Clinical trial results:
An open label, randomised controlled feasibility pilot study to evaluate whether nasal fentanyl alone and in combination with buccal midazolam give better symptom control to dying patients when compared with standard as needed medication

Summary

EudraCT number	2013-005009-30
Trial protocol	GB
Global end of trial date	26 February 2018

Results information

Result version number	v1 (current)
This version publication date	13 November 2021
First version publication date	13 November 2021
Summary attachment (see zip file)	Quantitative Results (Published paper.pdf) Qualitative Paper (bmjspcare-2020-002729.full.pdf)

Trial information

Trial identification

Sponsor protocol code	13/057/GHT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02009306
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov Identifier: NCT02009306, South Central-Berkshire Research Ethics Committee: 13/SC/0636

Notes:

Sponsors

Sponsor organisation name	Gloucestershire Hospitals NHS Foundation Trust
Sponsor organisation address	Leadon House, Gloucestershire Royal Hospital, Gloucester, United Kingdom, GL1 3NN
Public contact	Paul Perkins, Gloucestershire Hospitals NHS Foundation Trust and, +44 01242 230199, paul.perkins@suerydercare.org
Scientific contact	Paul Perkins, Gloucestershire Hospitals NHS Foundation Trust and, +44 01242 230199, paul.perkins@suerydercare.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2018
Global end of trial reached?	Yes
Global end of trial date	26 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We want to see how best to carry out a clinical trial to find out whether a medication known as fentanyl (given through the nose) given together with another medication known as midazolam (given through the lining of the mouth) are better (i.e. more effective) and faster at controlling the pain and agitation for patients dying in a hospice. The goal will be to use these medications for patients dying at home, leading to fewer nursing visits and lower healthcare costs.

We will assess the following:-
1. What is the time taken to control symptoms?
2. Did the patients need additional oral or injection medications?
3. How safe are the two medication when given together?

This is a pilot study meaning that we do not expect to have all answers to our research questions. It is to allow us to design a trial to confirm the trends we see in this trial.

Protection of trial subjects:

Patients could receive rescue as needed medication

Background therapy:

Background symptom relieving medication

Evidence for comparator:

Standard care (subcutaneous injections delivered by staff) - not great evidence for this standard care

Actual start date of recruitment	01 December 2016
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

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)	10
From 65 to 84 years	9
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment from December 2016 to Feb 2018 in UK

Pre-assignment

Screening details:

Inclusion criteria:
- Hospice in-patients 18 - 99 years old.
- Diagnosed with terminal cancer with an estimated prognosis of 1-2 weeks.
- Have carer/family member who would be willing to give the study medication to the patient AND likely to be at the hospice at least 25% of the time.

Period 1

Period 1 title	Titration
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nasal fentanyl and buccal midazolam

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PecFent
Investigational medicinal product code	EU/1/10/644/001
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Patients will be titrated with PecFent and Epistatus.
Efficacy of study drug will be determined 30 minutes after administration. A dose is deemed effective if the symptom is controlled AND there are no intolerable side effects.
If symptom control is achieved that dose will be administered as the effective treatment dose.
If symptom control is not achieved the patient will be administered a different dose on the PecFent or Epistatus titration schedule next time a dose of study drug is given:
- Next dose up if inadequate pain relief
- Next dose down if intolerable side effects

If patient has 2 consecutive doses of study drug at effective treatment dose followed by inadequate symptom relief consider:
- Giving next dose up on titration schedules if inadequate symptom relief
- Giving next dose down on titration schedules if intolerable side effects
- Patient stops trial

PecFent Titration - 100 mcg, 200mcg, 400mcg, 800mcg

Investigational medicinal product name	Epistatus
Investigational medicinal product code	M11
Other name	
Pharmaceutical forms	Oromucosal liquid
Routes of administration	Buccal use

Dosage and administration details:

Patients will be titrated with PecFent and Epistatus.
Efficacy of study drug will be determined 30 minutes after administration. A dose is deemed effective if the symptom is controlled AND there are no intolerable side effects.
If symptom control is achieved that dose will be administered as the effective treatment dose.
If symptom control is not achieved the patient will be administered a different dose on the PecFent or Epistatus titration schedule next time a dose of study drug is given:

- Next dose up if inadequate pain relief
- Next dose down if intolerable side effects

If patient has 2 consecutive doses of study drug at effective treatment dose followed by inadequate symptom relief consider:

- Giving next dose up on titration schedules if inadequate symptom relief
- Giving next dose down on titration schedules if intolerable side effects
- Patient stops trial

Epistatus Titration: 2.5, 5, 7.5, 10mg

Arm title	Standard as needed medication

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Diamorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

When the oral route becomes problematic it is standard practice for SANM to be administered via subcutaneous injection.
Subcutaneous SANM will include:

- Opioids for pain or dyspnoea
  - Diamorphine
  - Oxycodone
  - Fentanyl

The breakthrough dose of opioid is calculated according to the 24 hour background dose as is standard practice. Often it is 1/6th of the oral equivalent 24 hour dose although this can sometimes be different19.

- Benzodiazepine and / or anti-psychotic for agitation
  - Midazolam, usually 2.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
  - Haloperidol, usually 0.5 – 5mg
- Anti-emetic for nausea
  - Cyclizine, 50mg
  - Metoclopramide, 10mg
  - Haloperidol, usually 0.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
- Anti-secretory drug for respiratory secretions
  - Glycopyrronium, 200 – 400 mcg
  - Hyoscine butylbromide, 20mg
  - Hyoscine hydrobromide, 400 – 600mcg

Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

When the oral route becomes problematic it is standard practice for SANM to be administered via subcutaneous injection.
Subcutaneous SANM will include:

- Opioids for pain or dyspnoea
  - Diamorphine
  - Oxycodone
  - Fentanyl

The breakthrough dose of opioid is calculated according to the 24 hour background dose as is standard practice. Often it is 1/6th of the oral equivalent 24 hour dose although this can sometimes be different19.

- Benzodiazepine and / or anti-psychotic for agitation
  - Midazolam, usually 2.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
  - Haloperidol, usually 0.5 – 5mg
- Anti-emetic for nausea
  - Cyclizine, 50mg
  - Metoclopramide, 10mg
  - Haloperidol, usually 0.5 – 5mg

- o Levomepromazine, usually 6.25 – 25mg
- • Anti-secretory drug for respiratory secretions
- o Glycopyrronium, 200 – 400 mcg
- o Hyoscine butylbromide, 20mg
- o Hyoscine hydrobromide, 400 – 600mcg

Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

1/6th of total daily oxycodone SC dose up to hourly PRN SC

Investigational medicinal product name	Glycopyrronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

200 - 400 mcg PRN SC up to hourly

Investigational medicinal product name	Fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

25 - 50 mcg PRN SC up to hourly

Investigational medicinal product name	Levomepromazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

6.25 - 25 mg PRN SC up to hourly

Investigational medicinal product name	Haloperidol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

0.5 - 5 mg PRN SC up to hourly

Investigational medicinal product name	Hyoscine hydrobromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

200 - 400 mcg PRN SC up to hourly

Investigational medicinal product name	Hyoscine butylbromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

200 - 400 mcg PRN SC up to hourly

Arm title	Buccal Midazolam alone

Arm description:

In July 2017 the study team discussed a possible change to the study protocol. The study was recruiting on target but the 2 stage methodology meant that patients were not living long enough to receive Epistatus. Patients had to be titrated on PecFent before they could receive Epistatus. It was recognised that:

- The objective of this study is to evaluate the feasibility of a bigger study.
- The acceptability of administration of Epistatus for terminally ill patients and their families / carers is an important outcome for the study.

It was agreed that it would be more likely for the study to be able to collect useful feasibility data if a third observational arm could be added to the open label randomised control trial arms. Patients in this arm would receive Epistatus alone as the only experimental drug.

Arm type	Experimental
Investigational medicinal product name	Epistatus
Investigational medicinal product code	M11
Other name	
Pharmaceutical forms	Nasal spray, Oromucosal liquid
Routes of administration	Nasal use

Dosage and administration details:

For agitation, buccal Epistatus will be given instead of subcutaneous midazolam.
The Epistatus doses will be administered in time intervals not less than 4 hours.
If patient has agitation AND pain, they will be given:

- Standard analgesia for pain if agitation is assessed as likely to be secondary to pain
- Standard analgesia for pain and Epistatus buccally if pain and agitation are assessed as likely to be separate

Effectiveness of the dose will be assessed at 30 minutes post-dose. If deemed ineffective the following action should be taken:

- Consideration of administration of injection of opioid and benzodiazepine.
- Consideration of medical review.

Epistatus Titration: 2.5, 5, 7.5, 10mg

Number of subjects in period 1	Nasal fentanyl and buccal midazolam	Standard as needed medication	Buccal Midazolam alone
Started	9	9	2
Completed	6	9	2
Not completed	3	0	0
Patient died before receiving study drug	1	-	-
Lack of efficacy	2	-	-

Period 2

Period 2 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nasal fentanyl and buccal midazolam

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PecFent
Investigational medicinal product code	EU/1/10/644/001
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Nasal use

Dosage and administration details:

Patients will be titrated with PecFent and Epistatus.
Efficacy of study drug will be determined 30 minutes after administration. A dose is deemed effective if the symptom is controlled AND there are no intolerable side effects.
If symptom control is achieved that dose will be administered as the effective treatment dose.
If symptom control is not achieved the patient will be administered a different dose on the PecFent or Epistatus titration schedule next time a dose of study drug is given:
- Next dose up if inadequate pain relief
- Next dose down if intolerable side effects

If patient has 2 consecutive doses of study drug at effective treatment dose followed by inadequate symptom relief consider:
- Giving next dose up on titration schedules if inadequate symptom relief
- Giving next dose down on titration schedules if intolerable side effects
- Patient stops trial

PecFent Titration - 100 mcg, 200mcg, 400mcg, 800mcg

Investigational medicinal product name	Epistatus
Investigational medicinal product code	M11
Other name	
Pharmaceutical forms	Oromucosal liquid
Routes of administration	Buccal use

Dosage and administration details:

Patients will be titrated with PecFent and Epistatus.
Efficacy of study drug will be determined 30 minutes after administration. A dose is deemed effective if the symptom is controlled AND there are no intolerable side effects.
If symptom control is achieved that dose will be administered as the effective treatment dose.
If symptom control is not achieved the patient will be administered a different dose on the PecFent or Epistatus titration schedule next time a dose of study drug is given:
- Next dose up if inadequate pain relief
- Next dose down if intolerable side effects

If patient has 2 consecutive doses of study drug at effective treatment dose followed by inadequate symptom relief consider:
- Giving next dose up on titration schedules if inadequate symptom relief
- Giving next dose down on titration schedules if intolerable side effects
- Patient stops trial

Epistatus Titration: 2.5, 5, 7.5, 10mg

Arm title	Standard as needed medication

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Diamorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

When the oral route becomes problematic it is standard practice for SANM to be administered via subcutaneous injection.
Subcutaneous SANM will include:
- Opioids for pain or dyspnoea
  - Diamorphine
  - Oxycodone
  - Fentanyl

The breakthrough dose of opioid is calculated according to the 24 hour background dose as is standard practice. Often it is 1/6th of the oral equivalent 24 hour dose although this can sometimes be different19.
- Benzodiazepine and / or anti-psychotic for agitation
  - Midazolam, usually 2.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
  - Haloperidol, usually 0.5 – 5mg
- Anti-emetic for nausea
  - Cyclizine, 50mg
  - Metoclopramide, 10mg
  - Haloperidol, usually 0.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
- Anti-secretory drug for respiratory secretions
  - Glycopyrronium, 200 – 400 mcg
  - Hyoscine butylbromide, 20mg
  - Hyoscine hydrobromide, 400 – 600mcg

Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

When the oral route becomes problematic it is standard practice for SANM to be administered via subcutaneous injection.
Subcutaneous SANM will include:
- Opioids for pain or dyspnoea
  - Diamorphine
  - Oxycodone
  - Fentanyl

The breakthrough dose of opioid is calculated according to the 24 hour background dose as is standard practice. Often it is 1/6th of the oral equivalent 24 hour dose although this can sometimes be different19.
- Benzodiazepine and / or anti-psychotic for agitation
  - Midazolam, usually 2.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
  - Haloperidol, usually 0.5 – 5mg
- Anti-emetic for nausea
  - Cyclizine, 50mg
  - Metoclopramide, 10mg
  - Haloperidol, usually 0.5 – 5mg
  - Levomepromazine, usually 6.25 – 25mg
- Anti-secretory drug for respiratory secretions
  - Glycopyrronium, 200 – 400 mcg
  - Hyoscine butylbromide, 20mg
  - Hyoscine hydrobromide, 400 – 600mcg

Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details: 1/6th of total daily oxycodone SC dose up to hourly PRN SC	
Investigational medicinal product name	Glycopyrronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 200 - 400 mcg PRN SC up to hourly	
Investigational medicinal product name	Fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 25 - 50 mcg PRN SC up to hourly	
Investigational medicinal product name	Levomepromazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 6.25 - 25 mg PRN SC up to hourly	
Investigational medicinal product name	Haloperidol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 0.5 - 5 mg PRN SC up to hourly	
Investigational medicinal product name	Hyoscine hydrobromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 200 - 400 mcg PRN SC up to hourly	
Investigational medicinal product name	Hyoscine butylbromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 200 - 400 mcg PRN SC up to hourly	
Arm title	Epistatus alone
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Epistatus
Investigational medicinal product code	M11
Other name	
Pharmaceutical forms	Oromucosal liquid
Routes of administration	Buccal use

Dosage and administration details:

For agitation, buccal Epistatus will be given instead of subcutaneous midazolam.
The Epistatus doses will be administered in time intervals not less than 4 hours.
If patient has agitation AND pain, they will be given:
- Standard analgesia for pain if agitation is assessed as likely to be secondary to pain
- Standard analgesia for pain and Epistatus buccally if pain and agitation are assessed as likely to be separate

Effectiveness of the dose will be assessed at 30 minutes post-dose. If deemed ineffective the following action should be taken:
- Consideration of administration of injection of opioid and benzodiazepine.
- Consideration of medical review.

Epistatus Titration: 2.5, 5, 7.5, 10mg

Number of subjects in period 2	Nasal fentanyl and buccal midazolam	Standard as needed medication	Epistatus alone
Started	6	9	2
Completed	6	9	2

Baseline characteristics

Reporting groups	
Reporting group title	Nasal fentanyl and buccal midazolam
Reporting group description: -	
Reporting group title	Standard as needed medication
Reporting group description: -	
Reporting group title	Buccal Midazolam alone

Reporting group description:

In July 2017 the study team discussed a possible change to the study protocol. The study was recruiting on target but the 2 stage methodology meant that patients were not living long enough to receive Epistatus. Patients had to be titrated on PecFent before they could receive Epistatus. It was recognised that:

- The objective of this study is to evaluate the feasibility of a bigger study.
- The acceptability of administration of Epistatus for terminally ill patients and their families / carers is an important outcome for the study.

It was agreed that it would be more likely for the study to be able to collect useful feasibility data if a third observational arm could be added to the open label randomised control trial arms. Patients in this arm would receive Epistatus alone as the only experimental drug.

Reporting group values	Nasal fentanyl and buccal midazolam	Standard as needed medication	Buccal Midazolam alone
Number of subjects	9	9	2
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)	4	6	0
From 65-84 years	5	3	2
85 years and over	0	0	0
Gender categorical Units: Subjects			
Male	5	0	2
Female	4	9	0

Reporting group values	Total		
Number of subjects	20		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	10		
From 65-84 years	10		
85 years and over	0		
Gender categorical Units: Subjects			
Male	7		
Female	13		

End points

End points reporting groups

Reporting group title	Nasal fentanyl and buccal midazolam
Reporting group description: -	
Reporting group title	Standard as needed medication
Reporting group description: -	
Reporting group title	Buccal Midazolam alone

Reporting group description:

In July 2017 the study team discussed a possible change to the study protocol. The study was recruiting on target but the 2 stage methodology meant that patients were not living long enough to receive Epistatus. Patients had to be titrated on PecFent before they could receive Epistatus. It was recognised that:

- The objective of this study is to evaluate the feasibility of a bigger study.
- The acceptability of administration of Epistatus for terminally ill patients and their families / carers is an important outcome for the study.

It was agreed that it would be more likely for the study to be able to collect useful feasibility data if a third observational arm could be added to the open label randomised control trial arms. Patients in this arm would receive Epistatus alone as the only experimental drug.

Reporting group title	Nasal fentanyl and buccal midazolam
Reporting group description: -	
Reporting group title	Standard as needed medication
Reporting group description: -	
Reporting group title	Epistatus alone

Reporting group description: -

Primary: Time to symptom control from when medication needed

End point title	Time to symptom control from when medication needed

End point description:

End point type	Primary

End point timeframe:

Patients in experimental arm who had been successfully titrated

End point values	Nasal fentanyl and buccal midazolam	Standard as needed medication		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: Minutes				
median (inter-quartile range (Q1-Q3))	20 (17.5 to 29)	30 (25 to 38)		

Statistical analyses

Statistical analysis title	Quantitative outcome analysis

Statistical analysis description:

Quantitative outcome measures was undertaken using Stata v.15. Descriptive statistics were used to characterise the cohort. Multiple imputation by chain equations procedure in Stata25 was used to obtain twenty imputed datasets. The median time with interquartile range are reported for the main outcome measures.

Comparison groups	Nasal fentanyl and buccal midazolam v Standard as needed medication
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.5 [1]
Method	Not appropriate

Notes:

[1] - Small feasibility study - not appropriate to look for significance in results

Secondary: Time from medication needed to onset of symptom control

End point title	Time from medication needed to onset of symptom control

End point description:

End point type	Secondary

End point timeframe:

Patients in experimental arm who have been successfully titrated.

End point values	Nasal fentanyl and buccal midazolam	Standard as needed medication		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: Minutes				
median (inter-quartile range (Q1-Q3))	10 (9 to 16)	20 (16 to 30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from medication given to administration of next breakthrough medication

End point title	Time from medication given to administration of next breakthrough medication

End point description:

End point type	Secondary

End point timeframe:

Patients in experimental arm who have been successfully titrated.

End point values	Nasal fentanyl and buccal midazolam	Standard as needed medication		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: Minutes				
median (inter-quartile range (Q1-Q3))	380 (142.5 to 694)	275 (152.5 to 537)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: While patients participating in the study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24
Reporting groups	
Reporting group title	Nasal fentanyl and buccal midazolam
Reporting group description: -	
Reporting group title	Standard as needed medication
Reporting group description: -	
Reporting group title	Buccalmidazolam alone
Reporting group description: -	

Serious adverse events	Nasal fentanyl and buccal midazolam	Standard as needed medication	Buccalmidazolam alone
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	3	6	1
number of deaths resulting from adverse events	0	0	0
Product issues			
Incorrect dose administered	Additional description: A patient received four times the dose of nasal fentanyl they should have. We classified this as a serious adverse event. The patient was more sleepy after having the wrong dosage but was otherwise unharmed.		
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 1 (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

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

Non-serious adverse events	Nasal fentanyl and buccal midazolam	Standard as needed medication	Buccalmidazolam alone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	1 / 9 (11.11%)	0 / 1 (0.00%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 9 (33.33%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2017	which are needed: 1. To recruit up to 10 hospice in-patients into a study where they can receive Epistatus for agitation. The study will have different inclusion criteria to the main study and its conduct will not affect that of the main study. 2. Dr Jo Leonardi-Bee, Associate Professor in Medical Statistics and Independent Statistician Member of the TSG has suggested some rewording for the study objectives to make it clear that this is a feasibility study and the primary outcomes are about evaluating the feasibility of a larger study. 3. We would like to alter the titration and frequency of Epistatus. It has become clear from feedback from nursing staff that it is very unusual to give benzodiazepines half hourly (although they are often prescribed as such). We have reduced the frequency to hourly. We have also introduced another titration step of 7.5mg as it would be unusual to jump straight from 5mg to 10mg. 4. We have updated the membership of the TSG. 5. We have written some clearer guidance in conjunction with nursing staff administering trial drugs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32376759

http://www.ncbi.nlm.nih.gov/pubmed/33766820