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 no prior prophylaxis.

Summary

EudraCT number	2015-002041-59
Trial protocol	DE
Global end of trial date	18 July 2016

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	DP10018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02449291
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, 01223 875149, medinfo@acaciapharma.com
Scientific contact	Dr Gabriel Fox, Acacia Pharma Ltd, 01223 875149, 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	17 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2016
Global end of trial reached?	Yes
Global end of trial date	18 July 2016
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 no 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 provided 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	20 July 2015
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	Canada: 95
Country: Number of subjects enrolled	United States: 266
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 183
Worldwide total number of subjects	560
EEA total number of subjects	199

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)	505
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Planned (Consent):-2,500
Planned (Randomised):- 580
Analysed (Safety):-560
Intent-To-Treat:-560
Per Protocol:-542
Enrolled:- 1,988
Randomised and did not receive treatment and discontinued the study:- 8
Randomised and received treatment and completed the study:-552

Pre-assignment

Screening details:

The study consisted of a screening period from days –28 to 0 (day of 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

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 labeling purpose.

Arms

Are arms mutually exclusive?	Yes
Arm title	APD421 at 5mg

Arm description:

APD421 (Amisulpride) at 5mg is administered as a single slow intravenous (IV) push over a period of two minutes.

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 (Amisulpride) at 5mg administered as a single, slow intravenous (IV) push over a period of two minutes.

Arm title	APD421 at 10mg

Arm description:

APD421 (Amisulpride) at 10mg is administered as single slow intravenous push over a period of two minutes.

Arm type	Experimental

Investigational medicinal product name	Amisulpride
Investigational medicinal product code	ADP421
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

APD421 (Amisulpride) at 10mg administered as a single, slow intravenous (IV) push over a period of two minutes.

Arm title	APD421 IV Placebo

Arm description:

APD421 Placebo administered as a single dose, slow IV push over a period of two minutes.

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

Dosage and administration details:

APD421 Placebo administered as a single, slow IV push over a period of two minutes

Number of subjects in period 1	APD421 at 5mg	APD421 at 10mg	APD421 IV Placebo
Started	191	188	181
Completed	186	186	180
Not completed	5	2	1
Major Protocol Deviation	1	-	-
Lost to follow-up	4	2	1

Baseline characteristics

Reporting groups	
Reporting group title	APD421 at 5mg
Reporting group description:	
APD421 (Amisulpride) at 5mg is administered as a single slow intravenous (IV) push over a period of two minutes.	
Reporting group title	APD421 at 10mg
Reporting group description:	
APD421 (Amisulpride) at 10mg is administered as single slow intravenous push over a period of two minutes.	
Reporting group title	APD421 IV Placebo
Reporting group description:	
APD421 Placebo administered as a single dose, slow IV push over a period of two minutes.	

Reporting group values	APD421 at 5mg	APD421 at 10mg	APD421 IV Placebo
Number of subjects	191	188	181
Age categorical Units: Subjects			
Adults (18-64 years)	178	168	159
From 65-84 years	13	20	22
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.3	47.4	46.5
standard deviation	± 13.24	± 14.42	± 14.13
Gender categorical Units: Subjects			
Female	146	145	136
Male	45	43	45

Reporting group values	Total		
Number of subjects	560		
Age categorical Units: Subjects			
Adults (18-64 years)	505		
From 65-84 years	55		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	427		
Male	133		

Subject analysis sets

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

Subject analysis set description:

All subjects who have signed the informed consent form and been randomised into the study by virtue of receiving a dose of APD421 or placebo study medication.

Reporting group values	mITT		
Number of subjects	560		
Age categorical Units: Subjects			
Adults (18-64 years)	505		
From 65-84 years	55		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical Units: Subjects			
Female	427		
Male	133		

End points

End points reporting groups

Reporting group title	APD421 at 5mg

Reporting group description:

APD421 (Amisulpride) at 5mg is administered as a single slow intravenous (IV) push over a period of two minutes.

Reporting group title	APD421 at 10mg

Reporting group description:

APD421 (Amisulpride) at 10mg is administered as single slow intravenous push over a period of two minutes.

Reporting group title	APD421 IV Placebo

Reporting group description:

APD421 Placebo administered as a single dose, slow IV push over a period of two minutes.

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

Subject analysis set description:

All subjects who have signed the informed consent form and been randomised into the study by virtue of receiving a dose of APD421 or placebo study medication.

Primary: Incidence of complete response in the 24-hour period after treatment

End point title	Incidence of complete response in the 24-hour period after treatment

End point description:

The primary efficacy variable is the dichotomous variable: success or failure of initial PONV treatment, where success is defined as no emetic episodes (vomiting or retching) from 30 minutes 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 study medication

End point type	Primary

End point timeframe:

24hr period after study drug administration.

End point values	APD421 at 5mg	APD421 at 10mg	APD421 IV Placebo	mITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	191	188	181	560
Units: Comparison of the incidence of CR	60	59	39	560

Statistical analyses

Statistical analysis title	5 mg APD421 v placebo

Statistical analysis description:

The primary efficacy analysis was a comparison of the incidence of the primary efficacy variable between the two groups that received APD421 and the group that received placebo using Pearson chi-square test.

Comparison groups	APD421 at 5mg v APD421 IV Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [1]
Method	Chi-squared

Notes:

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

Statistical analysis title	10 mg APD421 v placebo
Comparison groups	APD421 at 10mg v APD421 IV Placebo
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [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 AE from randomisation, 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 at 5mg
Reporting group description: APD421 at 5mg administered as a single slow intravenous (IV) push over a period of two minutes.	
Reporting group title	APD421 at 10mg
Reporting group description: APD421 at 10mg is administered as a single slow intravenous IV push over a period of two minutes.	
Reporting group title	APD421 IV Placebo
Reporting group description: -	

Serious adverse events	APD421 at 5mg	APD421 at 10mg	APD421 IV Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 191 (2.62%)	4 / 188 (2.13%)	5 / 181 (2.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Pulmonary embolism			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 181 (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
Post procedural haematoma			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 181 (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			
subjects affected / exposed	1 / 191 (0.52%)	1 / 188 (0.53%)	0 / 181 (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
Procedural Pain			

subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 181 (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
Post-procedural bile leak			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 181 (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 anastomotic leak			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 181 (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
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 181 (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			
Abdominal Pain			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
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			

subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 181 (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
Respiratory, thoracic and mediastinal disorders			
Dysponea			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritonitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Abscess			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 181 (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

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

Non-serious adverse events	APD421 at 5mg	APD421 at 10mg	APD421 IV Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 191 (31.94%)	61 / 188 (32.45%)	63 / 181 (34.81%)
General disorders and administration site conditions			

Infusion site pain			
subjects affected / exposed	8 / 191 (4.19%)	13 / 188 (6.91%)	7 / 181 (3.87%)
occurrences (all)	8	13	7
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	24 / 191 (12.57%)	17 / 188 (9.04%)	21 / 181 (11.60%)
occurrences (all)	25	17	21
Nausea			
subjects affected / exposed	15 / 191 (7.85%)	18 / 188 (9.57%)	19 / 181 (10.50%)
occurrences (all)	17	18	22
Constipation			
subjects affected / exposed	14 / 191 (7.33%)	13 / 188 (6.91%)	16 / 181 (8.84%)
occurrences (all)	14	13	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2015	Non-substantial amendment was made specifically to only the French protocol (Version 1.1)- Three exclusion criteria was added.
07 September 2015	A non-substantial amendment was made specifically on the German Protocol (version 1.2)- one exclusion criteria was added.
23 September 2015	Protocol version 1.3 was developed for UK sites but not implemented as UK sites were not initiated.
29 October 2015	A non-substantial amendment was made for French specific protocol (version 1.4)- A change to laboratory tests/ assessments.
18 December 2015	A substantial amendment was made to all sites version 2.0- Amendments made to version 1.0 incorporated those made to country specific versions 1.1, 1.2 and 1.4. Changes made include the following:- Changes were made to study design Number of subjects and estimated recruitment Addition if the definition of randomisation and the change to randomisation for the drop dose selection Changes made to study centres Changes to exclusion criteria Redefinition of the primary study period Changes to laboratory tests/ assessments. Flexibilty around nominal study time points Change to labelling information Change to definitions Redefinition of primary efficacy analysis Redefinition of ITT analysis population Change to only one blinded data review at the end of the study Appendix 3 deleted Changes to the wording for the anti-emetic agents in appendix 4
04 February 2016	A non-substantial amendment was made to the German country specific protocol (version 2.1)- Changes were made to the one of the exclusion criteria of the protocol.

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: