SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Emend. For information on changes after approval please refer to module 8.

1. Introduction

Chemotherapy induced nausea and vomiting (CINV) remains a significant side-effect experienced by patients especially when these patients are treated with highly emetogenic regimens. One of the most emetogenic antineoplastic product is cisplatin when administered at doses superior to 50 mg/m^2. Without anti-emetic treatment essentially all patients experience CINV (for cisplatin emesis that has been documented to occur in more than 99% of patients). The chemotherapy associated emetic symptoms are categorised according to the temporal relation between the administration to emetogenic treatement and the emetic symptom phases, these symptoms are classified as acute or delayed CNIV. The acute phase of emesis is conventionally considered to last for 24 hours. In the particular case of cisplatin there is a peak in the risk of nausea and vomiting that occurs approximately 4 hours after the administration of the product followed by a period when virtually no emesis occur until about 16 to 18 hours after the administration of cisplatin. Despite the appropriate use of effective regimens for the prevention of CINV, about 25% of patients experience acute nausea and vomiting when treated with chemotherapeutic agents and about 50% experience delayed CINV.

The substances used to treat chemotherapy-induced nausea and vomiting include 5-HT_3 receptor antagonists also known as setrons, steroids and dopamine D2 antagonists. The combination of 5-HT_3 receptor antagonists with corticosteroids is recommended for the treatment of acute phase of high-risk CINV. There is substantial evidence to support their efficacy in this indication.

For the treatment of delayed emesis, clinical data show that dexamethasone given at 8 mg twice daily is effective. The role of 5-HT_3 antagonists for the control of the delayed CINV is much more controversial although they are recommended for use in recent therapeutic guidelines. The level of evidence in favour of activity of metoclopramide against delayed emesis is also considered weak

The active substance of EMEND is aprepitant (also know as MK-0869 or L-754030). Aprepitant is an antagonist of neurokinin 1 (NK1) receptor. The dominating natural ligand of this receptor is Substance P (SP), a neuropeptide from the family of tachykinins. Substance P is abundantly and widely distributed in the mammalian central nervous system and other tissues. Substance P itself is able to induce emesis. NK1 receptors are located the brain stem nuclei of the dorsal vagal complex, these regions of the brain are involved in the regulation of emesis.

The indication applied for EMEND by the Applicant is “prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin, in combination with other antiemetic agents”. The proposed regimen of aprepitant is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

EMEND is presented in the form of gelatine hard capsules filled with inert microcrystalline cellulose beads coated with 80 or 125 mg of aprepitant as active substance. Other ingredients are sucrose, hydroxypropyl cellulose, microcrystalline cellulose, sodium lauryl sulfate, gelatine, shellac, black iron oxide and titanium dioxide. The 125 mg capsule also contains red iron oxide and yellow iron oxide.

The capsules are packed in Aluminium blisters.

Active substance

Aprepitant is a white to off-white crystalline solid, and is practically insoluble in water. Aprepitant has the chemical name 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one.

Two crystalline forms exist but only one form (Form I), which is the most thermodynamically stable polymorph, is produced and used in the drug product. Satisfactory conformance has been provided that there is not any conversion to undesirable form (Form II).

Aprepitant is chiral, containing 3 asymmetric centres; and a defined pure stereoisomer is used in the finished product. Conversion to undesired stereoisomer is unlikely based on the molecular structure. Chiral purity is checked for one key intermediate during synthesis (chiral HPLC) and for the active substance (specific optical rotation).

Aprepitant is synthesized in two main steps: (1) the formation of the "secondary amine" (sec-amine) and (2) the synthesis of aprepitant drug substance from the sec-amine. The sec-amine is considered the starting material for the aprepitant synthesis as the material mainly contributes to the structure of the final drug substance. In the sec-amine, the absolute stereochemical configuration is already established and thereafter retained in the subsequent steps. Finally, aprepitant is purified from the crude substance by re-crystallization.

Modifications were made on the synthetic route during development concerning the synthesis of the secondary amine. Two major routes, which differ in the synthesis to form the sec-amine were used (Process 1 and Process 2). Further, a batch size modification has also been performed to the Process 2 in order to achieve the proposed synthetic route (Process 2B).

Sufficient data have been provided to show that there are not significant differences arising from these modifications.

Batch analysis data is provided on 5 batches produced with the proposed synthetic route and the current production batch scale. The batch analysis data confirm that the active substance can be manufactured reproducibly.

Adequate In-Process Controls are applied during the manufacture of aprepitant active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented.

Active substance specifications

The active substance specification includes tests for appearance, identity (IR spectroscopy, HPLC, specific rotation), assay (HPLC, weight %, 98.5 – 101.5%), impurities (HPLC, Area %), residual solvents (GC), water content (KF), heavy metals (ICP-MS), and residue ignition (Ph Eur).

The specifications reflect all relevant quality attributes of the active substance. However, the applicant committed to review the limits for assay when more manufacturing experience is being gained. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Stability

Stability studies under long term ICH conditions (25°C/60%RH and 40°C/75%) up to 9 months in three production-scale batches (plus additional data from pilot scale batches). Methods are validated and stability indicating. The parameters tested are characteristics, assay and impurities. Aprepitant drug substance appears to be very stable; there is no significant degradation at any of the conditions studied for the duration of the stability studies. Therefore, the data provided are sufficient to confirm the proposed re-test period.

Other ingredients

All excipients but the gelatine capsule shells and the printing ink are controlled for compliance to the corresponding monographs in the European Pharmacopoeia.

Certificates of analysis of the gelatine capsules demonstrating compliance to a satisfactory specification were provided. The suppliers of bovine gelatine are in the possession of Certificates of Suitability to Monographs of the European Pharmacopoeia.

The colorants used in the capsules, as well as the colorant used in the ink comply with Directive 95/45/EC.

The coating on the aluminum lidding that is in direct contact with the product meets the heavy metal requirements of the Packaging and Packaging Waste Directive (Commission Directive 94/62/EC). In addition, it complies with the requirements of the Monomers Directive (Commission Directive 2002/72/EEC), and the Framework Directive (Council Directive 89/109/EEC).

Product development and finished product

Due to the low aqueous solubility of the active substance, the product development has been focused on decreasing the active substance particle size to nanoscale in order to enhance the bioavailability of the substance. The product manufacture includes a wet-milling method to reduce the aprepitant particle size. The formulation includes excipients aiding in the reduction of the drug substance particle size, "forcing" the obtained nanoparticles to remain separated during and after coating of the microcrystalline cellulose beads, preventing agglomeration of beads and also allowing the drug substance particles to re-disperse from the beads in vivo with maintained small size. The product development and manufacture (including in-process controls and process validation) are satisfactorily accounted for. Excipients are well-known for medicinal products and satisfactorily controlled.

The manufacture comprises (1) production of a slurry of water, hydroxypropyl cellulose and aprepitant, (2) pre-milling (3) addition of an aqueous sodium lauryl sulphate dispersion, (4) media-milling to form a colloidal dispersion (5) addition of an aqueous sucrose dispersion, (6) spray-coating of microcrystalline cellulose beads with the colloidal dispersion (7) sieving of the coated beads, (8) blending of coated beads with micronised sodium lauryl sulphate and finally (9) encapsulation of the blended beads.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in thirteen production-scale batches (five batches of 80mg capsules and eight batches of 125mg capsules). The manufacturing process has adequately been validated and is satisfactory. The in process controls are adequate for this hard capsule preparation.

The batch analysis data show that the hard capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product Specification

The product specifications include tests by validated methods for appearance, identity (HPLC, NIR), assay (HPLC, 95.0-105.0% of the label), degradation products (HPLC), microbial purity (Ph. Eur.), dissolution, and content uniformity.

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data on three production-scale batches of each capsule strength confirm satisfactory uniformity of the product at release.

Stability of the Product

The shelf-life specifications for the finished products are appearance, assay (HPLC, 95.0% - 105.0% of label claim, the same as at release), degradates (HPLC), dissolution, etc.

Although, the following release parameters are not included in the shelf-life specifications: content uniformity, identity, and microbial limits, the finished product will meet these specifications, if tested.

Stability data for three full-scale production batches of each strength has been provides through 6 months at 25ºC/60% RH, 30ºC/65% RH, and 40ºC/75% RH packed in aluminium blisters. In addition data from pilot scale batches have been provided and based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The manufacturing process is demonstrated to give batch-to-batch reproducibility and compliance of finished product with specification.

The analytical methods have been validated and are suitable to ensure consistent quality of the active substance and the finished product.

The synthetic pathway is presented and the structure and impurity profile of the active substance are characterized and in line with current ICH guidelines. The stability data on the active substance supports the re-test period proposed by the applicant.

Due to the reduced particle size of aprepitant active substance the formulation shows reasonably good bioavailability despite the low solubility of the active substance.

At the time of the CPMP opinion, there were two minor unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

- *In vitro* studies.

The affinity of aprepitant to the NK1 receptor was evaluated on receptors from the species used in the non-clinical pharmacodynamic studies (ferret) and also in the majority of the species used in the toxicology studies. The structure of NK1 receptors is highly conserved between species. The affinity of aprepitant for these receptors was shown to be similar between species with the exception of the rat where the affinity was shown to be lower but still, this affinity was high (K_i in the nanomolar range of concentrations).

It was also shown that aprepitant is a selective NK1 receptor antagonist that penetrates into the central nervous system. With respect to central NK1 receptor occupancy, a PET study (positron emission tomography) performed in monkey showed that more than 80 % of the brain receptors were occupied when the plasma levels were superior or equal to 120 ng/ml. A relationship between plasma levels of aprepitant and the degree of central occupancy was demonstrated.

Aprepitant was more than 1000 times more selective for the NK1 receptor than for the NK2 and NK3 receptors and did not show any affinity for the serotonin $5HT_3$ and dopamine D_2 receptors (other systems of neurotransmitters involved in the control of emesis). It was shown that aprepitant had good functional selectivity with respect to the smooth muscle NK1 receptor and the central NK1 receptor antagonist activity was confirmed in functional studies *in vivo*.

- *In vivo* studies.

As far as the primary pharmacology of aprepitant is concerned, *in vitro* data showed that aprepitant slowly dissociates from the human NK1 receptor (t½ for receptor occupancy was equal to 154 min) and it was suggested that aprepitant, as a competitive antagonist, may also behave as a pseudo-irreversible antagonist. The inhibition of foot tapping in gerbils further indicated that aprepitant has a long central duration of action. Still, there are no *in vivo* data that actually studied the kinetics of the receptor-dissociation and the duration of the anti-emetic effect of aprepitant.

Aprepitant had a significant effect against acute and delayed cisplatin-induced emesis in ferrets and the effect of the combination with dexamethasone or $5HT_3$ receptor antagonists was additive.

Aprepitant is extensively metabolised especially in rodents. Some of its non-polar metabolites cross the blood brain barrier. All metabolites, including the primary metabolite L-755446, had decreased affinity for the human NK1 receptor compared with the parent compound. In ferrets, the emesis model, it has been shown that the main anti-emetic effect was closely related to aprepitant, not metabolites, since the main compound in the ferret brain was the parent molecule 48 hours after dosing. However, assuming that the properties of aprepitant and metabolites in human are similar to the properties observed in preclinical species, an additional pharmacological effect of L-755446 cannot be totally excluded. Still, in ferrets, the main anti-emetic effect was without doubt related to aprepitant, since the main compound in the ferret brain was still, after 48 hours, the parent molecule.

Tumour growth in athymic mice was not affected by aprepitant alone or in combination with cisplatin. The combination did not alter mortality rate and body weight as compared to the individual agents.

- General and safety pharmacology programme.

Aprepitant did not induce significant effects on cardiovascular, behavioural, central nervous system, respiratory, renal and gastric systems. Importantly, NK1 antagonism with aprepitant did not induce any relevant effects on gastro-intestinal motility. The minor cardiovascular effects that were observed in the safety pharmacology studies were similar to those described with the vehicle. In two repeated dose toxicity studies ECG measurements did not demonstrate any effects on the cardiovascular system in particular on the QT interval at exposures up to 80-fold over clinical exposure.

Pharmacokinetics

- Absorption and bioavailability.

Aprepitant is quite slowly absorbed. This absorption is saturable. It is widely distributed into tissues including the brain and extensively metabolised in all species studied. Bioavailability of aprepitant was 40-50 % in male rodents and 16 % in the dog; the half-life was approximately 3 and 6 hours in the respective species. The half-life in female rats was estimated to 8-14 hours. Clearance was slow and saturable in the dog and moderate in the male rat. Disposition kinetics and distribution of aprepitant were only evaluated in male rats. Data on the distribution of aprepitant to the female reproductive organs are lacking.

- Distribution.

More than 97-98 % of aprepitant is bound to proteins in all species tested. The protein binding of the non-polar/major metabolites has not been determined, but it is not likely that the metabolites will contribute to any significant pharmacological activity of aprepitant. Aprepitant, L-755446 and other metabolites are chiral molecules. It was shown with both chiral and non-chiral analytical methods that interconversion of aprepitant *in vivo* is unlikely. It can therefore be assumed that no additional pharmacological effect is to be expected due to interconversion of aprepitant or its metabolites.

Studies in mice suggested that aprepitant is a Pgp-substrate, while its primary metabolites are not since the brain concentrations of the major metabolite (L-755446) were independent of the presence or absence of Pgp in the animals. Neither ondansetron nor dexamethasone, which are Pgp substrates as well, had any significant effects on the brain levels of aprepitant.

Significant amounts of aprepitant pass the rat and rabbit placenta and rat milk contained 90 % of the parent plasma levels.

- Metabolism.

The metabolism of aprepitant is extensive. The metabolism of aprepitant was similar (on a qualitative viewpoint) across the different animal species. The major metabolites identified in human plasma were also present in rat, mouse or dog plasma. Aprepitant undergoes N-dealkylation and O-dealkylation resulting in the removal of the triazolone and bis-trifluoromethylphenyl-ether chains respectively (see molecular structure of aprepitant in part II of the report). Non-polar, polar, very polar metabolites and glucuronide conjugates of aprepitant were identified. The glucuronide conjugates are mainly excreted and non-clinical data does not indicate any significant recirculation of aprepitant. *In vitro* metabolism data were consistent with the *in vivo* data, confirming the proposed metabolic pathways for aprepitant.

There is a substantially higher rate of metabolism in male compared to female rats. The rate of metabolism further increased after repeated dosing (as studied in male animals only), probably due to an auto-induction of aprepitant metabolism via CYP3A. In dogs, there were no apparent gender differences, but data indicates a lower rate of metabolism in dogs than in rodents. There was no obvious accumulation, since a plateau in exposure was reached in the long-term toxicokinetic studies.
In vitro studies suggested that mainly CYP3A4 and possibly isoenzymes 1A2 and 2C19 were involved in the metabolism of aprepitant in man. In addition, these studies showed that aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4 and a very weak inhibitor of CYP2C9 and CYP2C19 and the main interactions are likely to occur with products that are metabolised through CYP3A4.

- Excretion.

Excretion was studied in male animals only. In rat and dog, aprepitant is eliminated mainly by excretion of metabolites via biliary and urinary excretion. Excretion is essentially independent of the route of administration. Only a small fraction of the dose is excreted as unchanged parent compound in bile and no intact drug was detected in urine of either species. A similar part of the dose is eliminated via urine following both IV and oral administration, suggesting that absorption is complete. However, absorption is approximately 40 % based on excretion in urine and bile following oral administration. These inconsistent results were probably due to the different formulations used in the two studies resulting in different degrees of absorption. In addition, time of bile-sampling was limited in the excretion study.

Toxicology

- Single dose toxicity.

Single dose toxicity studies in female mice and rats by the oral and intraperitoneal route indicated a low potential for acute toxic effects.

- Repeated dose toxicity (sub-acute and chronic toxicity).

After repeated dosing to **rats**, the target organs were thyroid (at exposures similar to, or lower than clinical exposures) and liver (at doses higher than 2.5 times the clinical dose). These changes are considered to be due to induction of microsomal enzymes in the liver and a subsequent increased thyroxine clearance with compensatory TSH elevation as confirmed in supplementary studies. Serum cholesterol was slightly increased in both sexes and serum triglycerides were slightly decreased in males. Effects on the morphology of erythrocytes were seen at the end of the chronic toxicity study.

The salient toxicity findings in the **mouse** studies were hepatocellular hypertrophy, increase of cholesterol and triglycerides, kidney hydropic tubular degeneration, and decrease of potassium.

In the dog, target organs were the reproductive organs (prostate, testis and ovaries) and thymus in the presence of decreased body weight gain. The thymic atrophy found in only one study was attributed to be secondary to stress. However this explanation seems improbable since the effect was dose-related; the effect might be related to a real immunomodulatory effect of aprepitant. However, this finding was only observed at high exposure levels (125 mg/kg twice daily i.e. more than 40-times the clinical

exposure) and is currently not considered of any clinical significance. In contrast to the degenerative changes in the other target organs, gross ovarian changes found in one study were not accompanied by microscopic changes. With respect to reproductive organ toxicity in the males (two studies) these findings were only observed at high exposure levels as well.

Even though the toxicological profile was very different in the species used in these toxicological studies, an increase in plasma cholesterol was observed in both rats and dogs. This was likely related to the significant hepatotoxicity in the rat, but not in the dog. The possible mechanism behind the increase in the latter species was not clear. Pronounced hepatic toxicity was also observed in mice (≥ 25 mg/kg, in the carcinogenicity study) and in rabbits (≥ 5 mg/kg, in the reproductive toxicity studies).

In none of the substantial number of studies conducted with aprepitant, recovery was assessed. The Applicant could not provide possible mechanisms for the increased cholesterol levels and testicular degeneration seen at high exposure levels in dogs, and the morphological changes of erythrocytes in rats. Considering the fact that EMEND is indicated for short-term use, these findings are probably not relevant for human use in the proposed indicationToxicokinetics.

In rats, no sufficient exposure to the substance was obtained. The doses administered resulted in a similar or lower exposure compared with the clinically expected exposure and there was evidence of a saturated absorption. Attempts were made to increase the exposure in this species, and for this indication, the low exposure in the rat is accepted. A sufficient margin of exposure was reached in the dog studies, already at the lowest dose tested (13-fold).

- Mutagenic potential.

Aprepitant was found non-genotoxic in appropriate studies.

- Carcinogenic potential.

The carcinogenicity studies submitted are not considered as being mandatory for the claimed indication due to the short duration of treatment. Kinetic evaluations from accessory studies suggest a low exposure to aprepitant also in these studies. Non-neoplastic and neoplastic changes (rat only) were observed in liver (mouse and rat) and thyroid (rat). The non-neoplastic effects on the liver in the mouse study were considered by the Applicant to be due to an increase in CYP enzymes, which is a well documented, rodent-specific effect of limited clinical significance. However, in the mouse, CYP-specific enzyme induction was not measured, but EFCOD (indicator of CYP1A and 2B) suggested an enzyme induction also in this species.

In the rat carcinogenicity study, the same non-neoplastic effects on liver and thyroid were observed as in the toxicity studies. Also in this species, both non-neoplastic and neoplastic changes were considered secondary to microsomal enzyme induction and subsequent alterations in thyroid hormone balance. In this species, induction of CYP3A and to some extent CYP2B was seen in both genders. Published data have shown a correlation between the induction of CYP2B and CYP3A with hepatocellular hypertrophy and hepatic tumours in rodents. It is therefore accepted that the liver tumours were due to the accelerated hepatic metabolism with CYP3A and 2B induction in the liver.

The thyroid follicular cell adenomas and carcinomas in the rat were considered as related to the increased thyroxine clearance and compensatory TSH elevation. The effect on the hypothalamic-pituitary-thyroid axis was confirmed in a mechanistic rat study. It is concluded that there is no clinical significance of this finding due to the large species differences between rats and humans in the inherent susceptibility to neoplasia secondary to hormone imbalance. Furthermore, severe thyroid dysfunction in a patient would most probably be observed before there is an increased risk for neoplasia in humans. In conclusion, the neoplastic findings in the carcinogenicity studies are likely not of any clinical significance.

- Embryo/foetal and perinatal toxicity.

In rat fertility studies systemic exposure was low, especially in male rats. Pharmacokinetic data also indicates a faster clearance with a shorter half-life in male rats compared to humans, and even with a twice-daily administration, sufficient exposure may not be obtained during the 24-hour period.

Aprepitant does not seem to have any dramatic adverse effects on embryo-foetal, pre- and postnatal development. No developmental treatment-related effects were observed at doses up to 2000 mg/kg/day in two studies conducted in rats. This contradicts the findings in the dose-ranging studies, where 1) pronounced maternal toxicity, 2) decreased numbers of implants (5 - 250 mg/kg), and 3) decreased postnatal pup survival and pup body weights (250 mg/kg) were observed. In the rabbit dose-range finding study at 25 mg/kg a slight pre- and post-implantation loss was observed, but also in this species in the final study, no effects were observed at this dose level. The findings in both studies were however limited, not seen in the pivotal studies and within the range of historical control data. Therefore, it is accepted that the increases in postnatal mortality in rats and post-implantation losses in rabbits were probably not related to the treatment. On the other hand, systemic exposure in both species was only similar to that of human exposure. In female rats, the half-life of aprepitant was similar to the half-life in humans, but the affinity for the NK1 receptor was 50 times lower compared to humans. The rabbit is reported to have high CYP3A levels. This may result in a rapid metabolism and a short half-life of aprepitant in this species. Consequently, there is no information on whether the rabbits are exposed during the full 24-hour period. This may be central during the critical period of organogenesis even though the rabbits were dosed twice daily. In addition, the affinity for the NK1-receptor in rabbits is not known As a result, data does not allow an adequate evaluation of the potential risks for the foetus during pregnancyPossible effect on immune system.

Substance P is a major modulator of the (neuro)immune system and regulates its action via the NK1 receptor, a receptor that is widely distributed. It is not known what consequences antagonism of the NK1 receptors may have on immune function. Being an antagonist of NK1 receptors, aprepitant is likely to retain immuno-pharmacological activity considering that NK1 receptors are present on various immune cells. No specific studies on the immunotoxic potential of aprepitant were performed. The fact that this issue was not addressed may be partly justified (in the present indication) since no increased susceptibility to infections was noted in the non-clinical studies. However, except for infection (studied in specific pathogen free animals which minimises the risk for infection),no overall cellular immune activity was considered as endpoint and a reduced immune activity in treated patients can not be excluded

A strong argument in favour of the relative low importance of immuno-pharmacological adverse effects of aprepitant is the short-term treatment schedule and the lack of neutropenia following 5 days treatment.

In conclusion, aprepitant has indeed the potential to affect immune activity, but such an activity has not become apparent and it is not clear whether blockade of NK1 receptors is beneficial or adverse in infection. No further studies are required. However, the immuno-pharmacological effects of long-term treatment with aprepitant are not known, and further research on immunotoxicity is needed if such treatment is indicated.

Discussion on toxico-pharmacological aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that aprepitant is a selective NK1 receptor antagonist that penetrates to the central nervous system. Aprepitant showed the desired mode of action in cisplatin-induced emesis in ferrets. The Applicant has however further committed to study the duration of action of aprepitant in vivo. The general pharmacology studies showed no significant effects on major organ systems.

Overall, the toxicology programme revealed a relatively low toxicity of aprepitant. However, it should be noted that systemic exposure in rodents was similar or even lower than therapeutic exposure in humans. Adverse effects of possible relevance to humans included effects on reproductive organs and thymus in dogs. These findings were however only seen at high exposure multiples and is currently not considered of any clinical significance. Reproduction toxicity studies did not allow an adequate evaluation of the potential risks for the foetus during pregnancy and no specific studies on the immunotoxic potential of aprepitant have been performed. For the present, short-term indication, these shortcomings are accepted.

This information is reflected in the summary of product characteristics.

4. Part IV: Clinical aspects

Clinical pharmacology

Human Pharmacodynamic studies

Using a specific NK1 receptor binding ligand, which is able to cross the blood brain barrier, it is possible to assess the displacement of the ligand by aprepitant. The relationship between plasma concentration and NK1 receptor occupancy in the central nervous system was evaluated in PET studies (positron emission tomography). The aprepitant concentration that results in 50% receptor occupancy was estimated to be 11.3 ng/ml. Plasma concentrations of approximately 100 ng/mL are predicted to produce brain NK1-receptor occupancy of approximately 90%. The maximum plasma concentration at the indicated doses is about 1500 ng/ml and trough levels were approximately 600 ng/ml on the third day of treatment. Provided that there is no lag phase, e.g., due to the blood/brain barrier, these data suggest very high receptor occupancy during the entire treatment period. No *in vivo* studies exploring the receptor dissociation in the central nervous system or the periphery have been submitted and the durability of dynamic effects put in relation to pharmacokinetics remains to be elucidated.

The possible contribution of peripheral NK_1 receptor blockade to the prevention of delayed emesis was not fully explored in the drug development programme.

Pharmacokinetics

- General.

The pharmacokinetics of aprepitant was extensively studied in a large number of clinical pharmacology studies in healthy volunteers.

Absorption. The absorption of aprepitant is relatively slow. Following oral administration of EMEND, maximum aprepitant plasma levels are obtained at approximately 4 hours. The absolute bioavailability of the 80 mg and 125 mg capsule under fasting conditions is 67% (95% CI 62-73%) and 59% (95% CI 53-65%), respectively. The effect of food on the pharmacokinetics of aprepitant after administration of the hard capsule is dose-dependent. In the therapeutic dose range a standard breakfast resulted in an up to 40% increase in AUC, which is not considered clinically relevant.

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the $AUC_{0\text{-}24hr}$ (mean±SD) was 19.6±2.5 µg·hr/ml and 21.1±6.3 µg·hr/ml on Day 1 and Day 3, respectively and the C_{max} was of 1.6±0.36 µg/ml and 1.4±0.22 µg/ml. The interindividual variability is low (CV% for AUC about 30% and for C_{max} about 23%) in relation to the large safety margins.

The formulation intended for marketing (nanoparticle capsule formulation) was used in phase IIb, phase III and late clinical pharmacology studies. Early studies with aprepitant were carried out with 3 tablet formulations, which had a relatively low bioavailability and a significant food effect. All tablet formulations had oral bioavailabilities inferior to the nanoparticle capsule formulation giving markedly lower exposure in a fasting state, but a smaller difference in the fed state.

Distribution. Aprepitant has a high protein binding, 97-98%. The mean apparent volume of distribution is approximately 66 Liters.

Elimination. Aprepitant is eliminated by metabolism. In the therapeutic dose range, clearance is 60-72 ml/min and the terminal half-life about 9-13 hours.

Metabolism. Aprepitant has a large number of metabolites. Seven metabolites have been identified in human plasma following oral administration of ^{14}C-aprepitant and 12 metabolites following IV administration of the water-soluble ^{14}C-L-758298 prodrug. CYP3A4 is the main CYP450 isoenzyme involved in the metabolism of aprepitant. CYP2C19 and CYP1A2 may also be involved to some extent. Some of these metabolites eventually undergo glucuronidation. The metabolite profile in urine

and faeces has been adequately evaluated. Aprepitant constitutes about 19% of the radioactivity in plasma over 72 h and is the largest component in plasma during the first 48 h. A large number of metabolites were detected in plasma, but the relative contribution of the metabolites to total radioactivity in plasma has not been determined, nor is the protein binding of the metabolites known. Radioactivity not accounted for in plasma seems to consist of a number of metabolites at low concentration. All of the metabolites have lower or no NK1 receptor affinity compared with aprepitant and none of the metabolites are likely to contribute significantly to the activity. Thus, the lack of detailed information regarding metabolites in plasma is considered acceptable. Aprepitant is an enantiomer, but does not undergo any interconversion *in vivo*.

Excretion. Following IV administration of a ^{14}C-labelled prodrug of aprepitant (L-758298), which is converted rapidly and completely to aprepitant, approximately 57% of the total radioactivity is excreted in the urine and 45% in faeces. No unchanged substance is excreted in urine.

Dose-linearity. The pharmacokinetics of aprepitant is not linear. Aprepitant displays dose- and time dependent pharmacokinetics. Clearance decreases with increased dose, likely due to saturable metabolism. Absolute bioavailability decreases as the dose increases. The decrease in clearance with dose is larger than the decrease in bioavailability resulting in a more than proportional increase in AUC with increased dose. Upon long-term administration, aprepitant induces its own metabolism resulting in decreased exposure over time beyond Day 7. Using the proposed EMEND administration schedule of 125 mg on day 1 and 80 mg/day on days 2 and 3, relatively stable aprepitant plasma levels are obtained from day 1 to 3.

- Pharmacokinetics in the patient population.

Limited data suggest that the pharmacokinetics is similar in patients and in healthy volunteers. However, a final study report of one pharmacokinetic study conducted in patients should be submitted as a follow-up measure.

- Special populations.

No pharmacokinetic data were obtained in children. Age, gender, weight and race have no clinically relevant influence on the pharmacokinetics of aprepitant. There is no clinically relevant change in pharmacokinetics in severe renal impairment or end stage renal disease. Aprepitant is not extracted during haemodialysis. Patients with mild hepatic impairment have similar pharmacokinetics as healthy volunteers, while the exposure is slightly increased in moderate hepatic impairment (Child-Pugh scores 7-8); AUC was increased by 18% on Day 3. However, the subjects included do not seem to be representative for patients with impaired hepatic cellular function. Conclusions regarding the effect of moderate hepatic impairment on the pharmacokinetics of aprepitant cannot be drawn from these data. Severe hepatic impairment has not been studied. The lack of data in moderate and hepatic impairment is acceptable for the present indication with 3-day administration.

- Interaction studies.

The interaction profile of aprepitant is complex. Aprepitant is a substrate and inhibitor of CYP3A4 and an inducer of CYP3A4, CYP2C9 and potentially other isoenzymes.

Aprepitant is metabolised by CYP3A4: effects of other substances on the pharmacokinetics of aprepitant.

Since aprepitant is metabolised through CYP3A4 the association of aprepitant with substance known to inhibit or conversely known to induce this isoenzyme will induce changes to the plasma levels of aprepitant. A 5 times increase in AUC was observed during concomitant administration of ketoconazole (a strong CYP3A4 inhibitor) and a reduction of the AUC with 91% during concomitant administration of rifampicin (a strong inducer of multiple P450 cytochromes including CYP3A4). The effect of the moderate CYP3A4 inhibitor diltiazem on aprepitant pharmacokinetics has been studied, but the results (2-fold increase in aprepitant exposure) cannot be extrapolated to the currently proposed posology for EMEND as this interaction was evaluated using an early tablet formulation.

Therefore, coadministration of EMEND with medicinal products that inhibit CYP3A4 activity will result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of EMEND with CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, clarithromycin, telithromycin) should be approached cautiously.

Concomitant use with substances known to strongly induce CYP3A4 such as rifampicin is likely to result in considerable loss of efficacy of aprepitant and should be avoided. Effects of other CYP3A4 inducers are also expected and concomitant administration should be approached cautiously.

Aprepitant is an inhibitor of CYP3A4: effects of aprepitant on the pharmacokinetics of other substances.

Aprepitant is an inhibitor of CYP3A4, but does not seem to inhibit CYP2C9 or P-gp. Therefore, a series of interaction studies between aprepitant and CYP3A4 substrates, i.e. midazolam, dexamethasone, methylprednisolone and granisetron were conducted. Aprepitant caused a 2-3-fold increase in AUC of concomitantly orally administered CYP3A4 substrates with the proposed dosage regimen. Based on these studies, dose-adjustments are proposed for methylprednisolone and dexamethasone, when administered in combination with EMEND. EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

Additional data provided show that the effect on CYP3A4 substrates administered intravenously was considerably lower, as demonstrated by a 34% increases in AUC of concomitantly administered IV methylprednisolone. Data on midazolam administered intravenously on Day 4, the first day after end of aprepitant treatment (25% increase in AUC) suggest that a somewhat larger effect of aprepitant on a sensitive CYP3A4 substrate than that observed on methylprednisolone could be expected. Chemotherapeutic agents are generally administered intravenously. Hence, the interaction potential is much less than if they had been administered orally. A clinically significant effect on irinotecan cannot be excluded.

Aprepitant is also an inducer of CYP2C9 and CYP3A4; effects of induction on pharmacokinetics of other substances.

Aprepitant induces one or several enzymes over long-term administration. In the 3-day CINV treatment regimen, aprepitant is a modest inducer of CYP2C9 with a likely maximum induction in the range 30-35% at approximately 7-10 days after start of treatment and duration of slightly more than two weeks. The effect on hepatic CYP3A4 is lower with a maximum decrease in AUC of about 20% and duration of less than two weeks. Aprepitant does not seem to induce P-gp. The effect of induction on pharmacokinetics of orally administered CYP3A4 substrates (including a number of possibly co-administered non-chemotherapeutics) is not known, but it is expected to be significantly greater than the effect on products administered intravenously. In addition, the effect of the combination of aprepitant and dexamethasone on the pharmacokinetics of drugs metabolised by CYP3A4 has not been studied. The applicant has committed to conduct a study characterising the effect of aprepitant in combination with dexamethasone on hepatic and intestinal CYP3A4 using an orally administered sensitive CYP3A4 substrate. The study should characterise the maximum extent of induction and duration of induction and should be conducted using the proposed Emend posology for three days together with the proposed dexamethasone posology for 4 days.

The efficacy of oral contraceptives during administration of aprepitant may be reduced. Alternative or back-up methods of contraception should be used for 2 months following the last dose of EMEND.

As far as the potential inductive effects on *chemotherapeutic agents* are concerned CYP2C9 does not seem to be involved in the metabolism of chemotherapeutic agents to any significant extent, but CYP3A4 is involved at least partly in the metabolism of several agents (etoposide, vinorelbine, docetaxel, and paclitaxel). No relevant inductive effects are expected on chemotherapeutic agents administered intravenously 3-4 weeks apart or for agents with a 3-4 day regimens given from day 1 of

aprepitant treatment. Small effects could be expected on agents administered intravenously at weekly intervals. Considering the small inductive effect on hepatic CYP3A4 (approximately 20% decrease in AUC), the effect of aprepitant alone on IV chemotherapeutic agents is unlikely to be of clinical relevance. It appears advisable, however, to study the effects of aprepitant combined with dexamethasone on the pharmacokinetics of vinorelbine administered once weekly.

Finally, concerning potential clinically relevant interactions involving other isoenzymes of CYP450 aprepitant was shown *in vitro* to be a very weak inhibitor of CYP2C19. Aprepitant was a very weak inhibitor of CYP2D6, CYP1A2, and CYP2E1 with IC_{50} values superior to 100 µM for reactions catalysed by these isozymes.

All the results from the interaction studies together with the interaction profile of aprepitant are summarised in the tables thereafter.

Summary of interaction studies performed with aprepitant

Product	N	Dose aprepitant	Dose concomitant product	Effect of aprepitant on product given concomitantly	Effect of concomitant product on aprepitant
CYP3A4 inhibitors					
Ketoconazole	11	125 mg single	400 mg (2x200mg) b.i.d. 10 days	-	AUC ↑ 4.8-fold Cmax ↑ 1.5-fold
Diltiazem	6	300 mg q.d. 5 days (tablet form B)	120 mg t.i.d. 13 days	AUC ↑ 1.7-fold Cmax↑ 1.5-fold	AUC ↑ 2-fold Cmax ↑ 2-fold
CYP3A4 inducer					
Rifampicin	11	375 mg single	600 mg (2x300mg) bid 14 days	-	AUC ↓ 91% Cmax ↓ 62%
CYP3A4 substrate					
Midazolam	16	125/ 80 mg 5d	2 mg p.o. single dose	AUC ↑ 3.3-fold Cmax ↑ 1.9-fold	-
Midazolam	12	125/ 80 mg 3d	2 mg i.v. single dose day 0, 4, 8, 15	Day 4: AUC ↑ 25% Day 8: AUC ↓ 19% Day 15: AUC ↓ 4%	-
CYP2C9 substrate					
Warfarin	22	125 / 80 mg 3d	Titrated to stable INR	34% decrease in S-warfarin **after** treatment (day 8) 14% decrease in INR	-
Tolbutamide	12	125/ 80 mg 3d	500 mg p.o. single dose day 0, 4, 8, 15	Day 4: AUC ↓ 23% Day 8: AUC ↓ 28% Day 15: AUC ↓ 15%	
CYP2D6 substrate					
Paroxetine	18	100 mg 4 d, 200 mg 10 d (form C)	20 mg 14 d	Day 14: AUC ↓ 26%	Day 14: AUC ↓ 27%
Antiemetics					
Dexamethasone (CYP3A4 substrate)	20	125/80 mg 5d	20 / 8 mg 5d	AUC ↑ 2.2-fold Cmax ↑ 1.5-fold	Day 1: 30% ↑ AUC Day 5: No change
Methylprednisolone (CYP3A4 substrate)	10	125/80 mg 3 d	125 iv/40 po 3d	Day 1: AUC ↑ 34% Day 3: AUC ↑ 150%	-
Ondansetron	15	375 / 250 mg 5d	32 mg iv	AUC ↑ 15%	-
Granisetron	18	125/80 mg 3 d	2 mg po	AUC ↑ 10%	-
P-gp					
Digoxine	11	125/80 mg 5 d	0.25 mg q.d. 13 d	AUC ↓ 7%	-
Other					
Oral contraceptives	6	100 mg q.d. 14d	35µg EE 1 mg NET	Day 14: EE AUC ↓ 43% NET AUC ↓ 8%	-

Table summarising the interaction profile of Aprepitant.

Product	Consequence of the interaction
Aprepitant is metabolised by CYP3A4: effects of other agents on the pharmacokinetics of aprepitant.	
CYP3A4 inhibitors (e.g. ritonavir, ketoconazole clarithromycin, telithromycin).	Concomitant administration of EMEND with CYP3A4 inhibitors results in increased plasma concentrations of aprepitant, the association should be approached cautiously.
Rifampicin (or other CYP3A4 inducers e.g. phenytoin, carbamazepine, phenobarbital, St John's Wort).	The association results in reduced plasma concentrations of aprepitant that may result in decreased efficacy of EMEND. Combination with strong CYP3A4 inducers should be avoided. Combination with St John's Wort is not recommended.
Aprepitant is an inhibitor of CYP3A4: effects of aprepitant on the pharmacokinetics of other agents.	
Pimozide, terfenadine, astemizole, or cisapride	EMEND should not be used concurrently with these substances. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.
Ergot alkaloid derivates	Coadministration of EMEND with ergot alkaloid derivatives, which are CYP3A4 substrates, may result in elevated plasma concentrations of these medicinal products. Therefore, caution is advised due to the potential risk of ergot-related toxicity.
CYP3A4 substrates	As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered medicinal products that are metabolised through CYP3A4. Caution is advised during concomitant administration with CYP3A4 substrates.
Dexamethasone	The usual oral dexamethasone doses should be reduced by approximately 50%.
Methylprednisolone	The usual intravenous administration methylprednisolone dose should be reduced by approximately 25%, and the usual oral methylprednisolone dose should be reduced by approximately 50%.
Aprepitant is also an inducer of CYP2C9 and CYP 3A4; effects of induction on pharmacokinetics of other agents.	
CYP3A4 substrates	As an inducer of CYP3A4, aprepitant can decrease plasma concentrations of intravenously administered CYP3A4 substrates within 2 weeks following initiation of dosing with EMEND. This effect may become apparent only after the end of treatment with EMEND. The inductive effect of aprepitant on orally administered CYP3A4 substrates has not been studied, but is expected to be larger. Caution is advised when oral medicinal products metabolised by CYP3A4 are

	administered during this time period.
CYP2C9 substrates	Aprepitant has been shown to induce CYP2C9. Coadministration of EMEND with medicinal products that are known to be metabolised by CYP2C9, such as warfarin, tolbutamide, phenytoin, may result in lower plasma concentrations of these medicinal products; therefore caution is advised.
Warfarin	In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored, in the 2 weeks following initiation of the 3-day regimen of EMEND with each chemotherapy cycle, to establish and maintain the required dose of warfarin.
Oral contraceptives	The efficacy of oral contraceptives during administration of EMEND may be reduced. Alternative or back-up methods of contraception should be used for 2 months following the last dose of EMEND.
Chemotherapeutic agents metabolised though CYP3A4 (e.g. etoposide, vinorelbine, docetaxel, and paclitaxel).	Caution is advised and additional monitoring may be appropriate in patients receiving such agents.

Discussion on Clinical Pharmacology

Clinical efficacy

All phase II and III studies were randomised, double-blind and recruited cisplatin naïve patients without concomitant therapy or complicating conditions likely to confound the assessment of efficacy.

Dose response studies

The phase II studies programme includes 5 dose and regimen finding studies (see table below).

Table summarising the Phase II (IIa and IIb) studies conducted with aprepitant.

Phase (Study title).	Protocol (ref.)	Dose	Duration of treatment	Number of patients/ patients enrolled	Study design. Description.
Phase IIa - monotherapy study (Safety & tolerability & efficacy in cisplatin-induced emesis).	P004L1	L-758298 was administered IV initially at 60 mg and increased to 100 mg. Ondansetron was given at 32 mg IV. Both products were infused over 30 minutes, beginning 60 minutes before the start of cisplatin infusion.	A 9- to 12-month initial study.	53	Double blind, multicentre, randomised, controlled study (ondansetron). The study enrolled cisplatin naïve male and female patients. Patients were stratified according to gender and emetogenic chemotherapy (cyclophosphamide or doxorubicin). Cisplatin was given at doses ranging from 50 to 100 mg/m^2. Based on an interim assessment of the first 9 patients at the 60-mg dose of L-758298, treatment at this dose level was stopped and the dose was increased to 100 mg for all patients who were subsequently randomised to the L-758298 treatment group; the investigators remained blinded to treatment. Rescue therapy was permitted for nausea or emesis at any time after cisplatin administration. Safety and tolerability were assessed through Day 22 by clinical evaluations and laboratory safety tests.
Phase IIa rationale for combination therapy (L-754030 in cisplatin-induced emesis).	P012	*4 groups*. Day minus 1: patients in group (C) received 400 mg L-754030 orally. Day 1: All patients received dexamethasone (20 mg orally). In addition, patients in group (A) received	Total patient monitoring time period of 17 to 29 days.	353	A double-blind, randomised, parallel-group study to investigate the safety, tolerability, and efficacy of L-754030 in cisplatin-induced emesis.

		Granisetron plus placebo, (B) granisetron plus L-754030, in (C) and (D) placebo plus L-754030. Granisetron was given at 10 µg/kg IV. Days 2 to 5: 300 mg L-754030 were given orally (groups B, C and D), patients in group A received placebo. Administration of metoclopramide in addition to dexamethasone as rescue therapy for Days 2 to 5 was also permitted.			
Phase IIa - rationale for combination therapy and dose duration (L-758298 plus dexamethasone in cisplatin-induced emesis).	P007L1	L-758298 100 mg IV or 32 mg IV of ondansetron both given with dexamethasone 20 mg IV on Day 1, followed by 300 mg of L-754030 or placebo once daily on Days 2 to 5.	A 9-month initial study.	177	Double-blind, randomised, controlled study (ondansetron plus dexamethasone). The study involved cisplatin-naïve patients. It was aimed at evaluating the efficacy of the product on prevention of both acute (0 to 24 hours) and delayed (Days 2 to 5) emesis after cisplatin IV ($\geq$70 mg/m^2).
Phase IIa - Dose duration (Efficacy in cisplatin-induced delayed emesis).	P007	All patients received granisetron 10 µg/kg intravenous and dexamethasone 20 mg orally) to control emesis before cisplatin on Day 1. In addition, patients were randomised to 1 of 3 treatment groups to receive: (A) daily doses of L-754030 on Days 1 to 5 (400 mg on Day 1 and 300 mg on Days 2 to 5 orally); (B) a single dose of L-754030 on Day 1 (400 mg orally) and placebo orally on Days 2 to 5; or (C) placebo (orally) on Days 1 to 5.	A 7-month initial study.	161	Double blind, randomised, parallel groups, placebo-controlled trial.

Phase IIb - dose selection (Dose finding study of MK-0869 for the prevention of acute and delayed chemo-induced emesis).	040/042	All patients were treated on Day 1 with a standard therapy regimen of ondansetron 32 mg given intravenously and dexamethasone 20 mg given orally prior to cisplatin administration, and subsequently dexamethasone 8 mg orally daily on Days 2 to 5. MK-0869 or placebo were administered orally over 5 days (375 mg day 1 prior to cisplatin and 250 mg days 2 to 5 **or** 125 mg day 1 and 80 mg days 2 to 5 **or** 40 mg day 1 and 25 mg days 2 to 5).	Oral antiemetic study therapy for 5 days following cisplatin infusion with option of treatment for a total of 6 cycles of cisplatin.	583	Multicentre, randomised, double-blind, parallel-group, controlled trial to assess the safety and efficacy of dosing regimens of MK-0869 in the prevention of emesis and nausea in cisplatin-naïve patients with histologically confirmed solid malignancies who were to be treated with a chemotherapy regimen that included cisplatin $\geq$70 mg/m^2.

Based on data from the clinical pharmacology studies and the phase II studies the following regimen was eventually retained and tested in the confirmatory studies:

Experimental regimen

Product			
Aprepitant 125 mg po	Day 1	Aprepitant 80 mg po once daily	Days 2 to 3
Ondansetron 32 mg IV	Day 1		
Dexamethasone 12 mg po	Day 1	Dexamethasone 8 mg po once daily	Days 2 to 4

It is acknowledged that for such a complex regimen involving three medicinal products, which may be administered in different dosages over variable time periods, it is difficult let alone impossible to explore all these possible combinations empirically. As discussed below, several important points were, however, addressed in the exploratory studies.

Aprepitant dosing: The 125/80-mg regimen was shown to be moderately more active than a 40/25-mg regimen. This is of some interest since the estimated blockade of NK1 receptors (not taking into account the crossing of the blood-brain barrier) at trough at a dose of 40/25 mg was between 80 and 89%. It was also shown that administration of aprepitant the day before chemotherapy does not enhance the antiemetic effects of combination therapy. This observation supports the view that there is no major lag phase as regards plasma/liquor levels of aprepitant. PET scan data after repeat administration are therefore of likely relevance also for receptor occupancy on the first day of administration. More than 90% occupancy is consequently predicted to occur on day 1. Altogether, this indicates that it was not meaningful to test higher dosages.

Loading dose concept: No results supported this approach and a uniform 80/80-mg regimen might be as efficient. Since there are no major dose-related safety concerns, this was not considered critical.

Duration of therapy: The need for further administration after day 1 was investigated in two studies. Trends were observed in both studies indicating that an administration after day 1 might be beneficial. In the study showing the strongest trend in favour of a prolonged administration, however, aprepitant was not given in association with 5-HT_3 antagonists, resulting in a poor control of acute emesis,. The need for further administration after day 1 was thus not considered firmly established.

In the phase II studies aprepitant was administered until day 5. In the confirmatory studies, however, only dosing days 1 to 3 was explored. There are no data comparing 3 vs. 5 days of aprepitant therapy, but as dosing only day 1 has a clear effect on delayed emesis, dosing days 1 to 3 is considered reasonable. Further studies aiming at optimising the duration of therapy should be considered, but due to the safety profile of aprepitant, this is understandably not a prioritised area of drug development

Associated medication: It was clearly shown that 5-HT_3 antagonists must be associated to aprepitant to obtain acceptable control of acute emesis. A lower dose of these products than the maximum recommended could be sufficient to control the symptoms. In general, administration of 5-HT_3 antagonists after day 1 is weakly supported by clinical studies therefore a unique administration on day 1 seems logical.

Fully recognising the established role of glucocorticosteroids for the control of acute and delayed CINV, it should be noted that the development programme was not specifically designed to address the need to co-administer steroids with aprepitant. Available phase II data provide poor support for the need of dexamethasone for the control of acute emesis and there are no relevant data to support its use over days 2 to 4. Finally, in order to compensate for the inhibition of metabolism of dexamethasone by aprepitant the formal dose of dexamethasone was lowered compared with the recommended standard doses. Further studies may be warranted

The possible role of metoclopramide in combination with aprepitant for the prophylaxis of delayed emesis was not explored.

Main studies (phase III = therapeutic confirmatory trials)

Two Phase III studies following essentially the same study design were conducted with aprepitant; Protocol 052 was conducted primarily in the United States and Europe and Protocol 054 was only conducted in Latin America. Both were multicentre, randomised, double-blind, parallel-group, controlled trials to assess the safety and efficacy of aprepitant in the prevention of CINV in cisplatin-naïve patients with histologically confirmed solid malignancies who were treated with chemotherapy regimens that included cisplatin given at doses superior to 70 mg/m^2 administered on a single day (see Table below).

Table summarising the main features of the two pivotal phase III studies conducted with aprepitant.

Phase (Study title).	Protocol (ref.)	Dose	Duration of treatment	Number of patients/ patients enrolled	Study design. Description.
Phase III (MK-0869 for chemotherapy-induced nausea and vomiting).	P052	The study had 2 treatment groups MK-0869 regimen vs standard therapy. MK-0869 Regimen = MK-0869 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg intravenous on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4. Standard therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.	MK-0869 regimen for 3 days (MK-0869 125 mg Day 1 and MK-0869 80 mg Days 2 and 3) in combination with ondansetron (Day 1) and dexamethasone (Days 1 to 4).	534	Multicentre, randomised, double-blind, parallel-group, controlled trial to assess the safety and efficacy of MK-0869 in the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who were naive to cisplatin chemotherapy and who were treated with a chemotherapy regimen that included cisplatin $\geq$70 mg/m2. The protocol had 2 components. The first component focused on the first cycle (Cycle 1) of chemotherapy. The second component consisted of an optional multiple-cycle extension for up to 5 subsequent cycles of chemotherapy (maximum of 6 cycles total).
Phase III (MK-0869 for chemotherapy-induced nausea and vomiting).	P054	Idem study P052.	MK-0869 regimen for 3 days (MK-0869 125 mg on Day 1 and MK-0869 80 mg on Days 2 and 3) in combination with ondansetron on Day 1 and Dexamethasone daily on Days 1 to 4.	569	Multicentre, randomised, double-blind, parallel-group, controlled trial.

These two studies had similar objectives and design. As far as the inclusion criteria are concerned a site-specific amendment allowed the enrolment of adolescents older than 12 years old (younger than 18 years of age and weighting more than 40 kg) in study P052.

The protocols had 2 components. The first component focused on the first cycle (Cycle 1) of chemotherapy. The second component consisted of an optional multiple-cycle extension for up to 5 subsequent cycles of chemotherapy (maximum of 6 cycles total).

The primary objective was in cycle 1, firstly to demonstrate that aprepitant as add on to standard therapy was superior to standard therapy in the control of chemotherapy-induced nausea and vomiting as measured by the proportion of patients with complete response in the 120 hours following the initiation of high-dose cisplatin chemotherapy. Secondly, the objective of the study was to evaluate the safety and tolerability of the proposed triple therapy with aprepitant.

The studies had 2 treatment groups:

The first group was the aprepitant regimen consisting of aprepitant 125 mg given orally on Day 1 followed by 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV (for adolescent patients ≥12 but <18 years of age, 3 doses of 0.15 mg/kg IV on Day 1) and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.

The second group of patients received a standard therapy consisting of ondansetron 32 mg IV (for adolescent patients ≥12 but <18 years of age, 3 doses of 0.15 mg/kg IV on Day 1) plus dexamethasone 20 mg given orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

1. Primary endpoints/assays

Clinical response was evaluated with a patient diary that was completed daily for 5 days after the administration of cisplatin (this was done during Cycle 1 only). The diary captured all emetic episodes, all use of rescue therapy (only taken for treatment of established nausea or emesis), and a daily nausea severity assessment. Patients were monitored for adverse experiences and tolerability at scheduled visits that occurred between Days 6 and 8 and Days 19 and 29 post cisplatin.

The primary endpoint was the proportion of patients with complete response in the overall phase in Cycle 1, defined as no emesis and no use of rescue therapy for treatment of either nausea or emesis in the 120 hours following the initiation of cisplatin chemotherapy in Cycle 1. In the optional multiple-cycle extension, the patient diary was not used. The patient was asked, at the Days 6 to 8 visit for each cycle that the patient entered, if any emetic episodes or nausea occurred since the start of chemotherapy for that specific cycle.

A secondary endpoint was the impact of chemotherapy induced nausea and vomiting on quality of life of patients assessed using the Functional Living Index—Emesis (FLIE) questionnaire during Cycle 1 only.

2. Statistical analysis

Patients were randomised using a stratified randomisation schedule based on gender and concomitant use of emetogenic chemotherapy in addition to cisplatin. Primary analyses were based on a modified intention-to-treat (MITT) approach. In addition, a supportive per-protocol analysis was done for the primary efficacy parameter.

The modified intention-to-treat (MITT) population for efficacy includes all patients who received cisplatin, took a dose of study drug, and had at least one post-treatment assessment. The Per-Protocol (PP) population excluded those patients who were identified as protocol violators. This population was considered only for the evaluation of the primary efficacy hypothesis.

The efficacy endpoints included complete response (primary endpoint: no emesis and no use of rescue medication to treat established nausea or emesis), no emesis (no vomiting or retching or dry heaves regardless of use of rescue medication), no significant nausea (maximum patient nausea self-assessed visual analog scale [VAS] rating <25 mm), no nausea (maximum nausea VAS rating <5 mm), complete protection (no emesis, no use of rescue medication, maximum nausea VAS rating <25 mm), and total control (no emesis, no use of rescue medication, maximum nausea VAS rating <5 mm). The impact of chemotherapy induced nausea and vomiting on patients' quality of life was assessed using the Functional Living Index—Emesis (FLIE) questionnaire during Cycle 1 only. For the efficacy endpoints, the proportions of patients having a favorable response were determined in the 2 treatment groups and the groups were compared using logistic regression models that included terms for treatment, gender, use of concomitant therapy, and region (U.S./non-U.S.). Time to first emesis and

time to first use of rescue medication were analysed using a log-rank test. The severity of nausea measured by the average VAS score was analysed using Wilcoxon rank-sum test. Exploratory (pre-specified and non-prespecified) analyses were also performed. In secondary analyses the overall phase (0-120 hours) was separated/divided into an acute phase (0-24 hours) and a delayed phase (25-120 hours).

The multiple-cycle exploratory analyses addressed the no emesis and no significant nausea endpoints using the log-rank test for treatment comparisons.

RESULTS

3. Study populations/accountability of patients

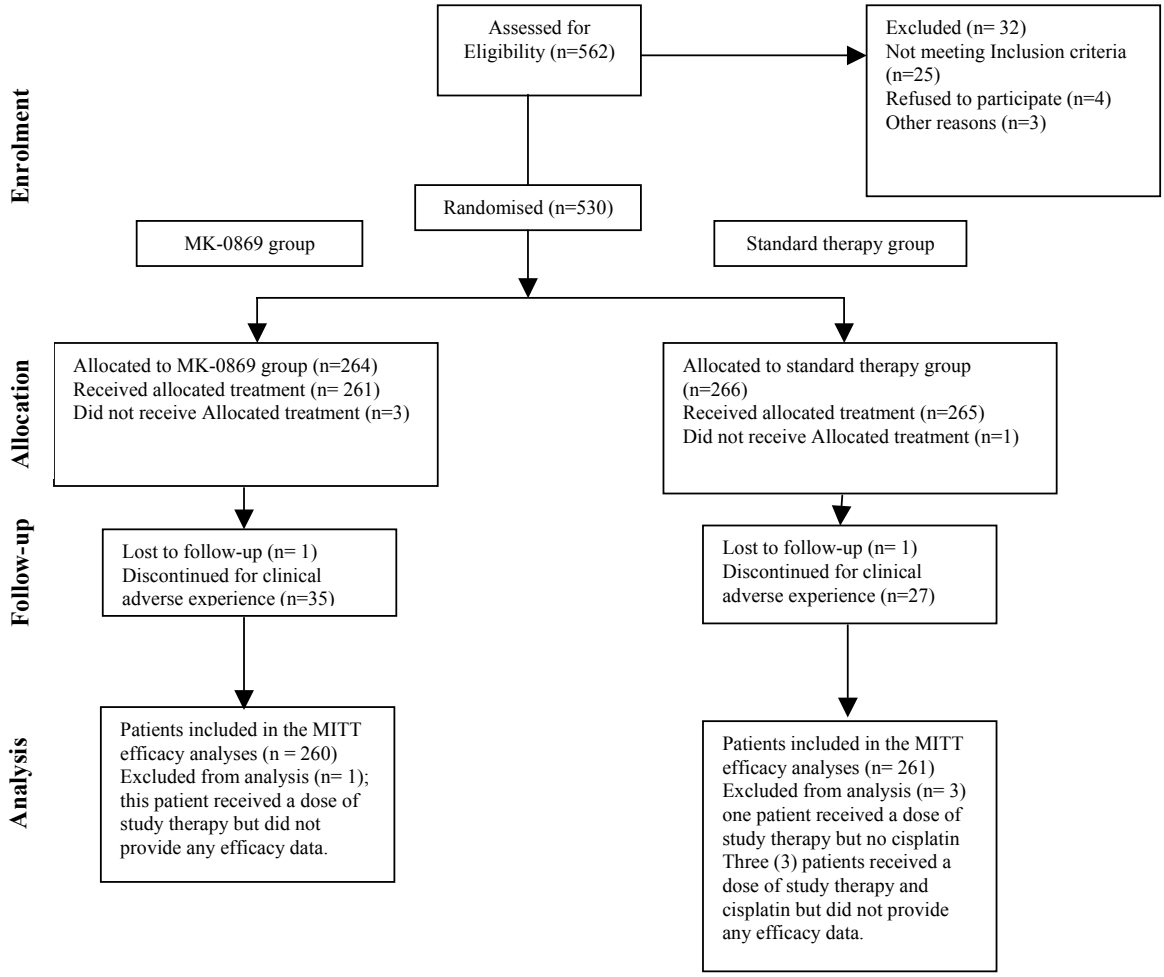
The baseline characteristics of the patients enrolled in studies P052 and P054 are displayed in the table below.

Baseline patient characteristics

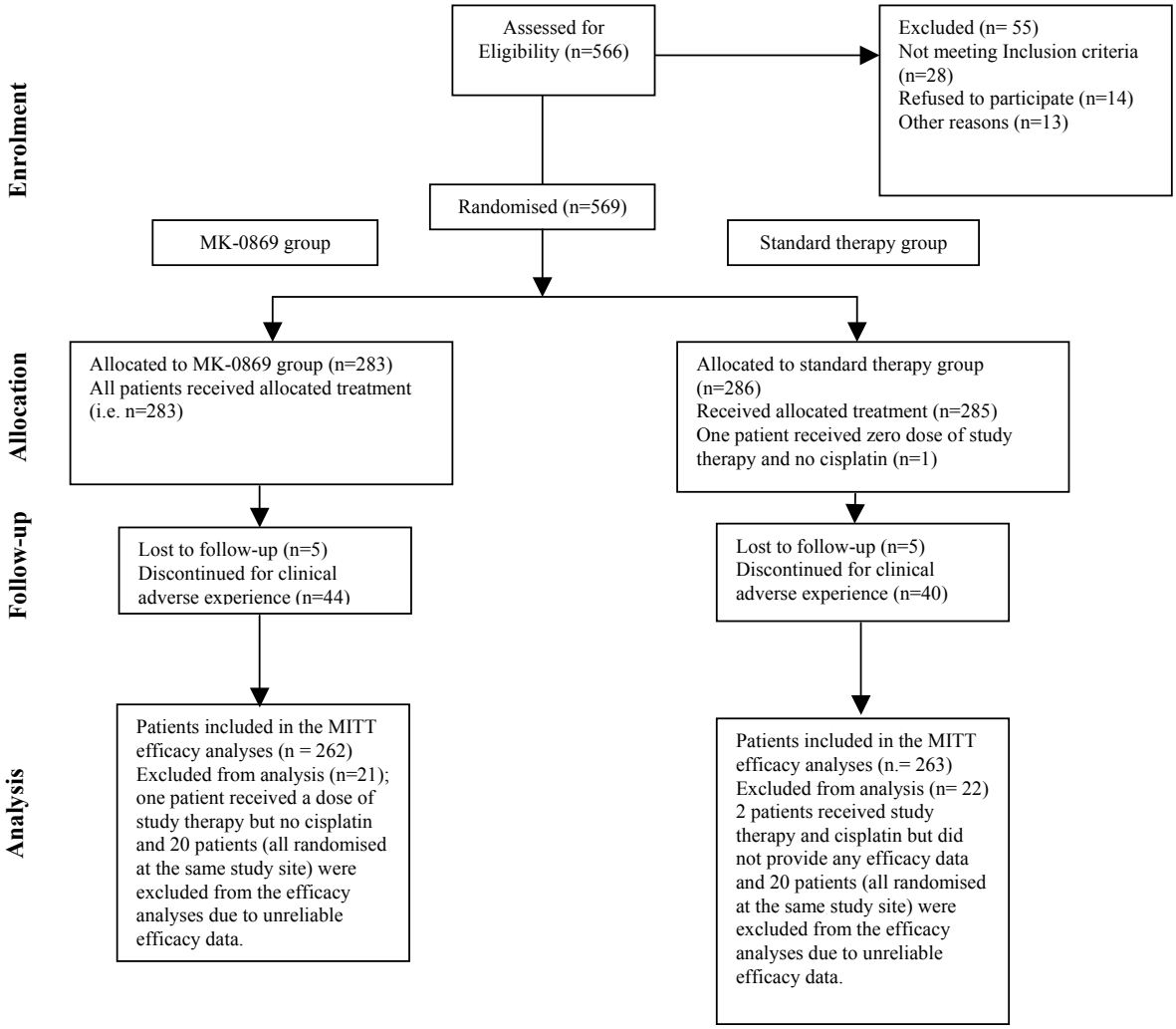
	P052						P054					
	Aprepitant (*N*=266)		Standard Th. (*N*=268)		Total (*N*=534)		Aprepitant (*N*=283)		Standard Th. (*N*=286)		Total (*N*=569)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender:												
Male	168	(63.2)	168	(62.7)	336	(62.9)	148	(52.3)	146	(51.0)	294	(51.7)
Female	98	(36.8)	100	(37.3)	198	(37.1)	135	(47.7)	140	(49.0)	275	(48.3)
Age (yrs):												
-17	2	(0.8)	2	(0.7)	4	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
18-64	165	(62.0)	178	(66.4)	343	(64.2)	212	(74.9)	220	(76.9)	432	(75.9)
65+	99	(37.2)	88	(32.8)	187	(35.0)	71	(25.1)	66	(23.1)	137	(24.1)
Alcohol Intake:												
No consumption	152	(57.1)	153	(57.1)	305	(57.1)	237	(83.7)	248	(86.7)	485	(85.2)
1-4 drinks/week	45	(16.9)	47	(17.5)	92	(17.2)	27	(9.5)	21	(7.3)	48	(8.4)
>4 drinks/week	62	(23.3)	56	(20.9)	118	(22.1)	19	(6.7)	17	(5.9)	36	(6.3)
Missing data	7	(2.6)	12	(4.5)	19	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
Cisplatin Dose:												
<70 mg/m^2	52	(19.5)	56	(20.9)	108	(20.2)	40	(14.1)	38	(13.3)	78	(13.7)
70-100 mg/m^2	187	(70.3)	185	(69.0)	372	(69.7)	231	(81.6)	235	(82.2)	466	(81.9)
>100 mg/m^2	24	(9.0)	25	(9.3)	49	(9.2)	11	(3.9)	12	(4.2)	23	(4.0)
No Cisplatin	3	(1.1)	2	(0.7)	5	(0.9)	1	(0.4)	1	(0.3)	2	(0.4)

It should be noted that differences between studies are notable as regards gender, alcohol intake age and percentage of patients receiving less than 70 mg/m2 of cisplatin (criteria for inclusion >70 mg/m^2). These covariates might influence outcome in study 052 in a favourable direction. There are, however, no important imbalances between study groups.

Accounting for patients in study P052.



Accounting for patients in study P054.



In addition, 4 adolescent patients were enrolled in study P052, 2 in each of the treatment arm (all these patients were male between 14-17 years old). These patients were not included in the analyses.

4. Efficacy results

The control regimen is an active and well-documented regimen with respect to acute and delayed emesis and the applicant's justification for not including metoclopramide and especially 5-HT_3 antagonists days 2 to 4 was considered to be reasonable.

In both studies, the proportion of patients with an overall complete response (no emesis and no use of rescue medication due to nausea) during the initial chemotherapy cycle (primary endpoint) was statistically significantly higher in the aprepitant group compared to the standard therapy group in both studies ($p<0.001$). The impact of chemotherapy induced nausea and vomiting on daily life was evaluated using the FLIE questionnaire. The table below displays the percentage of patients in each group with no or minor impact on daily life. Missing data was no problem for this first cycle of therapy.

Modified Intention-to-Treat Analysis, pooled analyses, first cycle of therapy

P052 and P054 combined							
		Aprepitant Regimen		Standard Therapy		Differences*	
Endpoint	Phase	x/n	%	x/n	%	%	(95% CI)
Complete Response:	Overall	352/520	67.7	250/523	47.8	19.9	(14.0-25.8)
	Acute	447/520	86.0	383/523	73.2	12.7	(7.9-17.6)
	Delayed	372/520	71.5	268/523	51.2	20.3	(14.5-26.1)
No Emesis:	Overall	374/520	71.9	260/523	49.7	22.2	(16.4-28.0)
	Acute	452/521	86.8	388/524	74.0	12.7	(8.0-17.5)
	Delayed	396/520	76.2	280/523	53.5	22.6	(17.0-28.2)
No Sign. Nausea:	Overall	373/517	72.1	339/522	64.9	7.2	(1.6-12.8)
	Delayed	384/519	74.0	350/523	66.9	7.1	(1.5-12.6)
FLIE Total Score	Overall	377/507	74.4	324/507	63.9	10.5	(4.8-16.1)

*calculated on raw data; the primary analysis according to protocol used a logistic model and odds ratios
x/n=number of patients with desired response/number of patients included in the analysis
FLIE Total Score: patients completed the questionnaire 5 days after receiving chemotherapy (Day 6)

In both the first 24 hours ("acute phase") and during the following 25-120 hours ("delayed phase") the percentage of complete responders was significantly higher in the aprepitant group compared to the standard therapy group in both studies ($p<0.001$). The results were supported by the per-protocol analysis.

In the analysis by phase of proportion of patients with no emesis the aprepitant regimen was shown to be statistically significant more effective, overall and during the acute and delayed phase respectively ($p<0.001$).

In both studies (P052, and P054 respectively) the proportion of patients with no impact of CINV on daily life was statistically significant higher in the aprepitant group compared to the standard therapy group ($p=0.021$ and $p=0.007$ respectively).

As regards emesis, the efficacy of aprepitant as add-on to standard therapy has been convincingly demonstrated. In the pooled analysis a statistically significant effect has also been shown as regards

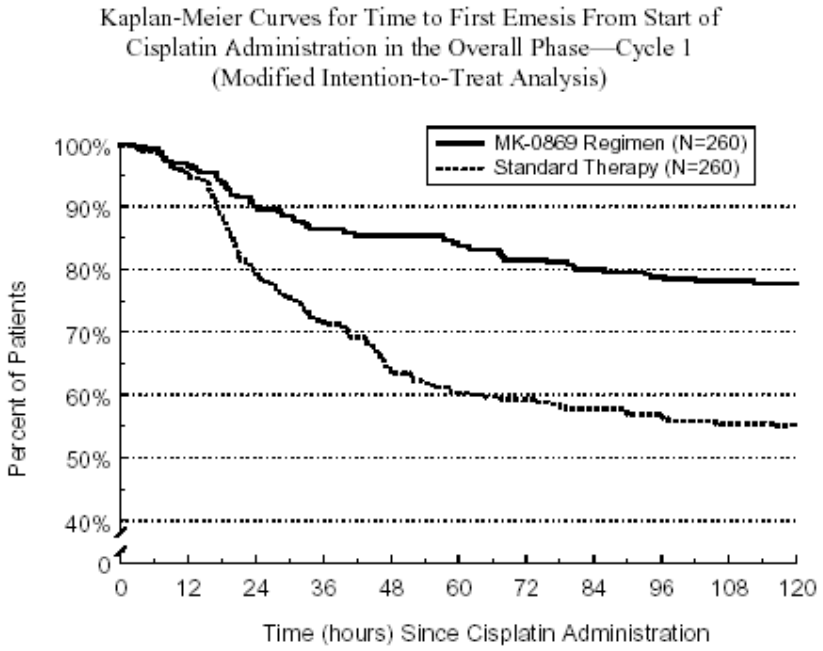
delayed nausea. In the individual studies, the effect on "no significant nausea" defined as <25 mm on a 100 mm visual analogue scale was however borderline.

Modified Intention-to-Treat Analysis, % Responders

Endpoint		P052		Difference	P054		Difference*
		Aprepitant	Standard	95% CI	Aprepitant	Standard	95% CI
No significant	Overall	73%	66%	-0%; +15%	71%	64%	-0%; +15%
Nausea	Delayed	75%	69%	-0%; +15%	73%	65%	-0%; +15%
No Nausea	Overall	48%	44%	-5%; +12%	49%	39%	+2%; +18%
	Delayed	51%	48%	-5%; +12%	53%	40%	+4%; +21%
* calculated on raw data							

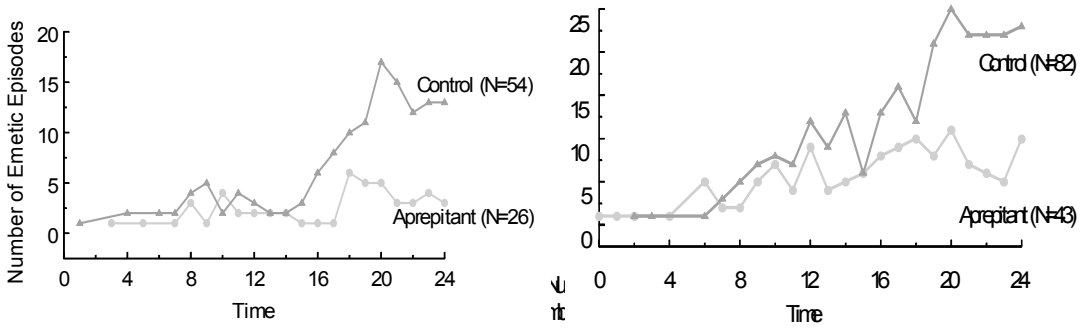
In general, the results in both treatment arms were slightly worse in the South American study, P054 and a higher percentage of women, about 48% vs. 37%, might at least partly explain this. The absolute difference between study arms, however, was similar with respect to emesis. As regards "no significant nausea" the results were also similar, while for "no nausea" a clearly significant difference between treatment arms was seen in P054, but not in P052. This "inconsistency" might be regarded as minor, but normally "no nausea" would appear easier to define with consequent less variability.

Kaplan-Meier Curves for Time to First Emesis (Study P052)



In both studies, the Kaplan-Meier curves start to diverge at about 16 hours. As discussed, the delayed phase of vomiting has previously been shown to emerge after about 16 to 18 hours after administration of cisplatin. The distinctive pattern of emetic events after approximately 16 hours is shown in the figure below. The figures below show all emetic events in the patients with acute emesis, not just the initial events shown in the Kaplan-Meier plots.

Study P052 Study P054



The observed pattern of emesis would support the interpretation that no add-on activity as regards the early phase of emesis is shown for aprepitant and that the early peak expected about 4 hours after the administration of cisplatin is almost completely abolished by standard therapy.

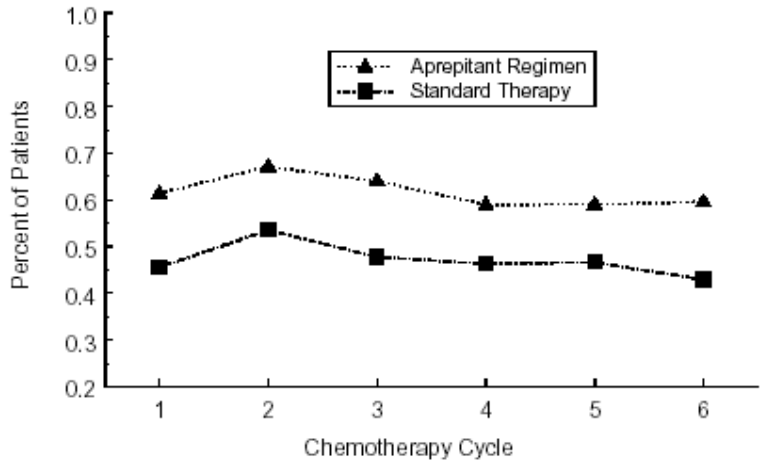
With respect to subgroups, data were presented for stratification variables. Of possible importance was the observed difference between studies as regards the effect of gender on study outcome. Otherwise, there were no notable differences in the subgroup analyses.

Modified-Intention-to-Treat Analysis, Complete Response (P052 and P054)

	P052		P054	
	Aprepitant	Standard	Aprepitant	Standard
Female	76/98 (78%)	38/98 (39%)	67/118 (57%)	51/121 (42%)
Male	113/162 (70%)	98/162 (61%)	96/142 (68%)	63/142 (44%)

The Phase III studies offered an optional multiple-cycle extension of up to 5 additional cycles of blinded treatment. The number of patients who entered cycle 2 varied from 97 (standard therapy group, P054) to 132 (aprepitant group, P052). As expected clearly fewer patients remained at cycle 6 and varied from 12 (standard therapy group, P052) to 31 (aprepitant group, P052).

Probability of a Favorable Response (No Emesis and No Significant Nausea) by Cycle and Treatment Group—Protocol 052 and Protocol 054 Combined—Cycles 1 to 6



Overall, the withdrawal pattern was similar comparing experimental and control arms, but after the first cycle, numerically more patients were withdrawn in the experimental arm due to adverse events

and withdrawn consent. This might be informative, but can hardly explain the seemingly sustained difference in activity.

A study specifically designed to show sustained activity over cycles of therapy would need re-randomisation after the first treatment cycle in order to protect the study from carry-over effects.

Discussion on clinical efficacy

The efficacy of aprepitant as add-on to standard therapy in the prevention of cisplatin induced CINV is considered convincingly demonstrated in terms of a clinically relevant reduction in delayed emesis and, less pronounced, as regards nausea.

In an attempt to increase the understanding of the activity of aprepitant, the apparent differences in efficacy between the pivotal studies were further explored.

Some risk factors are known to affect emetic control. It is generally more difficult to prevent and control emesis in female than in male patients particularly among women with a history of persistent or severe emetic symptoms during pregnancy. It is more difficult to prevent and control emesis in children and young adults than in older patients (the last factor, age, is a less consistent finding in trials) and in patients with a history of incomplete antiemetic control during prior treatments. Finally, patients who have chronically consumed alcohol (frequently defined as the ingestion of more than 100 g ethanol/day for several years) are more likely to have complete emetic control than are "non-drinkers".

An attempt to identify further *covariates* of importance for acute and delayed emesis and acute and delayed nausea (separately) was made. In addition to the covariates detailed above dose of cisplatin (>< median), concomitant emetogenic chemotherapy and control of acute phase emesis/nausea were considered. Similarly, a more detailed analysis and discussion as regards the apparently large gender related difference between studies was requested from the applicant.

In both studies, male and female patients receiving the aprepitant regimen consistently had a better outcome than male and female patients treated with the control regimen, though the magnitude of the advantage provided by the aprepitant regimen varied between studies.

Percent of Patients With Favorable Response by Gender
CINV Phase III Studies (Cycle 1)

Protocol 052

No Emesis	Gender	Aprepitant	Standard Therapy
Acute	Female Male	89/98 (90.8) 145/162 (89.5)	69/98 (70.4) 138/163 (84.7)
Delayed	Female Male	**84/98 (85.7)** **126/162 (77.8)**	**44/98 (44.9)** **109/162 (67.3)**

Percent of Patients With Favorable Response by Gender
CINV Phase III Studies (Cycle 1)

Protocol 054

No Emesis	Gender	Aprepitant	Standard Therapy
Acute	Female Male	97/118 (82.2) 121/143 (84.6)	75/121 (62.0) 106/142 (74.7)
Delayed	Female Male	**79/118 (67.0)** **107/142 (75.4)**	**59/121(48.8)** **68/142 (47.9)**

The variable magnitude of the advantage provided by the aprepitant regimen according to gender, however, could not be attributed to explored covariates.

As far as activity against acute emesis is concerned, more patients seem to report break-through emesis hours 8 to 16 in study P054. This difference is probably not informative concerning the activity of aprepitant as it was established prior to observable activity of the compound as add-on to standard therapy. Less effective control of acute chemotherapy induced nausea and vomiting may "explain" the overall poorer control of delayed nausea and vomiting in study P054. The differences, however, between the standard and experimental arms seemed reasonably similar as regards emesis during the time periods defined as "acute" (0-24h) and "delayed" (25-120h).

In order to illustrate the apparent relationship between control of acute and delayed emesis the following tables are presented.

Protocol 052

Categories of Delayed Emesis Among Patients Without Acute Emesis

	Aprepitant	Standard Therapy
	n/m (%)	n/m (%)
No emesis in delayed phase	202/234 (86.3)	143/206 (69.4)

Categories of Delayed Emesis Among Patients With Acute Emesis

	Aprepitant	Standard Therapy
	n/m (%)	n/m (%)
No emesis in delayed phase	8/26 (30.8)	10/54 (18.5)

The results were similar in study 054.

As regards the proposed indication, a major issue was whether it was appropriate or not to extrapolate from highly emetogenic cisplatin-based therapy to other highly emetogenic regimens. With respect to effects on acute CINV, cisplatin is generally regarded as a relevant model for other highly emetogenic regimens, while the experience as regards delayed emesis is much less extensive. Actually, among existing antiemetics only the activity of glucocorticosteroids is considered reasonably well established for the prevention of cisplatin induced delayed symptoms. The pathophysiology of CINV and especially delayed emesis is, in addition, rather ill defined, but differences in the emetic pattern comparing cisplatin with, *e.g.* high-dose cyclophosphamide might indicate underlying differences. . Furthermore no non-clinical studies were designed to explore the activity of aprepitant with respect to add-on activity to standard therapy using different highly emetogenic regimens. It is also notable that in clinical studies aprepitant in monotherapy appears inferior to 5-HT_3 antagonists as regards cisplatin-induced acute emesis but, in contrast, shows activity with respect to delayed emesis. Altogether these observations do not support a general extrapolation.

With respect to children and interactions, the applicant has committed to conduct further studies.

Finally, the Rapporteur acknowledged the proposed presentations which are consistent with the proposed posology and the treatment duration and regimen.

Clinical safety

Aprepitant is the first product in a new class of medicinal products. There is therefore a very limited clinical experience as regards adverse reactions outside the studies programme for aprepitant[1].

Patient exposure

The safety profile of aprepitant was evaluated in approximately 3300 individuals (see table below).

Number of Subjects enrolled in the Development Programme of aprepitant

	Aprepitant formulation D	Aprepitant, formulations a, b, c	L-758298* (iv.)	Total
Clinical Pharmacology	356	229	114	699
Phase II	397	369	149	547
Phase III	549	0	0	549
Total CINV	946	369	149	1464
Non-CINV	180	926	66	1172
Total	1482	1524	329	3335

*L758298 is a prodrug of aprepitant administered by the IV route.

[1] The terms adverse drug reactions and adverse events are used according to the current EU legislation. An adverse drug reaction is defined by a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. An adverse event does not necessarily have a causal relationship with the treatment. Finally, the term "severe" is not synonymous with serious. Severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe).

Frequencies are expressed according to the EU guideline on summary of product characteristics (Report from CIOMS Working Group III, Geneva 1995 terminology) Very common (>1/10) Common (>1/100, <1/10) Uncommon (>1/1,000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000), including isolated reports.

Number of Subjects Randomised to Aprepitant per Chemotherapy Cycle

Cycle	Number of Patients
1	1466
2	500
3	391
4	280
5	184
6	135
Total Cycles 1 to 6	2956

Adverse events and serious adverse event/deaths – discontinuation due to adverse reactions

Clinical Adverse Experience Summary – Clinical Pharmacological Studies

Number (%) of subjects with	Aprepitant or L-758298	Placebo
No adverse experience	305 (51%)	41 (35%)
Adverse drug reactions	178 (30%)	14 (12%)
Discontinued due to adverse drug reaction	6 (1%)	0
Serious adverse events	1*	0
Headache	22%	13%
Asthenia/fatigue	8%	2%
Dizziness	5%	1%

*Blurred vision

Clinical Adverse Experience Summary – CINV Phase III studies

	Aprepitant n=544 Number (%) of subjects	Control, n=550 Number (%) of subjects
Adverse drug reactions	93 (17%)	70 (13%)
Serious adverse events	73 (13%)	74 (13%)
Serious adverse drug reactions	2	4
Discontinued due to adverse drug reaction	3	2
Dizziness	7%	4%
Diarrhoea	10%	7%
Hiccups	11%	6%
Asthenia/fatigue	18%	12%

Further safety data were submitted in the applicant's response and these derived from a double-blind study (Protocol 039) in which aprepitant (final market image) was administered at daily doses up to 3-fold higher than the regimen for CINV for up to 8 weeks. In this study, patients (n=361) with major depression were randomised to receive aprepitant 250 mg, aprepitant 375 mg, paroxetine, or placebo. The proportion of patients who discontinued treatment due to a clinical adverse experience was higher in the active treatment groups than in the placebo group (respectively, 16.5, 13.5, and 15.1% versus 1.1%). Similar results were observed for the proportion of patients who discontinued treatment from each group due to a drug-related clinical adverse experience. Given the higher exposure and longer duration of therapy, these data confirm an acceptable tolerability profile for the CINV indication.

Infections and infestations (including safety possibly related to drug-drug interactions and other interactions)

There were signals in the exploratory studies that aprepitant might be associated with an increased incidence of infections, including neutropenic fever. In the phase II studies programme the most notable finding was an increased incidence of fever, about 5-6% compared with 1.5% in the control group. Actually, in study P040, the incidence of neutropenic fever was 6% in the experimental arm vs. 3% in the controls. These signals were attenuated in the confirmatory studies and during cycle 1 of the confirmatory studies altogether 10+10/282+261 (3.7%) infectious events were reported in the

aprepitant arms *vs.* 6+7/285+264 (2.4%), respectively. Phase II data may also have been confounded by a higher than expected exposure to glucocorticosteroids due enzyme inhibition by aprepitant.

An apparent increase in infectious events related to the administration of some anti-cancer medicinal products metabolised by CYP3A4 was, however, noted, especially etoposide (18% *vs.* 9%, aprepitant *vs.* control, n=106+91) and vinorelbine (18% *vs.* 12%, aprepitant *vs.* control, n=82+76). Further analyses using ANC as a measure of cytotoxicity did not provide evidence of enhanced cytotoxicity neither for chemotherapeutic agents in general metabolised by CYP3A4 or for the individual agents, *e.g.* etoposide or vinorelbine. These analyses were weakened by the non-ideal sampling intervals (baseline, days 6-8 and days 19-29).

As aprepitant is an inhibitor of P-gp *in vitro* results as regards anthracyclines were also detailed. There were no conspicuous findings and actually the interaction study conducted with digoxin indicates absence of relevant in vivo activity.

Immune system disorders

(See discussion in the non-clinical part of the report).

Nervous system disorders

In non-CINV studies, encompassing more than 1000 patients treated with aprepitant or L-758298 and close to 500 placebo subjects headache (17% vs. 12%) and somnolence (13% vs. 6%) appears to be aprepitant-related.

With respect to common, non-serious adverse reactions in CINV studies, there is a clear association between the use of aprepitant and asthenia/fatigue and dizziness. Headache might be related to duration of therapy, but this is not clear from the presentation of study data.

Cardiac disorders

Altogether 15 clinical pharmacology studies, mainly with automatic reading of ECGs, were reviewed without signals indicating QTc prolonging properties.

In the Phase IIb study (Protocol 040/042), patients were administered aprepitant (40-mg, 125-mg, or 375-mg capsules), plus ondansetron (32 mg IV) and dexamethasone (20 mg orally) on Day 1. Patients on Standard Therapy received placebo for aprepitant, plus ondansetron (32 mg IV) and dexamethasone (20 mg orally) on Day 1. Electrocardiograms (ECGs) were performed at baseline 3 to 5 hours after aprepitant dosing on Day 1, and at the Days 6 to 8 visits.

Summary Statistics For QT_c Interval (msec) Change From Baseline Data
Phase IIb Study (Protocol 040/042)

Aprepitant Dose	N	QT_c Interval at Baseline Mean	QT_c Interval Change From Baseline					
			Mean	Median	Min	Max	SD	95% CI
Aprepitant 40 mg	100	403.8	10.5	10.9	-247.7	141.7	44.3	(1.7, 19.2)
Aprepitant 125 mg	152	411.6	1.7	1.4	-149.8	129.2	40.5	(-4.8, 8.1)
Aprepitant 375 mg	8	445.7	-9.1	0.0	-57.5	29.7	32.7	(-36.4, 18.2)
Standard Therapy	149	401.0	12.8	11.1	-144.8	127.2	36.7	(6.8, 18.7)

From these data, no additional effect in terms of QTc prolongation was discernible.

Gastrointestinal disorders

An increased incidence of diarrhoea and hiccups was observed in the confirmatory studies in association with the use of aprepitant.

Skin and subcutaneous tissue disorders

One single case of Stevens-Johnson was observed in the clinical trials and confounding factors were present.

Investigations

A slightly higher incidence of grade 1 events (ALT, AST and ALP) was seen in aprepitant treated individuals around days 6 to 8.

Discussion on clinical safety

The signal as regards infectious events constitutes a remaining concern. Overall, however, the signal is considered rather weak, 3.7% *vs.* 2.4%, aprepitant and control, respectively in the confirmatory studies.

With respect to non-serious adverse reactions, there is an association between the use of aprepitant and central nervous system adverse reactions such as asthenia/fatigue and dizziness and gastrointestinal reactions such as diarrhoea and hiccups.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the summary of product characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact at the benefit/risk balance.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that aprepitant is a selective NK1 receptor antagonist that penetrates to the CNS. Aprepitant showed the desired mode of action in cisplatin-induced emesis in ferrets. The Applicant has however further committed to study the duration of action of aprepitant in vivo. The general pharmacology studies showed no significant effects on major organ systems.

Overall, the toxicology programme revealed a relatively low toxicity of aprepitant. However, it should be noted that systemic exposure in rodents was similar or even lower than therapeutic exposure in humans. Adverse effects of possible relevance to humans included effects on reproductive organs and thymus in dogs. These findings were however only seen at high exposure multiples and is currently not considered of any clinical significance. Reproduction toxicity studies did not allow an adequate evaluation of the potential risks for the foetus during pregnancy and no specific studies on the immunotoxic potential of aprepitant have been performed. For the present, short-term indication, these shortcomings are accepted.

This information is reflected in the summary of product characteristics.

Efficacy

As regards efficacy clinically relevant and statistically convincing effects on delayed CINV have been documented for aprepitant as add-on to standard therapy in patients exposed to highly emetogenic doses of cisplatin.

Safety

The signal as regards infectious events constitutes a remaining concern, otherwise the safety profile of aprepitant is reasonably well-documented.

Benefit/risk assessment

From a clinical perspective, the benefit risk relationship is considered favourable and there are no outstanding quality or non-clinical issues jeopardising this assessment. At least for short-term therapy, aprepitant was well tolerated also at doses considerably higher than recommended for the treatment of CINV and efficacy is convincingly demonstrated. The pharmacokinetic interaction profile is complicated including inhibition and induction, but quantitatively the effects are rather moderate, at least on parenterally administered compounds.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus decision that the benefit/risk profile of EMEND in the treatment of "Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin based cancer chemotherapy EMEND is given as part of combination therapy" was favourable and therefore recommended the granting of the marketing authorisation.