Clinical trial results:
Randomised, double-blind, dose-finding Phase II study to assess the efficacy of APD403 in the prevention of nausea and vomiting caused by cisplatin- or anthracycline/ cyclophosphamide (AC)-based chemotherapy

Summary

EudraCT number	2013-001635-51
Trial protocol	GB DE DK
Global end of trial date	16 February 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	DN10016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01857232
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acacia Pharma Ltd
Sponsor organisation address	Harston Mill, Harston, Cambridge, United Kingdom, CB22 7GG
Public contact	Dr Gabriel Fox, Acacia Pharma Ltd, 00234 1223875130, gabrielfox@acaciapharma.com
Scientific contact	Dr Gabriel Fox, Acacia Pharma Ltd, 00234 1223875130, gabrielfox@acaciapharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2015
Global end of trial reached?	Yes
Global end of trial date	16 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine how effective APD403 is at different doses at preventing sickness in patients given chemotherapy and to see if there is any relationship between the effectiveness and the dose.

Protection of trial subjects:

Before commencing the conduct of any of the pre-study procedures,the investigator or medical delegate explained the study fully to each patient. If the patient was willing to participate in the study they were requested to give written informed consent and sufficient time was given to consider their participation and the opportunity to ask further details.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	15 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 147
Country: Number of subjects enrolled	Denmark: 73
Country: Number of subjects enrolled	Germany: 108
Worldwide total number of subjects	328
EEA total number of subjects	328

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)	57
From 65 to 84 years	271
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Actual: 342 (320 completed).
Analysed (intent-to-treat [ITT]): 328 (Placebo 66, APD403 10 mg 63, 20 mg 68, 40 mg 65, DEX 66)
Analysed (per protocol [PP]): 318 (Placebo 65, APD403 10 mg 59, 20 mg 67, 40 mg 64,DEX 63)
Analysed (safety): 328 (Placebo 66, APD403 10 mg 63, 20 mg 68, 40 mg 65, DEX 66).

Pre-assignment

Screening details:

Patients were screened up to 14 days before the planned date of their operation and admitted to hospital on the day before or morning of their operation

Period 1

Period 1 title	Overall Trial (Overall Period) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1 (DEX)

Arm description:

IV Ondasetron 8mg + IV Fosaprepitant 150mg + IV Dexamethasone 12mg + PO Dexamethasone 8mg (Day2-4)

Arm type	Control
Investigational medicinal product name	Intravenous Dexamethasone
Investigational medicinal product code	IV DEX
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

12mg solution for IV injections

Investigational medicinal product name	Intravenous Fosaprepitant
Investigational medicinal product code	IV FOS
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

150 mg Solution for IV injection (Ivemend®; 1 mg/mL in normal saline)

Investigational medicinal product name	Ondansetron
Investigational medicinal product code	OND
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

OND was being used in line with its marketing authorisation and was not specifically under investigation in this study, so it did not meet the usual criteria defining an IMP, as described, for example, in 'The rules governing medicinal products in the EU. OND was not supplied separately for the study and was to be acquired by study sites according to their normal practice.

Investigational medicinal product name	Oral Dexamethasone
Investigational medicinal product code	PO-DEX
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone 8mg for oral use

Arm title	Arm 2 (Placebo)

Arm description:

IV Ondensotron 8mg + IV APD403 20mg + Oral Placebo of APD403 (Days 2-4)

Arm type	Experimental
Investigational medicinal product name	Ondansetron
Investigational medicinal product code	OND
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

OND was being used in line with its marketing authorisation and was not specifically under investigation in this study, so it did not meet the usual criteria defining an IMP, as described, for example, in 'The rules governing medicinal products in the EU. OND was not supplied separately for the study and was to be acquired by study sites according to their normal practice.

Investigational medicinal product name	IV APD403 20mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2omg dose of APD403 given via IV

Investigational medicinal product name	Oral Placebo of APD403
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules given via oral administration

Arm title	Arm 3 (APD403 10mg)

Arm description:

IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)

Arm type	Experimental
Investigational medicinal product name	Ondansetron
Investigational medicinal product code	OND
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

OND was being used in line with its marketing authorisation and was not specifically under investigation in this study, so it did not meet the usual criteria defining an IMP, as described, for example, in 'The rules governing medicinal products in the EU. OND was not supplied separately for the study and was to be acquired by study sites according to their normal practice.

Investigational medicinal product name	IV APD403 20mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2omg dose of APD403 given via IV

Investigational medicinal product name	Oral APD403 20mg od
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

APD403 20mg Capsule given Orally

Arm title	Arms 4 (APD403 20mg)

Arm description:

IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)

Arm type	Experimental
Investigational medicinal product name	Ondansetron
Investigational medicinal product code	OND
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

OND was being used in line with its marketing authorisation and was not specifically under investigation in this study, so it did not meet the usual criteria defining an IMP, as described, for example, in 'The rules governing medicinal products in the EU. OND was not supplied separately for the study and was to be acquired by study sites according to their normal practice.

Investigational medicinal product name	Oral APD403 20mg od
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

APD403 20mg Capsule given Orally

Investigational medicinal product name	IV APD403 20mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2omg dose of APD403 given via IV

Arm title	Arm 5 (APD403 40mg)

Arm description:

IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 40mg od

Arm type	Experimental
Investigational medicinal product name	Ondansetron
Investigational medicinal product code	OND
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

OND was being used in line with its marketing authorisation and was not specifically under investigation in this study, so it did not meet the usual criteria defining an IMP, as described, for example, in 'The rules governing medicinal products in the EU. OND was not supplied separately for the study and was to be acquired by study sites according to their normal practice.

Investigational medicinal product name	IV APD403 20mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

2omg dose of APD403 given via IV

Investigational medicinal product name	Oral APD403 40mg od
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

40mg capsules given orally

Number of subjects in period 1	Arm 1 (DEX)	Arm 2 (Placebo)	Arm 3 (APD403 10mg)
Started	66	66	63
Completed	61	65	63
Not completed	5	1	0
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	4	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Arms 4 (APD403 20mg)	Arm 5 (APD403 40mg)
Started	68	65
Completed	68	63
Not completed	0	2
Consent withdrawn by subject	-	-
Adverse event, non-fatal	-	-
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1 (DEX)
Reporting group description:	
IV Ondasetron 8mg + IV Fosaprepitant 150mg + IV Dexamethasone 12mg + PO Dexamethasone 8mg (Day2-4)	
Reporting group title	Arm 2 (Placebo)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral Placebo of APD403 (Days 2-4)	
Reporting group title	Arm 3 (APD403 10mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)	
Reporting group title	Arms 4 (APD403 20mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)	
Reporting group title	Arm 5 (APD403 40mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 40mg od	

Reporting group values	Arm 1 (DEX)	Arm 2 (Placebo)	Arm 3 (APD403 10mg)
Number of subjects	66	66	63
Age categorical Units: Subjects			
Adults (18-64 years)	50	45	48
From 65-84 years	16	21	15
Age continuous Units: years			
arithmetic mean	58.1	57.3	56.9
standard deviation	± 10.38	± 11.01	± 11.24
Gender categorical Units: Subjects			
Female	53	52	49
Male	13	14	14

Reporting group values	Arms 4 (APD403 20mg)	Arm 5 (APD403 40mg)	Total
Number of subjects	68	65	328
Age categorical Units: Subjects			
Adults (18-64 years)	55	52	250
From 65-84 years	13	13	78
Age continuous Units: years			
arithmetic mean	56.6	56.5	
standard deviation	± 11.24	± 10.59	-
Gender categorical Units: Subjects			
Female	54	54	262

Male	14	11	66

Subject analysis sets	
Subject analysis set title	Enrolled Patient Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who were randomised into the study	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled patients who received at least one dose of APD403 or DEX or the matching placebo. Patients were summarised according to the treatment actually taken	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who met the criteria for the ITT population and, in addition to the following:- - Had received a correct dose of day 1 study medication; and - had received the day 2 oral dose of study medication; and - were otherwise adherent to the protocol with no major protocol violations, as decided and documented prior to database lock	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
This is solely Identical to the ITT population.	

All enrolled patients were listed indicating their membership of each analysis population. The listing included the patient's randomisation number and reasons for exclusion from the analysis populations as appropriate.

Reporting group values	Enrolled Patient Population	ITT	PP
Number of subjects	328	328	318
Age categorical Units: Subjects			
Adults (18-64 years)	250	314	294
From 65-84 years	92	14	24
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	262	262	
Male	66	66	

Reporting group values	Safety Population		
Number of subjects	328		
Age categorical Units: Subjects			
Adults (18-64 years)	314		
From 65-84 years	14		

Age continuous Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female	262		
Male	66		

End points

End points reporting groups

Reporting group title	Arm 1 (DEX)
Reporting group description:	
IV Ondasetron 8mg + IV Fosaprepitant 150mg + IV Dexamethasone 12mg + PO Dexamethasone 8mg (Day2-4)	
Reporting group title	Arm 2 (Placebo)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral Placebo of APD403 (Days 2-4)	
Reporting group title	Arm 3 (APD403 10mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)	
Reporting group title	Arms 4 (APD403 20mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)	
Reporting group title	Arm 5 (APD403 40mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 40mg od	
Subject analysis set title	Enrolled Patient Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who were randomised into the study	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled patients who received at least one dose of APD403 or DEX or the matching placebo. Patients were summarised according to the treatment actually taken	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who met the criteria for the ITT population and, in addition to the following:- - Had received a correct dose of day 1 study medication; and - had received the day 2 oral dose of study medication; and - were otherwise adherent to the protocol with no major protocol violations, as decided and documented prior to database lock	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
This is solely Identical to the ITT population. All enrolled patients were listed indicating their membership of each analysis population. The listing included the patient's randomisation number and reasons for exclusion from the analysis populations as appropriate.	

Primary: Delayed phase complete response (CR)

End point title	Delayed phase complete response (CR)[1]
End point description:	
End point type	Primary
End point timeframe:	
Delayed phase complete response (CR), defined as an absence of emetic episodes and no rescue medication use in the period from 24 to 120 hours after the initiation of chemotherapy.	

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: To characterise the dose-response of oral APD403 for the prevention of delayed phase nausea and vomiting in male and female patients receiving cisplatin-based chemotherapy and female patients receiving anthracycline and cyclophosphamide (AC)-based chemotherapy, regimens both considered highly emetogenic.

End point values	Arm 1 (DEX)	Arm 2 (Placebo)	Arm 3 (APD403 10mg)	Arms 4 (APD403 20mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	66	63	68
Units: absence of emetic episodes and no rescue	37	13	27	21

End point values	Arm 5 (APD403 40mg)	Enrolled Patient Population	ITT	PP
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	342	328	318
Units: absence of emetic episodes and no rescue	20	118	118	118

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	328			
Units: absence of emetic episodes and no rescue	118			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any AE that was serious, occurring during the course of the study, irrespective of the treatment received by the patient, had to be reported to the pharmacovigilance contractor within 24 hours of its occurrence

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Arm 1 (DEX)
Reporting group description:	
IV Ondasetron 8mg + IV Fosaprepitant 150mg + IV Dexamethasone 12mg + PO Dexamethasone 8mg (Day2-4)	
Reporting group title	Arm 2 (Placebo)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral Placebo of APD403 (Days 2-4)	
Reporting group title	Arm 3 (APD403 10mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)	
Reporting group title	Arms 4 (APD403 20mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 20mg od (Days 2-4)	
Reporting group title	Arm 5 (APD403 40mg)
Reporting group description:	
IV Ondensotron 8mg + IV APD403 20mg + Oral APD403 40mg od	

Serious adverse events	Arm 1 (DEX)	Arm 2 (Placebo)	Arm 3 (APD403 10mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 66 (7.58%)	3 / 66 (4.55%)	0 / 63 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	1 / 66 (1.52%)	0 / 66 (0.00%)	0 / 63 (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
Gastrointestinal disorders			

Duodenal Obstruction			
subjects affected / exposed	1 / 66 (1.52%)	0 / 66 (0.00%)	0 / 63 (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
Vomiting			
subjects affected / exposed	1 / 66 (1.52%)	1 / 66 (1.52%)	0 / 63 (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
Musculoskeletal and connective tissue disorders			
Haemoptysis			
subjects affected / exposed	1 / 66 (1.52%)	1 / 66 (1.52%)	0 / 63 (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
Infections and infestations			
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 66 (1.52%)	1 / 66 (1.52%)	0 / 63 (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

Serious adverse events	Arms 4 (APD403 20mg)	Arm 5 (APD403 40mg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 68 (1.47%)	2 / 65 (3.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	0 / 68 (0.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal Obstruction			
subjects affected / exposed	0 / 68 (0.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 68 (1.47%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemoptysis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 68 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm 1 (DEX)	Arm 2 (Placebo)	Arm 3 (APD403 10mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 66 (34.85%)	17 / 66 (25.76%)	17 / 63 (26.98%)
Investigations			
Blood prolactin increased			
subjects affected / exposed	3 / 66 (4.55%)	1 / 66 (1.52%)	3 / 63 (4.76%)
occurrences (all)	3	2	3
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 66 (1.52%)	0 / 66 (0.00%)	0 / 63 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 66 (1.52%)	1 / 66 (1.52%)	1 / 63 (1.59%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 66 (3.03%)	0 / 66 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 66 (19.70%)	13 / 66 (19.70%)	13 / 63 (20.63%)
occurrences (all)	13	13	13
Malaise			
subjects affected / exposed	1 / 66 (1.52%)	0 / 66 (0.00%)	0 / 63 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 66 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Arms 4 (APD403 20mg)	Arm 5 (APD403 40mg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 68 (11.76%)	14 / 65 (21.54%)	
Investigations			
Blood prolactin increased			
subjects affected / exposed	1 / 68 (1.47%)	3 / 65 (4.62%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 68 (0.00%)	0 / 65 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 68 (2.94%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 68 (0.00%)	0 / 65 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 68 (7.35%)	11 / 65 (16.92%)	
occurrences (all)	5	11	
Malaise			

subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 65 (0.00%) 0	
Gastrointestinal disorders Gastritis subjects affected / exposed occurrences (all)	 0 / 68 (0.00%) 0	 0 / 65 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2013	Amendments made during this time are as follows:- •Restriction of 16 mg OND to patients with no evidence of moderate or severe hepatic impairment. • Changes to inclusion criterion 5 and exclusion criterion 4. • Changes to the wording for efficacy assessments relating to vomiting, retching and nausea. • Changes to the wording for ECG assessments. • Addition of a section to describe Rules for Early Termination of the Study if patients suffered specific AEs.
10 September 2013	Country specific amendments were made for UK and Denmark. They include the following:- • Changes to exclusion criterion 4. • Changes to the wording for efficacy assessments relating to vomiting, retching and nausea. • Changes to the wording for ECG assessments. • Additional text to the section describing the sample size determination.
15 October 2013	A country specific amendment was made to Germany which include the following:- •Changes to exclusion criterion 11 – addition of azithromycin and deletion of cisapride. • Additional text to the section describing the sample size determination. • Addition of Appendix 8 – insertion of a list of QT-prolonging drugs to be avoided as concomitant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported