CLINICAL DEVELOPMENT DEPARTMENT

FINAL STUDY REPORT SYNOPSIS

Study Number: DP10002

Randomised, double-blind, placebo-controlled, Phase II study to assess the safety and efficacy of different doses of intravenous APD405 (buspirone for IV injection) for the prevention of post-operative nausea and vomiting

Investigational Medicinal Product(s)	**APD405 (INN: buspirone)**	Version	**1.0**
		Date	**31 March 2010**
EUDRACT No	**2008-007770-37**	Principal Investigator	**Prof Martin Tramèr**

STUDY OUTLINE

Study Number	DP10002
Eudract Number	2008-007770-37
Study Title	Randomised, double-blind, placebo-controlled, Phase II study to assess the safety and efficacy of different doses of intravenous APD405 (buspirone for IV injection) for the prevention of post-operative nausea and vomiting
Study Design	Randomised, double-blind, parallel-group, placebo-controlled, dose-response study of a single administration of APD405 in post-operative patients at moderate to high risk of developing post-operative nausea and vomiting
Investigational Product	APD405
Comparator Product	Placebo
Indication	Prevention of post-operative nausea and vomiting
Development phase	Phase II
Overall Study Principal Investigator	Prof Martin Tramèr
Other Principal Investigators	
Sponsor	Acacia Pharma Ltd, Harston Mill, Cambridge, CB22 7GG, UK
Sponsor Contact	Dr Gabriel Fox
Telephone	
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Study Start Date	25 May 2009
Study Completion Date	28 October 2009
Date of Report	31 March 2010
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).	

SYNOPSIS

Sponsor Acacia Pharma Ltd	*(for National Authority use only)*
Name of Investigational Product APD405 for intravenous injection	
Name of Active Ingredient Buspirone hydrochloride	
Title Randomised, double-blind, placebo-controlled, Phase II study to assess the safety and efficacy of different doses of intravenous APD405 (buspirone for IV injection) for the prevention of post-operative nausea and vomiting.	
Investigators & Study Centres	
Study Period 25 May – 28 October 2009	**Phase of Development** II

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Objectives

Primary

To assess the efficacy of different doses of APD405 in the prevention of nausea and vomiting in the first 24 hours after surgery in patients at moderate to high-risk of PONV

Secondary

Efficacy: to assess

- 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 opiates
- Sub-groups of the above variables over time

Safety: to assess the nature and frequency of adverse events

Pharmacokinetics (PK): to assess the PK of APD405 in patients receiving general anaesthesia

Study Design

Multi-centre, double blinded, randomised, placebo controlled, parallel-group study.

Study Arms

Arm 1: placebo
Arm 2: APD405 at 0.3mg
Arm 3: APD405 at 1mg
Arm 4: APD405 at 2mg
Arm 5: APD405 at 3mg

Number of Subjects (planned and analysed)

Planned: 260
Analysed (modified intent-to-treat): 257
Analysed (per-protocol): 252

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Patient Population & Main Criteria for Inclusion

Adult patients (≥ 18 years), having freely given written informed consent, at moderate to high risk of PONV undergoing elective surgery under general anaesthesia for either hysterectomy (any surgical technique), cholecystectomy (any surgical technique) or "other" elective surgery scheduled to last at least one hour from induction of anaesthesia and requiring at least one overnight stay in hospital. Moderate to high risk of PONV defined as having at least 2 of the following risk factors for PONV:

- Past history of PONV and/or motion sickness
- Non-smoking status
- Female gender
- Planned opiate use for post-operative analgesia

Other Main Inclusion/Exclusion Criteria

- Adequate hepatic, renal and haematological function
- Not undergoing outpatient/day case surgery; surgery where post-operative ventilation is expected; or intra-thoracic, transplant or CNS surgery
- Not receiving exclusively a local anaesthetic or regional neuraxial (intrathecal or epidural) block
- Not diagnosed with Parkinson's disease, clinically significant cardiac arrhythmia or epilepsy

Investigational Medicinal Product (IMP)

APD405 (buspirone hydrochloride), batch number RX50401.002, for a single IV administration by slow push over 1 minute at time of completion of surgery (defined as up to 15 min before completion of wound closure but before extubation) at one of the following doses: 0.3mg; 1mg; 2mg; or 3mg

Comparator Product

Matched placebo, batch number RX50085.P.0001, for a single IV administration by slow push over 1 minute at the end of surgery (defined as above).

Randomisation

Patients randomised on a 1:1:1:1:1 basis between the 4 treatment doses and placebo. Randomisation stratified according to:

- Country
- Number of risk factors (2 vs 3 or 4)

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Analysis Populations

Modified Intention-to-Treat (mITT) Analysis Population

All subjects who signed informed consent, were randomised into the study, underwent an operation and received study medication are included in the mITT analysis.

Safety Analysis Population

All subjects who received the study medication, whether prematurely withdrawn from the study or not, are included in the safety analysis.

Per Protocol Population

All subjects who received the study medication and were essentially adherent to the protocol, with no major protocol violations as decided by the study medical monitor, are included in the per protocol analysis.

Pharmacokinetic Analysis Population

Approximately six subjects in each randomisation arm had blood samples taken for PK analysis. Subjects are included for PK analysis if they fulfilled per protocol population criteria. Subjects are excluded from the PK analysis population if they deviated significantly from the protocol or if data are unavailable or incomplete which could influence the PK analysis.

Intention-to-Treat (ITT) Analysis Population

All subjects who signed informed consent and were randomised into the study are included in the ITT population. After database closure, it was decided not to analyse this population, because the difference between it and the mITT population was accounted for by patients who did not receive study drug, for logistical reasons (such as cancellation of their operation), and for whom no efficacy or safety data were therefore available.

Cases excluded from any of the populations are documented together with the reason for exclusion. Apart from the non-analysis of the ITT population, all decisions on exclusions from analysis were made prior to database closure.

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Statistical and Analytical Methods

Primary Efficacy Analysis

The primary efficacy analysis is a comparison of the incidence of PONV between each treated group and the placebo group using Pearson's chi-square test with continuity correction.

Secondary Efficacy Analyses

The secondary efficacy analysis is logistic modelling of the incidence of PONV which (a) investigates the effects of adjustment for country, number of risk factors and type of operation and (b) characterises the nature and extent of any dose response.
Incidence of secondary efficacy variables (nausea, vomiting, rescue medication) is compared between treatment groups using Pearson's chi-square test with continuity correction. Time-to-event secondary efficacy variables (first vomiting) are compared between treatment groups using the log-rank test. Continuous secondary efficacy variables (severity of nausea) are compared between treatment groups using a Mann-Whitney group. These tests are repeated in the sub-group of patients receiving opiates for post-operative analgesia.

Hypothesis Testing

The threshold for determining statistical significance in comparisons of incidence of PONV between groups is a P-value of 10% one-sided.
The treated groups were tested against placebo in a pre-determined order, starting with the group with the highest dose such that it and all lower dose groups have an acceptable safety profile. Testing would stop if that group did not have a significantly lower incidence of PONV than placebo; otherwise testing would continue through the dose groups, in descending order, until a group did not have a significantly lower incidence of PONV or the lowest dose treated group had been tested.

Demographics & Baseline Characteristics

In total, 298 patients were screened, 281 randomised and 257 enrolled into the study: 51, 50, 49, 52 and 55 into the placebo, 0.3 mg, 1 mg, 2 mg and 3 mg groups respectively. The study arms were well balanced with respect to age, gender, race and BMI of subjects. The mean age was 50.6 years and 89.9% of patients were female. There were no significant differences between study arms in terms of past medical history, baseline physical examination, vital signs and the type of operation undergone. Hysterectomy was the commonest operation type (22.6% of patients). Laparoscopic surgery other than hysterectomy or cholecystectomy occurred in 19.8% of patients and breast surgery in 14.4%. All but one patient received an opioid anaesthetic agent and 54.5% received halogenated hydrocarbons.

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Efficacy Results

There was no significant difference from placebo for any dose of APD405 in the incidence of PONV in the 24 hours after surgery. The PONV rate for placebo was 49.0%, compared to 58.0% for APD405 0.3 mg, 40.8% at 1 mg, 57.7% at 2 mg and 50.9% at 3 mg. There was no significant difference in any other efficacy endpoint, including nausea rate and severity, vomiting incidence, time to first vomiting and use of rescue medication. No differences were seen between study arms in rates of PONV, nausea or vomiting in the time periods 0-2 h, 2-6 h and 6-24 h. In the subset of patients who received opioids post-operatively, there was no difference between the study arms in terms of PONV rate, or any other efficacy measure. APD405 was not an efficacious agent at any studied dose in the prevention of PONV.

Safety Results

There were no significant differences in the safety profile of APD405, at any dose, and placebo. The nature and frequency of adverse events and serious adverse events, as well as abnormalities in clinical laboratory parameters, vital signs and ECGs, were not significantly different between all study arms. There were no deaths on study and no subject withdrew as a result of an AE. Overall 90.7% of patients experienced at least one AE, but only 27.6% of patients experienced an AE at least remotely related to study medication. There were 11 SAEs in 8 patients, only one of which was considered at least remotely related to study drug. The post-operative Aldrete score showed a significantly greater decline from baseline with 0.3 mg and 1 mg doses of APD405 compared to placebo, suggesting delayed recovery from anaesthesia. However, this decline was not seen with 2 mg and 3 mg doses. The reason for this is unclear. APD405 was generally safe and well-tolerated in patients undergoing general anaesthesia.

Pharmacokinetics Results

PK data from a small sample of subjects in each arm were consistent with data obtained in Phase I from healthy volunteers, showing linear pharmacokinetics.

Conclusions

No difference was seen in the efficacy of APD405, at any dose evaluated, compared to placebo. The safety profile of a single IV dose of APD405 at all doses tested was similar to that of placebo. A single IV dose of APD405 is safe but has no role in the prevention of PONV in adult surgical patients.

Date of report: 31 March 2010

FINAL STUDY REPORT APPROVAL

Principal Investigator

Prof Martin Tramèr

Signature: Date: 31-Mar-2010

Author

Dr Gabriel Fox

Signature: Date: 31-Mar-2010

Sponsor

Chief Medical Officer

Dr Gabriel Fox

Signature: Date: 31-Mar-2010