Clinical trial results:
Open-label, ascending-dose, Phase II study to determine the minimum effective dose of APD421 (intravenous amisulpride) in the prevention of cisplatin-induced nausea and vomiting

Summary

EudraCT number	2010-022170-14
Trial protocol	GB DK
Global end of trial date	10 July 2012

Results information

Result version number	v1 (current)
This version publication date	19 May 2016
First version publication date	19 May 2016

Trial information

Trial identification

Sponsor protocol code	DN10007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01303978
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acacia Pharma Ltd
Sponsor organisation address	Harston Mill,, Cambridge, United Kingdom, CB22 7GG
Public contact	Dr Gabriel Fox, Acacia Pharma Ltd , 441223 875130, ITHelpdesk@acaciapharma.com
Scientific contact	Dr Gabriel Fox, Acacia Pharma Ltd , 441223 875130, ITHelpdesk@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	10 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2012
Global end of trial reached?	Yes
Global end of trial date	10 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the lowest dose of APD421 which shows an adequate level of effectiveness at preventing sickness in patients given cisplatin chemotherapy (compared to what would be expected based on historical data on other known anti-emetics).

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	10 March 2011
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: 20
Country: Number of subjects enrolled	Denmark: 31
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	29
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Planned: up to 54
Enrolled: 51
Analysed (intent-to-treat): 51
Analysed (per protocol): 51
Analysed (safety): 51
Per cohort:
Cohort 1 (2.5 mg APD421): 5 patients
Cohort 2 (7.5 mg APD421): 5 patients
Cohort 3 (20 mg APD421): 18 patients
Cohort 4 (20 mg APD421 + ondansetron): 23 patients

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 Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	APD421 (2.5mg)

Arm description:

Arm 1(Experimental): APD421 at 2.5mg

Arm type	Experimental
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	APD421
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

APD421 (amisulpride) for intravenous administration, given over 1-2minutes, 30 minutes prior to the administration of cisplatin.

Arm title	APD421 (7.5mg)

Arm description:

Arm 2 (Experimental): APD421 IV at 7.5mg

Arm type	Experimental
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	APD421
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

7.5mg dosage Amisulpride(APD421) given via intravenous(IV) administration over 1-2 minutes, 30 mins prior to administration of cisplatin.

Arm title	APD421 (20mg)

Arm description:	
Arm 3 (Experimental): APD421 IV at 20mg	
Arm type	Experimental
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	APD421
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
20mg dosage Amisulpride(APD421) given via intravenous(IV) administration over 1-2 minutes,30 mins prior to administration of cisplatin.	
Arm title	APD421 Combo with Ondansteron
Arm description:	
Arm 4: APD421 IV at 20mg in combination with a standard dose of IV ondansteron	
Arm type	Experimental
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	APD421
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
20mg dosage Amisulpride(APD421) given via intravenous(IV) administration over 1-2 minutes,30 mins prior to administration of cisplatin.	
Investigational medicinal product name	Ondansetron
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
Ondansetron give at a dose of 8-16mg according to usual site procedures	

Number of subjects in period 1	APD421 (2.5mg)	APD421 (7.5mg)	APD421 (20mg)
Started	5	5	18
Completed	5	5	18

Number of subjects in period 1	APD421 Combo with Ondansteron
Started	23
Completed	23

Baseline characteristics

Reporting groups

Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	51	51	
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)	26	26	
From 65-84 years	25	25	
85 years and over	0	0	
Age continuous Units: years			
median	64		
full range (min-max)	42 to 77	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	30	30	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who signed informed consent, enrolled into the study and received study drug were included in the ITT analysis.

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who received the study medication and adhered to the protocol with no major protocol violations, as decided and documented by the sponsor"s Chief Medical Officer, were included in a per protocol analysis. The reason for exclusion of any cases was documented.

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

This is identical to the ITT population, in the sense that all subjects who signed the informed consent and received study drug were included in the Safety Analysis.

Reporting group values	ITT	Per Protocol	Safety Analysis
Number of subjects	51	51	51
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)	26	26	26
From 65-84 years	25	25	25
85 years and over	0	0	0
Age continuous Units: years			
median	64	64	64
full range (min-max)	42 to 77	42 to 77	42 to 77
Gender categorical Units: Subjects			
Female	21	21	21
Male	30	30	30

End points

End points reporting groups

Reporting group title	APD421 (2.5mg)
Reporting group description:	
Arm 1(Experimental): APD421 at 2.5mg	
Reporting group title	APD421 (7.5mg)
Reporting group description:	
Arm 2 (Experimental): APD421 IV at 7.5mg	
Reporting group title	APD421 (20mg)
Reporting group description:	
Arm 3 (Experimental): APD421 IV at 20mg	
Reporting group title	APD421 Combo with Ondansteron
Reporting group description:	
Arm 4: APD421 IV at 20mg in combination with a standard dose of IV ondansteron	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who signed informed consent, enrolled into the study and received study drug were included in the ITT analysis.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received the study medication and adhered to the protocol with no major protocol violations, as decided and documented by the sponsor"s Chief Medical Officer, were included in a per protocol analysis. The reason for exclusion of any cases was documented.	
Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
This is identical to the ITT population, in the sense that all subjects who signed the informed consent and received study drug were included in the Safety Analysis.	

Primary: Incidence of emesis in the 24-hour period post Cisplatin

End point title	Incidence of emesis in the 24-hour period post Cisplatin
End point description:	
End point type	Primary
End point timeframe:	
24 hours	

End point values	APD421 (2.5mg)	APD421 (7.5mg)	APD421 (20mg)	APD421 Combo with Ondansteron
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	18	23
Units: Whole numbers	5	5	15	4

End point values	ITT	Per Protocol	Safety Analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	51	51	51	
Units: Whole numbers	29	29	29	

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis

Statistical analysis description:

The primary efficacy analysis was a description of the rate of complete response with a 90% confidence intervals at each dose of APD421 and in the combination therapy cohort adjusted with the possibility of stopping at the end of the first stage.

Comparison groups	APD421 (2.5mg) v APD421 (7.5mg) v APD421 (20mg) v APD421 Combo with Ondansteron
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AE encountered during the study will be reported in detail in the source documents and noted in the AE section of the CRF from the date of subject consent, throughout the clinical conduct and up to the follow-up visit.

Adverse event reporting additional description:

The nature and frequency of AEs in the study were recorded on the CRF by the investigator and were standardised by assigning terminology according to the Medical Dictionary for Drug Regulatory Affairs(MedDRA)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	2.5mg APD421
Reporting group description: -	
Reporting group title	7.5mg APD421
Reporting group description: -	
Reporting group title	20mg APD421
Reporting group description: -	
Reporting group title	20mg APD421 + Ondasetron
Reporting group description: -	

Serious adverse events	2.5mg APD421	7.5mg APD421	20mg APD421
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	5 / 18 (27.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension, Irregular heart beat, Renal disorder, Sepsis and Spinal Cord Compression	Additional description: Hypotension, Irregular heart beat, Renal disorder, Sepsis and Spinal Cord Compression		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 18 (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			
Pain	Additional description: The patient experienced moderate pain while taking part in the study.		
alternative assessment type: Systematic			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia Obstructive	Additional description: Patient experienced incarcerated hernia whist participating in the study.		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 18 (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			
Pulmonary embolism	Additional description: Pulmonary embolism		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	20mg APD421 + Ondasetron		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension, Irregular heart beat, Renal disorder, Sepsis and Spinal	Additional description: Hypotension, Irregular heart beat, Renal disorder, Sepsis and Spinal Cord Compression		

Cord Compression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain	Additional description: The patient experienced moderate pain while taking part in the study.		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hernia Obstructive	Additional description: Patient experienced incarcerated hernia whist participating in the study.		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: Pulmonary embolism		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
alternative assessment type: Systematic			

subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	2.5mg APD421	7.5mg APD421	20mg APD421
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	18 / 18 (100.00%)
Vascular disorders			
Increased Hypertension	Additional description: Increased Hypertension		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chills	Additional description: Chills		
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Infusion site pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 5 (80.00%)	4 / 5 (80.00%)	15 / 18 (83.33%)
occurrences (all)	4	4	15
Nausea			
alternative assessment type: Systematic			

subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	14 / 18 (77.78%)
occurrences (all)	5	5	14
Dry Mouth	Additional description: Dry Mouth		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Retching	Additional description: Retching		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	4 / 18 (22.22%)
occurrences (all)	1	0	4
Constipation	Additional description: Constipation		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Rash around eyes-puritus	Additional description: Rash around eyes-puritus		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Erythema of chest and upper back	Additional description: Erythema of chest and upper back		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Myalgia		
alternative assessment type: Systematic			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	20mg APD421 + Ondasetron		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 23 (30.43%)		
Vascular disorders			
Increased Hypertension	Additional description: Increased Hypertension		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Chills	Additional description: Chills		
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Infusion site pain			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	5		
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 23 (30.43%)		
occurrences (all)	7		
Dry Mouth	Additional description: Dry Mouth		
alternative assessment type: Systematic			

subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Retching	Additional description: Retching		
alternative assessment type: Systematic			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Constipation	Additional description: Constipation		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash around eyes-puritus	Additional description: Rash around eyes-puritus		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Erythema of chest and upper back	Additional description: Erythema of chest and upper back		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Myalgia		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2011	A substantial amendment to the protocol was approved on 02 June 2011 to enrol a further cohort of subjects to be given APD421 at the highest dose level showing signs of efficacy, in combination with a single dose of IV ondansetron (given according to its marketing authorisation),
14 June 2011	A substantial amendment to the protocol was approved on 14 June 2011 to allow the proactive collection of nausea data at 2, 4, 8, and 24 hours post-cisplatin in addition to reactively, when nausea was reported by the patient.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported