



Clinical trial results:

A randomised, double-blind controlled trial of ketamine versus placebo in conjunction with best pain management in neuropathic pain in cancer patients

Summary

EudraCT number	2007-002080-27
Trial protocol	GB
Global end of trial date	05 July 2014

Results information

Result version number	v1 (current)
This version publication date	03 May 2019
First version publication date	03 May 2019
Summary attachment (see zip file)	JAMA Oncology 2018 (jamaoncology_fallon_2018_id_180004.pdf)

Trial information

Trial identification

Sponsor protocol code	KPS 2008-01
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Additional study identifiers

ISRCTN number	ISRCTN49116945
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Clinical Research and Development Central Office, West Glasgow Ambulatory Care Hospital, Dalnair St, GLASGOW, United Kingdom, G3 8SW
Public contact	Dr Margaret Fegen, NHS Greater Glasgow and Clyde, margaret.fegen@ggc.scot.nhs.uk
Scientific contact	Dr Margaret Fegen, NHS Greater Glasgow and Clyde, margaret.fegen@ggc.scot.nhs.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, GLASGOW, United Kingdom, G12 8QQ
Public contact	Dr Debra Stuart, University of Glasgow, debra.stuart@glasgow.ac.uk
Scientific contact	Dr Debra Stuart, University of Glasgow, debra.stuart@glasgow.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2014
Global end of trial reached?	Yes
Global end of trial date	05 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish whether ketamine given in addition to best standard pain management improves malignant neuropathic pain compared to best standard pain management alone.

Protection of trial subjects:

As part of the study patients required to attend for additional clinic visits and investigations which would be above those considered to be standard care. The visit schedule and the number and type of investigations were fully explained to patients verbally and in writing via the patient information sheet to ensure patients were fully aware what was entailed in participating in the trial prior to them consenting to the study.

The patient information sheet also fully explained the design of the study and that half the patients would receive ketamine and half would receive placebo.

The side effects of ketamine were explained in the patient information sheet. All patients were closely monitored throughout the course of the study for adverse events and advised to report any side effects to their study nurse/doctor as they arose.

Background therapy:

Not Applicable

Evidence for comparator:

Subsequent human studies have established ketamine as a proven non-competitive antagonist of the NMDA receptor ion channel within the spinal cord. Ketamine blocks the NMDA receptor which subsequently acts by "winding down" and minimising pain transmission; which is particularly of benefit when a hyperexcitability state exists, commonly present in neuropathic pain states.

It has a proven role in neuropathic pain and pain secondary to critical limb ischaemia, however its use in neuropathic pain of malignant origin remains unsubstantiated. Through case reports some clinicians who are expert in the use of ketamine have reported good pain relief in situations where best standard approaches have failed. Examination of the use of ketamine in an objective, systematic fashion should enable equity of access to this treatment, if shown to be effective in a randomised controlled trial.

A pilot study was completed with s-ketamine, racemic ketamine and placebo in 65 patients. This double-blind randomised placebo controlled trial provides supporting evidence that ketamine may be superior to placebo in malignant neuropathic pain.

Actual start date of recruitment	21 May 2009
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: 214
Worldwide total number of subjects	214
EEA total number of subjects	214

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	149
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study opened to recruitment on 24 April 2009. 214 patients were randomised between 22 May 2009 and 29 April 2014.

Pre-assignment

Screening details:

513 patients were assessed for eligibility, 217 were registered, 214 completed run-in and were randomised. The purpose of the run-in period was to stabilise the opioid dose (individually) prior to randomisation to titration. During run-in, no SAEs were reported; 3 patients experienced non-serious AEs: 2x Drowsiness, 1x Extra pyramidal disorder.

Pre-assignment period milestones

Number of subjects started	513 ^[1]
Intermediate milestone: Number of subjects	Registered to run-in: 217
Number of subjects completed	214

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not registered: ineligible: 115
Reason: Number of subjects	Not registered: unhappy at option of placebo: 21
Reason: Number of subjects	Not registered: declined due to travel issues: 2
Reason: Number of subjects	Not registered: conflicting trial: 9
Reason: Number of subjects	Not registered: investigator decision: 65
Reason: Number of subjects	Not registered: patient too unwell: 29
Reason: Number of subjects	Not registered: patient declined for other reasons: 55
Reason: Number of subjects	Withdrew during run in: achieved pain control: 2
Reason: Number of subjects	Withdrew during run in: Unable to comply: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: The trial included a screening period, and a run-in period to allow the dose of opioid analgesia to be optimised prior to randomisation. Those starting the pre-assignment period are those that were screened into the study. The worldwide number enrolled considers randomised patients only due to this being pre-populated from the protocol information supplied to EudraCT.

Period 1

Period 1 title	Titration phase and assessment phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
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Arm title	Ketamine Hydrochloride
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ketamine Hydrochloride
Investigational medicinal product code	CAS: 1867-86-9 (ketamine hydrochloride)
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Titration period: Study drug will be administered under a set-dosing regimen. Each dose will be administered four times daily between the hours of 08:00 and 22:00. Under the dosing regimen study drug will be administered at seven dosing levels. Titration will stop when the McGill Pain Score drops by 5 points or side effects preclude further titration AND it is the opinion of the investigator that clinically meaningful analgesia has been attained. The dose level will be maintained for at least 48 hours before a further increment is made.

Table 1: Dose Schedule

Days	Dose Level	Total Daily Dose (mg)
1, 2	1	40
3, 4	2	80
5, 6	3	120
7, 8	4	160
9, 10	5	240
11, 12	6	320
13, 14	7	400

Assessment period: 16 day period of study drug at dose level reached during titration period

If patients complete the trial they will remain on either ketamine or placebo for a period of between 17 and 30 days.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Identical placebo capsules marked with the same range of dose levels as Ketamine arm.

Number of subjects in period 1	Ketamine Hydrochloride	Placebo
Started	107	107
Completed	24	26
Not completed	83	81
>30% increase in opioid dose (titration phase)	1	-
<5pt improvement in pain during assessment phase	18	17
<5pt improvement in pain during titration phase	26	16
Investigator declared treatment fail (titration)	31	41

>30% increase in opioid dose (assessment phase)	2	-
Investigator declared treatment fail (assessment)	5	7

Period 2

Period 2 title	Run-out phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose is reduced from assessment period over a period of 7 days.

Arm title	Ketamine Hydrochloride
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ketamine Hydrochloride
Investigational medicinal product code	CAS: 1867-86-9 (ketamine hydrochloride)
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose is reduced from assessment period over a period of 7 days.

Number of subjects in period 2	Placebo	Ketamine Hydrochloride
Started	26	24
Completed	48	49
Not completed	2	0
No run-out phase	2	-
Joined	24	25

Treatment failure during assessment phase	24	25
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Baseline characteristics

Reporting groups

Reporting group title	Ketamine Hydrochloride
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Ketamine Hydrochloride	Placebo	Total
Number of subjects	107	107	214
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	74	75	149
From 65-84 years	33	32	65
85 years and over	0	0	0
Age continuous			
Age at registration			
Units: years			
median	58	58	
standard deviation	± 10.12	± 10.91	-
Gender categorical			
Units: Subjects			
Female	67	66	133
Male	40	41	81
Current/previous analgesics			
Units: Subjects			
Gabapentin	31	32	63
Amitriptyline	17	18	35
>1 adj. analgesic	46	43	89
Pregabalin	12	12	24
Declined adj. analgesia	1	2	3
Site of primary tumour			
Units: Subjects			
Breast	30	29	59
Lung	15	7	22
Colorectal	23	34	57
Ovarian	7	2	9
Bone	2	1	3
Skin	1	3	4
Other	29	31	60
Presence of metastases			

Does the patient have metastases?			
Units: Subjects			
Yes	24	28	52
No	83	79	162
Prior chemotherapy			
Units: Subjects			
Yes	89	89	178
No	18	18	36
Prior radiotherapy			
Units: Subjects			
Yes	50	63	113
No	56	44	100
Missing	1	0	1
Prior hormone therapy			
Units: Subjects			
Yes	25	17	42
No	82	90	172
History of painful neuropathy			
Units: Subjects			
No	75	74	149
Yes, not problematic in last 3 months	3	2	5
Yes, problematic in last 3 months	29	31	60
History of chronic pain			
Units: Subjects			
No	87	88	175
Yes, not problematic in past 3 months	3	2	5
Yes, problematic in past 3 months	17	17	34
History of alcohol or drug dependence			
Units: Subjects			
Yes	3	5	8
No	104	102	206
Currently alcohol or drug dependent?			
Units: Subjects			
No	105	106	211
Missing	2	1	3
LANSS status			
Units: Subjects			
Positive	104	105	209
Negative	3	1	4
Missing	0	1	1
Primary method of diagnosis of side of index neuropathic pain			
Units: Subjects			
MRI	3	4	7
Clinical	102	100	202
Other	2	3	5
Index neuropathic pain associated with metastatic site?			
Units: Subjects			
Yes	2	10	12

No	105	97	202
BTPQ: background pain			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
0-3	4	7	11
4-6	33	31	64
>=7	47	47	94
Missing	23	22	45
BPTQ: Episodes			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
0 (zero)	10	5	15
1-5	33	46	79
6-10	20	17	37
>10	14	8	22
Missing	30	31	61
BPTQ: Severity			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
0-3	1	2	3
4-6	13	12	25
>=7	56	65	121
Missing	37	28	65
BPTQ: Episode duration			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
<1 min	4	9	13
1-15 mins	10	21	31
16-30 mins	13	13	26
31-60 mins	16	7	23
61-120 mins	7	8	15
>120 mins	18	15	33
Missing	39	34	73
BPTQ: onset to maximum intensity			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
Unpredictable	23	27	50
<10 sec	16	17	33
10 sec - 5 mins	18	17	35
6-30 mins	7	7	14
31-60 mins	5	4	9
>60 mins	1	1	2
Missing	37	34	71
BPTQ: Predictability			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
Never	41	43	84
Sometimes	21	23	44
Often	5	3	8
Almost always	7	8	15
Always	4	2	6

Missing	29	28	57
BPTQ: Use of analgesia			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
Every time	12	13	25
Most of the time	13	8	21
Some of the time	14	24	38
Hardly ever	7	5	12
Never	31	30	61
Missing	30	27	57
Breast metastases			
Units: Subjects			
No	107	105	212
Yes	0	2	2
Lung metastases			
Units: Subjects			
No	98	98	196
Yes	9	9	18
Colorectal metastases			
Units: Subjects			
No	106	107	213
Yes	1	0	1
Ovarian metastases			
Units: Subjects			
No	107	107	214
Liver metastases			
Units: Subjects			
No	104	100	204
Yes	3	7	10
Bone metastases			
Units: Subjects			
No	101	98	199
Yes	6	9	15
Brain metastases			
Units: Subjects			
No	106	106	212
Yes	1	1	2
Skin metastases			
Units: Subjects			
No	106	107	213
Yes	1	0	1
Other metastases			
Units: Subjects			
No	101	96	197
Yes	6	11	17
Baseline McGill sensory pain score			
Units: McGill sensory pain score			
median	19	17	
standard deviation	± 6.18	± 6.32	-
Weight			
Units: kg			

median	82.72	78.45	
standard deviation	± 19.46	± 17.19	-
Global pain score			
VAS (0-10)			
Units: Score			
median	7	6	
standard deviation	± 3.18	± 3.2	-
McGill sensory scale score			
0-33			
Units: Score			
median	18	17	
standard deviation	± 6.22	± 6.59	-
LANSS pain scale score			
0-24			
Units: Score			
median	19	19	
standard deviation	± 3.78	± 3.61	-
Index neuropathic pain worst score in past 24 hours			
VAS (0-10)			
Units: Score			
median	8	8	
standard deviation	± 1.57	± 1.55	-

Subject analysis sets

Subject analysis set title	Per protocol: Ketamine
Subject analysis set type	Per protocol

Subject analysis set description:

After blind review of the data, the Chief Investigators defined the per protocol population as all patients who, after randomisation, take at least 80% of the doses of prescribed trial treatment.

Subject analysis set title	Per protocol: Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

After blind review of the data, the Chief Investigators defined the per protocol population as all patients who, after randomisation, take at least 80% of the doses of prescribed trial treatment.

Reporting group values	Per protocol: Ketamine	Per protocol: Placebo	
Number of subjects	107	104	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	74	73	
From 65-84 years	33	31	
85 years and over	0	0	

Age continuous			
Age at registration			
Units: years			
median			
standard deviation	±	±	
Gender categorical			
Units: Subjects			
Female			
Male			
Current/previous analgesics			
Units: Subjects			
Gabapentin			
Amitriptyline			
>1 adj. analgesic			
Pregabalin			
Declined adj. analgesia			
Site of primary tumour			
Units: Subjects			
Breast			
Lung			
Colorectal			
Ovarian			
Bone			
Skin			
Other			
Presence of metastases			
Does the patient have metastases?			
Units: Subjects			
Yes			
No			
Prior chemotherapy			
Units: Subjects			
Yes			
No			
Prior radiotherapy			
Units: Subjects			
Yes			
No			
Missing			
Prior hormone therapy			
Units: Subjects			
Yes			
No			
History of painful neuropathy			
Units: Subjects			
No			
Yes, not problematic in last 3 months			
Yes, problematic in last 3 months			
History of chronic pain			
Units: Subjects			

No			
Yes, not problematic in past 3 months			
Yes, problematic in past 3 months			
History of alcohol or drug dependence			
Units: Subjects			
Yes			
No			
Currently alcohol or drug dependent?			
Units: Subjects			
No			
Missing			
LANSS status			
Units: Subjects			
Positive			
Negative			
Missing			
Primary method of diagnosis of side of index neuropathic pain			
Units: Subjects			
MRI			
Clinical			
Other			
Index neuropathic pain associated with metastatic site?			
Units: Subjects			
Yes			
No			
BTPQ: background pain			
BTPQ = Breakthrough pain questionnaire			
Units: Subjects			
0-3			
4-6			
>=7			
Missing			
BTPQ: Episodes			
BTPQ = Breakthrough pain questionnaire			
Units: Subjects			
0 (zero)			
1-5			
6-10			
>10			
Missing			
BTPQ: Severity			
BTPQ = Breakthrough pain questionnaire			
Units: Subjects			
0-3			
4-6			
>=7			
Missing			
BTPQ: Episode duration			
BTPQ = Breakthrough pain questionnaire			

Units: Subjects			
<1 min			
1-15 mins			
16-30 mins			
31-60 mins			
61-120 mins			
>120 mins			
Missing			
BPTQ: onset to maximum intensity			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
Unpredictable			
<10 sec			
10 sec - 5 mins			
6-30 mins			
31-60 mins			
>60 mins			
Missing			
BPTQ: Predictability			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
Never			
Sometimes			
Often			
Almost always			
Always			
Missing			
BPTQ: Use of analgesia			
BPTQ = Breakthrough pain questionnaire			
Units: Subjects			
Every time			
Most of the time			
Some of the time			
Hardly ever			
Never			
Missing			
Breast metastases			
Units: Subjects			
No			
Yes			
Lung metastases			
Units: Subjects			
No			
Yes			
Colorectal metastases			
Units: Subjects			
No			
Yes			
Ovarian metastases			
Units: Subjects			
No			

Liver metastases Units: Subjects			
No Yes			
Bone metastases Units: Subjects			
No Yes			
Brain metastases Units: Subjects			
No Yes			
Skin metastases Units: Subjects			
No Yes			
Other metastases Units: Subjects			
No Yes			
Baseline McGill sensory pain score Units: McGill sensory pain score median standard deviation	\pm	\pm	
Weight Units: kg median standard deviation	\pm	\pm	
Global pain score			
VAS (0-10)			
Units: Score median standard deviation	\pm	\pm	
McGill sensory scale score			
0-33			
Units: Score median standard deviation	\pm	\pm	
LANSS pain scale score			
0-24			
Units: Score median standard deviation	\pm	\pm	
Index neuropathic pain worst score in past 24 hours			
VAS (0-10)			
Units: Score median standard deviation	\pm	\pm	

End points

End points reporting groups

Reporting group title	Ketamine Hydrochloride
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ketamine Hydrochloride
Reporting group description: -	
Subject analysis set title	Per protocol: Ketamine
Subject analysis set type	Per protocol
Subject analysis set description: After blind review of the data, the Chief Investigators defined the per protocol population as all patients who, after randomisation, take at least 80% of the doses of prescribed trial treatment.	
Subject analysis set title	Per protocol: Placebo
Subject analysis set type	Per protocol
Subject analysis set description: After blind review of the data, the Chief Investigators defined the per protocol population as all patients who, after randomisation, take at least 80% of the doses of prescribed trial treatment.	

Primary: Malignant neuropathic pain

End point title	Malignant neuropathic pain
End point description: To establish whether ketamine given in addition to best standard pain management improves malignant neuropathic pain compared to best standard pain management alone. This is assessed using the sensory component of the McGill Short Form Questionnaire (SF-MPQ). The primary comparison will be in terms of time to treatment "failure" (as defined in 5.1.1) between the study arms. This comparison will be made using the log-rank test. The differences in the "success" rates between the arms at the day 16 assessment point will be estimated and presented together with associated 95% confidence intervals. Treatment failure reasons: - Greater than 30% increase in 24 hour morphine equivalent daily dose - Less than 5 point drop from baseline McGill pain score - Investigator decision due to clinical reasoning or lack of efficacy	
End point type	Primary
End point timeframe: From the end of the run in period (prior to randomisation) to any one of the assessment time points (end of titration period, assessment period: day 1, day 4, day 8, day 12, day 16).	

End point values	Ketamine Hydrochloride	Placebo	Per protocol: Ketamine	Per protocol: Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	107	107	107	104
Units: Time to treatment failure number (not applicable)				
Event (treatment failure)	83	81	83	78
Censor (no treatment failure)	24	26	24	26

Statistical analyses

Statistical analysis title	Time to treatment failure
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.692
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.952
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.294

Notes:

[1] - Cox regression model is performed as a secondary confirmatory analysis of log rank test.

Statistical analysis title	Time to treatment failure: per protocol
Statistical analysis description:	
Per protocol comparison, secondary analysis	
Comparison groups	Per protocol: Placebo v Per protocol: Ketamine
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.594
Method	Logrank

Secondary: Initial treatment benefit

End point title	Initial treatment benefit
End point description:	
To compare initial treatment benefit (at day 4 of assessment period of 16 days) using the sensory component of the SF-MPQ.	
End point type	Secondary
End point timeframe:	
Day 4 of assessment period of 16 days	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Success rate				
number (not applicable)	34	39		

Statistical analyses

Statistical analysis title	Difference in proportion
Statistical analysis description: Ketamine - Placebo	
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.471
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Difference in proportion
Point estimate	-0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.174
upper limit	0.08

Secondary: Overall pain (global pain score: VAS)

End point title	Overall pain (global pain score: VAS)
End point description:	
End point type	Secondary
End point timeframe:	
VAS pain score completed daily throughout run in, titration and assessment period.	

End point values	Ketamine Hydrochloride	Placebo	Per protocol: Ketamine	Per protocol: Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	107	107	107	104
Units: Number of patients	107	107	107	104

Statistical analyses

Statistical analysis title	Area under curve analysis
Statistical analysis description: AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.	
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.917
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Percentage change from baseline (ITT)
Statistical analysis description: Change: Number of patients (K=Ketamine, P=Placebo) Increased: K=10, P=17 No change: K=33, P=32 Decreased: K=62, P=50 N.B. 10 patients excluded: 9 patients had baseline score of 0 so not possible to calculate % change; 1 patient had no end of assessment period score.	
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.13
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Percentage change from baseline (PP)
Statistical analysis description: Change: Number of patients (K=Ketamine, P=Placebo) Increased: K=10, P=16 No change: K=33, P=30 Decreased: K=62, P=50 N.B. 201 patients included (105 K; 96 P)	
Comparison groups	Per protocol: Ketamine v Per protocol: Placebo
Number of subjects included in analysis	211
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.196
Method	Wilcoxon (Mann-Whitney)

Secondary: Index site pain (worst pain score: VAS)

End point title	Index site pain (worst pain score: VAS)
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End point description:

End point type	Secondary
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End point timeframe:

VAS pain score completed daily throughout run in, titration and assessment period.

End point values	Ketamine Hydrochloride	Placebo	Per protocol: Ketamine	Per protocol: Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	107	107	107	104
Units: Number of patients	107	107	107	104

Statistical analyses

Statistical analysis title	Area under curve analysis
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Statistical analysis description:

AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.

Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Percentage change from baseline (ITT)
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Statistical analysis description:

Change: Number of patients (K=Ketamine, P=Placebo)

Increased: K=12, P=13

No change: K=22, P=21

Decreased: K=73, P=73

Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.984
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Percentage change from baseline (PP)
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Statistical analysis description:

Change: Number of patients (K=Ketamine, P=Placebo)

Increased: K=12, P=12

No change: K=22, P=21

Decreased: K=73, P=71

Comparison groups	Per protocol: Ketamine v Per protocol: Placebo
Number of subjects included in analysis	211
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.999
Method	Wilcoxon (Mann-Whitney)

Secondary: Patient distress

End point title	Patient distress
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End point description:

End point type	Secondary
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End point timeframe:

NCCN Distress Thermometer completed at end of run in period (prior to randomisation) and day 1, 4, 8, 12 and 16 of assessment period.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Number of patients	107	107		

Statistical analyses

Statistical analysis title	Area under curve analysis
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Statistical analysis description:

AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.

Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.635
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of Life (EuroQol thermometer)

End point title	Quality of Life (EuroQol thermometer)
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End point description:

End point type	Secondary
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End point timeframe:

EuroQoL Thermometer completed at end of run in period (prior to randomisation) and day 1, 4, 8, 12 and 16 of assessment period.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Number of patients	107	107		

Statistical analyses

Statistical analysis title	Area under curve analysis
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Statistical analysis description:

AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.

Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.893
Method	Wilcoxon (Mann-Whitney)

Secondary: Anxiety (HADS)

End point title	Anxiety (HADS)
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End point description:

End point type	Secondary
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End point timeframe:

HADS completed at end of run in period (prior to randomisation) and day 1, 4, 8, 12 and 16 of assessment period.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Number of patients	107	107		

Statistical analyses

Statistical analysis title	Area under curve analysis
Statistical analysis description: AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.	
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	Wilcoxon (Mann-Whitney)

Secondary: Depression (HADS)

End point title	Depression (HADS)
End point description:	
End point type	Secondary
End point timeframe: HADS completed at end of run in period (prior to randomisation) and day 1, 4, 8, 12 and 16 of assessment period.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Number of patients	107	107		

Statistical analyses

Statistical analysis title	Area under curve analysis
Statistical analysis description: AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.	
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663
Method	Wilcoxon (Mann-Whitney)

Secondary: Daily opioid requirement (MEDD)

End point title	Daily opioid requirement (MEDD)
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End point description:	
MEDD: morphine equivalent daily dose	
End point type	Secondary
End point timeframe:	
Over titration and assessment periods	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Average daily MEDD				
arithmetic mean (standard deviation)	75.95 (± 236.95)	73.74 (± 216.66)		

Statistical analyses

Statistical analysis title	Area under curve analysis
Statistical analysis description:	
AUC calculated over the assessment/titration period, divided by number of days on assessment/titration and with the baseline value subtracted.	
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585
Method	Wilcoxon (Mann-Whitney)

Secondary: Quantitative sensory testing: Brush

End point title	Quantitative sensory testing: Brush
End point description:	
QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.	
End point type	Secondary
End point timeframe:	
Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Brush				
Increased	10	9		
Reduced	9	8		
No difference than control	6	11		
Missing	82	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative sensory testing: Von Frey filaments - detection threshold

End point title	Quantitative sensory testing: Von Frey filaments - detection threshold
End point description: QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.	
End point type	Secondary
End point timeframe: Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Detection threshold				
Increased	5	9		
Reduced	19	17		
No difference than control	8	7		
Missing	75	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative sensory testing: Von Frey filaments - pain threshold

End point title	Quantitative sensory testing: Von Frey filaments - pain threshold
End point description: QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period	

analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

End point type	Secondary
End point timeframe:	
Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Pain threshold				
Increased	12	17		
Reduced	6	8		
No difference than control	14	7		
Missing	75	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative sensory testing: Von Frey filaments - cool

End point title	Quantitative sensory testing: Von Frey filaments - cool
End point description:	
QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.	
End point type	Secondary
End point timeframe:	
Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Cool				
Increased	14	10		
Reduced	11	20		
No difference than control	5	3		
Missing	77	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative sensory testing: Von Frey filaments - warm

End point title	Quantitative sensory testing: Von Frey filaments - warm
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

End point type	Secondary
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End point timeframe:

Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Warm				
Increased	8	8		
Reduced	15	22		
No difference than control	7	3		
Missing	77	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative sensory testing: Von Frey filaments - pin prick

End point title	Quantitative sensory testing: Von Frey filaments - pin prick
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

End point type	Secondary
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End point timeframe:

Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Pin prick				
Increased	15	14		
Reduced	11	12		
No difference than control	5	7		
Missing	76	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative sensory testing: Von Frey filaments - wind up

End point title	Quantitative sensory testing: Von Frey filaments - wind up
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

End point type	Secondary
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End point timeframe:

Quantitative sensory testing (QST) at the end of the assessment period. Summarising test area compared to control area.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Wind up				
Increased	14	19		
Reduced	10	8		
No difference than control	6	5		
Missing	77	75		

Statistical analyses

No statistical analyses for this end point

Secondary: QST change in sensation: Brush

End point title	QST change in sensation: Brush
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period

analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
End point timeframe:	
Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	6	9		
No change	14	16		
Normal to abnormal	3	0		
Missing	84	82		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219
Method	Wilcoxon (Mann-Whitney)

Secondary: QST change in sensation: detection threshold

End point title	QST change in sensation: detection threshold
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
End point timeframe:	
Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	5	4		
No change	25	23		
Normal to abnormal	1	4		
Missing	76	76		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.411
Method	Wilcoxon (Mann-Whitney)

Secondary: QST change in sensation: pain threshold

End point title	QST change in sensation: pain threshold
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
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End point timeframe:

Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	9	4		
No change	21	23		

Normal to abnormal	0	4		
Missing	77	76		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035 ^[2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Not adjusted for multiple testing. Adjusted p=0.245

Secondary: QST change in sensation: cool

End point title	QST change in sensation: cool
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
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End point timeframe:

Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	1	1		
No change	26	29		
Normal to abnormal	2	2		
Missing	78	75		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Ketamine Hydrochloride v Placebo

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Wilcoxon (Mann-Whitney)

Secondary: QST change in sensation: warm

End point title	QST change in sensation: warm
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
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End point timeframe:

Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	4	3		
No change	21	27		
Normal to abnormal	3	2		
Missing	79	75		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.863
Method	Wilcoxon (Mann-Whitney)

Secondary: QST change in sensation: pin prick

End point title	QST change in sensation: pin prick
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
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End point timeframe:

Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	4	6		
No change	22	24		
Normal to abnormal	2	2		
Missing	79	75		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.728
Method	Wilcoxon (Mann-Whitney)

Secondary: QST change in sensation: wind-up

End point title	QST change in sensation: wind-up
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End point description:

QST was introduced approximately 1 year after study open. Only patients completing the 16 day assessment period (i.e. "responders") can be included in the change at end of assessment period analysis. Therefore the comparison between arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.

[Abnormal sensation is increased or reduced sensation in test area compared to control area; normal sensation is no difference between test and control areas]

End point type	Secondary
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End point timeframe:

Summarising change from abnormal sensation in test areas compared to control areas to normal sensation, and vice-versa, between end of run-in and day 16 assessment.

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Change in sensation				
Abnormal to normal	5	4		
No change	22	27		
Normal to abnormal	1	0		
Missing	79	76		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.856
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Malignant neuropathic pain (exploratory definition of treatment failure)

End point title	Malignant neuropathic pain (exploratory definition of treatment failure)
End point description:	As per primary endpoint but treatment failure based on opioid dose includes the prescribed background opioid dose as per primary endpoint, and ALSO recorded breakthrough (PRN) dose.
End point type	Other pre-specified
End point timeframe:	As per primary endpoint

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Time to treatment failure				
number (not applicable)				
Event (Treatment failure)	83	81		
Censor (no treatment failure)	24	26		

Statistical analyses

Statistical analysis title	Time to treatment failure
Statistical analysis description: As per primary analysis with updated definition of treatment failure.	
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.694
Method	Logrank

Post-hoc: Break through pain questionnaire

End point title	Break through pain questionnaire
End point description: Only patients who complete the 16 day assessment period ('responders') can be included in the end of assessment period analysis. Note also that this restriction to "responders" means that the comparison between the arms does not reflect the initial randomisation and is therefore biased and difficult to interpret.	
End point type	Post-hoc
End point timeframe: At end of assessment period	

End point values	Ketamine Hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Patients	107	107		

Statistical analyses

Statistical analysis title	Mann-whitney U test: Background pain
Comparison groups	Ketamine Hydrochloride v Placebo

Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.523
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-whitney U test: Episodes
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.506
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-whitney U test: Severity
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.79
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-whitney U test: Episode duration
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.574
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-whitney U test: Onset to max intensity
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.669
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-whitney U test: Predictability
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.857
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Mann-whitney U test: Use of analgesia
Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.38
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Background pain
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.399
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Episodes of pain
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.697
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Severity of pain
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.735
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Episode duration
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.589
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Onset to max intensity
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.909
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Prediction of flare-up
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.999
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change from baseline: Use of analgesia
Comparison groups	Placebo v Ketamine Hydrochloride
Number of subjects included in analysis	214
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.889
Method	Wilcoxon (Mann-Whitney)

Post-hoc: McGill pain score	
End point title	McGill pain score
End point description:	
End point type	Post-hoc

End point timeframe:

Baseline (end of run-in) and end of assessment period.

End point values	Ketamine Hydrochloride	Placebo	Per protocol: Ketamine	Per protocol: Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	94 ^[3]	87 ^[4]	94	87
Units: Number of patients	94	106	94	87

Notes:

[3] - 13 patients had only a baseline score

[4] - 19 patients had only a baseline score

1 patient had baseline score of 0

Statistical analyses

Statistical analysis title	Percentage change from baseline (ITT)
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Statistical analysis description:

Change: Number of patients (K=Ketamine, P=Placebo)

Increase: K=24, P=13

No change: K=5, P=2

Decreased: K=65, P=72

Comparison groups	Ketamine Hydrochloride v Placebo
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.039 ^[5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Unadjusted.

Adjusted p-value=0.118

Statistical analysis title	Percentage change from baseline (PP)
Comparison groups	Per protocol: Ketamine v Per protocol: Placebo
Number of subjects included in analysis	181
Analysis specification	Post-hoc
Analysis type	superiority ^[6]
P-value	= 0.039 ^[7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Change: Number of patients (K=Ketamine, P=Placebo)

Increase: K=24, P=13

No change: K=5, P=2

Decreased: K=65, P=72

[7] - Unadjusted.

Adjusted p-value=0.118

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were recorded from study entry throughout the study period and for at least 30 days after discontinuation of study medication. All adverse events were followed until resolution.

Adverse event reporting additional description:

Specifically, opioid toxicity was recorded at the end of the Run-In Period.

For each subject, the worst grade of each AE during each resporting period was recorded hence the number of subjects and number of occurrences is the same.

For the serious adverse events "causally related" has been defined as a relationship of at least 'Possible'

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Ketamine Hydrochloride (Titration)
Reporting group description: -	
Reporting group title	Placebo (Titration)
Reporting group description: -	
Reporting group title	Ketamine Hydrochloride (Assessment)
Reporting group description: -	
Reporting group title	Placebo (Assessment)
Reporting group description: -	
Reporting group title	Ketamine Hydrochloride (Run-out)
Reporting group description: -	
Reporting group title	Placebo (Run-out)
Reporting group description: -	

Serious adverse events	Ketamine Hydrochloride (Titration)	Placebo (Titration)	Ketamine Hydrochloride (Assessment)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 107 (3.74%)	3 / 107 (2.80%)	0 / 49 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alkaline phosphatase			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ALT			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GGT			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AST			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular arrhythmia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Confusional state			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurology other			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Infection			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Obstruction GU			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (Assessment)	Ketamine Hydrochloride (Run- out)	Placebo (Run-out)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)	4 / 45 (8.89%)	2 / 44 (4.55%)
number of deaths (all causes)	2	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Alkaline phosphatase			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ALT			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GGT			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AST			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular arrhythmia			

subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Confusional state			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurology other			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 50 (2.00%)	4 / 45 (8.89%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Vomiting			
subjects affected / exposed	0 / 50 (0.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Obstruction GU			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ketamine Hydrochloride (Titration)	Placebo (Titration)	Ketamine Hydrochloride (Assessment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 107 (61.68%)	37 / 107 (34.58%)	13 / 49 (26.53%)

General disorders and administration site conditions			
Nightmare			
subjects affected / exposed	3 / 107 (2.80%)	6 / 107 (5.61%)	0 / 49 (0.00%)
occurrences (all)	3	6	0
Constitutional symptoms			
subjects affected / exposed	4 / 107 (3.74%)	1 / 107 (0.93%)	1 / 49 (2.04%)
occurrences (all)	4	1	1
Fatigue			
subjects affected / exposed	6 / 107 (5.61%)	2 / 107 (1.87%)	0 / 49 (0.00%)
occurrences (all)	6	2	0
Fever			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	1 / 107 (0.93%)	3 / 107 (2.80%)	2 / 49 (4.08%)
occurrences (all)	1	3	2
Pain			
subjects affected / exposed	10 / 107 (9.35%)	11 / 107 (10.28%)	0 / 49 (0.00%)
occurrences (all)	10	11	0
Rigors/ chills			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Allergic Reaction			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 107 (0.00%)	3 / 107 (2.80%)	0 / 49 (0.00%)
occurrences (all)	0	3	0
Psychiatric disorders			
Insomnia			

subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	2 / 107 (1.87%) 2	0 / 49 (0.00%) 0
Investigations			
Alkaline phosphatase subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 107 (0.00%) 0	0 / 49 (0.00%) 0
ALT subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	0 / 107 (0.00%) 0	0 / 49 (0.00%) 0
AST subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	0 / 107 (0.00%) 0	0 / 49 (0.00%) 0
GGT subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	0 / 107 (0.00%) 0	0 / 49 (0.00%) 0
Cardiac disorders			
Hypertension subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 107 (0.93%) 1	0 / 49 (0.00%) 0
Supraventricular arrhythmia subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	0 / 107 (0.00%) 0	0 / 49 (0.00%) 0
Nervous system disorders			
Confusional state subjects affected / exposed occurrences (all)	5 / 107 (4.67%) 5	2 / 107 (1.87%) 2	0 / 49 (0.00%) 0
Hallucination subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	3 / 107 (2.80%) 3	0 / 49 (0.00%) 0
Cognitive disturbance subjects affected / exposed occurrences (all)	13 / 107 (12.15%) 13	4 / 107 (3.74%) 4	4 / 49 (8.16%) 4
Dizziness subjects affected / exposed occurrences (all)	32 / 107 (29.91%) 32	6 / 107 (5.61%) 6	6 / 49 (12.24%) 6
Involuntary movement			

subjects affected / exposed	3 / 107 (2.80%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
Mood altered			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Neurology other			
subjects affected / exposed	6 / 107 (5.61%)	2 / 107 (1.87%)	0 / 49 (0.00%)
occurrences (all)	6	2	0
Sensory neuropathy			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Personality change			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	4 / 107 (3.74%)	3 / 107 (2.80%)	0 / 49 (0.00%)
occurrences (all)	4	3	0
Speech impairment			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Vasovagal episode			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Ocular			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	4 / 107 (3.74%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	4	1	0
Dry mouth			
subjects affected / exposed	2 / 107 (1.87%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	2	1	0
Dysphagia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
GI			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Heartburn			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Mucositis			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	8 / 107 (7.48%)	9 / 107 (8.41%)	1 / 49 (2.04%)
occurrences (all)	8	9	1
Obstruction			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	2 / 107 (1.87%)	2 / 107 (1.87%)	0 / 49 (0.00%)
occurrences (all)	2	2	0

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Sweating			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Obstruction GU			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Urinary frequency			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal other			
subjects affected / exposed	3 / 107 (2.80%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
Infections and infestations			
Nasal/ paranasal reaction			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo (Assessment)	Ketamine Hydrochloride (Run- out)	Placebo (Run-out)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 50 (28.00%)	16 / 45 (35.56%)	7 / 44 (15.91%)
General disorders and administration site conditions			
Nightmare			

subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Constitutional symptoms			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Fever			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	4 / 50 (8.00%)	1 / 45 (2.22%)	1 / 44 (2.27%)
occurrences (all)	4	1	1
Pain			
subjects affected / exposed	4 / 50 (8.00%)	2 / 45 (4.44%)	2 / 44 (4.55%)
occurrences (all)	4	2	2
Rigors/ chills			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergic Reaction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Investigations			

Alkaline phosphatase subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
ALT subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
AST subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
GGT subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Cardiac disorders			
Hypertension subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Supraventricular arrhythmia subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Nervous system disorders			
Confusional state subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Hallucination subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Cognitive disturbance subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	2 / 45 (4.44%) 2	0 / 44 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0
Involuntary movement subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0
Mood altered			

subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Neurology other			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Sensory neuropathy			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Personality change			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Speech impairment			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Vasovagal episode			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Ocular			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed	2 / 50 (4.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	2	0	0
Dry mouth			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
GI			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Heartburn			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Mucositis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	4 / 50 (8.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	4	1	0
Obstruction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)	1 / 45 (2.22%)	0 / 44 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0

Sweating subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Renal and urinary disorders			
Obstruction GU subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Renal failure subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Urinary frequency subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal other subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Infections and infestations			
Nasal/ paranasal reaction subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 45 (0.00%) 0	0 / 44 (0.00%) 0
Metabolism and nutrition disorders			
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 45 (2.22%) 1	0 / 44 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2009	*Protocol clarifications *Addition of Quantitative Sensory Testing (QST) Questionnaire *Addition of new sites (Royal Lancaster / St John's Hospice) *Removal of site (Royal Brompton Hospital) *Update to Patient Information Sheet/Consent Form and GP Letter
25 March 2010	*Addition of a site (St Catherine's Hospice)
08 April 2010	Restart after Temporary Halt
25 June 2010	*Addition of a Site (St George's Hospital)
27 October 2010	*Eligibility criteria amendment to state that patients need to have been offered a trial of an adjuvant analgesic. Clarification that written informed consent must be obtained within 28 days prior to study entry. *Administrative changes updating participating sites and change in contact details. *Typo corrected in section 7.2.2 Secondary efficacy analysis (weeks should read days) *Changes to patient information sheet to inform patients that the titration phase could possibly last more than 14 days and also that the number of trial sites has changes *Changes to the consent form to remove 'Centre No' as centre numbers are not used in this study (this has been changed to 'Site' *Administrative changes updating participating sites and change in contact details. *Updated patient information sheet and consent form
06 January 2011	*Addition of Site (Nottingham)
11 February 2011	Temporary Halt of Study *Recruitment stopped 10/02/2010 Shortage of IMP meant that no new patients could be recruited into the study in order that the patient already on treatment could continue until completion
18 February 2013	*Removal of a site (St George's Hospital)
11 April 2013	*Removal of a site (St Catherine's Hospice)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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10 February 2010	Interruption due to a shortage in IMP which resulted in no new patients being able to start treatment in order that patients currently on study could complete treatment	22 February 2010
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Notes:

Limitations and caveats

None reported