Clinical trial results:
Effentora® for Dyspnoea (EffenDys) - Fentanyl buccal tablet (FBT) for the relief of episodic dyspnoea (ED) in cancer patients: an open label, randomized, morphine-controlled, crossover, phase II trial

Summary

EudraCT number	2011-005797-32
Trial protocol	DE
Global end of trial date	29 October 2014

Results information

Result version number	v1 (current)
This version publication date	26 October 2020
First version publication date	26 October 2020
Summary attachment (see zip file)	EffenDys summary report [German] (Abschlussbericht-EffenDys-FINAL_all signed.pdf)

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1412

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: 00004353

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Prof. Dr.med Raymond Voltz Zentrum für Palliativmedizin Center for Integrated Oncology (CIO), University Hospital Cologne Zentrum Palliativmedizin, raymond.voltz@uk-koeln.de
Scientific contact	Prof. Dr. med. Steffen Simon Zentrum für Palliativmedizin Center for Integrated Oncology (CIO), University Hospital Cologne Zentrum Palliativmedizin, steffen.simon@uk-koeln.de

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	29 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2014
Global end of trial reached?	Yes
Global end of trial date	29 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the time to onset of meaningful dyspnoea relief of fentanyl buccal tablet (FBT) in comparison to immediate-release morphine (IRM)

Protection of trial subjects:

none further specific measures; Patient’s usual rescue medication for the relief of dyspnoea will be used as rescue medication. Rescue medication is allowed at any time of the study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2013
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	Germany: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	7
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between March 2013 and October 2014 (20 months, extended from a planned 12 month period) in 3 hospitals (palliative care and oncology wards) in Germany.

Pre-assignment

Screening details:

Around 1.000 patients were screened in a 20 month recruitment phase. 25 patients were considered eligible and offered participation. 10 patients provided informed consent and were included.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fentanyl buccal tablet (FBT; Effentora®)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fentanyl 100/200/400/600µg
Investigational medicinal product code	SUB02129MIG
Other name	Effentora®
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage: 100µg - 600 µg (to be determined by titration)

Arm title	Immediate release morphine (IRM)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Morphin Merck Tropfen 2%
Investigational medicinal product code	SUB14596MIG
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

Dosage: Start with a minimum of 5mg (to be determined by titration)

Number of subjects in period 1	Fentanyl buccal tablet (FBT; Effentora®)	Immediate release morphine (IRM)
Started	5	5
Efficacy phase	5	4
Completed	5	4
Not completed	0	1
Disease progression	-	1

Period 2	
Period 2 title	Second (cross-over) treatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Fentanyl buccal tablet (FBT; Effentora®)

Arm description:

Second treatment period with FBT after receiving IRM in period 1

Arm type	Experimental
Investigational medicinal product name	Fentanyl 100/200/400/600µg
Investigational medicinal product code	SUB02129MIG
Other name	Effentora®
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

Dosage: 100µg - 600 µg (to be determined by titration)

Arm title	Immediate release morphine (IRM)

Arm description:

Second treatment period with IRM after receiving FBT in period 1

Arm type	Active comparator
Investigational medicinal product name	Morphin Merck Tropfen 2%
Investigational medicinal product code	SUB14596MIG
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

Dosage: Start with a minimum of 5mg (to be determined by titration)

Number of subjects in period 2	Fentanyl buccal tablet (FBT; Effentora®)	Immediate release morphine (IRM)
Started	4	5
Efficacy phase	2	4
Completed	2	4
Not completed	2	1

Consent withdrawn by subject	1	-
Disease progression	1	-
Detoriation of health status	-	1

Baseline characteristics

Reporting groups	
Reporting group title	First treatment period
Reporting group description:	
Patients randomized into the trial after being successfully screened	

Reporting group values	First treatment period	Total	
Number of subjects	10	10	
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)	7	7	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	58.0		
standard deviation	± 11.3	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	6	6	

Subject analysis sets	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all randomized patients	

Reporting group values	Intention-to-treat		
Number of subjects	10		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over	7 3		
Age continuous Units: years arithmetic mean standard deviation	 58.0 ± 11.3		
Gender categorical Units: Subjects			
Female Male	4 6		

End points

End points reporting groups

Reporting group title	Fentanyl buccal tablet (FBT; Effentora®)
Reporting group description: -	
Reporting group title	Immediate release morphine (IRM)
Reporting group description: -	
Reporting group title	Fentanyl buccal tablet (FBT; Effentora®)
Reporting group description: Second treatment period with FBT after receiving IRM in period 1	
Reporting group title	Immediate release morphine (IRM)
Reporting group description: Second treatment period with IRM after receiving FBT in period 1	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: all randomized patients	

Primary: Time to onset of meaningful dyspnoea relief

End point title	Time to onset of meaningful dyspnoea relief[1]
End point description:	
End point type	Primary

End point timeframe:

Time to onset of meaningful dyspnoea relief will be measured by stopwatch: time in minutes between administration of study medication and onset of meaningful dyspnoea relief.
'Meaningful dyspnoea relief' is defined by the patient.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary analysis of the trial is a comparison of periods in a cross-over design that cannot be properly documented in the results database. Additionally planned methods were adjusted in the SAP because the planned sample size was not reached.
Data from both periods were available for 6 patients. The mean difference (FBT minus IRM) is -14.2 min with 95% confidence interval -27.1 to -1.4 min, p=0.036 (paired t-test). See PDF summary report for details and secondary endpoints.

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: whole	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First Treatment until 3 days after last application of study drug

Adverse event reporting additional description:

Signs or symptoms of expected progression of the underlying disease or worsening of pre-existing conditions were exempt from AE reporting unless meeting SAE criteria or being CTCAE Grade>2. Also, treatment measures planned before start of the trial were exempt from reporting.
Death from underlying disease was considered an AE but not an SAE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Intention-to-treat

Reporting group description:

Note that the 3 (fatal) serious adverse events reported were not considered serious events in the study (death from underlying disease). Numbers were adjusted in this section to be able to pass result validation.

Serious adverse events	Intention-to-treat		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
General disorders and administration site conditions			
Death	Additional description: Death from underlying disease. Note that death from underlying disease was not considered a serious adverse event in the study but only an adverse event. Events were moved to this section to pass result validation.		
subjects affected / exposed	3 / 10 (30.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		

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

Non-serious adverse events	Intention-to-treat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
Nervous system disorders			

Coma subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2013	Changes in Exclusion criteria (protocol version V9-02-F, 10-sep-2013): Deletion of „Severe chronic obstructive pulmonary disease (COPD; GOLD classification stage III or IV or long term oxygen therapy (LTOT, defined as oxygen therapy at least 16 hours per day))" Change of „History of opioid abuse (as reported by the patient, referring physician or investigator)" to "Ongoing opioid abuse (as reported by the patient, referring physician or investigator)".
01 July 2014	(protocol version V10-01, 15-apr-2014) Changes in exclusion criteria - use of a monoamine oxidase inhibitors, "..SSRIs or SNRIs ...".within the previous 14 days updated SmPC for Fentanyl buccal tablet (FBT; Effentora®)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Despite best efforts only 10 of 30 planned patients could be enrolled and only 6 received both treatment periods. This severely limits both efficacy and safety conclusions The main result is that this design is not feasibile in this population.

Notes: