SCIENTIFIC DISCUSSION

I. INTRODUCTION

Emend (aprepitant) is an oral neurokinin 1 (NK-1)-receptor antagonist. Substance P (SP) is the dominating natural ligand to this receptor and belongs to the neuropeptide family of tachykinins. SP is abundantly and widely distributed in the mammalian CNS and other tissues. Mammalian tachykinin SP that binds to the NK-1 receptor has been associated with numerous inflammatory conditions, mediation of the emetic reflex and modulation of central nervous system disorders. By blocking the NK-1 receptors, aprepitant prevents SP from interacting with the receptor and thus provides a novel mechanism of action for the prevention of induced nausea and vomiting.

On 12 November 2003, the European Commission issued a Marketing Authorisation valid throughout the European Union. The initial approved indication was: "*Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy. EMEND is given as part of combination therapy"*.

In September 2004, the MAH submitted results from one pivotal study conducted in patients treated with moderately emetogenic chemotherapy regimens in order to broaden the indication to encompass emetogenic chemotherapies in general. On 16 March 2005, the European Commission issued a Marketing Authorisation valid throughout the European Union. The currently approved indication is:

> *"Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.*
>
> *Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.*
>
> *EMEND is given as part of combination therapy (see section 4.2)."*

On 6 October 2005, the MAH submitted the present Type II variation requesting an extension of the indication for aprepitant to include the prevention of post-operative nausea and vomiting (PONV) in the 40 mg strengh. The application is based on data from two large, three-armed (aprepitant 125 mg, 40 mg, or ondansetron) studies.

This variation concerns an extension of the indication for aprepitant to include the prevention of post-operative nausea and vomiting (PONV) in the 40 mg strengh.

> "*EMEND is indicated for the prevention of postoperative nausea and vomiting"*

This indication in based on data from two large, three armed, dose and active reference studies, which have been conducted by the MAH under the same protocol (one in US and one non-US site). The MAH has submitted in parallel with this type II variation, an extension application (X/15) for Emend 40 mg, which is intended to be used for PONV. The PONV indication only concerns the 40 mg strength.

PONV constitutes an important remaining clinical issue despite availability of active therapies. Ondansetron and other 5-HT3 antagonists are considered to provide a better prophylaxis against emesis than nausea. To increase the activity, 5-HT3 antagonists may be administered in combination with dexamethasone or droperidol.

Ondansetron may be administered prior to induction of anaesthesia or at end of surgery and the selected dose, 4 mg seems to be the most widely licensed, though a higher dose (8mg) is recommended in some EU Member States in patients with a history of PONV, etc. Some studies also indicate that the activity of ondansetron might be higher if administered at end of surgery, but this posology seems not to be licensed in most Member States.

II. NON-CLINICAL ASPECTS

In the present application, the dose is lowered to 40 mg, which is a dose that lowers the human exposure ~ 2.6-fold (AUC = 7751 ng.h/ml) compared to the previous 125 + 80 mg posology in Chemotherapy Induced Nausea and Vomiting (CINV). The exposure margins to the clinically expected exposure are re-calculated to take the lower clinical exposure for this indication into account.

III. CLINICAL ASPECTS

Pharmacokinetics

The effect of a single dose of Emend 125 mg on iv midazolam (2 mg infused 1 h after Emend administration) was evaluated. Midazolam AUC increased with 47%, which is less than the effect on oral midazolam observed in previous studies (127% increase). In previous studies it has been shown that Emend 40 mg increased oral midazolam AUC by 22% and dexamethasone by 45%.

Clinical Studies

The clinical development of aprepitant for the PONV indication was based on two studies (Protocol 090 and Protocol 091). These phase 3 trials were identical with respect to study design, study population, study treatments, efficacy and safety assessments, but differed in study hypotheses, and efficacy analyses. Therefore, efficacy data from the studies was presented separately, while safety data was combined.

Additionally, the MAH submitted an interaction study evaluating the effect of a single dose of Emend 125 mg on i.v. administered midazolam (P108).

Good Clinical Practice (GCP) Procedures

Both clinical studies, Protocol 091 and Protocol 090, were conducted according to Good Clinical Practice (GCP) guidelines and considerations for the ethical treatment of human subjects. Three investigative sites (Sites 0002 and 0029 in Protocol 091, and Site 0024 in Protocol 090) were identified as non-compliant with GCP requirements based on data review, routine monitoring, and/or site audits. Consequently, efficacy data from these study sites was not included in the primary mITT efficacy analyses, while safety data was included in all safety displays and analyses.

Study 090

Methods

Study 090, which was conducted between 26-Sep-2003 and 24-Nov-2004, is a randomized, double-blind, active comparator-controlled, parallel group study, which was designed to examine the safety, tolerability, and efficacy of 2 doses of aprepitant (125 mg, 40 mg) for the prevention of postoperative nausea and vomiting. This study was conducted in 29 centres across the USA.

- Inclusion criteria

- Patient scheduled to undergo open abdominal surgery requiring overnight hospital stay (24-hour hospital stay after end of surgery).
- Patient scheduled to receive general anaesthesia, with the following general anaesthetic regimen:
    - Premedication with benzodiazepine (e.g., IV midazolam 1 to 3 mg) or nil
    - Induction with any anaesthetic agent
    - Narcotics (e.g., fentanyl, morphine, or hydromorphone)
    - Neuromuscular blocking agents
    - Maintenance with N2O (50 to 70%) with volatile anaesthetic
    - Neostigmine 2 to 5 mg (A minimum dose of 2.5 mg was recommended.)
- Patient scheduled to receive postoperative opioids (e.g., morphine, or fentanyl) IM or IV, or patient controlled analgesia (PCA).
- Patient had an American Society of Anesthesia (ASA) physical status of I–III

- Exclusion criteria

- Patient scheduled to receive propofol for maintenance of anaesthesia.
- Placement of nasogastric or oral gastric tube intra- or postoperatively.
- Patient expected to receive neuroaxial anaesthesia such as epidural, spinal, etc.
- Patient expected to be transferred to the Intensive Care Unit (ICU) or step-down unit after surgery.
- Evidence of any clinically significant respiratory, metabolic, hepatic, renal dysfunction, or cardiovascular condition or congestive heart failure (CHF).
- Patient had vomited within 24 hours prior to surgery.
- Patient was taking, or had taken within 7 days of surgery the following CYP3A4 substrates: terfenadine, cisapride, astemizole, mozidem.
- Patient was taking, or had taken within 30 days of surgery the following CYP3A4 inducers: phenytoin or carbamazepine, barbiturates, rifampicin or rifabutin
- Patient was taking, or had taken within 7 days of surgery the following CYP3A4 inhibitors: clarithromycin, ketoconazole, itraconazole
- Abnormal laboratory values: AST >2.5 x upper limit of normal (ULN), ALT >2.5 x ULN, bilirubin >1.5 x ULN, creatinine >1.5 x ULN
- Pregnancy or breast-feeding
- Patient had taken an antiemetic within 24 hours before surgery, or was scheduled to receive an antiemetic during the study period

Both, Protocol 090 and Protocol 091, were multi-centre, double-blind, randomised, active comparator-controlled trials. Both trials included 3 arms (aprepitant 125 mg PO, aprepitant 40 mg PO, and ondansetron 4 mg IV, all three as a single dose). Aprepitant was administered orally 1 to 3 hours before the expected induction of anaesthesia. Ondansetron was administered intravenously immediately before induction of anaesthesia in accordance with prescribing information.

Both studies, Protocol 091 and Protocol 090, had the same original primary efficacy hypothesis that aprepitant is superior to ondansetron with respect to Complete Response during the first 24 hours after surgery. The endpoint of Complete Response was selected because this was also the primary endpoint in the placebo-controlled, pivotal studies of the 5-HT3 antagonists that supported registration for PONV.

- Study medication

Aprepitant Dose Selection and Timing of Administration:
Both studies tested the 2 doses of aprepitant (125 mg and 40 mg) to permit assessing dose-dependent effects of aprepitant on the prevention of PONV. Data from the aprepitant CINV program had previously demonstrated a similar dose response between these 2 doses. Hence, these studies suggested that doses greater than 125 mg would not provide an additional benefit, while doses lower than 40 mg would not be sufficient to demonstrate a clinical beneficial. Since there were no other clinical studies conducted on the dose effect of aprepitant for the prevention of PONV, a similar dose range as applied for CINV was investigated.

The recommended time point of administration of aprepitant is within3 hours prior to induction of anaesthesia. This recommendation is consistent with previously accepted recommendations for oral 5-HT3 antagonists for prevention of PONV even when in the pivotal clinical trials the drug was administered at a fixed time in relation to surgery. The relatively long time interval was proposed in order to limit the number of patients excluded from the trial after administration of aprepitant due to changes in surgery start time

- Comparator Selection

Ondansetron, selected as active comparator was administered intravenously in both, Protocol 091 and Protocol 090. Presently, ondansetron is the standard of care and the most commonly used agent for prevention of PONV. In earlier well-controlled studies, prophylaxis with ondansetron was associated with approximately a 20 to 30% absolute reduction in the incidence of PONV compared with placebo.

- Treatments
  - Single oral administration of aprepitant (125 mg or 40 mg) 1 to 3 hours prior to induction of surgery.
  - Single IV administration of ondansetron (4 mg) immediately prior to induction of anaesthesia.

Patients were randomized to 1 of 3 treatment groups (aprepitant 125 mg, 40 mg, or ondansetron) at each site using a stratified randomization schedule based on gender. Patients were treated with study medication only on Day 1 preoperative. Aprepitant (and placebo) capsules were supplied in 1 bottle ("Bottle A"), and ondansetron (or placebo) were dispensed in 1 vial ("Vial B"). Each patient received 2 capsules (aprepitant and placebo, or 2 placebo capsules) and an IV (ondansetron or placebo) on the day of surgery.

- Objectives and Endpoints

The *primary objective* was to demonstrate that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with Complete Response in the 24 hours following end of surgery. The primary endpoint was complete response, defined as no vomiting and no rescue medication given.

The secondary objective was to demonstrate that aprepitant (125 mg, 40 mg) is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with:

1. No Vomiting (0 to 24 hours)
2. No Rescue (0 to 24 hours)
3. No Vomiting (0 to 48 hours)

- Definitions

Vomiting was defined as one or more continuous vomits or retches/dry heaves. Episodes of vomiting were recorded by health care providers. Rescue therapy was offered to: (i) patients who requested it; (ii) patients who experienced more than 1 emetic episode; or (iii) patients who had nausea lasting for more than 15 minutes. No Rescue was defined as no use of rescue medications. Type of rescue therapy was not defined in the protocol.
Nausea was assessed using the 11-point nausea verbal rating score (VRS). Zero (0) equals no nausea, and 10 equals nausea as bad as it could be. Nausea assessments were recorded by study personnel at prespecified times (2, 6, 24, and 48 hours postsurgery) and unscheduled times (prior to administration of rescue, and if the patient complained of nausea).
Patients who did not vomit and did not take rescue medications were defined as patients with Complete Response. Efficacy assessments were recorded for 48 hours from end of surgery, but the time frame of primary interest was the first 24 hours after the end of surgery.

- Statistical methods

All hypotheses were used at a 2-sided significance level of 0.05 with the exception of the non-inferiority and superiority hypothesis with regard to the Complete Response endpoint of Protocol 091, which was tested using respectively the lower bound of a one-sided 95% confidence interval and the upper bound one-sided significance level of 5%.

A closed testing procedure was used to account for multiplicity related to the 2 primary hypotheses and a two-part hypothesis (non-inferiority followed by superiority) related to Complete Response in Protocol 091. A closed testing procedure was also used for the two treatment comparisons (aprepitant 125 mg versus ondansetron, and aprepitant 40 mg versus ondansetron) in both studies 091 and 090.

Comparisons between aprepitant (125 mg, 40 mg) and ondansetron were made using logistic regression that included factors for treatment, gender and study sites. A step-down procedure was used to account for multiple tests (2 doses compared to ondansetron) within the primary hypothesis.

The primary population used to assess efficacy was the mITT population, which included all patients who were randomized, took study drug, underwent surgery under general anaesthesia, and had at least 1 post-treatment assessment. The patients were included in the treatment group to which they were randomized.

The per-protocol (PP) population excluded patients who were identified as protocol violators (identified prior to unblinding of the study). The definition of protocol violators included patients who did not receive N_2O or postoperative opioids, patients who received propofol for maintenance of anaesthesia or neuroaxial anaesthesia, patients who received placement of nasogastric or oralgastric tube, patients who vomited within 24 hours prior to surgery and patients who took an antiemetic within 24 hour prior to surgery, or during the initial 24 hours after the end of surgery for emetic prophylaxis.

Kaplan-Meier curves were generated for each of the treatment groups to describe the time to first vomiting (0-48 hours) in studies 091 and 090, the time to first vomiting or first use of rescue medication (0-24 hours) in study 091, and the time to first use of rescue medication to treat established nausea or vomiting (0-24 hours) in studies 091 and 090. A log-rank test was used for treatment comparisons.

For the nausea analysis, an individual peak nausea score was calculated over the first 24 hours following the end of surgery. All scheduled and unscheduled nausea assessments over the first 24 hours were included in this calculation. The single highest VRS score was used as the peak value. The Wilcoxon rank-sum test was used in comparing the treatment groups.

Careful review of the outcome of study 090 led to the decision to revise the hypothesis structure, including the Data Analysis Plan (DAP) for study 091 prior to completion of this study and un-blinding of the database. The revised protocol had two primary efficacy hypotheses. The first was that aprepitant is superior to ondansetron as measured by the proportion of patients with No Vomiting in the 24 hours following end of surgery. This endpoint was selected because previous PONV studies as well as Protocol 090 indicate that it is an objective and clinically relevant assessment in the surgical setting. The second primary efficacy hypothesis was that aprepitant is non-inferior to ondansetron as measured by the proportion of patients with Complete Response in the 24 hours following end of surgery. Based on published ondansetron - placebo comparative studies in women, the non-inferiority margin was set at an odds ratio of 0.65. The study had other exploratory objectives, such us, proportion of patients with “no rescue” 0 to 24 hours, distribution of peak nausea score 0 to 24 hours, time to first vomiting 0 to 48 hours, time to first vomiting or use of rescue 0 to 24 hours and time to first use of rescue 0 to 24 hours.

Study 091 (Principle study)

Study 091, conducted between 28-May-2004 and 20-April-2005, was a randomized, double-blind, active comparator-controlled, parallel group study, performed to examine the safety, tolerability, and efficacy of 2 Doses of aprepitant for the prevention of postoperative nausea and vomiting. This study was a multinational study with 42 sites.

Methods

- Patient population

A total of 922 patients from 16 countries worldwide including the US and the EU met the eligibility criteria at the screening visit and were enrolled in the study and randomized into 1 of 3 treatment groups (307 were in the aprepitant 40-mg group, 313 were in the aprepitant 125-mg group and 302 were in the ondansetron group). A total of fifty-six patients were not included in either the safety or in the mITT efficacy analyses thereof 30 as they did not receive study drug, all of them due to discontinuation prior to scheduled administration of study drugs and this mainly due to change in planned surgery or anaesthesia.

- Statistical plan

See study 090

Due to the outcome of study 090, the study protocol was revised 17 March 2005. The first step in the analysis was to show that aprepitant was superior to ondansetron with respect to "no vomiting". If significantly better (p=0.05), the second step would be to show "non-inferiority" in terms of "complete control" (no vomiting, no use of rescue). Based on published ondansetron - placebo comparative studies in women, the non-inferiority margin was set at an odds ratio of 0.65.

Primary objectives: "No vomiting" (superiority) and "complete control", as defined in study 091 (non-inferiority)

Secondary objective: "No vomiting" for 48 hours (superiority)
Exploratory objectives: Proportion of patients with "no rescue" 0 to 24 hours.
Distribution of peak nausea score 0 to 24 hours.
Time to first vomiting 0 to 48 hours
Time to first vomiting or use of rescue 0 to 24 hours
Time to first use of rescue 0 to 24 hours

Results for Studies Protocol 090 and 091

- Study population

The study population of both protocols 091 and 090 consisted of patients receiving general anaesthesia (nitrous oxide, volatile anaesthetics and intra- and postoperative opioids) for open abdominal surgery requiring an overnight, post-surgery hospital stay. The majority of patients (~ 85%) were women undergoing gynaecological surgeries (81% and 92%, in Protocol 091 and 090, respectively). Populations were similar to those enrolled in previous pivotal PONV studies with 5-HT3 antagonist ondansetron.
Specific exclusion criteria were 'epidural anaesthesia' and the use of a 'nasogastric (NG)', or oral-gastric (OG) tubing. Surgeries requiring routine use of an NG/OG tube were not permitted in order to avoid any potential impairment of the absorption of orally administered aprepitant. Likewise, epidural anaesthesia was not allowed in order to ensure consistent exposure to postoperative opioids, an important risk factor for PONV.

Based on the specific eligibility criteria, the majority of patients consisted of women undergoing gynaecological surgeries. In both studies, the most common category of surgery was hysterectomy plus salpingo-oophorectomy, and the specific types of surgery were generally similar across treatment groups.

- Sample Size

The premeditated sample size for both studies was 720 patients, consisting of 240 patients per arm. Following revision of the primary hypotheses of Protocol 091, the sample size of study 091 was increased to 840 patients, with 280 patients per arm, to get an anticipated magnitude of statistical power of at least 80% of the two primary hypotheses.

Initially Protocol 090 enrolled 805 patients in the US. In fact, the Modified Intent To Treat (MITT) population for all endpoints within the first 24 hours after surgery consisted of 866 patients (of 922 randomized) for Protocol 091 and 733 patients (of 805 randomized) for Protocol 090. The MITT population for endpoints up to 48 hours after surgery consisted of 861 and 728 patients, respectively. Supportive per-protocol (PP) analyses were also conducted for the primary and secondary endpoints.

- Clinical Efficacy

The great majority of randomized patients in both PONV studies completed the studies. The completion rate for all randomized patients was 96% in Protocol 091 and 93% in Protocol 090. The majority of patients who discontinued the study did so prior to receiving study drug, most commonly because the surgery was cancelled or rescheduled, the surgical or anaesthesia plans had changed, or

the patient became “ineligible” for the study. In Protocol 091, four dosed patients discontinued the study due to a clinical adverse experience.

The US study (Protocol 090) failed to meet its primary objective to show superiority compared with ondansetron in terms of complete control of PONV (no emesis, no use of rescue, odds ratio about 1), but based on available data it is concluded that aprepitant is active in the prevention of PONV. The superiority objective, however, was met by the non-US study (091) (odds ratio 1.4). With respect to baseline characteristics, including type of surgery there are no obvious differences between studies.

In protocol 090, aprepitant, although not meeting the statistical criteria for establishing superiority, was numerically better than ondansetron for Complete Response and was statistically not inferior based on a post hoc non-inferiority analysis during the first 24 hours after surgery. Aprepitant was also superior to ondansetron for the prevention and control of postoperative vomiting during the first 24 hours ($p<0.001$) and 48 hours ($p<0.001$) after surgery.

Table 1. Complete Response in Study 090 (a) and 091 (b)

a) Study 090 Complete Response (no emesis, no use of rescue), MITT

Treatment	n/m (%)	Odds Ratio	Lower Bound of 2-sided 95% CI
Aprepitant 125	103/239 (43.1)	1.0	0.72
Ondansetron	104/246 (42.3)		
Aprepitant 40	111/248 (44.8)	1.1	0.77
Ondansetron	104/246 (42.3)		

b) Study 091 Complete Response (no emesis, no use of rescue), MITT

Treatment	n/m (%)	Odds Ratio	Lower Bound of 2-sided 95% CI
Aprepitant 125 mg	184/293 (62.8)	1.4	0.99
Ondansetron	154/280 (55.0)		
Aprepitant 40 mg	187/293 (63.8)	1.4	1.02
Ondansetron	154/280 (55.0)		

A difference between both studies with regards to the use of rescue therapy was shown. Rescue therapy has been used more frequently across all study arms in the US study (Protocol 090), about 55% vs. 35%, despite very similar nausea scores prior to administration of rescue. The percentage of patients without vomiting was also slightly higher in the US study, especially in the aprepitant groups. This might have been the effect of a more frequent use of rescue therapy in the US study. These data are also compatible with the seemingly better effect of rescue concerning vomiting in aprepitant-pretreated patients.

If study data are pooled the overall complete response rate in the aprepitant (40 mg) group 298/541 is slightly better than in the ondansetron group 258/526 (95% CI +12%; +0.0%).

Table 2. Complete Response' MITT Population Pooled PONV Studies– Protocols 091 – 090

	Aprepitant 40 mg		Aprepitant 125 mg		Ondansetron	
	n/m	(%)	n/m	(%)	n/m	(%)
Overall	298/541	(55.1)	287/532	(53.9)	258/526	(49.0)
Gender						
Female	265/499	(53.1)	251/489	(51.3)	233/494	(47.2)
Male	33/42	(78.6)	36/43	(83.7)	25/32	(78.1)

A reasonable interpretation of the overall results would be that aprepitant is at least as effective as ondansetron for the prophylaxis of PONV. With regards to the dose, the 40 mg dose appears to be as effective as the 125 mg dose.

An issue regarding section 5.1 of the SPC was identified. The MAH claims that aprepitant is superior to ondansetron in terms of its anti-emetic properties (and control of nausea). Following a request of CHMP in January 2006 the MAH addressed the issue of a potentially confounding effect by the use of rescue medication on the individual outcome measures (nausea and emesis). In order to provide further information possibly supporting claims related to superior effects as regards prevention of emesis, time to first emesis may be analysed censoring patients at time of rescue medication (studies 091 and 090). Alternative ways to handle the confounding effects of rescue were requested from the MAH. The same analysis was also requested for nausea. The MAH agreed that, while the proportion of patients using rescue was similar between all treatment groups, the effectiveness of rescue medication theoretically may have varied depending on the randomized treatment received. The MAH performed three additional analyses:

1. The time to first vomiting or first rescue analysis incorporates patients who used rescue medication or had an emetic episode as treatment failures.
2. An analysis, which ignores the use of rescue medication in determining the time to first emetic episode.
3. An analysis in which the patient is censored at the time of rescue use.

Protocol 091

The time to first vomiting or first rescue analysis (1) was analysed using the Kaplan-Meier plot.

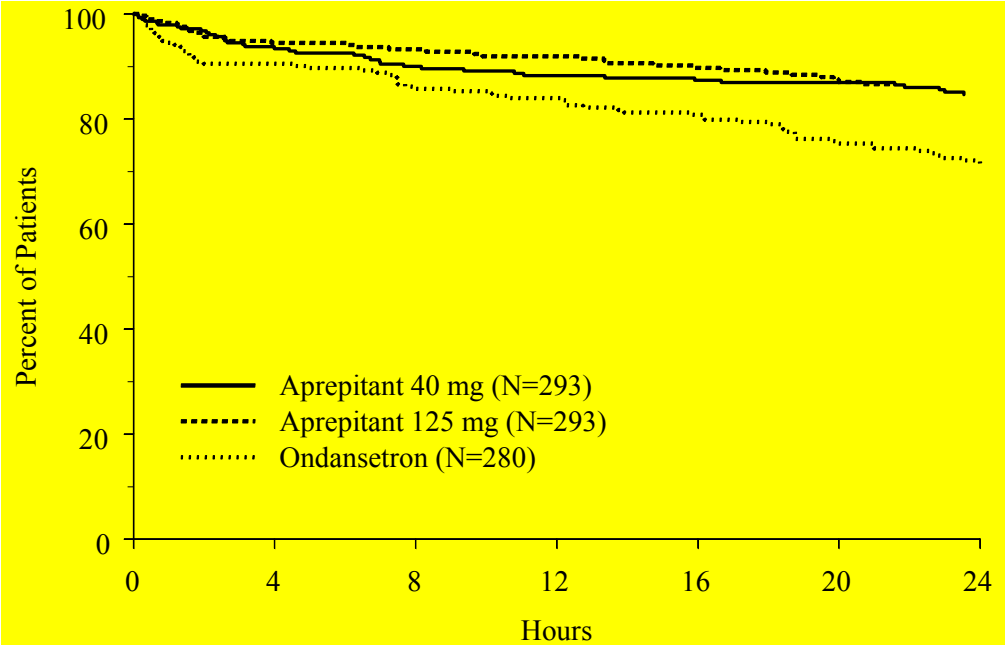

Figure 1. Kaplan-Meier Curves for Time to First Vomiting During the 24 Hours Following End of Surgery Patients Censored at Time of Rescue, Modified Intention-to-Treat Analysis

Pairwise Comparison	Analysis 1	Analysis 2	Analysis 3
Aprepitant 40mg vs. Ondansetron			
Hazard Ratio	0.764	0.522	0.513
Relative Risk Reduction (RRR)	23.6%	47.8%	48.7%
95% C.I. for RRR	(1.1%, 41.0%)	(25.1%, 63.6%)	(23.6%, 65.5%)
Aprepitant 125mg vs. Ondansetron			
Hazard Ratio	0.774	0.438	0.452
Relative Risk Reduction (RRR)	22.6%	56.2%	54.8%
95% C.I. for RRR	(0.0%, 40.1%)	(35.9%, 70.0%)	(31.7%, 70.1%)

Table 3. Hazard Ratios and Reduction in Risk for No Vomiting Analyses, Protocol 091

These three analyses show alternative ways to treat the use of rescue therapy: as an endpoint (=emetic episode), ignoring the use of rescue in the time to emesis analysis and censoring at the time of use of rescue. The results from all these analyses favour aprepitant. The outcome with respect to the protocol defined endpoint "percentage of patients without emesis" neglecting use of rescue is considered to be qualitatively supported by these analyses. The estimated effect size according to the protocol analyses (odds ratio 2 – 3, $p<0.001$), however, should be interpreted with caution, nevertheless it is accepted to state that aprepitant provides better prevention against emesis than ondansetron.

No analyses have been submitted supporting the claim with regards to superior control of nausea. No attempts were made by the MAH to support the claim in the originally submitted SPC that aprepitant, irrespective of use of rescue, provides better protection against nausea.

The protocols were identical, but due to the non-superiority results of study 090, the analysis plan for study 091 has been revised. For the presentation of study data in 5.1, however, it was proposed that the results should be pooled and that results should be reported as "percentage of patients with complete response" (no use of rescue, no emesis), i.e. the original primary endpoint for both studies should be reported. It could be added that aprepitant offered a better prevention against emesis without further qualifications, as it is hard to define the optimal measure due to the confounding effect of use of rescue. The CHMP was of the opinion that the term nausea should be deleted from section 5.1.

With reference to the secondary and exploratory end points, rescue therapy was considered effective in the case of PONV. Both nausea and vomiting may trigger the use of rescue. A nausea score VRS>0 was high enough to prompt the use of rescue if requested by the patient with consequent effects on vomiting and peak nausea. Similarly, early vomiting at a relatively low nausea score followed by administration of rescue may lead to a reduced peak nausea score. Provided that there is no major difference in the activity of rescue, the confounding effect of use of rescue should tend to reduce differences in terms of effects on the individual variables vomiting and nausea. In this study, however, rescue appears to be more active in the aprepitant arms resulting in "no vomiting".

If the possibly confounding effect of rescue is not accounted for, aprepitant appears to be more active against both emesis and nausea. Therefore, it is reassuring that there appears to be more patients with nausea score 0 in the aprepitant arms, i.e. an outcome measure unlikely to be confounded by use of rescue. It is notable that close to 50% of the patients reported a high nausea score (≥7/10) prior to the administration of rescue. The distribution of nausea scores prior to the administration of rescue was very similar to the distribution seen in study 090 despite less common use of rescue in study 091 (about 35% vs. 55%) and despite a higher peak nausea score in study 090. The difference in use of rescue was established early and at 2 hours about 25% of the patients in the US study had received rescue versus about 15% in the non-US study.

No vomiting (0-24 hours)

Both studies demonstrated that aprepitant compared to ondansetron improved prevention of vomiting, and exhibited better anti-emetic control in the 24 hours following end of surgery, as indicated by the frequency of emetic events across treatment groups. In Protocol 091, on average, for each emetic episode recorded in each aprepitant group, there were about 2 episodes recorded in the ondansetron group. In Protocol 090, on average, for every emetic episode recorded in the aprepitant groups, there were at least 4 episodes recorded in the ondansetron group.

Complete response (0-24 hours)

The Complete Response aim comprises 2 separate hypotheses of non-inferiority and superiority.
In Protocol 090, the primary hypothesis was that aprepitant is superior to ondansetron with respect to Complete Response. Although aprepitant gave numerically better Complete Response than ondansetron, the hypothesis was not met with statistical significant evidence.

Post hoc analysis of data from Study 090 demonstrates that both doses of aprepitant were statistically non-inferior to ondansetron with respect to the proportions of patients with Complete Response in the 24 hours following end of surgery (0.76 and 0.81 lower bound of the 95% confidence interval for aprepitant 40 mg versus ondansetron and aprepitant 125 mg versus ondansetron, respectively).

In both protocols, per-protocol analyses of Complete Response (0 -24 hours) supported the primary analyses. Additional post hoc analyses for Complete Response were also conducted in both protocols using the lower bound of the 2-sided 95% confidence interval as the decision rule for non-inferiority / superiority. Results of study 091 are sufficient to conclude that aprepitant has shown non-inferiority to ondansetron. Study 091 was considered confirmative for the hypotheses generated in study 090.

No vomiting (0-48 hours)

The results of the secondary endpoint of No Vomiting in the 48 hours following end of surgery in Protocol 091 are summarised in Table below. Results obtained in Protocol 091 were consistent with the results obtained in Protocol 090 and consistent with the Kaplan-Meier curves for the time to first emesis during the 48 hours following end of surgery for both studies.

Treatment	With No Vomiting			Aprepitant Versus Ondansetron	
	n/m	%	95% CI	Odds Ratio[†]	p-Value
Aprepitant 40 mg	238/292	81.5	(76.6, 85.8)	2.3	<0.001
Aprepitant 125 mg	246/290	84.8	(80.2, 88.8)	2.9	<0.001
Ondansetron	185/279	66.3	(60.4, 71.8)		

[†] Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favours Aprepitant over Ondansetron.

The model included terms for treatment and investigative sites.

n/m = Number of patients with desired response/number of patients included in analysis.

Table 4. Number and Percentage (%) of Patients With No Vomiting by Treatment Group in the 48 Hours Following End of Surgery in the Modified-Intention-to-Treat Analysis of Protocol 091

Other efficacy endpoints

No Rescue (0-24 hours)

The percentages of patients with no use of rescue medication in the 24 hours following end of surgery were similar across treatment groups in both Protocol 091 and Protocol 090. However, the proportions of patients with No Rescue during the first 24 hours after surgery were higher in Protocol 091 (67%, 65%, and 63% in the aprepitant 40 mg, aprepitant 125 mg and ondansetron group, respectively), compared with Protocol 090 (45%, 44%, and 46% in the aprepitant 40 mg, aprepitant 125 mg and ondansetron group, respectively). In Protocol 091 the peak nausea Verbal Rating Score (VRS) was lower with aprepitant 125 mg and 40 mg compared with ondansetron, while in Protocol 090 there were no significant differences in the distribution of peak nausea verbal rating scores between treatment groups.

Time to First Emesis

Kaplan-Meier curves for the time to first emesis during the 48 hours following end of surgery for Protocol 091 and Protocol 090 depict the cumulative percentage of patients who did not have emesis. Kaplan-Meyer estimates indicate that the proportions of patients who had a first vomiting episode within 2 hours following the end of surgery were more than double in the ondansetron group (9% and 8% in Protocol 091 and protocol 090, respectively) compared to the aprepitant 40 mg (2% and 3% in Protocol 091 and Protocol 090, respectively), and the aprepitant 125 mg (4% and 2% in Protocol 091 and Protocol 090, respectively) groups.

Summary of Efficacy Results

Results are consistent with those of previous preclinical studies and clinical data with NK1 receptor antagonists other than aprepitant that had suggested that NK1 receptor antagonists would be more effective than 5-HT3 receptor antagonists in preventing PONV. Therefore, by virtue of its novel mechanism of action, aprepitant has demonstrated and increased efficacy in the prevention of PONV. This effect is considered important in medical practice.

Clinical Safety

- Adverse events (AE)

Aprepitant is licensed for the treatment of chemotherapy induced nausea and vomiting at a dose of 125 (day 1) + 80 mg (Days 2 and 3). Overall aprepitant is well tolerated. In patients receiving cisplatin-based chemotherapy the most commonly observed adverse reactions include: hiccups (5%), asthenia/fatigue (3%), ALT increased (3%), constipation (2%), headache (2%), anorexia (2%)**.**

- ADR reported from PONV studies (Protocol 90 and 91)

Out of 1727 randomized patients in the pooled PONV studies, 1120 patients received aprepitant and were included in the safety analysis. Both single doses of aprepitant were generally well tolerated. Clinical adverse experiences occurred in 60% of the patients in the aprepitant 40 mg group, and 64% of the patients in the aprepitant 125 mg group. Common clinical adverse experiences that occurred more frequently in the aprepitant 125 mg group compared with the aprepitant 40 mg group include: headache (5.0% in the aprepitant 40 mg group and 8.1% in the aprepitant 125 mg group), and tachycardia (0.7% in the aprepitant 40 mg group, and 2.0% in the aprepitant 125 mg group).

One hundred forty two (142) of the 1658 randomized patients who received active study drug had one or more serious clinical adverse experiences. The most common criteria for the definition of 'serious adverse events' were hospitalisation and prolonged hospitalisation.

	Aprepitant 40 mg (N = 564)		**Aprepitant 125 mg** (N = 556)		**Ondansetron** (N = 538)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	336	(59.6)	354	(63.7)	344	(63.9)
With no adverse experience	228	(40.4)	202	(36.3)	194	(36.1)
With drug-related adverse experiences[†]	24	(4.3)	30	(5.4)	33	(6.1)
With serious adverse experiences	49	(8.7)	43	(7.7)	50	(9.3)
With serious drug-related adverse experiences	0	(0.0)	2	(0.4)	1	(0.2)
Who died	1	(0.2)	1	(0.2)	1	(0.2)
Discontinued due to adverse experiences	1	(0.2)	2	(0.4)	1	(0.2)
Discontinued due to drug-related adverse experiences	0	(0.0)	1	(0.2)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	1	(0.2)	1	(0.2)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably or definitely drug related.

Table 5. Clinical Adverse Experience in Pooled PONV Studies with Protocols 090 and 091

- Serious adverse events and deaths

There were three deaths, one in each of the treatment groups, none of these cases were reported to be drug related. The most common criteria for defining an AE as serious was hospitalization/prolonged hospitalization.

The most common serious clinical adverse experiences were gastrointestinal disorders: 9 (1.6%) patients in the aprepitant 40-mg group, 15 (2.7%) patients in the aprepitant 125-mg group, and 14 (2.6%) in the ondansetron group.

Three serious adverse experiences were considered by the investigator as possibly related to study therapy (2 cases of constipation that required prolonged hospitalization and 1 case of development of subileus also required prolonged the hospitalization). The incidences of specific laboratory AEs were essentially similar between treatment groups. An increase in ALT levels e.g. was observed in 8/543 (aprepitant 40mg), 7/528 (aprepitant 125mg) and 8/521 (ondansetron).

Out of the 1658 randomized patients receiving study medications, two patients in the aprepitant 125 mg group and one patient in the ondansetron group had one serious clinical adverse experience of special interest (hypoventilation, respiratory arrest). None of these serious events of special interest were considered possibly, probably, or definitely related to study drugs by the investigator. In the aprepitant 40 mg group, one patient developed respiratory depression, one patient had decreased respiratory rate, and one patient developed an over sedation. No formal analysis was conducted to assess the risk associated with administration of aprepitant 40 mg because a single 40 mg dose of aprepitant induces a weak inhibition of CYP3A4.

The incidence of specific laboratory adverse experiences was similar between the 3 treatment groups. The most frequent laboratory abnormality reported as laboratory adverse experience was a decrease in haemoglobin: 20 patients (3.8%) in the aprepitant 40-mg group, 28 patients (5.3%) in the aprepitant 125-mg group, and 22 patients (4.2%) in the ondansetron group. Two patients who received study drug experienced a laboratory adverse experience that the investigator considered serious. The overall adverse event profile is similar to ondansetron. Administration of aprepitant 40 mg prior to induction of anaesthesia was well tolerated.

The safety and tolerability of aprepitant in surgical patients was assessed in the combined safety database from both Study 091 and 090. Aprepitant (125 mg and 40 mg) was well tolerated when administered in the preoperative setting. The clinical and laboratory safety profile of aprepitant was similar to that of ondansetron and consistent with previous experience in cancer patients, as reflected in the current labelling. No new safety concerns have emerged in the PONV development program. Specifically, no definitive dose-dependent drug interaction concerns were identified, even though preoperative administration of aprepitant 125 mg may alter the metabolism of orally administered CYP3A4 substrates.

The MAH was also requested to address the risk for pharmacodynamic interactions. The CHPM enquired if dose adjustments of anaesthetic agents were required in the aprepitant arm compatible with a pharmacokinetic/pharmacodynamic interaction.

The receptor selectivity profile of aprepitant and its metabolites has been examined in a series of radioligand-binding assays at ion channels and receptors. These studies were conducted to characterize its NK1 receptor specificity and antagonist activity. Aprepitant had high affinity (IC50 0.1nM) and was highly selective for the G-protein coupled NK1 receptor. In contrast, the principal effects of general anaesthetics are thought to be mediated by ligand-gated (rather than voltage-gated) ion channels.

Aprepitant was shown to be only a weak inhibitor of [3H] diltiazem binding to skeletal muscle L-type calcium channels (IC50 8000 nM) compared to diltiazem (IC50 370 nM). Therefore aprepitant had only a very weak *in vitro* functional effect on Ca2+ mediated contraction in guinea pig LM/MP preparation (Ka 5.5). The activity of aprepitant against acetyl cholinesterase and cyclooxygenase was not studied. These data suggest that a direct interaction between aprepitant and anaesthesia-related medications is unlikely.

There have been no specifically designed experiments to address pharmacodynamic interactive effects between anaesthetic agents and aprepitant in humans. However, some data from the aprepitant PONV clinical program may be relevant. While intra-operative changes in anaesthetic doses were not measured, there were no reports of adverse experiences of intra-operative anaesthetic over-dose. The rate of recovery from anaesthesia serves as a surrogate marker for both pharmacodynamic and pharmacokinetics drug interactions. The awakening times and duration of recovery were similar in aprepitant and ondansetron groups. Serious adverse experiences related to excessive sedation were prescribed as being of special interest; in the 40 mg group, there was only 1 serious adverse experience adjudicated as excessive sedation. Finally, there was no clinically meaningful effect on other physiological parameters.

CHMP concluded on the basis of these data that an interaction on receptor levels is not expected. Doses of anaesthetic agents were not specifically monitored, however, there were no reports of adverse experiences of intra-operative anaesthetic over-dose. Time to awakening and duration of recovery were followed according to the protocol.

III. DISCUSSION

The MAH has submitted an application to propose aprepitant for the prevention of PONV as an alternative treatment option. Aprepitant is an NK1 receptor antagonist that blocks the emetic reflex induced by substance P, which is a novel bio-mechanistic approach to PONV. Other available anti-

emetics antagonise one of the four neurotransmitter receptors implicated in the aetiology of nausea and vomiting: serotonin (5-HT3 receptor antagonists), dopamine (butyrophenones, benzamides, phenothiazines), acetylcholine (anticholinergics), and histamine (antihistamines). Ondansetron, a 5-HT3 receptor antagonist, is presently the standard of care for the prevention of PONV.

The clinical development program consisted of two studies (studies 090/91) including more than 1500 patients, who received general balanced anaesthesia. Study 090 did not meet its primary objective. Additional post hoc analyses of this study generated hypotheses that were subject to confirmatory tests in study 091.
Overall, the clinical effects of 2 doses of aprepitant (125 mg and 40 mg) were evaluated in more than 1000 surgical patients, and compared with the efficacy provided by ondansetron IV. In both studies, the primary population used to assess efficacy was the mITT population, which included all patients who were randomized, took study drug, underwent surgery under general anaesthesia, and had at least 1 post-treatment assessment. The rationale for using a mITT population for the primary analysis was based on ensuring consistency with respect to the emetogenic stimulus, similarly to the approach followed in the aprepitant CINV studies.

Study 091 demonstrated that aprepitant was not inferior to ondansetron with respect to 'Complete Response' rate. Even though the defined non-inferiority margin was questioned, the lower limit of the Confidence Interval was far above the defined non-inferiority margin.

When administered as a single dose prior to surgery, the two doses of aprepitant had similar efficacy. In contrast, a pivotal CINV dose-range defining study observed maximal anti-emetic efficacy with the 125 mg regimen, compared to sub-maximal efficacy observed with the 40-mg dose regimen. The MAH argues that different dose-response curves observed in cancer chemotherapy patients and in surgical patients may be due to the different intensity of the emetic stimulus. This explanation has been considered acceptable by the CHMP.

The recommended dose of aprepitant for the prevention of PONV is a single 40 mg dose prior to anaesthesia. In comparison to a higher dose of 125 mg, the lower 40 mg dose had similar anti-emetic and anti-nausea efficacy. However, the 40 mg dose may have a slightly better safety profile and it is likely to have a lower drug-interaction potential.

Aprepitant 40 mg prior to induction of anaesthesia is considered to be well tolerated, as the adverse event profile for aprepitant was similar to ondansetron and. Nonetheless, the MAH was required to provide additional information on older subjects. The MAH was requested to submit information on differentiated Awakening Time/Duration of Recovery/Excessive Sedation and Respiratory Depression for younger and older patients in Studies 090 and 091. The MAH is in agreement that physiological changes associated with ageing such as renal and hepatic dysfunction and cognitive decline can complicate treatment options and pose a difficult challenge to surgeons due to higher incidences of co-morbidity and poly-pharmacy. The MAH evaluated the following:

- Awakening time (time interval between the placement of the last suture and the patient's ability to obey commands) was assessed every minute.
- The duration of recovery (time interval between the placement of the last suture and the patient's achievement of the postanaesthesia recovery score ≥8 on a scale of 0 to 10) was assessed every 15 minutes.

Other than a weak signal of prolonged awakening time in patients above 65 years of age treated with aprepitant 125mg, there are no signs of a dose – response relationship when comparing aprepitant 40 and 125mg. In study 090 there were only 9 individuals over 65 and treated with aprepitant 125mg and mean awakening time was only 0.16 hours in this group. The available limited data do not support the notion that there is an interaction between age, use of aprepitant and sedation.

In addition, the MAH has submitted a brief overview on the pharmacology of aprepitant and anaesthesia-related medications. These data do not indicate that an interaction on receptor level is expected.

The adverse event profiles were dominated by events expected in the postoperative setting and few events were regarded as drug related by the investigators. Dizziness, bradycardia and gastrointestinal events were reported for aprepitant and are labelled. No new signals classified as serious or general were identified. The overall adverse event profile for aprepitant was similar to ondansetron and aprepitant 40 mg prior to induction of anaesthesia and was considered to be well tolerated.

CONCLUSION

It is concluded that aprepitant offers a positive benefit risk ratio in the "Prevention of post-operative nausea and vomiting (PONV)" and that the newly formulated strength of 40mg may offer advantages to the indicated population.