CLINICAL DEVELOPMENT DEPARTMENT

FINAL STUDY REPORT

Study Number: DP10006

Randomised, double-blind, placebo-controlled, Phase II study to assess the safety and efficacy of different doses of intravenous APD421 (amisulpride for IV injection) for the prevention of post-operative nausea and vomiting

Investigational Medicinal Product(s)	**APD421 (INN: amisulpride)**	Version	**1.0**
		Date	**01 Nov 2012**
EUDRACT No	**2011-004267-71**	Principal Investigator	**Prof Peter Kranke**

FINAL STUDY REPORT

Study No	DP10006
Eudract No	2011-004267-71
Study title	Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Safety and Efficacy of Different Doses of Intravenous APD421 (Amisulpride for IV Injection) for the Prevention of Post-Operative Nausea and Vomiting
Study design	Ascending dose, randomised, double-blind, placebo-controlled study.
IMP(s)	APD421
Comparator product	Placebo
Development phase	Phase II
Principal investigator	Professor Peter Kranke Department of Anaesthesia and Critical Care University Hospitals of Würzburg Germany
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Study start date	17 Jan 2012 (first patient screened)
Study completion date	25 Apr 2012
Date of report	01 Nov 2012
This study was conducted in accordance with the European Good Clinical Practice (GCP) guideline as issued by the European Community (EU Directive 2001/20/EC, including the subsequent amendments 2003/94/EC and 2005/28/EC), the Medicines for Human Use regulations (SI 2004/1031, 2006/1928 and 2008/941) and the Committee of Proprietary Medicinal Products (CPMP) and International Conference on Harmonisation (ICH) 1997 guideline on GCP (CPMP/ICH/135/95) and the principles enunciated in the Declaration of Helsinki (October 1996).	

1 Study Synopsis

Name of Sponsor/Company: Acacia Pharma Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Study Treatment: APD421		
Name of Active Ingredient: APD421		

Title of Study: Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Safety and Efficacy of Different Doses of Intravenous APD421 (amisulpride for IV injection) for the Prevention of Post-Operative Nausea and Vomiting

Investigators:

France: Professor Hervé Bouaziz, Nancy; Dr Ngai Liu, Paris; Professor Dominique Chassard, Lyon; Professor Pierre Diemunsch, Strasbourg

Germany: Professor Peter Kranke (Principal Investigator), Würzburg; Professor Leopold Eberhart, Marburg; Dr Jan Wallenborn, Aue; Dr Johann Motsch, Heidelberg; Dr Didier Keh, Berlin

USA: Professor TJ Gan, Durham NC

Study Centres: 4 sites in France (Nancy, Paris, Lyon and Strasbourg), 5 sites in Germany (Würzburg, Marburg, Aue, Heidelberg and Berlin) and 1 site in the USA (Durham NC)

Publication (Reference): None

Studied Period: 17 Jan 2012 to 25 Apr 2012	**Phase of Development:** II

Objectives:

The primary objective of the study was to assess the efficacy of different doses of APD421 in the prevention of post-operative nausea and vomiting (PONV) in patients at moderate to high risk of PONV, in terms of the proportion of patients with no vomiting/retching and no use of rescue medication during the first 24 hours after completion of surgery.

The secondary objectives of the study were:

- To assess the efficacy of APD421 in terms of:
  - the incidence of total response (absence of vomiting/retching and nausea and no requirement for rescue medication during the first 24 hours after completion of surgery)
  - the incidence and severity of nausea
  - the incidence of vomiting
  - time to first vomiting
  - the frequency of use of rescue medication
  - the above variables in a sub-group of patients receiving opioids for post-operative analgesia
  - sub-groups of the above variables over time
- To assess the nature and frequency of adverse events (AEs) of APD421 patients at risk of PONV.

Methodology:

This was a multi-centre, double-blind, randomised, placebo-controlled study with 4 treatment groups of patients at moderate to high risk of PONV.

Patients were screened up to 14 days before the planned date of their operation and admitted to hospital on the day before (Day -1) or morning of (Day 0) their operation.

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Study medication was given at induction of anaesthesia. Assessments were conducted during the 24 hours following study drug administration. Patients were discharged 24 hours after the end of their operation. Patients who had met the criteria for experiencing PONV could have been discharged any time from 16 hours after completion of surgery, at the discretion of the investigator, provided that nominal 24-hour procedures were completed prior to discharge. Patients who did not fail prophylaxis could also have been discharged any time from 16 hours after completion of surgery, provided that they had completed an overnight stay, they had not suffered any significant nausea or vomiting since waking on Day 1, and nominal 24-hour procedures were completed prior to discharge. Telephone follow-up was conducted 7 days after the operation.

Number of Patients (Planned and Analysed):

Planned: 208

Enrolled: 223

Analysed (intent-to-treat): 215

Analysed (per protocol): 199

Analysed (opiates): 140

Analysed (safety): 215

Diagnosis and Main Criteria for Inclusion:

Adult patients (≥18 years) who had freely given informed consent, were at moderate to high risk of PONV and were undergoing elective surgery under general anaesthesia for hysterectomy, cholecystectomy or other elective surgery that required overnight admission to hospital and was scheduled to last at least 1 hour from induction of anaesthesia. Moderate to high risk of PONV was defined as having at least 2 of the following risk factors:

- Past history of PONV or motion sickness
- Habitual non-smoking status
- Female
- Planned opioid use for post-operative analgesia

Test Product, Dose and Mode of Administration, Batch Number:

APD421 (amisulpride), batch number RX501138.005, for single intravenous (IV) administration by slow push over 1 to 2 minutes at induction of anaesthesia at one of the following doses: 1 mg, 5 mg or 20 mg.

Duration of Treatment:

Single dose

Reference Therapy, Dose and Mode of Administration, Batch Number:

Matching placebo, batch number RX501138.005, for single IV administration by slow push over 1 to 2 minutes at induction of anaesthesia.

Criteria for Evaluation:

Efficacy

The occurrence of any vomiting/retching and the occurrence and severity of any nausea was recorded. The patient's opinion of the severity of the nausea was

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measured using an 11-point verbal rating scale, where 0 represented no nausea and 10 represented the worst nausea imaginable.

In addition to the recording of any spontaneous reports of nausea, patients were asked about the presence (and severity, if applicable) of nausea at 0.5, 1, 1.5, 2, 6 and 24 hours after completion of surgery.

The use of any rescue anti-emetic medication and opioid analgesics during the 24 hour post-operative period was recorded.

Safety

The safety and tolerability of APD421 were assessed by monitoring AEs, vital signs, laboratory tests, electrocardiograms (ECGs) and performing general physical and specific neurological examinations.

Statistical Methods:

Primary Efficacy Analysis

The primary efficacy variable was the proportion of patients in each treatment group experiencing PONV, defined as the occurrence of an emetic episode (vomiting or retching) or receipt of rescue anti-emetic medication.

The primary efficacy analysis was a comparison of the incidence of the primary efficacy variable between each treated group and the placebo group using Pearson's chi-squared test with Yates' continuity correction on a one sided significance level of 10%.

For the highest treatment group (ie APD421 group with the highest occurrence of PONV) and placebo, the null hypothesis of independence between treatment and the occurrence of PONV was tested. For this analysis missing values of this variable was imputed with "yes". If the first null hypothesis was rejected, the next lower treatment group was tested with placebo. Testing was to continue, descending to the lowest treatment group, but stopped as soon as the null hypothesis could not be rejected for the first time.

Secondary Efficacy Analysis

The occurrence of PONV was further analysed using a logistic regression model including the following explanatory variables: country, number of risk factors, type of operation and treatment group.

For the secondary efficacy variables such as occurrence of nausea, occurrence of vomiting, use of rescue medication, occurrence of significant nausea and occurrence of total response, pairwise comparisons between each APD421 dose group and the placebo group were performed.

For the variable time to first vomiting (censored), pairwise comparisons between each APD421 dose group and the placebo group were performed.

The maximum severity of nausea was calculated for each patient for the 24-h post-operative period and also by time interval depending on the time of onset of the episode with the maximum severity ie 0 to 2 h, 2 to 6 h and 6 to 24 h. In addition, the maximum severity was calculated for each time interval (ie 0 to 2 h, 2 to 6 h and 6 to 24 h) on a per patient basis. Descriptive statistics were used and no formal statistical testing was performed on these data.

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Where applicable, secondary efficacy analyses were repeated for restricted intervals 0 to 2 h, 2 to 6 h and 6 to 24 h and for the subgroup of patients receiving opiates for post-operative analgesia.

Summary – Conclusions:

Efficacy Results

Occurrence of PONV

The occurrence of PONV was lowest in the 5 mg APD421 group (36.17%) followed by the 1 mg and 20 mg APD421 groups (45.28% and 51.06%) and placebo (67.31%). The occurrence of PONV was statistically lower for the 5 mg and 1 mg APD421 dose groups compared with placebo (p = 0.004 and 0.038, respectively); however, there was no significant difference between the 20 mg APD421 dose group and the placebo group (p = 0.15).

The time at which 50% of patients had PONV was 231, >1440, >1440 and 905 min for placebo, 1 mg, 5 mg and 20 mg APD421, respectively. Overall, the time to the first episode of PONV was significantly longer in all APD421 dose groups compared with placebo (p = 0.008, 0.002 and 0.078 for 1 mg, 5 mg and 20 mg APD421, respectively).

The breakdown of PONV by country revealed a higher incidence of PONV in the APD421 dose groups in German compared to non-German sites, although there is no obvious explanation for this effect, particularly as it was not apparent in the placebo dose group. No consistent trends were apparent when reviewing the incidence of PONV by number of risk factors or previous history of motion sickness or PONV.

Occurrence of Vomiting

The occurrence of vomiting was lowest in the 5 mg APD421 group (14.89%) followed by the 20 mg and 1 mg APD421 groups (17.02% and 28.30%, respectively) and placebo (36.54%). The occurrence of vomiting was significantly lower for the 5 mg and 20 mg APD421 dose groups compared with placebo (p = 0.027 and 0.051, respectively); however, this was not demonstrated for the 1 mg APD421 dose group (p = 0.49). It would appear that the increased occurrence of vomiting in the 1 mg APD421 group compared with the 5 mg APD421 group differentiates the 5 mg dose as more efficacious than the 1 mg dose.

The time at which 50% of patients had a vomiting episode was greater than 1440 min for all dose groups. Overall, the time to the first episode of vomiting was significantly longer in the 5 mg (p = 0.014) and 20 mg APD421 (p = 0.027) dose groups compared with placebo; however, this was not observed for the 1 mg APD421 dose group (p = 0.31).

Occurrence of Rescue Medication Use

The occurrence of rescue medication use was lowest in the 5 mg APD421 group (34.04%) followed by the 1 mg and 20 mg APD421 groups (43.40% and 48.94%, respectively) and placebo (65.38%). The occurrence of rescue medication use was significantly lower for the 5 mg and 1 mg APD421 dose groups compared with placebo (p = 0.004 and 0.039, respectively); however, this was not demonstrated for the 20 mg APD421 dose group (p = 0.15). It would appear that the increased rescue medication use in the 20 mg APD421 group compared with the 1 mg and 5 mg

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APD421 groups differentiates the 1 mg and 5 mg dose as more efficacious than the 20 mg dose.

The time at which 50% of patients had used rescue medication was 259 min in the placebo group and was greater than 1440 min for all APD421 groups. Overall, the time to the first rescue medication was significantly longer in all APD421 dose groups compared with placebo (p = 0.009, 0.001 and 0.086 for 1 mg, 5 mg and 20 mg APD421, respectively).

Occurrence of Nausea

The occurrence of nausea was lowest in the 1 mg APD421 group (37.74%) followed by the 5 mg and 20 mg APD421 groups (38.30% and 51.06%, respectively) and placebo (69.23%). The occurrence of nausea was significantly lower for the 1 mg and 5 mg APD421 dose groups compared with placebo (p = 0.002 and 0.004, respectively); however, this was not demonstrated for the 20 mg APD421 dose group (p = 0.10). In addition, there was some evidence that the maximum severity of nausea was highest in the placebo group (mean (standard deviation [SD]) = 3.7 [3.1]) and lowest in the 5 mg APD421 dose group (mean [SD] = 2.3 [3.3]), although, this was not statistically analysed.

Safety Results

There appeared to be a slightly higher incidence of TEAEs in the placebo group compared with the APD421 dose groups (96.3%, 86.2%, 78.0% and 86.8% in the placebo, 1 mg, 5 mg and 20 mg APD421 groups, respectively); however, when vomiting and nausea events were excluded, there was no difference between placebo and the APD421 groups in the incidence of TEAEs (83.3%, 79.3%, 74.0% and 77.4%, respectively). Similarly, there was no notable difference in the incidence of TEAEs between the APD421 dose groups (1 mg, 5 mg and 20 mg APD421). In all dose groups, the majority of TEAEs were mild and unrelated to study drug. Procedural pain was the most common TEAE across all dose groups (approximately 50% in each dose group) followed by nausea (39.1% overall) and vomiting (22.3% overall). The incidence of nausea and vomiting was higher in the placebo group (51.9% and 33.3%, respectively) than the APD421 dose groups (32.8%, 26.0% and 45.3% for vomiting and 24.1%, 14.0% and 17.0% for nausea in the 1 mg, 5 mg and 20 mg APD421 groups, respectively). There was no notable difference between placebo and APD421 in the nature of TEAEs, with the exception of insomnia, procedural hypotension and hypertension, which were all reported by more patients in the APD421 groups (5.2% to 10.0% for insomnia, 4.0% to 5.7% for procedural hypotension and 1.7% to 5.7% for hypertension) than the placebo group (1.9%, 31.9% and 1.9% for insomnia, procedural hypotension and hypertension, respectively).

Five patients experienced serious adverse events but these were all associated with surgical procedures and none was considered related to study drug.

APD421 had no adverse effect on clinical laboratory assessment, vital signs or ECG measurements.

Conclusions

- The occurrence of PONV was significantly lower and the time to the first episode of PONV was significantly longer in the APD421 dose groups compared with

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placebo. There was no dose-related response in the occurrence of PONV or time to first episode of PONV, with 5 mg APD421 appearing to be the most efficacious, followed by 1 mg and 20 mg APD421.

- The occurrence of vomiting was significantly lower and the time to the first episode of vomiting was significantly longer in the 5 mg and 20 mg APD421 dose groups compared with placebo. There was no significant difference between the 1 mg APD421 dose and placebo in terms of vomiting.
- The occurrence of rescue medication use was significantly lower in the 5 mg and 1 mg APD421 compared with placebo and the time to the first rescue medication use was significantly longer in all APD421 dose groups compared with placebo. There was no dose-related response in the occurrence of rescue medication use or time to first rescue medication use, with 5 mg APD421 appearing to be the most efficacious.
    - A single IV dose between 1 mg, 5 mg or 20 mg APD421 was generally safe and well tolerated with no notable difference between placebo and APD421, and no notable difference between the APD421 dose groups.

Date of Report: 01 Nov 2012