Ocular hyperaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	5 / 18 (27.78%)	
occurrences (all)	2	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	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. Provides further guidance that blood samples can now be taken from a central line as well as an indwelling cannula. Clarifies that hospitals can use their own internal protocol with respect to the use of Naloxone Hydrochloride.
20 February 2009	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 ≥15kg. The study will now be conducted in two phases with subjects weighing ≥25kg 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 ≥15kg and <25kg 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. As this study will now be only conducted in children weighing ≥15kg, this leads to a change in study title. The study title now is: 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 severe mouth pain secondary to chemotherapy induced mucositis 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. 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

21 April 2009	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. 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: 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 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.
12 April 2010	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. It was discussed and agreed that subjects weighing ≥10kg could safely be recruited into the study (current weight limit ≥15kg) and that subjects of any weight could be recruited initially (currently recruiting only subjects weighing ≥25kg). It was felt by all of the clinicians present that neither of these two changes would compromise subject safety. It was also decided that the measurement of PCO2 andoxygen saturation levels during the study would be discretionary as this intervention was not normally part of clinical practice in these subjects.

04 July 2011	Instigated following the meeting of the Independent Data Monitoring Committee (IDSMC) on 01 July 2011. 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. 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. The IDSMC suggested the following modifications to the protocol, which form the basis of this amendment: • Increase the lower age limit to 2 years • Increase the lower weight limit to 12 kg • 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). • 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 • 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) • A further meeting of the IDSMC to be convened after the next 15 patients have been recruited with the revised protocol 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.
06 September 2011	Instigated following a recommendation from the UK Ethics Committee (letter dated 15 August 2011). 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.

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.

Notes: