Clinical trial results:
Randomised, double-blind, placebo-controlled study of APD421 (amisulpride for IV injection) as treatment of established post-operative nausea and vomiting, in patients who have had prior prophylaxis

Summary

EudraCT number	2015-003992-30
Trial protocol	DE
Global end of trial date	20 January 2017

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	DP10019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02646566
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acacia Pharma Ltd
Sponsor organisation address	Harston mill, Harston, United Kingdom, cb22 7gg
Public contact	Dr Gabriel Fox, Acacia Pharma Ltd, Medinfo@acaciapharma.com
Scientific contact	Dr Gabriel Fox, Acacia Pharma Ltd, Medinfo@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	31 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2017
Global end of trial reached?	Yes
Global end of trial date	20 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of 5 mg and 10 mg APD421 to placebo as treatment of established PONV, in adults who have had prior PONV prophylaxis

Protection of trial subjects:

The investigator or individuals designated by the investigator (where acceptable by regulations) was responsible for ensuring that each patient were provided a signed and dated written informed consent before participating in the study. Each patient who attended a pre-study visit was provided with a written explanation of the study giving details of the investigational drug, study procedures and objectives, potential hazards involved and overall requirements for study subjects

Background therapy:

N/A

Evidence for comparator:

Placebo

Actual start date of recruitment	08 February 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	France: 28
Country: Number of subjects enrolled	Germany: 158
Country: Number of subjects enrolled	Canada: 142
Country: Number of subjects enrolled	United States: 374
Worldwide total number of subjects	702
EEA total number of subjects	186

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)	638
From 65 to 84 years	63
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Planned (consent): 2,500
Planned (randomised): 700 (to give at least 690 evaluable patients, 230 in each of the three treatment arms)
Planned (per country, randomised): Germany, 190; France, 15; Canada, 100; USA, 395
Enrolled (consented): 2,285

Pre-assignment

Screening details:

The study consisted of screening from days –28 to 0 (day of operation); a primary study period, which was the period beginning with the first episode of PONV (emesis and/or a request by the patient for anti-emetic medication to treat nausea) and ending 24 hours after administration of study medication, safety follow-up continued up to Day 7.

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, Data analyst

Blinding implementation details:

The randomisation information was not available to the sponsor or to any personnel at any study site or at the CRO. The randomisation list was made available to the appropriate Qualified Person at the clinical packaging contractor for the study labelling Purpose

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Study medication (APD421/placebo) was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula

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

Dosage and administration details:

Study medication (APD421/placebo) was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula

Arm title	APD421 at 5mg

Arm description:

APD421 (Amisulpride) at 5mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.

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:

APD421 at 5mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.

Arm title	APD421 at 10mg

Arm description:

APD421 at 10mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.

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:

APD421 at 10mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.

Number of subjects in period 1	Placebo	APD421 at 5mg	APD421 at 10mg
Started	235	237	230
Completed	230	231	226
Not completed	5	6	4
Lost to follow-up	5	5	4
Dropped out	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Study medication (APD421/placebo) was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula	
Reporting group title	APD421 at 5mg
Reporting group description:	
APD421 (Amisulpride) at 5mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.	
Reporting group title	APD421 at 10mg
Reporting group description:	
APD421 at 10mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.	

Reporting group values	Placebo	APD421 at 5mg	APD421 at 10mg
Number of subjects	235	237	230
Age categorical Units: Subjects			
Adults (18-64 years)	217	215	206
From 65-84 years	18	22	23
85 years and over	0	0	1
Age continuous Units: years			
arithmetic mean	46	45.8	46.9
standard deviation	± 13.38	± 13.12	± 13.03
Gender categorical Units: Subjects			
Female	212	213	208
Male	23	24	22

Reporting group values	Total		
Number of subjects	702		
Age categorical Units: Subjects			
Adults (18-64 years)	638		
From 65-84 years	63		
85 years and over	1		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	633		
Male	69		

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population was considered the primary efficacy analysis population and included all patients who had signed the ICF, were randomised into the study and received a dose of either APD421 or placebo.

Reporting group values	mITT		
Number of subjects	702		
Age categorical Units: Subjects			
Adults (18-64 years)	638		
From 65-84 years	63		
85 years and over	1		
Age continuous Units: years			
arithmetic mean	46.3		
standard deviation	± 13.17		
Gender categorical Units: Subjects			
Female	633		
Male	69		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Study medication (APD421/placebo) was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula

Reporting group title	APD421 at 5mg

Reporting group description:

APD421 (Amisulpride) at 5mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.

Reporting group title	APD421 at 10mg

Reporting group description:

APD421 at 10mg was administered to each patient in a double-blind fashion, by slow IV push over about two minutes into a peripheral or central venous cannula.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT population was considered the primary efficacy analysis population and included all patients who had signed the ICF, were randomised into the study and received a dose of either APD421 or placebo.

Primary: Number of Complete Responders in a 24-hour period after study drug administration

End point title	Number of Complete Responders in a 24-hour period after study drug administration

End point description:

The primary efficacy endpoint defined as success or failure of initial study treatment (complete response), where success was defined as no emetic episodes (vomiting or retching) from 30 minutes (to give time for the study medication to take effect) to 24 hours after administration of study medication and no administration of anti-emetic rescue medication at any time in the 24-hour period after administration of study medication.

End point type	Primary

End point timeframe:

24 hour period after study drug administration

End point values	Placebo	APD421 at 5mg	APD421 at 10mg	mITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	235	237	230	702
Units: Number of Complete Responders	67	96	80	702

Statistical analyses

Statistical analysis title	Pearson's chi-squared test

Statistical analysis description:

Analysis 1: Primary efficacy analysis comparison of the incidence of the primary efficacy variable between the group that received 5mg APD421 and the group that received placebo using Pearson’s chi-squared test.

Comparison groups	APD421 at 5mg v Placebo
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109 [1]
Method	Chi-squared

Notes:

[1] - One-sided p-value,adjusted for multiplicity using the Hommel procedure.

Statistical analysis title	Pearson's chi-squared test

Statistical analysis description:

Analysis 2: Primary efficacy analysis comparison of the incidence of the primary efficacy variable between the group that received 10mg APD421 and the group that received placebo using Pearson’s chi-squared test.

Comparison groups	Placebo v APD421 at 10mg
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [2]
Method	Chi-squared

Notes:

[2] - One-sided p-value,adjusted for multiplicity using the Hommel procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any Adverse events from randomization, throughout the clinical conduct and up to the follow-up visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	APD421 IV at 5mg

Reporting group description:

APD421 given intravenously at 5mg

Reporting group title	APD421 IV at 10mg

Reporting group description: -

Reporting group title	APD421 IV Placebo

Reporting group description: -

Serious adverse events	APD421 IV at 5mg	APD421 IV at 10mg	APD421 IV Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 100 (6.00%)	3 / 99 (3.03%)	5 / 113 (4.42%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Gastrointestinal anastomotic leak			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 113 (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
Postoperative ileus			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 113 (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
Cardiac disorders			
Acute Myocardial Infaction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 113 (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
Blood and lymphatic system disorders			
Leukocytosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 113 (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
Eye disorders			
Periorbital fat herniation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 113 (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			
Colitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 113 (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
Gastrointestinal inflammation			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra abdominal Haematoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural atomic bile leak			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 113 (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
Infections and infestations			
Pelvic abscess			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 113 (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
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 113 (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

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

Non-serious adverse events	APD421 IV at 5mg	APD421 IV at 10mg	APD421 IV Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 100 (33.00%)	28 / 99 (28.28%)	32 / 113 (28.32%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 100 (10.00%)	10 / 99 (10.10%)	17 / 113 (15.04%)
occurrences (all)	10	10	17
General disorders and administration site conditions			
Infusion site pain			
subjects affected / exposed	8 / 100 (8.00%)	12 / 99 (12.12%)	10 / 113 (8.85%)
occurrences (all)	8	12	10
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	30 / 100 (30.00%)	27 / 99 (27.27%)	30 / 113 (26.55%)
occurrences (all)	33	28	32
Flatulence			
subjects affected / exposed	13 / 100 (13.00%)	13 / 99 (13.13%)	18 / 113 (15.93%)
occurrences (all)	13	13	18
Constipation			
subjects affected / exposed	13 / 100 (13.00%)	11 / 99 (11.11%)	17 / 113 (15.04%)
occurrences (all)	13	11	17
Vomiting			
subjects affected / exposed	11 / 100 (11.00%)	10 / 99 (10.10%)	13 / 113 (11.50%)
occurrences (all)	14	11	13
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 100 (7.00%)	10 / 99 (10.10%)	13 / 113 (11.50%)
occurrences (all)	7	10	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2016	Country specific changes for France version 1.1- Change to exclusion criteria, addition of electrocardiogram and addition of ECG information.
05 October 2016	Substantial Amendment- Change to number of patients and estimated recruitment, change to expected number of study centers, change to exclusion criteria, expansion of secondary efficacy variable to include measures of the time course of nausea, addition of sensitivity analysis to secondary efficacy analysis, Change in sample size statement to include revised patient numbers and difference in response rate between treatments. Addition of electrocardiogram (This is applicable to France only) and addition of ECG information, including timing, equipment requirements, review and storage of tracings. Addition of ECG information.

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.

None reported

Notes: