

# I.V. APD421 (amisulpride) prevents postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled, multicentre trial

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## Editor's key points

- This is a dose-finding study to investigate amisulpride for i.v. injection (APD421), a D<sub>2</sub>/D<sub>3</sub>-antagonist, in postoperative nausea and vomiting (PONV) prophylaxis.
- This study demonstrates that a 5 mg dose of APD421 reduced PONV from 69 to 40%, compared with placebo.
- A lower dose of APD421 (1 mg) also reduced PONV significantly ( $P < 0.05$ ) but higher dosages did not.

**Background.** Postoperative nausea and vomiting (PONV) remain significant clinical problems for patients, especially nausea. The D<sub>2</sub>-antagonist droperidol was popular for prophylaxis until safety concerns limited its use. In early testing, APD421 (amisulpride for i.v. injection), a D<sub>2</sub>/D<sub>3</sub>-antagonist, has shown promising antiemetic efficacy at very low doses. We conducted a randomized, double-blind, dose-finding study to investigate APD421 in PONV prophylaxis.

**Methods.** Adult surgical patients with  $\geq 2$  Apfel risk factors for PONV undergoing surgery expected to last  $\geq 1$  h and receiving standard inhalation anaesthesia were randomized to receive placebo or one of three doses of APD421 (1, 5, or 20 mg) as a single i.v. administration at anaesthesia induction. The primary endpoint was PONV (vomiting/retching or antiemetic rescue) in the 24 h period after surgery.

**Results.** Two hundred and fifteen patients received study drug, 92% female and 60% with  $\geq 3$  risk factors. Groups were well balanced for baseline characteristics and risk factors. The PONV incidence was 37/54 [69%; 90% confidence interval (CI), 57–79%] in the placebo group; 28/58 (48%; 90% CI, 37–60%) with 1 mg APD421 ( $P=0.048$ ); 20/50 (40%; 90% CI, 28–53%) with 5 mg ( $P=0.006$ ); and 30/53 (57%; 90% CI, 44–68%) with 20 mg ( $P>0.1$ ). APD421 at 5 mg also significantly improved vomiting, rescue medication use, and nausea rates. The safety profile of APD421 was similar to that of placebo at all doses, with no significant central nervous system (CNS) or cardiac side-effects.

**Conclusions.** APD421 given i.v. before surgery is safe and effective at reducing PONV in moderate/high-risk adult surgical patients. The optimal dose tested was 5 mg.

**Trial Registration.** ClinicalTrials.gov identifier: NCT01510704. <http://www.clinicaltrials.gov/ct2/show/NCT01510704?Term=APD421&rank=1>.

**Keywords:** antiemetics; postoperative nausea and vomiting; randomized controlled trial; sulpiride/\*analogues and derivatives, amisulpride

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Vomiting and nausea, especially the latter, remain important issues after surgery, despite the availability of numerous antiemetic agents. Dopamine (D<sub>2</sub>), serotonin (5-HT<sub>3</sub>), and histamine

(H<sub>1</sub>) antagonists are commonly used as prophylactic agents, as is the corticosteroid dexamethasone, but the incidence of postoperative nausea and vomiting (PONV) is still appreciable. The

D<sub>2</sub>-antagonist droperidol was an especially valued agent, described as the 'overwhelming first choice for PONV prophylaxis' in international consensus guidelines,<sup>1,2</sup> until safety concerns, particularly QT-interval prolongation, led to its withdrawal or disuse in many countries. New agents are therefore still required, especially those with good activity against nausea.

APD421 is an i.v. formulation of amisulpride for the new use of prevention and treatment of nausea and vomiting. Amisulpride is an anti-psychotic agent first launched as Solian<sup>®</sup> tablets (Laboratoires Delagrangre, now sanofi-aventis) in France in 1986 and now approved in oral form in > 50 countries worldwide. It is a potent but 'atypical' D<sub>2</sub>-antagonist with a very low tendency to cause the side-effects which have plagued older members of the class, such as QT-interval prolongation and extra-pyramidal signs and symptoms.<sup>3</sup> It is, furthermore, a potent antagonist at D<sub>3</sub> receptors, which have also been implicated in the emetic response.<sup>4</sup>

In pre-clinical testing, APD421 showed a significant anti-emetic effect against challenges with the D<sub>2</sub>-agonist apomorphine, with cisplatin and with morphine. We, therefore, conducted this double-blind, placebo-controlled study with the primary objective of assessing the efficacy of different doses of i.v. APD421 as PONV prophylaxis.

## Methods

### Study design

This double-blind, placebo-controlled, parallel-group study was conducted between January and April 2012 at 10 sites, predominantly University Hospitals, in Germany, France, and the USA, each centre obtaining prior approval from an authorized ethics committee and their national regulatory authority. The trial was registered on EudraCT (ref.: 2011-004267-71) and ClinicalTrials.gov (ref.: NCT01510704).

Adults who had given written informed consent were enrolled if they were due to have an in-patient operation [other than intra-thoracic, transplant, or central nervous system (CNS) surgery], expected to last at least 1 h, under general anaesthesia, and had at least two of the following risk factors for developing PONV: (i) female sex; (ii) non-smoking status; (iii) a prior history of PONV or motion sickness; and (iv) being expected to receive postoperative opioid analgesia.

Adequate haematological, renal, and hepatic function (haemoglobin  $\geq 9$  g dl<sup>-1</sup>; white cells  $\geq 3 \times 10^9$  litre<sup>-1</sup>; platelets  $\geq 100 \times 10^9$  litre<sup>-1</sup>; creatinine  $< 2 \times$  upper limit of normal (ULN); bilirubin  $< 3 \times$  ULN; and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both  $< 5 \times$  ULN) were required. Patients were not eligible if they were expected to require postoperative ventilation or need a naso- or oro-gastric tube *in situ* after surgery, or if they had Parkinson's disease, a pre-existing vestibular disorder or history of dizziness, a history of alcohol abuse, a clinically significant cardiac arrhythmia, or epilepsy.

Subjects were randomized to one of four parallel groups: 1, 5, or 20 mg of i.v. APD421 or placebo, on a 1:1:1:1 basis. The randomization was stratified by centre and by the number of risk factors (2 vs 3 or 4), the latter intended to give as homogeneous as possible a risk of PONV in each of the groups, within the

constraints of the sample size. The APD421 dose range was determined partly by reference to data generated in an ongoing clinical trial of APD421 in patients receiving cisplatin chemotherapy and partly by extrapolation from pre-clinical efficacy data. Each site was supplied with vials of i.v. APD421 (at strengths of 0.5, 2.5, and 10 mg ml<sup>-1</sup> to maintain equal volume of study drug) and matching placebo containing the same excipients but no active ingredient, manufactured specifically for the study. All vials were identically labelled except for an individual subject number derived from a master randomization list available to the contract manufacturer of the study medication, but not to the sponsor, any site research personnel, or study participants. An internet-based randomization system provided sites on demand with a subject number for each patient randomized, which could then be matched to the subject number on the appropriate vial of study medication held at the site. A 2 ml aliquot of study medication was administered by slow i.v. push over 2 min at the time of induction of anaesthesia.

Pre-medication and anaesthetic regimens were at investigators' discretion, except that total i.v. anaesthesia with propofol, which would have significantly reduced the control PONV rate, was not permitted, nor was it allowed to give any anti-emetic apart from study drug before operation. The investigator's usual institutional practice was also followed for other aspects of peri- and postoperative care, such as analgesia. Rescue medication, specified as the investigator's choice of 5-HT<sub>3</sub>-antagonist, was available to any patient who retched, vomited, or experienced nausea from which they wanted relief. One or more additional agents of a different class could be added at the discretion of the investigator in the event of PONV which was not, or was considered likely not to be, controlled by the 5-HT<sub>3</sub>-antagonist.

### Assessments

The primary population for both efficacy and safety analysis was the intention-to-treat (ITT) population, defined as all subjects who signed the informed consent form, were randomized into the study, and received study medication. A per-protocol analysis population was defined as a subset of the ITT population with no major protocol violations. A major violation was considered one that could reasonably be considered to have had a material impact on the subject's outcome, such as inadvertent use of antiemetics or use of excluded anaesthetic techniques or agents. The final constitution of study analysis populations was determined on a fully blinded basis before database closure.

The primary endpoint of the study was the incidence of PONV, defined as any episode of vomiting, retching, or any use of rescue antiemetic medication in the 24 h period after the end of surgery, timed from the completion of wound closure. Secondary efficacy endpoints included incidence and severity of nausea, time to PONV, and the use of antiemetic rescue medication. Nausea was measured using an 11-point verbal rating scale (VRS) running from 0 (no nausea at all) to 10 (the worst nausea imaginable). Any nausea spontaneously

reported by the patient was recorded, and in addition, patients were asked for a nausea score at times 0.5, 1, 1.5, 2, 6, and 24 h after surgery. Secondary analyses were conducted by time period (0–2, 2–6, and 6–24 h after surgery) and by post-operative opioid analgesia use. Safety was analysed in terms of the nature and incidence of adverse events, changes in vital signs and laboratory parameters, and changes in electrocardiogram (ECG) parameters.

Efficacy variables were compared between each APD421 dose group and the placebo group, using Pearson's  $\chi^2$  test with Yates's continuity correction. Secondary efficacy comparisons were exploratory and no adjustment was made for multiplicity. Kaplan–Meier estimations of time to PONV were prepared, with data censored to 24 h where no PONV event occurred. A sample size of 50 per group was calculated to give a power of 87% to detect a reduction from 50 to 25% in PONV incidence, at a one-sided significance level of 0.1, considered appropriate for this stage of development. Calculations were done using SAS version 8.2.

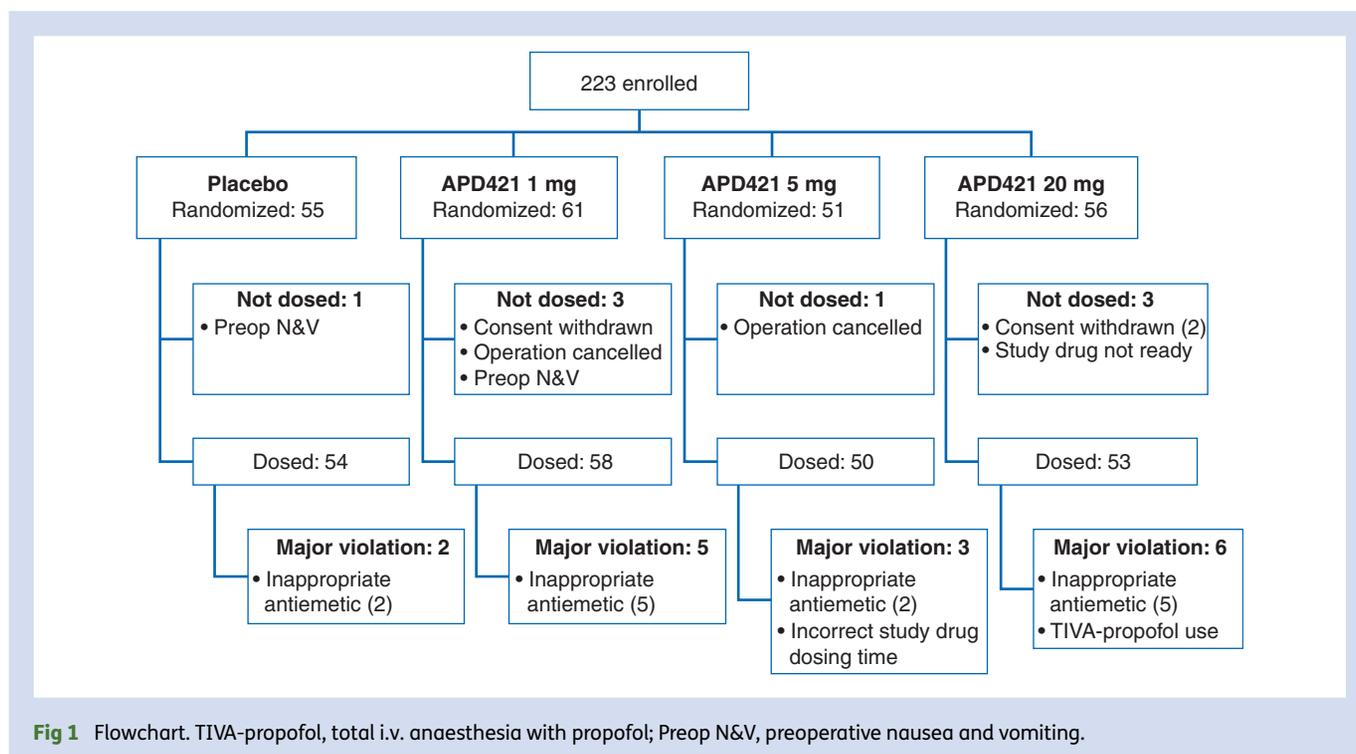
## Results

Two hundred and twenty-three subjects were randomized into the study (Fig. 1), eight not receiving study drug, mostly because of withdrawal of consent, cancellation of surgery, or a preoperative episode of nausea and vomiting. The ITT and safety analysis populations, therefore, comprised 215 individuals. Study arms were generally well balanced for age, body mass index, and PONV risk factor profile (Table 1). Most patients were female (92%) and non-smokers (77%), including ex-smokers who had ceased > 2 yr previously. Two-thirds of the population had three or four risk factors.

There were no significant differences between study groups in terms of type of surgery, with 69% overall being abdominal operations and 24% being breast or axillary surgery. A laparoscopic technique was used in a quarter of the operations. There was little difference in duration of surgery between the study groups, the mean time from incision to completion of wound closure being 108 min (range 16–485 min), with 73% of operations lasting at least 60 min. The average time between study drug administration and start of surgery was 33 min. The anaesthetic technique was similar across the study groups, with sevoflurane used in 58% of patients and desflurane in 42%. Four patients received N<sub>2</sub>O. Propofol induction was used in 99% of patients, though in only one instance was total i.v. anaesthesia with propofol used (a major protocol violation), and 79% received fentanyl, remifentanyl, or sufentanil during the anaesthetic procedure. Neostigmine was used for reversal of neuromuscular block in 5% of patients.

## Efficacy

In the placebo group, the mean 24 h incidence of PONV was 69% [90% confidence interval (CI): 57–79%], while that in the 5 mg APD421 treatment arm was significantly lower at 40% (90% CI: 28–53%;  $P=0.006$ ) (Table 2), a relative risk of 0.58. The degree of improvement in vomiting and nausea separately was similar to that for the composite PONV endpoint. The relative risk for vomiting between the placebo and 5 mg arms was 0.40, and for any nausea (a score  $\geq 1$  on the VRS) was 0.61. Significant improvement was also seen in terms of use of rescue medication and clinically significant nausea (a score  $\geq 4$  on the VRS). The other APD421 dose groups



**Table 1** Baseline patient characteristics. BMI, body mass index; MS, motion sickness

	Placebo		APD421 1 mg		APD421 5 mg		APD421 20 mg	
Number of subjects	54		58		50		53	
Median age (range)	50.0 (19–75)		48.5 (22–83)		50.5 (20–80)		51.0 (22–82)	
Median BMI (range)	25.8 (18–40)		25.6 (17–46)		26.1 (18–40)		26.2 (20–43)	
Female	47	87%	53	91%	48	96%	49	92%
History of PONV/MS	21	39%	21	36%	20	40%	20	38%
Non-smoker	46	85%	37	64%	42	84%	40	75%
Opioid analgesia use	33	61%	39	67%	31	62%	37	70%
Two risk factors	16	30%	24	41%	14	28%	19	36%
Three risk factors	23	43%	22	38%	20	40%	22	42%
Four risk factors	15	28%	12	21%	16	32%	12	23%

**Table 2** Incidence of PONV, vomiting, rescue medication use and nausea in the 24 h postoperative period. 90% CIs in parentheses. PONV, postoperative nausea and vomiting. \* $P < 0.05$ , \*\* $P < 0.01$  (compared with the placebo group). †Score  $\geq 4$  on 0–10 VRS. ‡Score  $\geq 1$  on 0–10 VRS

	Placebo	APD421 1 mg	APD421 5 mg	APD421 20 mg
Number of subjects	54	58	50	53
PONV	69% (57–79%)	48%* (37–60%)	40%** (28–53%)	57% (44–68%)
Vomiting	35% (25–47%)	28% (18–39%)	14%* (7–25%)	17% (9–28%)
Rescue medication use	67% (55–77%)	47% (35–58%)	38%** (27–51%)	55% (43–66%)
Significant nausea†	48% (36–60%)	41% (30–53%)	24%* (15–36%)	43% (32–56%)
Any nausea‡	72% (60–82%)	45%** (34–56%)	44%** (32–57%)	57% (44–68%)

showed a less marked benefit over placebo, but for the 1 mg dose, this was statistically significant for PONV and any nausea.

A Kaplan–Meier analysis of time to the first incidence of PONV (Fig. 2) showed a clear separation of the active and placebo curves before 100 min after operation. The curves for the 1 and 5 mg dose groups overlapped up to around the 10 h mark and then separated.

In the subgroup of 140 patients who received an opioid in the 24 h postoperative period, but before any episode of PONV, the same response pattern was observed, with a difference of  $\sim 20$  percentage-points between the PONV rate in the placebo arm and that in the 1 and 5 mg APD421 arms.

A range of other subgroup analyses was conducted on the per-protocol population, revealing no significant differences from the primary data (Table 3). Among the 142 highest risk patients, those with three or four risk factors as estimated at study entry, the PONV rate was 71% for placebo and 42% for 5 mg APD421 ( $P = 0.02$ ). In the subgroup of 136 patients undergoing abdominal operations, the PONV rate was 61% in the placebo group and 32% in the 5 mg group.

## Safety

The incidence and profile of treatment-emergent adverse events were similar across all the study groups and there was no evidence of any of the toxicities of concern commonly associated with D<sub>2</sub>-antagonists as a class, such as extrapyramidal signs and symptoms, cardiotoxicity, and psychological disturbance.

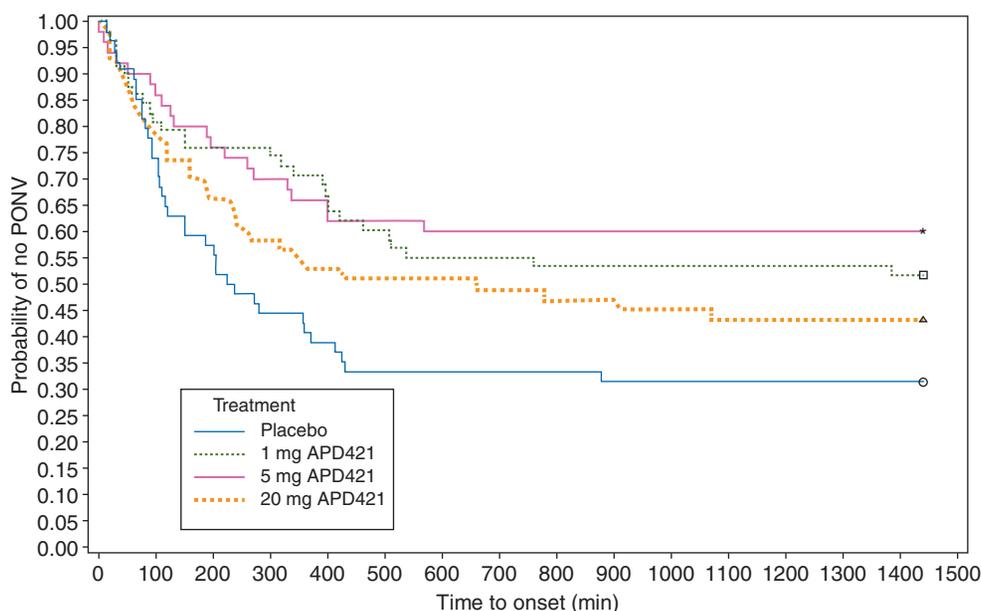
Even after excluding nausea and vomiting adverse events, a lower proportion of patients in the APD421 arms than in the placebo arm experienced at least one adverse event (Table 4). Overall, 11 events were classed as severe and 1 (an episode of vomiting in the placebo group) as life-threatening. Five serious adverse events were reported, all of them clearly complications of surgery (four instances of postoperative haemorrhage or haematoma and one of postoperative pain).

Insomnia or sleep disorder occurred numerically more commonly in the active treatment groups than in placebo, being reported in 19/161 patients (12%) receiving APD421 compared with 3/54 (6%) receiving placebo, a difference which was not statistically significant. Of the 23 events reported, 22 were rated as mild and 1 as moderate. Only two episodes of insomnia or sleep disorder occurred during the first postoperative night, most occurring during the third or fourth. There were more episodes of headache in the APD421 1 mg group than in placebo ( $P = 0.07$ ) but not in the higher APD421 dose groups.

There were no differences between the study groups in ECG parameters, including heart rate-corrected QT interval, at 1 and 24 h after surgery; nor were there any significant differences in any vital signs or clinical laboratory parameters.

## Discussion

This study demonstrates a significant benefit for low-dose APD421 in the prevention of PONV. At 5 mg, all efficacy measures—the composite measure of PONV and vomiting,



**Fig 2** Time to first incidence of PONV.

**Table 3** PONV rates in different sub-populations and by time period. \* $P < 0.05$  (compared with the placebo group)

	Placebo	APD421 1 mg	APD421 5 mg	APD421 20 mg
Opioid sub-population	20/33 (61%)	16/39 (41%)	13/31 (42%)	20/37 (54%)
Patients with two risk factors	10/16 (63%)	12/24 (50%)	5/14 (36%)	9/19 (47%)
Patients with three or four risk factors	27/38 (71%)	16/34 (47%)	15/36 (42%)*	21/34 (62%)
0–2 h postoperative	20/54 (37%)	12/58 (21%)	8/50 (16%)*	13/53 (25%)
2–6 h postoperative	12/34 (35%)	5/46 (11%)*	9/42 (21%)	12/40 (30%)
6–24 h postoperative	5/22 (23%)	11/41 (27%)	3/33 (9%)	5/28 (18%)

nausea (both significant nausea and any nausea at all), and requirement for rescue medication—were reduced by a similarly substantial magnitude. Both the 1 and 20 mg doses appeared less effective than the 5 mg dose, suggesting a bell-shaped dose–response.

The study followed a well-established and robust methodology<sup>5</sup> and the randomly allocated groups were well balanced for risk factors. The study population was typical of that in which antiemetic prophylaxis is most relevant and the range of operations and anaesthetic techniques was representative of real-world surgical practice. The incidence of PONV seen in the placebo group, 69%, is highly consistent with that seen in many other recent studies involving such moderate-to-high-risk patients, suggesting good comparability of these data with the latest literature. For example, in two large studies of palonosetron in patients with at least two PONV risk factors undergoing elective abdominal or breast surgery, the rates of PONV in the placebo arms were 64 and 74%,<sup>6,7</sup> while that seen in a similarly designed study of rolapitant was 73%.<sup>8</sup>

In a study of > 5000 patients, Apfel and colleagues<sup>9</sup> demonstrated that the benefit of a range of antiemetic interventions, including ondansetron, dexamethasone, and droperidol, was similar, with a relative risk reduction of ~25% compared with the absence of that intervention, equating to an absolute reduction of 15–20 percentage points on a typical baseline PONV rate in the range 65–75%. This magnitude of benefit has been seen with many antiemetics in separate, placebo-controlled trials, including ondansetron,<sup>10,11</sup> palonosetron,<sup>6,7</sup> and droperidol.<sup>10</sup> A Cochrane Collaboration meta-analysis of 737 studies involving 103 237 patients found that eight agents tested were effective antiemetics, with relative risk reductions in the range 20–40%.<sup>12</sup> The benefit seen with 5 mg APD421 is a 42% relative risk reduction, or 30 percentage-points in absolute terms, which is promising.

It is interesting that the Kaplan–Meier curves for the 1 and 5 mg dose groups overlap up to ~10 h but then separate. This suggests that APD421 does have significant antiemetic potential even at a dose as low as 1 mg, but that a 5 mg dose

**Table 4** Summary of treatment-emergent adverse events (AE) excluding nausea and vomiting, and individual events occurring in at least 3% of the patient population. \* $P=0.07$ , comparison with the placebo group, Pearson's  $\chi^2$  test with Yates's continuity correction

	Placebo		APD421					
			1 mg		5 mg		20 mg	
Number of subjects	54		58		50		53	
Subjects with any AE (excl. PONV)	45	83%	46	79%	37	74%	41	77%
Any SAE	2	4%	1	2%	0	0%	2	4%
Any life-threatening AE	0	0%	0	0%	0	0%	0	0%
Any severe AE	3	6%	1	2%	1	2%	2	4%
Anaemia	2	2%	2	3%	0	0%	4	8%
Constipation	6	11%	6	10%	6	12%	6	11%
Dizziness	2	4%	1	2%	0	0%	3	6%
Flatulence	7	13%	7	12%	4	8%	4	8%
Headache	0	0%	4*	7%	0	0%	2	4%
Hypertension	1	2%	1	2%	2	4%	3	6%
Insomnia/sleep disorder	3	6%	6	10%	7	14%	6	11%
Pain/procedural pain	33	61%	37	64%	30	60%	33	62%
Procedural hypotension	1	2%	3	5%	2	4%	3	6%
Pyrexia	0	0%	3	5%	1	2%	0	0%

may be needed to ensure supra-therapeutic levels for the full 24 h postoperative period.

Also of interest is the bell-shaped dose–response suggested by the data. This is consistent with data from pre-clinical testing in a standard ferret model, where APD421 efficacy tailed off somewhat with the highest dose tested against emetic challenges with both morphine and cisplatin. Similar findings have been reported with oral APD421 in the treatment of schizophrenia<sup>13</sup> and with other centrally acting receptor antagonists, such as 5-HT<sub>3</sub>-antagonists used in CNS indications such as anxiety and migraine.<sup>14</sup> No improvement was seen for 3 mg over 1 mg of i.v. granisetron in a randomized, dose-ranging PONV study<sup>15</sup> and an absence of dose–response was reported in meta-analyses of the antiemetic effects of the D<sub>2</sub>-antagonists droperidol<sup>16,17</sup> and haloperidol,<sup>18</sup> while nausea and vomiting are both listed as ‘common’ (1–10% incidence) in the product labelling for the higher-dose haloperidol injection used in psychiatric indications. The underlying mechanism is unknown.

The efficacy shown for APD421 appeared not to be at the expense of any significant toxicity. Overall, fewer patients receiving APD421 than placebo experienced one or more adverse events, even after subtracting PONV events, which were much commoner in the placebo group. This presumably reflected the generally better postoperative course experienced by patients who received active prophylaxis. Of note, no extra-pyramidal toxicity was seen at any dose of APD421. Extra-pyramidal side-effects such as akathisia and tardive dyskinesia are not uncommonly seen with older D<sub>2</sub>-antagonists such as droperidol when used in psychiatric practice and have also been reported at the lower doses used against PONV.<sup>19–21</sup> A feature of newer, ‘atypical’ D<sub>2</sub>-antagonists is a much lower propensity to cause such reactions. At doses

used for the management of schizophrenia with predominant negative symptoms, which range from 50 to 300 mg day<sup>-1</sup> by mouth, given in most cases for many weeks or months, the rate of these reactions has been reported to be <5% and not significantly different from that in placebo.<sup>3,22</sup>

The risk of cardiotoxicity appears also to be much lower with APD421 than with older D<sub>2</sub>-antagonists. Prolongation of the QT interval has been considered a class effect of D<sub>2</sub>-antagonists resulting from their binding to hERG potassium channels in the heart. Droperidol exhibits a high affinity for such channels,<sup>23</sup> but that of APD421 has been shown to be more than a thousand-fold lower in *in vitro* testing.<sup>24</sup> Although the ECG data obtained in this study are not sufficiently detailed to exclude an effect on the QT interval, they are consistent with the absence of cardiac toxicity noted in safety studies.<sup>25</sup>

Insomnia or sleep disorder appeared to be commoner with APD421 than with placebo, though there was no relationship to dose. Insomnia has been reported in association with amisulpride in psychiatric use, though in placebo-controlled studies it was not seen more commonly than with placebo.<sup>3</sup> In this study, most cases of insomnia occurred >48 h after study drug administration, which is considerably more than five times the half-life of i.v. amisulpride (7.5 h).<sup>26</sup> It is, therefore, unclear to what extent APD421 contributes to sleep disorders in this setting. Headache occurred more commonly with 1 mg APD421 than with placebo, but this may have been a spurious finding, as there were no instances at the 5 mg dose, and furthermore, headache is not listed as an undesirable effect in the summary of product characteristics of marketed amisulpride preparations.

APD421 has several attractive features for use in the general surgical population. It has a very low propensity for drug interactions,<sup>27</sup> being neither a substrate for nor an inhibitor of

cytochrome P450 isoenzymes.<sup>28</sup> It can safely be used in elderly individuals, in whom the pharmacokinetic profile matches that in younger adults,<sup>29</sup> and in patients with renal failure, which does increase the plasma concentration<sup>30</sup> but to a modest degree unlikely to represent a clinical issue at the low doses shown to be effective in this trial.

This study provides a promising initial indication of efficacy in a typical at-risk surgical population. Larger trials are warranted to confirm the value of APD421 as an antiemetic.

## Acknowledgements

The protocol was developed in collaboration with the coordinating investigator for each country (Germany: P.K.; France: P.D.; USA: T.J.G.) with input from all investigators. There was a *pre hoc* agreement that the investigators would have the right to examine the data independently and to submit a manuscript for publication without first obtaining the consent of the sponsor and that the results of this study would be published as a full report in their entirety and not as individual centre data. P.K. had full access to all the data and coordinated the decision to submit for publication. All the authors participated in writing the manuscript.

## Declaration of interest

G.F. is an employee of Acacia Pharma Ltd. P.K. had been the Lead Investigator of the reported trial and Principal Investigator in Germany. The Department received payment per case to conduct the reported research activities. P.K. also received travel fee/lecture fees from FreseniusKabi AG and ProStrakan Ltd. and has consulted for Acacia Pharma Ltd. The other authors have no interest to declare.

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