23 February 2017
EMA/239011/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Varuby

International non-proprietary name: rolapitant

Procedure No. EMEA/H/C/004196/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

5-HT	Serotonin
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration x time curve
BA	Bioavailability
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CEC	Concomitant emetogenic chemotherapy
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CIC	Chronic idiopathic cough ?
CINV	Chemotherapy-induced nausea and vomiting
Cmax	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CPP	Critical process parameter
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EU	European Union
FLIE	Functional Living Index-Emesis
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEC	Highly emetogenic chemotherapy
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IV	Intravenous

Kb	Equilibrium dissociation constant
KF	Karl Fischer titration
Ki	Inhibition constant
LDPE	Low density polyethylene
LOD	Loss on drying
MEC	Moderately emetogenic chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
NCCN	National Comprehensive Cancer Network
NF	National Formulary
NK1	Neurokinin-1
NMT	Not more than
NV	Nausea Vomiting
PAR	Proven Acceptable Range
PD	Pharmacodynamics
PET	Positron emission tomography
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PO	Oral administration
PONV	postoperative nausea and vomiting
PSD	Particle Size Distribution
QC	Quality Control
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RH	Relative Humidity
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t½	Terminal half life
Tmax	Time to maximum plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
VAS	Visual analogue scale
Vd	Volume of distribution
WBC	White blood cell
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Tesaro UK Limited submitted on 2 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Varuby, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2015.

The applicant applied for the following indication:

Prevention of nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy in adults

Varuby is given as part of combination therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that rolapitant was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0047/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0047/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance rolapitant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 26 January 2006. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis (up to February 2017) and Alexandre Moreau (from February 2017 onwards)

Co-Rapporteur: Patrick Salmon

- The application was received by the EMA on 2 March 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 June 2016.
- During the meeting on 7 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 6 July 2016.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2016.

The applicant submitted the responses to the CHMP consolidated List of Questions on 9 September 2016.

- In cases when a pre-authorisation inspection has been conducted, please reflect the following steps (include/delete information as applicable).
- The following GCP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at one investigator site in Korea and the sponsor site in US between 1 and 26 August 2016. The outcome of the inspection carried out was issued on 12 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 October 2016.
- During the PRAC meeting on 27 October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 25 October 2017.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 November 2016.
- During the CHMP meeting on 10 November 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 January 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 February 2017.
- During the meeting on 20-23 February 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Varuby on 23 February 2017.

2. Scientific discussion

2.1. Problem statement

Despite the availability of effective prevention, many patients still suffer from chemotherapy-induced nausea and vomiting (CINV), particularly delayed and often in the form of nausea. CINV can interfere with treatment adherence, functional activity and quality of life in patients treated with cytotoxic chemotherapy.

2.1.1. Disease or condition

CINV plays a significant role in cancer patients' morbidity and is associated with significant clinical, social and economic burden. Although the direct mortality of CINV is low, there is significant morbidity, including premature or inadequate termination of effective chemotherapy as well as negative impact on quality of life and daily functioning and increased healthcare costs (National Cancer Institute (NCI, 2015);Wiser W, 2005; Bloechl-Daum B, 2006; Navari RM, 2007).

2.1.2. Epidemiology and risk factors

Emetogenicity classification of chemotherapeutic agents

The frequency of chemotherapy induced emesis depends on the emetogenic potential of the specific chemotherapeutic agents used. A 1997 classification scheme gained broad acceptance and was utilized as the basis for treatment recommendations by guideline panels. Chemotherapy agents were divided into five levels: level 1 (<10% of patients experience acute [<or = 24 hours after chemotherapy] emesis without antiemetic prophylaxis); level 2 (10% to 30%); level 3 (30% to 60%); level 4 (60% to 90%); and level 5 (>90%). For combinations, the emetogenic level was determined by identifying the most emetogenic agent in the combination and then assessing the relative contribution of the other agents. (Hesketh PJ 1997)

A modification of this scheme was proposed at the 2004 Perugia Antiemetic Consensus Guideline meeting that reflected the likelihood of emesis developing following treatment (Roila et al 2006) and was incorporated into the most recent MASCC/ESMO 2010 guidelines for the prevention CINV .This modified classification divides chemotherapy agents into four categories

- Highly emetic – >90 percent risk of emesis
- Moderately emetic – >30 to 90 percent risk of emesis
- Low emetogenicity – 10 to 30 percent risk of emesis
- Minimally emetic – <10 percent risk of emesis

The objective of antiemetic therapy is the complete prevention of CINV, and this should be achievable in the majority of patients receiving chemotherapy, even with highly emetic agents.

Incidence and risk factors for CINV

More than 90% of patients receiving highly emetic chemotherapy (HEC) will have episodes of vomiting. With prophylactic antiemetic therapy, vomiting will be prevented or substantially decreased in about 70% of cases. Nausea is however more difficult to control.

Multiple factors influence the incidence and severity of CINV (Grunberg SM, 2004; Hesketh PJ, 2008), including:

- Chemotherapy regimen (type of agent and dosage, route of administration.)
- Females and patients aged <65 and particularly those <50yrs are at high risk for CINV compared to males and patients aged ≥65
- Poorly managed CINV during the 1st cycle (significantly increased the risk for subsequent CINV by 6-8 fold)
- Incomplete control of CINV during cycle 1 (increased the risk for incomplete response by 6 fold during the cycle 2)
- Incomplete control of CINV during cycle 2 (further increased the risk for incomplete response by 8 times during cycle 3)
- History of pregnancy-induced nausea and vomiting;
- History of limited alcohol intake;
- History of motion sickness;
- History of anxiety-related disorder.

2.1.3. Biologic features, aetiology and pathogenesis

Two phases of CINV mediated by neurotransmitter- driven mechanisms have been defined.

The acute emesis is mediated in part by chemotherapy-induced increases in serotonin (5-HT) release and activation of 5-HT3 receptors on vagal afferent neurons located primarily in the gastrointestinal tract. The 5HT3 receptors have been shown to play a significant role in acute-onset CINV. 5-HT3 receptor antagonists such as granisetron and ondansetron are clinically effective in reducing the incidence of CINV in the acute phase, particularly when given in combination with a corticosteroid such as dexamethasone.

Delayed emesis, involves the production of substance P, which binds to NK1 receptors in the vomiting centre of the brain, leading to nausea and vomiting. Although NK-1 signalling has some role in acute chemotherapy-induced nausea and vomiting (≤24 h), delayed emesis has primarily been linked with substance P mediated stimulation of neurokinin 1 receptors within the central and peripheral nervous systems. Blocking both receptors is required to achieve optimal control of CINV (Hesketh et al., 2003).

2.1.4. Clinical presentation, diagnosis.

The acute phase, which most commonly begins within one to two hours of chemotherapy and usually peaks in the first four to six hours which represents the first 24 hours following chemotherapy,

The delayed phase of CINV, occurs more than 24 hours after chemotherapy – usually 2 to 5 days following the initiation of chemotherapy.

2.1.5. Management

Current recommendations for antiemetics used to prevent CINV

Antiemetic therapy should be initiated before chemotherapy. Three categories of drugs are routinely used for the management of CINV: type three 5-hydroxytryptamine (5-HT3) receptor antagonists, the neurokinin-1 receptor antagonists (NK1 RA), and glucocorticoids to prevent acute nausea and vomiting following chemotherapy of high emetic risk.

A three-drug regimen including single doses of a 5-HT3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. A number of agents are licensed for the prevention of CINV including the first- and second generation 5HT3 receptor antagonists ondansetron, granisetron and palonosetron and NK1 receptor antagonists aprepitant, fosaprepitant, and netupitant.

Evidence-based guidelines for CINV prophylaxis have been published by different contemporary sources, (ESMO/MASCC 2010; NCCN 2016;ASCO.There are some differences between these guidelines but they generally recommend a 5HT3 receptor antagonists plus corticosteroid for patients receiving moderately emetogenic chemotherapy (MEC), and combination treatment with an NK-1RA and 5HT3 receptor antagonist plus a corticosteroid for patients receiving HEC.

Chemotherapy Antiemetic guidelines MASCC /ESMO Recommendation (Roila 2010)

Risk Level	Chemotherapy	Antiemetic Guidelines
High (>90%)	Cisplatin and other HEC	Day 1: 5-HT3 receptor antagonist + DEX 12 mg + (fos)aprepitant Days 2–3: DEX + aprepitant Day 4: DEX
Moderate (30%–90%)	AC	Day 1: 5-HT3 receptor antagonist + DEX + (fos)aprepitant Days 2–3: aprepitant
	Non-AC MEC	Day 1: Palonosetron + DEX 8mg

DEX, dexamethasone; AC, combination of an anthracycline (doxorubicin or epirubicin) and cyclophosphamide. (fos)aprepitant: either i.v. or oral form of the NK1 receptor antagonist.

No differences between the 5-HT3 receptor antagonists, dolasetron, granisetron, ondansetron, tropisetron exist in terms of efficacy. There is no consensus on the dose of dexamethasone to be used in delayed emesis. A single 20 mg dose before chemotherapy is recommended based on the observations that the 20-mg dose had the highest numerical efficacy.

Unmet need

Although antiemetic prophylaxis has been improving continuously, significant numbers of patients still continue to experience CINV. Compliance with current emetic guidelines can be suboptimal. Treatment of nausea remains a challenge.

Currently approved treatments have limitations. NK1 receptor antagonists, aprepitant and netupitant are inhibitors of cytochrome P450 (CYP) 3A4, with aprepitant also having CYP3A4 and CYP2C9 induction potential

and inhibition of other CYP enzymes induction potential. Dosage adjustment of concomitantly administered drugs is required including dexamethasone.

About the product

Rolapitant is a potent, selective, competitive NK1 receptor antagonist with no known activity at other pharmacologic targets. It is proposed to be given as part of a regimen that includes dexamethasone and 5-HT3 receptor antagonist.

Two tablets should be administered orally approximately 1 to 2 hours prior to initiation of each chemotherapy cycle but at no less than 2-weeks intervals.

The following regimens are recommended for the prevention of nausea and vomiting associated with emetogenic cancer therapy:

Highly Emetogenic Chemotherapy Regimen:

	Day 1	Day 2	Day 3	Day 4
Rolapitant	180 mg; approx. 1 to 2 hours prior to chemotherapy			
Dexamethasone	20 mg; 30 min prior to chemotherapy	8 mg twice daily	8 mg twice daily	8 mg twice daily
5-HT3 receptor antagonist	Standard dose of 5-HT3 receptor antagonist			

Moderately Emetogenic Chemotherapy Regimen:

	Day 1	Day 2	Day 3	Day 4
Rolapitant	180 mg; approx. 1 to 2 hours prior to chemotherapy	None		
Dexamethasone	20 mg; 30 min prior to chemotherapy	None		
5-HT3 receptor antagonist	Standard dose of 5-HT3 receptor antagonist	See the prescribing information for the co-administered 5-HT3 receptor antagonist for appropriate information.		

Type of Application and aspects on development

An agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and on the granting of a waiver for rolapitant (EMEA-001768-PIP02-15) is addressed in March 2016. PIP is not required for this application concerning the adults.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 90 mg rolapitant (as hydrochloride salt monohydrate) as active substance.

Other ingredients are:

Tablet content: lactose monohydrate, pregelatinised starch, microcrystalline cellulose (E460), povidone K-30, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate.

Tablet coating: partially hydrolysed polyvinyl alcohol, titanium dioxide, polyethylene glycol talc, FD&C Blue No. 2 Indigo Carmine Lake (E132) and polysorbate 80.

The product is available in polyvinyl chloride/polychlorotrifluoroethylene/aluminium foil twinned blister as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of rolapitant hydrochloride is (5*S*,8*S*)-8-[[(1*R*)-1-[3,5-*bis*(trifluoromethyl)phenyl] ethoxy]methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride monohydrate corresponding to the molecular formula $C_{25}H_{26}F_6N_2O_2.HCl.H_2O$. It has a relative molecular mass of 554.96 g/mol and the following structure:

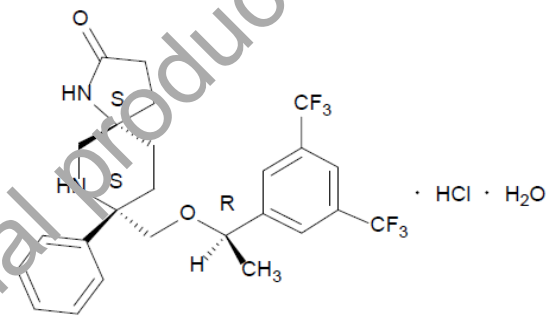


Figure 1 – Structure of rolapitant hydrochloride

The chemical structure of rolapitant was confirmed by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, elemental analysis, infrared spectroscopy and ultraviolet spectroscopy. Absolute control of stereochemistry is inferred from the known absolute configurations of raw materials. Epimerisation has been shown not to occur. Chiral HPLC methods have been developed to control starting materials and the active substance. Relative stereochemistry around the piperidine ring was confirmed by ^{1}H nuclear magnetic resonance spectroscopy.

The active substance is a white to off-white, slightly hygroscopic crystalline powder. It exhibits pH dependent solubility in aqueous media with maximum solubility between pH 2-4. It is a BCS class II molecule, exhibiting dissolution rate–limited absorption when dosed orally.

Rolapitant exhibits stereoisomerism due to the presence of three chiral centres, all of which originate in raw materials. Enantiomeric purity is controlled routinely by chiral HPLC in both the active substance and starting materials' specifications.

Polymorphism has not been observed for rolapitant hydrochloride monohydrate. Two non-hydrated forms have been detected by DSC but convert back to the hydrated form in the presence of moisture. The crystallisation process ensures routine production of the monohydrate form which is conformed routinely by XRPD.

Rolapitant is considered to be a new active substance. The applicant demonstrated that neither it, nor its derivatives and salts have ever been active substances in products authorised in Europe.

Manufacture, characterisation and process controls

Rolapitant is synthesized from well-defined starting materials with acceptable specifications. The starting material was re-defined during the procedure in responses to a major objection from CHMP as not enough of the process had been included for the regulator to understand the control and fate of impurities. The revised process, along with impurity (including genotoxic impurities) fate and purge studies ensures that sufficient steps are included in the process description, and that the control strategy is adequate to ensure the quality of the active substance.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The starting material specifications contain tests for genotoxic impurities with limits set to ensure these are not carried through to the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. A new process to that used to provide material for phase I and II clinical trials was introduced to facilitate the increased material requirements needed for phase III. The same process will be used commercially. Changes introduced have been presented in sufficient detail and have been justified. It has been demonstrated that the changes did not have a significant impact on the quality of the product.

The active substance is packaged in LDPE bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, identification (IR, HPLC), chloride identity (precipitation) and assay (titration), assay (HPLC), impurities (HPLC), stereomeric impurities (chiral HPLC), residual solvents (GC), water content (KF), heavy metals (turbidimetric), residue on ignition (gravimetric), particle size (laser diffraction) and polymorphic form (XRPD).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 13 production scale batches of the active substance manufactured by the proposed route were provided, 7 of which were manufactured by the proposed commercial manufacturer. The results are within the specifications and consistent from batch to batch. The microbiological quality of 13 batches of active substance was consistently below 100 cfu/g (TAMC) and 10 cfu/g (TYMC) and given the oral route of administration, no routine test is required. Impurities limits are all set below the qualification threshold.

Stability

Stability data from three pilot scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, identity, water content, assay, impurities, particle size (only for long term batches) and microbial limits. The analytical methods used were the same as for release, except for the microbial limit tests which use the Ph. Eur. method, and are stability indicating. The polymorphic form had already been shown to be stable so no testing was deemed necessary. Particle size remained constant under long term conditions so was not tested under accelerated conditions. All tested parameters were within the specifications and no significant trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch showing that the active substance is not photosensitive. Forced degradation studies were carried out by exposing the active substance to heat, light, acid, base and oxidative conditions. Rolapitant hydrochloride monohydrate is stable in the solid state but degrades in aqueous solution at high pH or when treated with an oxidant.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container under the proposed conditions.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Varuby is a blue film coated immediate release tablet, debossed with T0101 on one side and 100 on the other, containing 100 mg rolapitant hydrochloride monohydrate, equivalent to 90 mg rolapitant free base.

Studies were aimed at developing a robust and stable formulation allowing immediate release and dissolution of the active substance. Rolapitant hydrochloride is a stable BCS class II molecule with absorption limited by its dissolution rate. Accordingly, the active substance is micronized.

Phase 1-3 clinical trials were carried out using a 50 mg capsule formulation. Following identification of the efficacious dose as 200 mg, development began on a solid dosage form with higher active substance content. A series of prototype dosage forms were investigated in order to identify a bioequivalent formulation. The final commercial formulation is a 100 mg film coated tablet, shown to be bioequivalent following optimisation of content for manufacturability. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The dissolution method was developed using compendial apparatus. Various parameters were optimized resulting in a method able to achieve sink conditions. The QC method was shown to be discriminatory with respect to manufacturing changes shown to impact the performance of the finished product and is considered to have sufficient discriminatory power.

Additional process development studies were carried out and process parameters optimized using a series of design of experiment studies to study the granulation, drying and milling, and lubrication, compression and coating steps. Target set-points were thus defined for individual process parameters and proven acceptable ranges set. Active substance batches with particle size distributions at the extremes of the proposed specification were also investigated and the proposed limits shown to be suitable. This series of experiments also demonstrated the robustness of the process. Scale up of the process was shown to deliver finished product of adequate quality.

A bioequivalence study was performed showing bioequivalence between the 50 mg capsule used in clinical trials and the proposed commercial 100 mg tablets.

The primary packaging is polyvinyl chloride/polychlorotrifluoroethylene/aluminium foil twinned blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: de-lumping and mixing of intra-granular materials, wet granulation followed by drying and milling, blending with extra-granular excipients and lubrication, compression to form tablets, film coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by manufacturing three consecutive production scale batches using the intended processing conditions. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and comprise tests for description, identity (FT-IR, HPLC), assay (HPLC), impurities (HPLC), uniformity of dosage units (USP), dissolution (HPLC), moisture (KF) and microbial enumeration (USP).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for the three production scale validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. In addition, batch analysis data from 23 previous batches of a range of tablet and capsule strengths (from 2.25-180 mg) used throughout clinical development was provided as supporting information.

Stability of the product

Stability data from 3 pilot scale batches of finished product (and an additional batch with a white film coat) stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Other than the white batch, the batches of Varuby are identical to those proposed for marketing, except that they were printed with black ink rather than debossed, and were packed in the primary packaging proposed for marketing. The difference in appearance was not considered likely to enhance stability. Samples were tested for description, water content, dissolution, assay, related substances and microbial enumeration. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed, other than a slight increase in water content over time under long term conditions. Since this doesn't impact any of the other quality attributes, it is not a concern.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes to any of the measured parameters were observed under the above conditions. Therefore, Varuby is photostable.

Samples were also exposed to freeze/thaw cycles (between -20 and 50 ^{o}C) and thermal stress (85 ^{o}C). A bulk storage study was carried out on one batch packaged in double LDPE bags for up to 12 months under ambient conditions. No degradation was observed other than under thermal stress where some minor degradants were observed.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption, and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

The magnesium stearate is of plant origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The majority of pharmacokinetic studies and all primary pharmacology studies were non-GLP studies.

All pivotal toxicology studies and the safety pharmacology studies were carried out in compliance with Good Laboratory practice (GLP) regulations except *in vitro* hERG in mouse L-929 cells (SN-08107, SN-46553) and cardiovascular isolated canine Purkinje fibers study (SN05255), cardiovascular study in cynomolgus monkeys (SN-08107, SN-46553) and central nervous system and respiratory renal and gastrointestinal studies in rats (SN-46553).

CHMP Scientific advice was sought regarding the nonclinical programme.

2.3.2. Pharmacology

Primary pharmacodynamic studies

***In vitro* studies** *(*D-46896, GR 73632, 100000503)

Table 1: in vitro pharmacology studies. Affinity of rolapitant and it major metabolite (M19) for NK1, NK2 and NK3 receptor

GLP aspect	Type of study	Test system	Noteworthy Findings
no GLP D-46896 study	Affinity of rolapitant for NK1 receptor	Gerbil, rabbit and monkey striata and cells expressing cloned rat mouse and guinea pig NK receptors. Chinese hamster ovary cells transfected with the recombinant human NK1 receptor	Human recombinant NK1 : Ki = 0.66 nM Gerbil NK1 receptor : Ki = 0.13 nM Guinea pig NK1 receptor : Ki = 0.72 nM Monkey NK1 receptor : Ki = 2.5 nM Rabbit NK1 receptor : Ki = 31.7 nM Mouse NK1 receptor : Ki = 64.4 nM Rat NK1 receptor : Ki = 78.6 nM Human recombinant NK2 : Ki > 1200 nM Human recombinant NK3 : Ki = 4050 nM
no GLP 100000503 study	Affinity of major metabolite (M19) of rolapitant for NK1, NK2 and NK3 receptors	Human NK1, NK2 and NK3 receptor	NK1 : IC50<10 nM (Ki = 0.42 nM) NK2 : IC50=20 000 nM NK3 : IC50=1700 nM

***In vivo* studies**

Table 2: In vivo pharmacology studies with rolapitant

Type of study No of animals/dose GLP aspect	Doses (mg/kg)	Major findings
Induced Foot-Thumping in Gerbils		
Foot thumping induced by an NK1 agonist (GR 73632) 3F /group No GLP D-46896 SN04917	Oral by Gavage 0.03- 1 mg/kg	Rolapitant blocked NK1 agonist induced foot thumping => ED90 = 0.3 mg/kg. Plasma concentration of rolapitant (4 hours after administration of the ED90 dose of 0.3 mg/kg) = 34 ng/ml (68 nM).
Foot thumping induced by an NK1 agonist (GR 73632) 3F/group No GLP D-46896	Oral by gavage and IV 0.3 mg/kg PO 1.0 mg/kg IV	Rolapitant blocked NK1 agonist induced foot thumping for up to 24 hours.
Emesis studies in Ferrets		
Ferrets Acute apomorphine induced retching and vomiting 4M/group No GLP D-46833	Oral by Gavage 0.01 – 0.3 mg/kg + apomorphine	Rolapitant produced a significant dose related inhibition of emesis induced by apomorphine =>ED50 = 0.03 mg/kg.
Ferrets Acute cisplatin-induced retching and vomiting 4M/group No GLP D-46833	Oral by Gavage 0.03 – 0.3 mg/kg + cisplatin	Rolapitant produced a significant dose related inhibition of emesis induced by cisplatin => ED50 = 0.07 mg/kg.
Ferrets Acute and delayed cisplatin-induced retching and vomiting	Oral by Gavage 1 mg/kg	A single dose of rolapitant at 1 mg/kg administered 4 hours prior to cisplatin produced 95% inhibition of retching and vomiting over 72 hours. Daily treatment with rolapitant produced 95% inhibition of retching and vomiting over 72 hours.

4M/group D-46833	+ cisplatin	

Secondary pharmacodynamic studies

In vitro pharmacology assays, rolapitant has > 1000-fold lower affinity for a panel of 115 other receptors, transporters, enzymes, or channels. Rolapitant has a little affinity for norephinephrine or dopamine transporters or Cl- channel. Rolapitant has > 200-fold lower affinity for glucocorticoid receptor, the closest receptor by affinity, than for the NK1 receptor. The major active metabolite M19 has > 1000-fold lower affinity for a panel of 86 other receptors, transporters, enzymes, or channels against which it was tested.

The secondary pharmacodynamics experiments indicate that rolapitant and M19 are selective for NK1 over the related NK2 and NK3 receptors (>1000-fold lower affinity). Furthermore, rolapitant and the metabolite M19 were screened against a large panel of other receptors, enzymes and ion channels, the results of which indicate that based on lower affinity, rolipitant is unlikely to achieve sufficient clinical concentrations in humans to affect other receptor/ion channel activity, including the closest receptor by affinity, the glucocorticoid receptor (>200-fold lower affinity).

Safety pharmacology programme

Table 3: Safety pharmacology studies with rolapitant and its metabolite M19

Type of study GLP aspect	Doses/concentrations	Major findings
Ex vivo		
Cardiovascular Isolated, canine Purkinje fibers Non-GLP SN05255	ROLAPITANT 1.19 and 8.04 µM	8.04 µM: small but statistically significant shortening of action potential duration at all pacing frequencies (APD60 and APD90: -14.0% and -9.5%, respectively). NEL = 1.19 µM.
In vitro		
Cardiovascular hERG: Mouse L-929 cells stably transfected with human hERG Non-GLP SN-46553 SN-08207 (M19)	ROLAPITANT: 0, 0.4, 2.46, 7.18 µM M19: 0.3, 1.0, 3.0, 10, 20µM	hERG : IC50 = 1.05 µM (rolapitant) and = 5.8 µM (M19) Rolapitant at 1.05 µM ⇨ Safety margin = 278
In vivo		
Cardiovascular Cynomolgus Monkeys (Telemetry) Cardiovascular: 5M/group	Oral, by gavage ROLAPITANT Cardiovascular: 0, 1, 2, 5 mg/kg	Cardiovascular: No treatment related effects on blood pressure, heart rate, ECG. At 6 hours post-dose, plasma drug levels at 2 and 5 mg/kg were 290 and 820 ng/mL, respectively.

Non-GLP SN-08107 SN-46553		
Cardiovascular Cynomolgus Monkeys Telemetry 6M/Group GLP SN03125	Oral, by gavage ROLAPITANT Single dose : 0, 5, 15 mg/kg	No changes in heart rate, blood pressure, or ECG intervals or ECG morphology NOEL =15 mg/kg
CNS, Respiratory, Renal, GI: Sprague-Dawley Rats 6/sex/group SN-03124 (GLP) SN-03123 (GLP) SN-46553 (Non-GLP)	Oral, by gavage CNS (Irwin), Respiratory, Renal, GI (SN-46553) : ROLAPITANT : 0, 5, 10 mg/kg in M only Respiratory (SN-03123): ROLAPITANT single oral dose in M 5, 25, or 100 mg/kg or in F 1, 5, or 25 mg/kg CNS (SN-03124): ROLAPITANT single oral dose :1, 5, or 25 mg/kg in F; 5, 25, or 100 mg/kg in M	CNS: No significant findings in behavioral or autonomic endpoints. Respiratory: No test-article related effects on respiratory rate, tidal volume, minute volume or arterial pH, blood gases, or bicarbonate levels. Renal: No test-article-related effects on urine volume, urinary electrolyte excretion, serum creatinine or 24-hour creatinine clearance. GI: No test-article-related effects on gastric emptying or intestinal transit.

M: male ; F: female; PK: pharmacokinetic; plasma fu : free fraction of drug in plasma; NEL: no effect level

The SN05255, SN46553 and SN08107 studies concern also the evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) regarding rolapitant or it major metabolite M19 and were not conducted under GLP conditions. For that reason, the Applicant performed two new studies in December 2016 and in January 2017 for both rolapitant (SN 1000-09-003) and its M19 metabolite (SN 1000-09-004) under GLP conditions (subject to pending final report). The results of all studies are consistent. In addition, a QTc study of rolapitant in humans was conducted at 4x the therapeutic dose, and no QT signal was observed in this study.

In vitro rolapitant and M19 weakly inhibited hERG (potassium) current with an IC50 of 1.05 µM and 5.8 µM, respectively.

Furthermore, a canine Purkinje fiber assay indicated that small but statistically significant shortening of action potential duration at all pacing frequencies occurred in fibers exposed to the high concentration of 8.04 µM of rolapitant (APD60 and APD90 were shortened slightly by 14.0% and 9.5%, respectively) but no test article related effects were reported at lower concentrations or on other action potential parameters at any concentration.

In vivo safety pharmacology studies were conducted to evaluate the safety of rolapitant in core organ systems including rat studies of central nervous, respiratory, renal/urinary and gastrointestinal systems and a monkey cardiovascular study. No test-article related effects of concern were observed on neurologic or respiratory function at doses up to 25 mg/kg in female rats and 100 mg/kg in male rats or on gastrointestinal or renal function in male rats at single oral doses of up to 10 mg/kg rolapitant (SN03123, SN03124, D-46553). However, the binding affinity of rolapitant for rat NK1 receptor is >100-fold less than for human NK1 receptor.

Rolapitant administered at doses ranging from 1 to 15 mg/kg to male conscious telemetered cynomolgus monkeys did not affect arterial blood pressure, heart rate, ECG intervals or ECG morphology in vivo (D-46553, SN03125). In addition, no ECG intervals or morphology changes including QTc intervals were observed in repeat-dose GLP toxicity studies up to an oral dose of 30 mg/kg/day for 9 months and up to an IV dose of 15 mg/kg/day for 14 days in monkeys. Taken together with the in vitro study results, these data suggest that rolapitant does not delay cardiac ventricular repolarization.

Pharmacodynamic drug interactions

Non clinical studies on pharmacodynamic drug interactions were not submitted.

2.3.3. Pharmacokinetics

Quantitative methods using protein precipitation followed by reverse phase HPLC coupled with triple quadruple mass spectrometry (MS/MS) was developed and validated for the quantitatively analyses of rolapitant and the metabolite M19 in several non clinical matrices (mouse plasma, rat plasma, monkey plasma).

Table 4: Representative Validated LC-MS/MS Assays Used to Determine Rolapitant and Metabolite M19 (M19) Concentration in Mouse, Rat, and Monkey Plasma

Reference	Species	Analyte	Range (ng/mL)	LLOQ (ng/mL)	Accuracy (% Diff)	Precision (% CV)
DM27321 Non-GLP	Mouse	Rolapitant	50 to 50000	50	-3.5 to 3.0	2.5 to 7.7
		M19	5 to 5000	5	-2.4 to 3.0	2.0 to 9.5
DM27320 Non-GLP	Rat	Rolapitant	50 to 50000	50	-5.0 to 2.8	1.7 to 12.5
		M19	5 to 5000	5	-4.2 to 4.0	2.5 to 12.0
DM27322 Non-GLP	Monkey	Rolapitant	50 to 50000	50	-6.0 to 6.0	1.8 to 9.1
		M19	5 to 5000	5	-4.7 to 6.5	1.2 to 11.8

Absorption

Single dose studies:

Table 5: Bioavailability of rolapitant after single dose in preclinical species

Species	Formulation	Dose (mg/kg) Route	Gender (N)	Cmax (ng/mL)	Tmax (hr)	AUC $_{0-\infty}$ (ng*hr/mL)	F (%)
Rat	Amorphous HCl Salt	5 i.v.	M (3)	ND	ND	10400	
		5 p.o.	M (17)	556	3.6	4840 - 7000	47 -71 %
	Crystalline HCl monohydrate salt	5 p.o.	M (20)	379	5.0	5410 (0-24 hr)	
		5 p.o.	F (10)	723	8.0	14900 (0-24 hr)	
Monkey	Amorphous HCl Salt	2 i.v.	M (3)	ND	ND	5200	
		2 p.o.	M (3)	467	2.7	6540	≈100%
	Crystalline HCl monohydrate salt	2.5 p.o.	M (3)	590	4.0	11700 (0-72 hr)	

Distribution

In Vitro Protein Binding- Plasma Protein Binding

Rolapitant is highly plasma protein-bound (99.7-99.9% in mice, rabbits, rats, dogs, monkeys, and humans). Consistently, the metabolite M19 exhibits the same marked binding with the rat, monkey and human plasma proteins (≥ 99.0%).

Both rolapitant and the active metabolite M19 are highly non-specifically bound, resulting in the free fraction available for the potential interactions with biological targets likely in the order of 1% or less of the total compounds in the brain.

In Vivo Studies

The volume of distribution (Vdss) of rolapitant is considered high in rats (Vdss =7.7 L/kg) and moderate in monkeys (Vdss =3.9 L/kg).

A quantitative whole-body autoradiography (QWBA) study was conducted following a single oral dose of 14C-rolapitant (25 mg/kg) to both the albino (Sprague-Dawley) and pigmented rats (Long-Evans). 14C-rolapitant was absorbed rapidly into the blood. The majority of tissues reached peak radiocarbon concentrations at the 8-hr time point, the tissues that had the highest radiocarbon concentrations, at this time point were the liver, lung, pancreas harderian, adrenal, and the wall of the small intestine (range; 18100 to 88900 SCH 619734 ng equiv/g). The lens of the eye had fallen below the limit of quantification in all genders and strains at the 8-hr time point and the tissue-to-blood concentration ratios were on average between 3.5- and 6.2-fold higher than the time-matched blood concentrations. Since the amount of radioactivities was one of the lowest in the ocular tissues among all solid tissues examined in both pigmented and albino rats, the binding affinity of rolapitant to melanin-containing tissues appears to be negligible. Radioactivities were not detected in ocular tissues after 48 hours postdose.

Brain Distribution

Table 6 : Brain distribution in gerbils and rats

Studies	Rolapitant brain to plasma concentration ratio	M19 brain to plasma (AUC) ratio
RAT 5 mg/kg	2.4 to 5 (24 h post dose) 0.2 to 2.5 (48 h post dose)	
RAT 10 mg/kg	1.2 (48 h post dose)	0.682 (24 h post dose)
RAT 25 mg/kg		0.627 1.2 (24 h post dose)
RAT 100 mg/kg	1.2 (48 h post dose)	

The elimination kinetics appeared to be comparable between brain (t½ ~ 4.2-4.4 hr) and plasma (t½ ~ 4.5-5.3 hr) in rats.

Multiple dose studies

Table 7: Rolapitant Pharmacokinetic Parameters after Repeated Oral Dosing to Rats and Monkeys

Species	Formulation	Dose (mg/kg) Per os	Duration (day)	Gender (N)	Cmax (ng/mL)	Tmax (hr)	AUC $_{0\text{-}24h}$ (ng*hr/mL)
Rat	Crystalline HCl monohydrate salt	5	7	M (20)	417	2	4680
		5	7	F (10)	1118	2	22500
		5	30	M (10)	551	8	8660
		5	30	F (10)	551	8	40600
Monkey	Amorphous HCl Salt	5	15	M (4)	1300	1.8	12700
		5	30	M (4)	1353	2.5	14054

Metabolism

In vitro studies:

14C-rolapitant metabolism was investigated, in a cofactor NADPH-dependent manner, using human liver subcellular fractions (microsomal preparations, S9 and cytosolic fractions), and human recombinant metabolic enzymes including 19 recombinant P450 members and 3 human flavin monooxygenases. Recombinant human CYP3A4 and CYP3A5, to a less extent, catalyzed the formation of M19 from rolapitant.

In vivo studies:

None of the metabolites detected appear to possess discernible structural alerts for bioactivation specifically, glutathione (GSH) or acyl glucuronide conjugates formed with rolapitant and the metabolites in the nonclinical species (rats and monkeys) were not evidently detected.

Table 8: Comparaison of plasma metabolites in mice, rats and monkeys given a single dose of rolapitant

Metabolite	Peak Area Relative to Rolapitant (%)				
	Mouse	Rat		Monkey	Human
	Male	Male	Female	Male + Female	
M4 Dihydroxy-*O*-desalkyl-SCH 619734	NR	24.5	ND	ND	NA*
M4a Hydroxy-*O*-desalkyl- SCH 619734	NR	24.5	ND	ND	NA*
M6 Hydroxy-*O*-desalkyl- SCH 619734	NR	26.0	ND	ND	NA*
M19 (M19) Hydroxy- SCH 619734	1.1	50.4	3.8	11 -17	50
M21 Hydroxy- SCH 619734	5.8	4.0	5.0	ND	NA*
ROLAPITANT	100	100	100	100	NA*

ND, not detected on Day 1 but detected in Day 5 plasma ; NR, not reported as detected by either MS or on-line 14C radiometric detection
NA*: No details available in Humans, wathever the other metabolites their plasma exposure are < 10%

Excretion

Table 9 : Excretion of rolapitant (SN04917 (No GLP))

Species	N	Dose (mg/kg)	Route	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
Rat	2a	5	IV	14.9	NC	25.5	40.3	0-24
	3	5	IV	34.1	54.6	NC	92.9	0-168
	2a	15.6	PO	10.1	NC	22.3	32.4	0-24
	3	5	PO	31.3	51.8	NC	87.8	0-168
Monkey	2a	2	IV	7.5	NC	48	55.5	0-48
	3	2	IV	18.6	58.4	NC	77.3	0-240
	2a	10	PO	5.2	NC	31.8	37.0	0-48
	3	2	PO	18.1	56.9	NC	75.7	0-240
Humans		180 mg Single dose	PO	14.2	73			6 weeks

a : bile duct-cannulated animals

Milk excretion

Table 10 : Pharmacokinetic Parameters of Rolapitant in Dams and Pups after Oral Administration (25 mg/kg) to Postpartum Female Rats

Parameter	Dams			Pups	
	Blood	Plasma	Milk	Blood	Plasma
C_{max} (ng equiv/g)	4470	5990	14100	356	369
T_{max} (hr)	8	8	12	22	22
AUC_{0-48hr} (ng equiv*hr/g)	124000	156000	331000	11500	12000

2.3.4. Toxicology

Single dose toxicity

Table 11 : Summary of acute toxicity studies performed with rolapitant

Species/ Sex/Number/Group Study ID GLP aspect	Dose/Route (mg/kg)	Approx. Lethal dose / observed max non-lethal dose	Major findings
Mouse 3 days 5M & 5F SN 05220 GLP	Oral, by gavage 300, 450, 900, 1800		Mortality: 2M & 3F at 450 mg/kg, 4M & 4F at 900 mg/kg, 5M & 3F at 1800 mg/kg found dead after single dose. 1F at 300 mg/kg and 2F at 1800 mg/kg euthanized after single dose. Physical Signs: In M & F at all doses, convulsions, hypoactivity, impaired equilibrium, intermittent tremors and/or convulsions, partial closure of eyes, prostration.
Rat 3M & 3F SN 03101 GLP	Oral, by gavage M: 0, 0, 100, 500, 1000, 2000 F: 0, 0, 50, 250, 500, 1000	Observed Maximum Non lethal Dose (mg/kg) F: 100 M: 1000 Approximate Lethal Dose (mg/kg) F: 500 M: 2000	Mortality: 1/3 F at 500 mg/kg, 3/3 F at 1000 mg/kg; 1/3 M at 2000 mg/kg Physical Signs: Hunched appearance, hypoactivity, tremors in F at ≥250 mg/kg and M at ≥500 mg/kg. Ataxia, abnormal stool M&F at 500 and 1000 mg/kg and M at 2000 mg/kg. Labored breathing, coolness to touch, chromorhinorrhea and salivation in M at 2000 mg/kg.
Rat 3M&3F SN 03102 GLP	Intraperitoneal M: 0, 125, 250, 500, 1000 F: 0, 125, 250, 500	Observed Maximum Nonlethal Dose (mg/kg) F: 250 M: 500 Approximate Lethal Dose (mg/kg) F: 500 M: 1000	Mortality: 1/3 F at 500 mg/kg; 3/3 M 1000 mg/kg. Physical Signs: Hypoactivity ≥250 mg/kg. Ataxia and hunched posture F at 250 mg/kg, M&F at 500 mg/kg, and M at 1000 mg/kg. Abnormal stool. Chromodacryorrhea and fecal M at 500 mg/kg. Labored breathing and urogenital staining in F at 500 mg/kg. Tremors in M&F at 500 mg/kg and M at 1000 mg/kg. clonic convulsions, prostration M at 1000 mg/kg.

Monkey/ Cynomolgus 1M&1F SN 03126 GLP	Oral, by gavage 25, 50, 75, 100, 150, 200	Observed Maximum Nonlethal Dose (mg/kg) F: 100 M: 200 Approximate Lethal Dose (mg/kg) F: 100 M: 200	Mortality: F at 200 mg/kg Clinical Signs: F at 200 mg/kg: convulsions, emesis, hypothermia, prostration, and morbidity. At 150 mg/kg, excessive vocalization in M, hyperactivity in F, face rubbing in M&F.
Monkey/ Cynomolgus 8F SN 08134 GLP	Oral, by gavage 100	Observed Maximum Nonlethal Dose (mg/kg) F: 100	Emesis, hypoactivity, and abnormal posture.

BWG = body weight gain, F = female, M = male, NA = not applicable, TK = toxicokinetics

a All rolapitant doses as hydrochloride monohydrate salt

Repeat dose toxicity

Table 12 : Summary of repeat-dose toxicity studies

Species/Sex/ Number/Group Study ID/ GLP aspects	Dose (mg/kg/day) / Duration /Route	NOAEL (mg/kg/day)	Major findings
IV INFUSION			
Rat 14 days toxicity study Tox 10M&10F TK: 12M&12F SN 07395 GLP	IV infusion Saline, Vehicle, 4.5, 18, 36	NOAEL = 18	- At 36 mg/kg/day: sacrificed after the first dosing due to inability to infuse such volume (20 mL/kg) reliably. - in 4.5 and 18 mg/kg/day group : no findings
Monkey/ Cynomolgus 14 days toxicity study 4M&4F SN 07393	IV infusion Saline, vehicle, 5, 10, 20	NOAEL : F = 5 M < 5	Mortality: 14 monkeys pre-terminally euthanized due to clinical observation findings: 4M/4 at the 5 mg/kg, 8/8 at 20 mg/kg; 1M/4 +1 F/4 at 10 mg/kg : hunched posture, prostration, hypoactivity, ataxia, pulling hair, no food consumption, coughing/gagging, vomitus, excessive salivation, and retching. 2M sacrificed on D10 at 5 mg/kg : ↓ in red cell

GLP			mass and albumin with ↑ cholesterol and triglycerides, 1M with notable ↓ in reticulocyte and platelet counts.
Monkey/ Cynomolgus 14 days toxicity study Main study: 4M&4F Recovery: 2M&2F for Groups 2 and 5 only SN-2013-009 GLP	IV infusion Saline, vehicle, 3, 10, 20/15	NOAEL =10 (30 minute infusion) NOAEL = 15 (45 minute infusion)	20mg/kg/day: convulsions, decreased activity, recumbency, and ataxia ⇨ resulted in a dose reduction to 15mg/kg/day and a lengthening of the infusion time to 45 minutes (20/15 mg/kg, 45 minutes infusion).
ORAL (GAVAGE)			
Mouse 3 months toxicity study Toxicity: 10M&10F TK: 30M&30F SN 03665 GLP	Oral, by gavage 0, 25, 75, 150	NOAEL = 75	Organ wt (changes listed as relative to body wt) • ↑Liver wt in M&F at ≥75 mg/kg • ↓Uterine wt (-19%) at 150 mg/kg Histopathology • Liver: centrilobular hepatocellular hypertrophy in M at ≥25 mg/kg and F at ≥75 mg/kg P450 Gene Expression • Induction of CYP 2B1/2B2 and CYP 3A1 in M (~7-fold for both) and F (~4- and ~9-fold, respectively) – only HD investigated
Rat 3 months toxicity study Toxicity : 10M&10F TK : 30M&30F SN 03409 GLP	Oral, by gavage M : 0, 5, 25, 100 F : 0, 1, 5, 25	NOAEL = 5	Body weights: ↓BWG: in M at 100 mg/kg Biochemistry: ↑ protein, albumin, and globulin at 25 mg/kg; ↓A/G and ↑calcium at 100 mg/kg Organ weights: ↑liver wt. in M at 100 mg/kg. Histopathology: Epididymes: vacuolation of epithelium at ≥25 mg/kg
Rat 3 months toxicity study	Oral, by gavage	NOAEL M = 75	Clinical signs: dose-related peri-oral food-like material associated with salivation at ≥50 mg/kg, convulsions on F43 to termination in 1F at 125

Toxicity: 10M&10F TK: 15M&15F P450 Gene Expression : 5M&5F control and high dose only SN 03664 GLP	0, 50, 75, 125	(based on histo-pathology & organ wt) F = 50 (based on organ wt).	mg/kg <u>Body weights:</u> ↓BWG in F at 125 mg/kg <u>Food consumption:</u> transient↓ on D7 at ≥ 50 mg/kg. <u>Hematology:</u> slight ↓ RBC, Hb, Hct, microcytosis (↓MCV, MCH) in F at 125 mg/kg <u>Biochemistry:</u> ↑protein, ↑globulin at 125 mg/kg in M and at ≥75 mg/kg in F, ↓TG at 125 mg/kg in M and at ≥50 mg/kg in F <u>Organ weights:</u> ↑Liver at ≥50 mg/kg, ↑Thyroid and adrenal in M at 125 mg/kg, ↑Kidney wt in M at ≥50 mg/kg, ↓Uterus wt in F at 125 mg/kg. <u>Histopathology:</u> • Liver: centrilobular hypertrophy at ≥50 mg/kg, multinucleated hepatocytes in 2/10 M at 125 mg/kg • Thyroid: follicular cell hyperplasia in M at 125 mg/kg • Adrenal gland: hyperplasia of zona fasciculate in 1/10 M at 125 mg/kg • Kidney: focal hyperplasia of tubular cells in outer stripe of kidney in M at ≥75 mg/kg <u>Ultrastructural Pathology (selected control and high-dosed M only):</u> proliferation of smooth endoplasmic reticulum in tubular epithelial cells of pars recta of kidney, compatible with enzyme induction. <u>P450 Gene Expression:</u> induction of hepatic CYP 2B1/2B2 (~7- to 13-fold) and CYP 3A1 (~12- to 44-fold) mRNA at 125 mg/kg.
Rat 6 months toxicity study Toxicity : 15/sex/group TK 3/sex/group/time point SN 03115 GLP	oral by gavage 0, 25, 50, 100	NOAEL = 100	- Physical signs: ↑ incidence of salivation in M&F 50 and 100 mg/kg/day. - ↓ BWG on D184 in F 25, 50, and 100 mg/kg/day (-20.4, -21.4. and -20.6%, respectively) - Serum Biochemistry: a slight to mild ↓ in total and conjugated bilirubin in all dosage level in M&F, with a dose-related trend only in M. Minimal ↑ Cholesterol F all dose groups. Mildly ↓TG in all doses with dose-related trend only in males. – Organ wt: ↑ liver weight correlated with hepatocellular hypertrophy. ↓ absolute uterus weight in all dosage level. - Histopathological findings : • Liver: minimal to moderate centrilobular hepatocellular hypertrophy with an apparent dose-related increase in incidence and severity, multinucleated hepatocytes at 50 and 100 mg/kg/day, single cell necrosis at 50 and 100 mg/kg/day, eosinophilic cell focus at 100 mg/kg/day in

			M, ↑ incidence of minimal to slight hepatocellular vacuolation in M. • Thyroid: minimal to slight follicular cell hypertrophy at 50 and 100 mg/kg/day in M&F • Epididymes: a minimal vacuolation of the tubular epithelium (in all M at all doses) ⇨ Vacuolation of epithelial cells is a common degenerative change in the epididymis of aged rats.
Monkey/ Cynomolgus 28 days toxicity study 4M&4F SN 05015 GLP	Oral, by gavage 0, 30, 60, 100	NOAEL =30	Mortality: All animals at 60 and 100 mg/kg euthanized after 2 and 3 day dosing due to treatment-related clinical signs. At ≥60 mg/kg, loose/soft stool, emesis, hypoactivity, weakness, coolness to touch, hunched appearance, ataxia, prostration, and/or convulsions. Stress-related ↑WBC, neutrophils and ↓lymphocytes ≥60 mg/kg. Histopathology: • Pancreas: at ≥60 mg/kg, vacuolar degeneration of pancreatic acinar cells and • Stomach: vacuolar degeneration of glandular epithelium of stomach. • Heart: Mild focal arteriolar degeneration of the heart in 1 M at 60 mg/kg possibly secondary to seizures. ↳Traumatic injuries secondary to convulsive activity ≥60 mm/kg.
Monkey/ Cynomolgus 3 months toxicity study 4M&4F SN 03098 GLP	Oral, by gavage 0, 1, 5, 15	NOAEL =15	None
Monkey/ Cynomolgus 9 months toxicity study 4M&4F SN 03663 GLP	oral by gavage 0, 2.5, 15, 30	NOAEL =30	Minimal focal necrosis in the liver of 3 out of 4 high-dose (30 mg/kg/day) in M.

A/G = albumin/globulin ratio, BWG = body weight gain, ECG = electrocardiogram, F = female, Hb = hemoglobin, Hct = hematocrit, M = male, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, PBS = phosphate buffered saline, RBC = red blood cells, TK = toxicokinetics WBC = white blood cells, wt = weight, w/v = weight to volume ratio. D: day

In rodents, rolapitant was tested in repeated dose oral toxicity studies up to 26-weeks in duration, and the liver, thyroid, kidneys, epidymis and uterus were identified as target organs.

Liver weight increased with dose-dependent, which correlated with histopathological findings such as hepatocellular hypertrophy. In the thyroid, the incidence of follicular cell hypertrophy was increased at all doses and relative thyroid weights were increased at the high dose. The changes in the liver and thyroid appear to be related to the activation of drug metabolizing enzymes (increased CYP gene expression (CYP2B1/2B2 and CYP 3A1) and may not be relevant to humans. In the 3-month dose range-finding study, additional observations in males at 125 mg/kg/day consisted of hyperplasia of the tubular cells of the outer stripe of the kidney that was associated with endoplasmic reticulum proliferation, and minimal hyperplasia of the zona faciculata in the adrenal gland, both considered consistent with enzyme induction. Moreover treatment-related minimal vacuolation in the epididymis was not considered adverse since the changes were minimal and did not increase in severity with longer duration treatment. Decreased absolute uterus weight occurred in 3-months repeated doses studies in mice from dose of 1 mg/kg/day and in rats from dose of 50 mg/kg/day and in 6-months repeated doses study in rat from dose of 25 mg/kg/day.

In monkeys, the oral administration of rolapitant at dosage levels as high as 15 mg/kg/day for 3 months and 30 mg/kg/day for 9 months resulted in no treatment-related findings. However in an oral one month study, all animals in the 60 and 100 mg/kg/day dosage levels were euthanized due to treatment-related clinical signs, including convulsions. In addition, convulsions were observed in mice oral doses of 300 mg/kg/day and intraperitoneal doses of 125 mg/kg/day. In rats, convulsions occurred following a single IP dose of 1000 mg/kg and in a single animal given 125 mg/kg/day in a 3-month oral toxicity study.

Given the differences in half-lives and the difference in dosing in animals (repeated daily dosing) and in humans (single dose per treatment cycle), the Applicant considered for the safety margin calculation that direct comparison of steady-state AUC0-24h values in animals to AUC0-∞ values following a single dose in humans to be misleading. Thus, to allow for a comparison of cumulative total exposure in animals relative to the total exposure in humans over the same timeframe, animal "AUC Projected" values by multiplying the daily, steady state AUC0-24h values for rolapitant and metabolite M19 in animals by a factor of 14. This approach, comparing projected human steady state exposure for two weekly dosing intervals to cumulative exposure in the non-clinical species over the same time period is reasonable when considering the significant difference in half-lives of the drug and major metabolite M19 between non-clinical species and humans.

Genotoxicity

Table 13 : Summary of genotoxicity studies performed with rolapitant:

Type of test/study ID/GLP	Test system Method of administration	Concentrations/ Concentration range/ Metabolising system	Results
In vitro			
Ames Gene mutations in bacteria SN 03113 GLP	Salmonella typhimurium TA 1535, TA97a, TA98, TA100, TA102, WP2uvrA	31.2 to 5000 µg/plate +/- S9	negative
Chromosome aberration SN 03114 GLP	Human peripheral blood lymphocytes	-S9: 2.93 to 23.4 µg/mL (4-hour treatment) and 10 to 40 µg/mL (19-hour treatment). +S9: 5.86 to 46.9 µg/mL (4-hour treatment) and 40 to 70 µg/mL (4-hour treatment)	negative
In vivo			
Micronucleus test	Mouse	0, 31.25, 62.5, 125 mg/kg for 2	negative

SN 03261 GLP	6 M + 6F /group **IP** Micronuclei in bone marrow cells	days Mortality at ≥ 250 mg/kg, Clinical signs at ≥ 62.5 mg/kg/day : hypoactivity and/or flattened posture Bone marrow toxicity at 125 mg/kg/day at the 48-hour harvest.	

The dose ranges evaluated in the GLP bacterial gene mutation study were based on an exploratory study which identified excessive cytotoxicity in Salmonella typhimurium strains, at higher doses. Rolapitant was negative for revertant colony counts in all strains tested with or without metabolic activation indicating that rolapitant is negative for bacterial gene mutations. Rolapitant was also negative for chromosomal aberrations in human peripheral blood lymphocytes with or without metabolic activation in a GLP-compliant assay. A dose-range finding study was performed for the *in vivo* bone marrow micronucleus assay and doses of 15.6, 31.3, 62.5, and 125 mg/kg/day were selected for the definitive micronucleus assay based on the significant mortality observed at ≥ 250mg/kg/day. Rolipitant was negative in the in vivo bone marrow micronucleus study in CD1 mice dosed with rolapitant ip.

The pharmacologically active primary metabolite, M19 was also assessed for genotoxicity in a GLP-compliant bacterial mutagenicity test and a GLP compliant chromosomal aberration study. M19 was negative in the bacterial mutagenicity study with or without metabolic activation and negative for chromosomal aberrations in cultured in human peripheral blood lymphocytes with or without metabolic activation.

Table 13b : Summary of M19 genotoxicity studies

Type of test/study ID/GLP	**Test system Method of administration**	**Concentrations/ Concentration range/ Metabolising system**	**Results**
In vitro			
Ames Gene mutations in bacteria SN 08101 GLP	Salmonella typhimurium TA 1535, TA97a, TA98, TA100, TA102, WP2uvrA	78 (strain 1535 –S9) to 5000 µg/plate +/- S9	negative
Chromosone aberration SN 08102 GLP	Human peripheral blood lymphocytes	-S9: 15 to 23.4 µg/mL (4-hour treatment) and 7.5-60 µg/mL (19-hour treatment). +S9: 30 to 100 µg/mL (4-hour treatment)	Negative Doses limited by cytotoxicity

Carcinogenicity

Table 14 : Summary of carcinogenicity studies

Species/Sex/ Number/Group Study ID/ GLP aspects	**Dose (mg/kg/day) / Duration /Route**	**NOAEL (mg/kg/day)**	**Major findings**
Mouse (CD-1) Two-Year Oral Carcinogenicity Study	oral gavage once daily 0 (control), 0 (control), 25, 75, 150	NOAEL = 150 mg/kg/day	- Non-neoplastic findings : - Glandular stomach : ↑incidence/severity of lymphoid aggregates in F at 150 mg/kg, ↑incidence/severity of mucosal hyperplasia at 150 mg/kg

age 7-week old Toxicology groups (50/sex/group) Toxicokinetic groups (20/sex/group) SN 03662 GLP	mg/kg/day		
Rat SD Two-Year Carcinogenicity Study age 6-7 weeks Toxicology groups (50/sex/group except for group 250 mg/kg only 50 M) Toxicokinetic groups (10/sex/group except for group 250 mg/kg only 10 M) SN 03361 GLP	Oral gavage once daily 0, 0, 25, 50, or 100 mg/kg. On study days 0 through 10, rats in the 25, 50, and 100 mg/kg dose groups received 5, 25, and 75 mg/kg, respectively. An additional group of male rats was administred with 250 mg/kg daily for 9 days.	NOAEL = 25 mg/kg/day for male NOAEL = 50 mg/kg/day for female	- ROLAPITANT-related mortality only in males dosed at 250 mg/kg/day. This group was terminated and carcasses discarded without necropsy or tissue collection on study Day 9 due to mortality and adverse clinical signs including hypoactivity, impaired equilibrium, intermittent tremors, dermal atonia, thin body, cool to touch, and rales. - Lower mean body weights and cumulative body weight gains noted at Week 104 in the 50 and 100 mg/kg/day M&F, compared to controls. - ROLAPITANT-related increased survival was statistically significant at 50 mg/kg/day in M and at 25, 50, and 100 mg/kg/day in F. - ROLAPITANT-related decreases in the incidences of palpable masses and animals with multiple masses, and ROLAPITANT-related increases in the mean number of days to first mass at 25, 50, and 100 mg/kg/day in F. - Macroscopically: • Benign pheochromocytomas (adrenal glands) : ↑ incidence at 50 and 100 mg/kg/day in M and • Thyroid glands: ↑ incidence at 100 mg/kg/day in M&F; follicular cell adenomas : ↑ incidence of follicular cell carcinomas at 100 mg/kg/day in M. ROLAPITANT-related <u>non-neoplastic findings</u>: • adrenal glands at 100 mg/kg/day in M. Cystic cortical degeneration at 100 mg/kg/day M • liver of both sexes at all doses. Findings included multinucleated hepatocytes in both sexes at 50 and 100 mg/kg/day, focus(i) of cellular alteration, eosinophilic cell, in females at all doses, focus(i) of cellular alteration, basophilic cell, in M at all doses and centrilobular hypertrophy in both sexes at all doses. However, these non-neoplastic findings in the liver were not accompanied by higher incidences of liver tumors.

D = day; M = mâle; F = female

Table 15 : SD Rat 140 weeks carcinogenic study: principal neoplastic findings according to tissue or organ of origin

Sex:	Males					Females				
Dose (mg/kg/day):	**0**	**0**	**25**	**50**	**100**	**0**	**0**	**25**	**50**	**100**
Organ/Findings	Incidence[a]									
Adrenal Gland	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
-pheochromocytoma [B]	6	5	8	12*	14*	1	4	1	3	0
Thyroid Gland	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
-follicular cell adenoma [B]	2	3	3	3	7*	2	1	3	2	5*
-follicular cell carcinoma [M]	0	1	0	2	2	0	0	1	0	1
Mammary Gland	(28)	(28)	(28)	(30)	(25)	(47)	(45)	(41)	(37)	(36)
-fibroadenoma [B]	0	2	0	0	0	11	18	2*	1*	1*
-adenoma [B]	0	0	0	1	0	3	1	0*	0*	0*
-adenocarcinoma [M]	0	0	0	1	0	9	12	0*	0*	0*
Pituitary Gland	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
-pars distalis adenoma [B]	28	30	23	29	22	42	43	33*	29*	21*

[B] = Benign tumor; [M] = Malignant tumor; * = considered test article-related
[a] Incidence = Number of animals affected
[b] () = Number of animals examined

Table 16: Estimated exposure multiples for rolapitant at the highest doses in the mouse carcinogenicity study vs. the single 200 mg oral dose in humans.

Species	Study Duration	Study Number	Dose (mg/kg/day)	Steady State Mean Rolapitant Values			Exposure Multiple	
				C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Mouse	3-month	03665	M = 150 F = 150	13.50 8.83	128.0 113.0	2,688 2,373	13.8 9.0	22.2 19.6
Human	Single-dose	P04852	200 mg total	0.977	121.0[b]			

[a]AUC Projected is AUC_{0-24hr} multiplied by 21; [b]$AUC_{0-\infty}$ from the single 200 mg oral dose

Table 17: Estimated exposure multiples for rolapitant at the highest doses in the rat carcinogenicity study vs. the single 200 mg oral dose in humans.

Species	Study Duration	Study Number	Dose (mg/kg/day)	Steady State Mean Rolapitant Values at Varied Dose			Exposure Multiple at Varied Dose	
				C_{max} (µg/mL)	$AUC_{0\text{-}24hr}$ (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Rat	6-month	03115	M = 25 F = 25	3.58 5.28	46.2 65.2	970.2 1,369.2	3.7 5.4	8.0 11.3
			M = 50 F = 50	4.90 5.78	55.7 80.2	1,169.7 1,684.2	5.0 5.9	9.7 13.9
			M = 100 F = 100	5.53 5.90	79.7 72.0	1,674 1,512	5.7 6.0	13.8 12.5
Human	Single-dose	P04852	200 mg total	0.977	121.0[b]			
[a]AUC Projected is $AUC_{0\text{-}24hr}$ multiplied by 21; [b]$AUC_{0\text{-}\infty}$ from the single 200 mg oral dose								

In mice, no carcinogenic findings were associated with rolapitant following 2 years daily oral administration of doses up to 150mg/kg/day in CD-1 mice. In rats, non-neoplastic findings were observed in the adrenal glands of males (cystic cortical degeneration) at 100mg/kg/day and in the liver of males and females (multinucleated hepatocytes, foci of cellular alteration, eosinophilic cell and basophilic cell, centrilobular hypertrophy) at all doses but liver findings were not associated with higher incidence of liver tumour and were considered a result of P450 enzyme induction. Rolapitant-related neoplastic findings included a decrease in absolute incidence of mammary gland neoplasms (fibroadenomas, adenomas and malignant adenocarcinomas) and adenomas of the pituitary gland (benign pars distalis adenoma), attributed to the decrease in body weight and body weight gain. A higher absolute incidence of benign pheochromocytomas in the adrenal gland of rolapitant-dosed 50 mg/kg/day and 100 mg/kg/day males and a higher absolute incidence of follicular cell adenomas in the thyroid glands in 100 mg/kg/day-dosed males and females, as well as follicular cell carcinomas (malignant) in the thyroid glands of 100 mg/kg/day-dosed males were reported but these findings were not statistically significant. Hyperplasia of follicular cells of the thyroid gland was previously noted in rats in a 3-month dose range-finding study at 125 mg/kg/day and in a 6-month study at 50 and 100 mg/kg/day. In both of these previous studies as well as in the present study, this change was associated with centrilobular hypertrophy in the liver, consistent with P450 induction. The administration of rolapitant has been shown to result in a significant elevation of cytochrome P450s in rats. The association of follicular cell hypertrophy/hyperplasia and subsequent thyroid gland neoplasia with centrilobular hepatocellular hypertrophy is a well-known rat-specific phenomenon that occurs secondarily after P450 enzyme induction and was considered of no clinical relevance. The safety margin (AUC) at NOAEL for rat carcinogenicity study is estimated at 8 for males and 13.9 for females.

Reproductive and Developmental Toxicity

Table 18 : Summary of Fertility and early embryonic development studies

Species (number) Study ID GLP aspect	Route/ Duration/ Dose	NOAEL (mg/kg/d)	Major findings
Male Rats Fertility and Early Embryonic Developmental Toxicity Study (22 M+F/group) SN 05078 GLP	Oral by Gavage 0, 5, 25, 100 mg/kg/day For 4 weeks prior to cohabitation period through the day prior to schedule sacrifice. Females (22/group) were not dosed.	NOAEL for paternal toxicity = 25 mg/kg/ NOAEL for male mating and fertility and early embryonic development =100 mg/kg/day	- ≥25 mg/kg/day: peri-oral substance. -100 mg/kg/day from Day 0 to 3: ↓ transient mean body weight with an associated ↓ in food consumption, but was not affected during the remainder of dosing period. -100 mg/kg/day: ↓mean absolute weights of the prostate gland and seminal vesicles ⇨ No effects on male mating and fertility indices and early embryonic development.
Female Rats Fertility and Early Embryonic Developmental Toxicity Study 25F/group SN 03117 GLP	Oral by Gavage 0, 1, 5, 10 mg/kg/day oral gavage for at least two weeks prior to and during the cohabitation period and through gestation Day 7	NOAEL for maternal toxicity = 5 mg/kg/day. NOAEL for female fertility =1 mg/kg/day NOAEL for early embryonic development = 5 mg/kg/day	- 10 mg/kg/day: ↑pre- and post-implantation losses (↑ in early resorptions) - 5 and 10 mg/kg/day: Significant ↓ in the number of corpora lutea compared to the control group, but below the historical control range (15.3 to 16.6). - 5 mg/kg/day: ↓ in the number of implantation sites attributed to the decrease in the number of corpora lutea.
Rat (SD) Investigative Study of the Effects on Rat Hormone Levels during Pregnancy: Reversibility of Effects on Female Fertility and Early Embryonic Development 20F/group SN 06533 GLP	Oral by gavage 0, 25 mg/kg/day Male rats not dosed. Female rats dosed once on GD 0-7 (Phase 1) or on GD 0-7 after the first mating (Phase 2).		• Phase 1 and 2: ↓ in BWG and ↓ food consumption, relative to control rats. After re-mating (Phase 2), without administration of rolapitant did not affect BWG or food consumption ⇨ reversible. • <u>Phase 1</u> : ↓ pregnancies, ↓ implantation sites, ↓ numbers of corpora lutea, and probable pre-implantation loss. • <u>Phase 2</u>: administration of rolapitant: ↓pregnancies ↓ litters. Prolongation of gestation (≈ 8 days). After re-mating (Phase 2), without administration of rolapitant: no persistent effects on fertility and development => reversible. • <u>Prolactin, estradiol, and progesterone levels</u> unaffected by rolapitant on gestation Day 5 during Phase 1 and after re-mating during Phase 2.

Table 19 : Estimated exposure multiples for rolapitant at 1 mg/kg/day in the rat female fertility study vs. the single 200 mg oral dose in humans.

Species	Study Duration	Study Number	Dose (mg/kg/day)	Steady State Mean Rolapitant Values			Exposure Multiple	
				C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Rat	3-month	03409	F = 1 F = 5	0.45 1.29	7.37 21.9	154.7 459.9	0.46 1.32	1.3 3.8
Human	Single-dose	P04852	200 mg total	0.977	121.0[b]			

[a]AUC Projected is AUC_{0-24hr} multiplied by 21; [b]$AUC_{0-\infty}$ from the single 200 mg oral dose

Table 20 : Summary of embryo-foetal development studies

Species (number) Study ID GLP aspect	Route/ Duration/ Dose	NOAEL (mg/kg/d)	Major findings
Pregnant rats Embryo-Fetal Developmental Toxicity Study (25/group) SN 03118 GLP	oral gavage 0, 5, 15 or 25 mg/kg/day on GD 6 - 17	NOAEL for maternal toxicity = 5 mg/kg/day based on the effects on body weight and food consumption NOAEL for embryo and fetal toxicity in rats = 25 mg/kg/day	- 15 or 25 mg/kg/day exhibited evidence of maternal toxicity: ↓ BWG and/or BW loss and concomitant ↓ in food consumption during the first week of dosing. -No test article-related effects on placental findings, reproductive parameter findings, fetal body weight, fetal sex determination, fetal external findings, fetal visceral findings, and fetal skeletal examination findings.
Pregnant Rabbits (NZW) Embryo-Fetal Developmental Toxicity and Toxicokinetic study (20/group) SN 03119 GLP	oral gavage 0 (vehicle control), 5, 15 or 30 mg/kg/day on GD 7 - 19	NOAEL for maternal toxicity in rabbits = 15 mg/kg/day NOAEL for embryo-fetal toxicity = 30 mg/kg/day	- 30 mg/kg/day: 2 rabbits exhibited maternal toxicity: ↓ food consumption and concomitant ↓ in fecal output. - All doses: no observations of embryo-fetal toxicity or teratogenicity. No test article-related effects on placental findings, reproductive parameter findings, fetal body weight, fetal sex determination, fetal external findings, fetal visceral findings, and fetal skeletal examination findings.

GD: gestation day

Table 21 : Estimated exposure multiples for rolapitant at NOAEL rat and rabbit embryo-fetal toxicity study vs. the single 200 mg oral dose in humans.

Species	Study Number	Dose (mg/kg/day)	Steady State Mean Rolapitant Values			Exposure Multiple	
			C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Rat	SN 03118 and SN 2013-010	25	4.45	60.7	728.4	4.6	6.0
Rabbit	SN 03119	30	0.863	11.0	143.0	0.9	1.2
Human	P04852	200 mg total	0.977	121.0[b]			

[a]AUC Projected is AUC_{0-24hr} multiplied by 12 for the rat study and 13 for the rabbit study; [b]$AUC_{0-\infty}$ from the single 200 mg oral dose

In an oral fertility and early embryonic development study, male mating and fertility indices were not affected at 100 mg/kg/day. However the decreased female fertility was identified at dose of 10 mg/kg/day in rats. The critical period for the reproductive effects (no viable fetuses, decreased number corpora lutea resulting in increased pre-implantation loss at 25 mg/kg/day) was identified at GD 0-7. In a separate fertility and early embryonic development study, rolapitant was administered for at least 2 weeks prior to and during cohabitation and through GD 7. At the time of implantation no changes in maternal serum prolactin, estradiol, and progesterone levels were found. These changes in fertility were shown to be reversible, i.e., when the dams are re-mated after the first pregnancy and are not dosed, no adverse effect on fertility are observed. The female decreased fertility is rolapitant dose related and the mechanism was not identified.

The potential embryo and fetal toxicity of rolapitant was assessed in pregnant rats administered daily oral doses up to 25 mg/kg/day. The NOAEL for maternal toxicity is 5 mg/kg/day based on the effects on body weight and food consumption. As no embryo and fetal toxicity are occurred, the NOAEL for embryo and fetal toxicity in rats is 25 mg/kg/day. The estimated exposure multiple based on the maternal AUC (projected) as compared to that after a single 200 mg oral dose in human is 6.

In pregnant rabbits, the potential maternal, embryo and fetal toxicity of rolapitant was further assessed administered daily oral doses up to 30 mg/kg/day. At all doses examined, there were no observations of embryo-fetal toxicity or teratogenicity. The NOAEL for maternal toxicity in rabbits is 15 mg/kg/day, and the NOAEL for embryo-fetal toxicity is 30 mg/kg/day. The estimated exposure multiple based on the maternal AUC as compared to that after a single 200 mg oral dose in human is 1.2.

In an oral pre- and postnatal development study in rats, the NOAEL for F0 maternal toxicity was 10 mg/kg/day rolapitant based on mortality/moribund condition, total litter loss, prolonged parturition, decreased gestation length, increased number of unaccounted-for implantation sites. The NOAEL for offspring (F1) effects was 2.5 mg/kg/day rolapitant based on decreased postnatal survival and body weight gain at 25 mg/kg/day, decreased pup body weights at 10 and 25 mg/kg/day (at this one all pups was euthanized), and effects on memory (Biel swim maze) at 10 mg/kg/day.

Toxicokinetic data

Comparative systemic exposure ratios

Table 22 : Estimated Exposure Multiples for Rolapitant at the Oral NOAEL in Animals vs. the Single 200 mg Oral Dose in Humans.

Species	Study Duration	Study Number	NOAEL (mg/kg/day)	Steady State Mean Rolapitant Values at NOAEL			Exposure Multiple at the NOAEL	
				C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Mouse	3-month	03665	M≥150 F = 75	13.50 7.06	128.0 69.5	2,688 1,459	13.8 7.2	22.2 12.1
Rat	3-month	03664	M = 75 F = 50	3.14 5.01	40.0 62.9	840 1,321	3.2 5.1	6.9 10.9
	6-month	03115	100	M: 5.53 F: 5.90	M: 79.7 F: 72.0	1,674 1,512	5.7 6.0	13.8 12.5
Monkey	1-month	05015	30	3.66	64.2	1,348	3.7	11.1
	3-month	03098	≥15	3.55	52.0	1,092	3.6	9.0
	9-month	03663	≥30	4.33	70.1	1,472	4.4	12.2
Human	Single-dose	P04852	200 mg total	0.977	121.0[b]			

[a]AUC Projected is AUC_{0-24hr} multiplied by 21; [b]$AUC_{0-\infty}$ from the single 200 mg oral dose

Table 23 : Estimated Exposure Multiples for M19 at the Oral NOAEL in Animals vs. the Single 200 mg Oral Dose in Humans.

Species	Study Duration	Study Number	NOAEL (mg/kg/day)	Steady State Mean M19 Values at NOAEL			Exposure Multiple at the NOAEL	
				C_{max} (µg/mL)	AUC_{0-24hr} (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Rat	6-month	03115	100	M: 1.03 F: 0.312	M: 14.3 F: 4.73	312.9 100	5.6 1.7	4.3 1.4
Monkey	1-month	05015	30	0.542	10.8	226.8	2.8	3.1
Human	Single-dose	P04852	200 mg total	0.183	73.23[b]			

[a]AUC Projected is AUC_{0-24hr} multiplied by 21; [b]$AUC_{0-\infty}$ from the single 200 mg oral dose

Local Tolerance

An independent local tolerance study was performed in male rabbits for the clinical intravenous formulation. This local tolerance study for the IV formulation is not relevant to the oral administration of the proposed marketed product in humans

Other toxicity studies

Table 24 : Summary of other toxicity studies

Species (number) Study ID GLP aspect	Dose	Major findings
In vitro Human Blood Compatibility Study 3M+3F SN 6000033 GLP	Rolapitant : 0.01, 0.025, 0.1 mg/mL Incubated at 37oC for 1 hour.	No hemolysis was observed for the test article, placebo and saline control while significant hemolysis was observed for the positive control 20% saponin.
Chemical solutions of rolapitant and M19 **UV-Visible absorption spectrum Scan** SN XBL 11073 No-GLP		Rolapitant and its major metabolite M19 do not absorb UVB, UVA, or visible radiation

Antigenicity

Rolapitant is a small molecule and no antigenicity is expected. Therefore, no antigenicity study was performed.

Immunotoxicity

No immunotoxic effects (histopathologic examination of the spleen, mandibular and mesenteric lymph nodes, gut-associated lymphoid tissue, and thymus) were observed in the toxicology program, including the pivotal 6 month rat study and 9 month monkey study.

Dependence

Table 25 : Summary of dependence studies

Species (number) Study ID GLP aspect	Route / Duration / Dose	NOAEL (mg/kg/d)	Major findings
Rhesus Monkey 4 M SN 2013-001 GLP	**IV Self-administration** 0, 0.1, 0.5, 1.0, 1.5 mg/kg /injection 3-5 Days per dose cycle		Rhesus monkeys were conditioned to self-administer 0.18 mg/kg/injections of cocaine under a fixed-ratio 20 schedule of drug deliveries in daily 2-hour unlimited access. The reinforcing properties of rolapitant were assessed from a saline-extinction baseline. **Rolapitant did not initiate, sustain, or maintain lever-press responding for rolapitant drug deliveries for 3 or 5 daily sessions preceded by saline extinction trials ⇨ low potential for abuse.**
Rhesus Monkey 4M SN 2013-002 GLP	**Oral (once daily)** 0, 7.5, 25 mg/kg/day for 28 days		No significant clinical change within the activity/arousal, neuromuscular, sensory motor, or autonomic domains of a standardized and validated non-human primate functional observational battery. **Abrupt cessation of daily dosing did not induce a measurable or definable discontinuation syndrome in male rhesus monkeys**.

2.3.5. Ecotoxicity / environmental risk assessment

Table 26: Summary of main study results

Substance : ROLAPITANT			
CAS-number : 5522922-08-7			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	**Log P partition coefficient**	**5.3 in n-octanol / 0.15N KCl**	**Above 4.5 threshold Consider PBT screening**
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0081	µg/L	**> 0.01 threshold (Y) Phase II not required**

Rolapitant PEC $_{surfacewater}$ is below the action limit of 0.01µg/L but log Kow exceeds 4.5 therefore an estimation of Persistence, Bioaccumulation and toxicity (PBT index) is required and will be submitted as a post-authorisation measure.

With reference to the guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (European Medicines Agency, 2006 [EMEA/CHMP/SWP/4447/00]), the applicant is recommended to conduct a specific risk with regard to a step-wise fashion for Persistence, Bioaccumulation and toxicity (PBT index), since log Kow value for rolapitant is above 4.5 and provide a planning for these studies.

2.3.6. Discussion on non-clinical aspects

Primary and secondary pharmacodynamic in vitro studies completed by the sponsor demonstrate that rolapitant (SCH 619734) is a potent, highly selective and competitive NK1 receptor antagonist that binds with high affinity to the human NK1 receptor, as does its primary metabolite M19 (SCH 720881) which is also pharmacologically active. Rolipitant shows similar affinity toward the gerbil, guinea pig and monkey NK1 receptor, while it is significantly less potent toward the rabbit, rat and mouse NK1 receptor. In vivo, rolapitant is active in ferret models of chemotherapy-induced emesis, supporting proof of principle for the proposed indication for rolapitant. Two additional studies showed consistent results. In addition, a QTc study of rolapitant in humans was conducted at 4x the therapeutic dose, and no QT signal was observed in this study.

Safety pharmacology studies performed in rats evaluated central nervous, respiratory, renal/urinary and gastrointestinal systems and indicated no cause for concern following the administration of rolapitant. Cardiovascular safety pharmacology was completed in the monkey and similarly did not indicate a cause for concern.

From the pharmacokinetic point of view, the monkey was the most relevant species for non-clinical assessment based on the similarities in binding affinity, oral bioavailability and metabolism. The rat is also a relevant species, despite the evidence that the binding affinity of rolapitant for rat NK1 receptor is >100-fold less than for human NK1 receptor. The M19 metabolite is also the primary metabolite in rats.

Rolapitant is rapidly absorbed after oral administration in mice, rats, and monkeys with maximum plasma concentrations (Cmax) being reached within 2 hours. The bioavailability across a series of single dose studies was approximately 50-70% in rats and was higher in monkeys, consistent with the near 100% bioavailability observed in humans. Gender-related differences in exposure were found in rats, with an exposure consistently higher in the female than the male (4 fold in average) following repeated dosing of rolapitant. The gender differences in the pharmacokinetics of rolapitant observed are likely due to the gender differences in CYP3A isoenzyme concentrations in rats. In addition, this is not observed in humans.

The half-lives of rolapitant are markedly longer in humans (t1/2= 7 days) than in cynomolgus monkeys and rat (t1/2= 6-8 h). The in vitro intrinsic clearance or lipophilicity alone cannot fully explain the significant difference of half-life. In the SmPC it is stated that the mechanism of the significant difference of half-lives observed between the rat and monkey (6-8 h) and human (7 days) is not elucidated.

Rolapitant is highly plasma protein-bound (99.7-99.9% across rat, monkey, and human). In rat studies, rolapitant was found to be extensively distributed. The distribution to ocular tissues is very low and transient, suggesting lack of melanin binding. Rolapitant crosses the blood-brain barrier (BBB) and supports the proposed mechanism of action of NK1 receptor antagonism. Liver metabolism, largely oxidative biotransformation, appeared to be the major clearance mechanism of rolapitant in rats and monkeys. A common major circulating active metabolite is M19 in both rat and human. Biliary excretion into the faeces was the major route of elimination for rolapitant in rats and monkeys following oral and intravenous administration. Rolipitant was also rapidly transferred to the milk of lactating rats and section 4.6 of the

SmPC appropriately reports the presence of rolipitant in the milk of lactating rats treated orally with rolipitant and breast-feeding is not recommended during treatment with Varuby. Rolapitant pass through the placenta.

All pivotal toxicology studies were GLP compliant and included repeat-dose toxicity studies of up to 6 months in duration rats and 9 month duration in monkeys. Supportive toxicokinetic analyses were also performed for these studies. Mortality was reported in mice at ≥450mg/kg, in rats at 500mg/kg and 1000mg/kg for females and males respectively, and in monkeys at 200mg/kg. Target organs for toxicity identified included the liver and uterus in mice and rats, with increased weight and histopathological findings also reported in the kidneys, adrenal and thyroid glands in rats. The effect on liver was considered a result of enzyme induction leading to centrilobular hypertrophy and similarly the findings in the kidney, adrenal and thyroid glands were considered associated with P450 enzyme induction after repeated dosing. Clinical signs in rats at ≥ 250mg/kg included hunched appearance, hypoactivity, tremors, ataxia, dehydration and abnormal stool. Similarly in monkeys, abnormal stool and decreased food consumption occurred at ≥ 75mg/kg with convulsions, emesis, hypothermia, morbidity and prostration occurring at the highest dose of 200mg/kg. Severe acute toxicity, including convulsions, was reported at 60 and 100mg/kg/day in one month repeat-dose toxicity testing in monkeys. The mechanism underlying the convulsions is likely to be common in all species. The finding is probably due to reversible interaction with target sites in the central nervous system. However since the target site in brain involved in the convulsions is not identified, the relevance of these findings in humans is unknown. (See SmPC point 5.3.) The calculations for safety margins is based on body surface area comparison between human and non-clinical species, producing approximate 6x and 5.8x margins based on convulsive doses in rat and monkey studies respectively.

Potential M19 related toxicity has been assessed as part of the toxicology studies is not justified when considering that the proportion of M19 exposure relative to rolapitant+M19 exposure in terms of AUC ranges from 6-15% in the non-clinical species in these studies, whereas in humans, the reported M19 exposure relative to rolapitant+M19 based on AUC is from 30- 37% (P04328, P04852) following the 180mg dose.

A complete package of genotoxicity and carcinogenicity studies indicated rolipitant was negative for genotoxicity and 2 year carcinogenicity studies in rats and mice did not reveal a carcinogenic risk of relevance to humans. The pharmacologically active primary metabolite, M19 was also negative in 2 GLP compliant genotoxicity tests for bacterial mutagenicity, mammalian chromosomal aberration.

In a fertility and early embryonic development study in female rats, rolapitant hydrochloride at an oral dose equivalent to 9 mg/kg per day free base (approximately 0.5 times the recommended human dose on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a dose equivalent to 4.5 mg/kg per day free base (approximately 0.2 times the recommended human dose on a body surface area basis), there were decreases in the number of corpora lutea and implantation sites (See section 5.3. of the SmPC).

In a pre- and post-natal development rat study, maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg per day free base (approximately 1.2 times the recommended human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg per day rolapitant free base (approximately 0.5 times the recommended human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

Overall, the toxicology programme revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, teratogenic potential and carcinogenic potential. Relevant information has been reflected in the SmPC indicating the relevance of these findings to clinical use.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical pharmacology studies provided adequate evidence that rolapitant (SCH 619734) is a potent, highly selective and competitive NK1 receptor antagonist. The general pharmacology studies showed proof of principle for the proposed indication for rolapitant in the prevention of CINV for highly or moderately emetogenic chemotherapy. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, teratogenic potential, and carcinogenic potential.

The CHMP considered the following recommendations for further development on non-clinical aspects:

- The applicant is recommended to perform an estimation of Persistence, Bioaccumulation and toxicity (PBT index) in accordance with the guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (European Medicines Agency, 2006 [EMEA/CHMP/SWP/4447/00])

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 27: Tabular overview of clinical studies

Study ID	Design	Study Posology	Study Objective	Subjs by arm planned/actual/ compl.	Duration	Gender M/F Median Age
P04351	Phase 2, MC, R, DB, Active control, dose finding	Rolapitant 10, 25, 100, or 200mg single dose or placebo in combination with ondansetron and dexamethasone PO	Efficacy: Prevention of CINV Safety and tolerability	Overall: 450/454/416 Rolapitant: 360/363/332 Control: 90/91/84	Maximum: 6 cycles Median number of cycles: NR Cycle length (range): 16 to 78 days	Overall: M=244; F=210 Overall: 53.7 yrs (18-86)
P04832	Phase 3, MC, R, DB, Active control	Rolapitant 200 mg single dose or placebo in combination with granisetron and dexamethasone PO	Efficacy: Prevention of CINV Safety and tolerability	Overall: 530/526/491 Rolapitant: 265/264/251 Control: 265/262/240	Maximum: 6 cycles Median number of cycles: 2.0 Median cycle duration: 21-22 days Cycle length (range): 13 to 70- days	Overall: 57.3 yrs (20-90) Overall: M=304; F=222
P04833	Phase 3,	Rolapitant 200 mg single	Efficacy:	Overall:	Maximum: 6	Overall:

	MC, R, DB, Active control	dose or placebo in combination with granisetron and dexamethasone PO	Prevention of CINV Safety and tolerability	530/544/518 Rolapitant: 265/271/259 Control: 265/273/259	cycles Median number of cycles: 3.0 Median cycle duration: 21-23 days Cycle length (range): 13 to 42 days	58.5 yrs (18-83) Overall: M=369; F=175
P04834	Phase 3, MC, R, DB, Active control	Rolapitant 200 mg single dose or placebo in combination with granisetron and dexamethasone PO	Efficacy: Prevention of CINV Safety and tolerability	Overall: 1350/1332/1276 Rolapitant: 675/666/636 Control: 675/666/640	Maximum: 6 cycles Median number of cycles: 4.0 Median cycle duration: 21 days Cycle length (range): 12 to 62 days	Overall: 56.7 yrs (22-83) Overall M=265; F=1067

Abbreviations: CINV = chemotherapy-induced nausea and vomiting; CR = complete response; DB = double-blind, F = female; HEC = highly emetogenic chemotherapy; IV = intravenous; M = male; MC = multicentre; MEC = moderately emetogenic chemotherapy; MITT = modified intent-to-treated; NR = not reported; PO = oral administration; R = randomised

a Duration of treatment is presented maximum number of cycles planned, median number of cycles administered, and actual range of days per cycle reported.

b Actual refers to the MITT population for Studies P04832, P04833 and P04834 and for Study P04351 was based on all randomised subjects who received cisplatin-based chemotherapy and a dose of study medication and had at least one post-treatment efficacy assessment in Cycle 1 recorded.

c Completed primary endpoint of Cycle 1.

d Subjects were to receive a first course of one or more of the following agents IV: cyclophosphamide (<1500 mg/m2), or doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine (>1 g/m2).

2.4.2. Pharmacokinetics

Absorption

Orally administered rolapitant was completely bioavailable (~100%), rapidly absorbed, and slowly metabolised and eliminated.

Following single oral dose administration of 5 to 200 mg in the fasted state, mean time to maximum plasma concentration (Tmax) of rolapitant ranged from 2 to 4 hours. At the 200 mg dose, the mean maximum plasma concentration (Cmax) is approximately 1000 ng/mL. The variability in exposure (Cmax and AUC) was low to moderate with coefficients of variation ranging from 10% to 47%.

Following multiple oral doses (9 to 45 mg once daily) of rolapitant, accumulation of rolapitant is approximately 5-fold.

Influence of food

An Open-Label, Randomized, Pivotal Bioequivalence and Food Effect Study of Oral Rolapitant carried out an analysis of the effect of food on the PK of the 100-mg tablet formulation. For the comparison of 2 x 100-mg tablets fed vs. 2 x 100-mg tablets fasting, the geometric mean ratios were 1.16, 1.05, 1.04, and 1.06 for Cmax, AUC0-t, AUC0-∞ and AUC0-120, respectively. The rolapitant peak exposure (Cmax) was increased when 2 x 100-mg tablets were administered with food; however, for overall exposure (AUC0-t, AUC0-∞ and

AUC0-120), there was no effect when rolapitant was administered with or without food. The 90% CIs for the test/reference ratios were within the acceptable range of 80% to 125% for the comparison for AUC0-t, AUC0-∞ and AUC0-120, and outside the range for Cmax.

Distribution

Rolapitant and its metabolite M19 are highly protein-bound to human plasma with unbound (free) fractions of <1%. The apparent volume of distribution (Vd) of rolapitant is high (~ 460 L). Given a 100% absolute bioavailability observed, the apparent Vd would be representative of true Vd, indicating an extensive tissue distribution of rolapitant.

Human NK1 receptor occupancy study indicates that rolapitant crosses blood brain barrier.

Elimination

Rolapitant is extensively biotransformed via oxidation, primarily to M19, a pharmacologically active metabolite exhibiting an inhibitory potency similar to the parent compound against human neurokinin-1 (NK1) receptor. The pharmacokinetics of the major metabolite M19 were well characterised in humans. Following administration of a single oral 200-mg dose of [14C]-rolapitant (180 mg of rolapitant monohydrate), total radioactivity recovered in the urine accounted for 14.2% (range 9.11% to 20.0%) of the dose and total radioactivity recovered in the faeces was 72.7% (range 51.8% to 88.7%) of the dose based on interpolation of the excreta data. Rolapitant is slowly eliminated, primarily through the hepatic/biliary route.

Renal elimination represents a minor route, which is consistent with non-clinical studies demonstrating no significant changes in exposure of rolapitant in 5/6 nephrectomised rats.

Following single oral doses (4.5 to 180 mg) of rolapitant, the mean terminal half-life (t1/2) ranges from 169 to 183 hours (~7 days) and is independent of dose. In the human ADME study following administration of a single oral 200-mg dose of [14C]-rolapitant, the mean terminal half-life (t1/2) is 186 hours and apparent total clearance of rolapitant is 1.74 L/hr. Given the 7-day half-life of rolapitant, the accumulation of rolapitant is expected to be minimal following either once every two weeks (q2w) or once every three weeks (q3w) regimen.

Metabolism

Hepatic metabolism is the major clearance mechanism in nonclinical species. Oxidation appears to be the primary metabolic pathways in rats, monkeys and human. Rolapitant is extensively metabolised by CYP3A4 via oxidation primarily to M19. This metabolite is structurally elucidated as a C4-pyrrolidine-hydroxylated rolapitant.

In human ADME study, M19 was identified as the major circulating metabolite of rolapitant in plasma. The exposure ratio of M19 to rolapitant was approximately 50% in plasma.

Dose proportionality and time dependencies

After oral administration, rolapitant was rapidly and completely absorbed with a dose-proportional increase in exposure**.** The PK of rolapitant is approximately linear across the dose range of 5 to 200 mg. Exposure to

rolapitant (Cmax and area under the concentration - time curve [AUC]) following single or multiple oral doses was dose-proportional).

Intra- and inter-individual variability

The inter-individual variability of plasma rolapitant concentrations was low to moderate

Population pharmacokinetics

A population PK study was performed in 482 subjects who received Rolapitant. One objective of the analysis was to develop a population pharmacokinetic model for Rolapitant and its metabolite and to identify factors that may influence the disposition of the drug in cancer patients.

The data consisted of 8858 valid Rolapitant concentration measurements from 482 cancer subjects.

Measures of organ function were also considered in the analysis and included clinical chemistries such as ALT, AST, alkaline phosphatase, albumin, total bilirubin, and creatinine clearance. In addition, Karnofsky performance score, rescue medication, and neutrophil counts were also evaluated. The relationship between concentrations of Rolapitant (predicted AUC) and efficacy measures was investigated graphically.

The demographic subpopulations showed that the majority of the population was male (54.6 %). The majority of subjects were Caucasian (62%) or Multiracial (27.4%), followed by Asian (6%), American Indian (1.7%), Black (0.4%), and Native Hawaiian (0.2%).

A one-compartment sub-model was used to describe the PK of the metabolite, M19. The typical estimate for the apparent CL of M19 was 1.83 L/hr.

Rolapitant disposition was characterized by a two compartment model with an estimated typical value for apparent CL of 0.962 L/hr and a large apparent V2, estimated to be 214 L. The apparent Q and apparent V4 were estimated to be 2.79 L/hr and 164 L respectively, indicating extensive tissue distribution.

None of the covariates investigated (body surface area, age, gender, race, chemotherapy regimen, Karnofsky performance score, creatinine clearance, ALT, AST, alkaline phosphatase, albumin, bilirubin, rescue medication, and neutrophil count) had a significant impact on the pharmacokinetics of Rolapitant.

Subject body weight did influence the volume of distribution parameters. The covariate analysis showed a 39% decrease in V2/F for subjects at the low end of the weight range (38 kg) compared to subjects at the median weight (68.8 kg). A 67% increase in V2/F was evident for the heaviest subjects (WT=128 kg). Similarly, over the weight range seen in the studies, V4/F was 71% lower for the lightest subjects (WT=38 kg) and was 213% higher for patients at the highest weight (128 kg) when compared to subjects with median weight.

Special populations

Impaired renal function

In population pharmacokinetic analyses, creatinine clearance (CLcr) at baseline did not show a significant effect on rolapitant pharmacokinetics in cancer patients with mild (CLcr: 60 to 90 mL/min) or moderate (CLcr: 30 to 60 mL/min) renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal impairment. The pharmacokinetics of rolapitant was not studied in patients with end-stage renal disease requiring haemodialysis.

Impaired hepatic function

The PK profiles of rolapitant were evaluated in subjects with mild and moderate hepatic impairment as compared to normal healthy subjects. The PK profiles and exposure parameters were generally similar in subjects with mild impairment compared to normal subjects. The PK profiles and exposure parameters in subjects with moderate impairment were slightly lower, especially for Cmax, than those in normal subjects.

The ratio of the geometric means of Cmax and AUCs (i.e. AUC0-120hr and AUC0-last) comparing subjects with mild impairment to normal subjects ranged from 92% to 96%. The ratio of the geometric means of Cmax and AUCs comparing subjects with moderate impairment to normal subjects ranged from 75% to 100%.

Although the 90% CIs for these parameters (moderate vs. normal) were not fully contained within the 80% to 125% interval, the possible effect of moderate hepatic impairment on the elimination of rolapitant was not considered clinically meaningful.

There was no formal study of rolapitant in patients with severe hepatic impairment (Child-Pugh score >9), however baseline serum albumin, AST, total bilirubin, and ALT levels did not have a clinically important effect on rolapitant pharmacokinetics in patients with various degrees of hepatic impairment.

Gender

Based on the population PK analysis from pooled CINV studies (P04351, TS-P04832 and TS-P04833), gender had no significant impact on the pharmacokinetics of rolapitant.

Therefore, no dosing adjustments based on any patient variables are recommended.

Race

Based on the population PK analysis from pooled CINV studies (P04351, TS-P04832 and TS-P04833), race had no significant impact on the pharmacokinetics of rolapitant. Therefore, no dosing adjustments based on any patient variables are recommended for rolapitant.

Weight

Based on the population PK analysis from pooled CINV studies (P04351, TS-P04832 and TS-P04833), age, gender, and race had no significant impact on the pharmacokinetics of rolapitant. Body weight was shown to have an influence on the central and peripheral volume of distribution, with heavier subjects exhibiting a larger volume of distribution. However, no clear trend was observed between body weight and rolapitant clearance. Therefore, no dosing adjustments based on any patient variables are recommended for rolapitant.

Elderly

Table 28: Number of elderly patients included in clinical pharmacology studies

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	85/95	9/95	1/95

Pharmacokinetic interaction studies

In vitro, CYP3A4 is the main enzyme involved in rolapitant metabolism. According to the results, CYP2B6, 2C8 and 2J2 are also implicated since the inhibition of these enzymes decreases more than 50 % the

metabolism of rolapitant. Furthermore, the estimated high bioavailability of rolapitant in vivo (F~100%), translates the low impact of the first pass metabolism and the low hepatic extraction ratio of rolapitant. This is confirmed by a DDI study performed with ketoconazole, a strong CYP3A4 inhibitor, that shows a slight but significant effect of ketoconazole on rolapitant exposure (increase of rolapitant exposure ca-20%) stressing the low involvement of CYP3A4 in rolapitant hepatic clearance. Therefore, the co-administration of rolapitant with strong and moderate CYP3A4 inhibitors is not expected to be clinically relevant.

Rolapitant is competitive inhibitor for most of CYP450, CYP3A4, 2C8, 2C9, 2C19, 2D6 and 2B6, except for CYP1A2, and a time-dependent inhibitor for CYP1A2, CYP2A6, CYP2D6, and CYP3A4/5. As regards its active metabolite, it does not exhibit any inhibitory potential towards these CYPs except CYP2B6. Nonetheless, at therapeutic concentrations, this effect is unlikely: its IC50 is far higher the worst estimated concentrations of 50*Cmax,u or 0,15 µM.

Based on these data, the Applicant carried out dedicated clinical DDI studies with probe CYP3A (midazolam and ondansetron), 2D6 (dextromethorphan), CYP2C (tolbutamide, omeprazole for CYP2C9 and CYP2C19 respectively), CYP2C8 (repaglinide) and CYP2B6 (efavirenz) substrates.

Rolapitant and its active metabolite, M19, are not P-gp, BCRP, OATP1B1 and 1B3 substrates.
Despite some limits in the dedicated in vitro studies, it can be concluded that rolapitant is a P-gp and BCRP inhibitor with an IC50= 7,4µM and =0,172 µM, respectively. No additional in vitro investigation is requested since clinical studies have been carried out (see in vivo part).

In vivo

Based on in vitro data, clinical interaction studies were conducted to assess the magnitude of the potential interactions with rolapitant:

Table 29: Rolapitant as a perpetrator

Midazolam *(*CYP3A4 substrate)	
+ rolapitant low dose (study P03670) + rolapitant 200 mg (study PR-10-5002-C)	With rolapitant low dose, midazolam exposure slightly decreases but with a single dose of 20 mg, no induction or inhibition of CYP3A4 by rolapitant or its active metabolite is evidenced.
Dexamethasone (CYP3A4 substrate)	No significant effect of rolapitant on dexamethasone exposure.
Ondansetron (CYP3A4 substrate)	No significant effect of rolapitant on ondansetron exposure.
Digoxin (P-gp substrate)	Rolapitant significantly alters digoxin $C_{ss,max}$ about 71 %, and its AUC about 30%. Even though no pharmacodynamics effect was observed in healthy volunteers, in the clinical setting, this effect may be clinically relevant notably in women patients in whom the therapeutic margin for digoxin is narrower than in men. Furthermore, rolapitant will be administered to patients the renal status of whom would be probably altered either due to the age and/ or to combined chemotherapies (e.g. cisplatin). Therefore, it cannot be ruled out that digoxin exposure may increase in a greater extent.

Dextromepthorphan (CYP2D6 substrate)	Rolapitant is a CYP2D6 inhibitor since its increases about 2,6-fold dextromethorphan exposure at D7 and about 3,3-fold at day 14. However, the clinical relevance of this increase is questionable. This is far lower than the effect of cinacalacet, a well-known strong CYP2D6 inhibitor, on dextromethorphan exposure, the latter increasing about 11-fold in extensive metabolisers (Nakashima D. and al; J Clin Pharmacol 2007).
Efavirenz (*CYP2B6 substrate)*	In vitro both rolapitant and its active metabolite inhibit CYP2B6. Even though this effect is expected to be low in vivo, a clinical DDI study has been carried out in order to invalidate or confirm it. Based on the observed results, rolapitant does not exhibit any clinically relevant CYP2B6 inhibition.
Omeprazol (CYP2C19 substrate) ***Tolbutamide (CYP2C9 substrate)***	When rolapitant is co-administered with omeprazole or tolbutamide, no significant change in their AUC and Cmax is observed. It can be concluded that rolapitant is not expected to alter the pharmacokinetics of drugs the metabolism of which is CYP2C9 or CYP2C19-dependant.
Repaglinide (CYP2C8 substrate)	AUC and C_{max} of repaglinide does not significantly change when rolapitant is co-administered simultaneously. Interestingly, 7 days after the co-administration with rolapitant, repaglinide AUC and C_{max} significantly increase, about 24% and 29%.
Sulfasalazine (BCRP substrate)	Rolapitant increases sulfasalazine (a BCRP substrate) exposure about-2-fold and about 32 % 7 days after the co-administration compared to sulfasalazine given alone.

Table 30: Rolapitant as a victim drug

Ketoconazole	Rolapitant AUC significantly increases with a strong CYP3A4 inhibitor, about 21% with a 90% CI of [1,04- 1,41], nonetheless this is not expected to be clinically relevant.
Rifampicine	Results show a substantial decrease in both rolapitant and its metabolite M19 about 87% and 89% respectively. Based on the data available on rolapitant metabolism and absorption (notably, its high bioavailability and low hepatic extraction ratio likely < 0,3), and according to outcomes observed with ketoconazole, these results are puzzling. Therefore, the Applicant should further discuss the mechanisms behind this interaction since CYP3A4 induction does not appear to be the main explanation. Rifampicin is a well-known potent inducer and does not limit its inducing effect, via PXR activation, to CYP3A.

Others DDI comments / issues

Two NK1 receptor antagonists are currently launched in the prevention of nausea and vomiting induced by highly and moderate emetogenic cancer chemotherapy, netupitant (fixed-does combination with palonosetron) and aprepitant. Since no efficacy and safety data allows NT1 receptor antagonists to be combined, the mention of a statement that not recommend the simultaneous use of these drugs with rolapitant is raised in order to avoid any off-label use.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

No specific clinical pharmacology studies have been performed to qualify the suggested mechanism of action of rolapitant.

Primary and Secondary pharmacology

Two studies were performed to evaluate the PK and PD effects of rolapitant, including a PET study (P04078) and a thorough QT/QTc study (P04852).

PET Study in Healthy Volunteers

This study showed that the NK1 receptor occupancy in the cortex was related with rolapitant dose and the plasma concentration

This study showed that at rolapitant dose of 200 mg, mean NK1 receptor occupancy was over 90% for at least 120 hour.

Thorough QT Study in Healthy Volunteers

A thorough QT study investigated the effect of rolapitant on corrected QT interval. The study was designed according to the ICH E14 guidance, according to a parallel group design and using moxifloxacin as a positive control.

The resulting study is a randomized, double-blind, parallel-group, placebo-controlled study involving four study groups (placebo, SCH 619734 50mg ; SCH 619734 200 mg ; SCH 619734 800 mg)

A total of 84 subjects were enrolled.

As a result, for the largest time-matched difference (QTcF), which is the main endpoint of the study, its one - sided confidence interval was always constrained within 10 ms. The time matched analysis for the QTcF endpoint revealed that the moxifloxacin group met the assay sensitivity criteria outlined in the statistical plan with several time points > mean of 5 ms, as moxifloxacin duly prolonged the QTcF ~ 10 ms at its estimated Cmax (with an upper limit of the 95 CI between 10 and 13 ms).

The time matched results for QTcF (as well as QTcI) showed that at no time point did rolapitant dose groups exceed the upper confidence interval of 10 ms. As for categorical values with QTcF there was no subject with ≥ 30 ms change from baseline in the low or high dose or placebo groups. One volunteer had [30-60] ms change from baseline with moxifloxacin. QTcI are matching these results. There was no significant gender effect.

The relationship between concentrations of Rolapitant and efficacy measures was investigated graphically using the data available from the Phase 2 and 3 studies. Measures of exposure (predicted AUC) for Rolapitant were correlated with efficacy (as measured by complete response, emesis, nausea, significant nausea, and complete protection) variables via a graphical exploratory approach to visually determine if any correlations between drug exposures and these parameters were evident. These plots demonstrate that there does not appear to be any overt relationship or trend between exposure parameters for Rolapitant and response for the subjects in the Phase 2 and 3 studies included in this population analysis.

2.4.4. Discussion on clinical pharmacology

Following a single dose administration of 180 mg rolapitant under fasting conditions to healthy subjects, rolapitant was measurable in plasma between 30 minutes and the peak plasma concentration (C_{max}) for rolapitant which was reached in about 4 hours and mean C_{max} was 968 ng/mL (%CV:28%). It was rapidly absorbed with mean time to maximum plasma concentration (Tmax) ranging from 2 to 4 hours. At the 200 mg dose, the mean maximum plasma concentration (Cmax) is approximately 1000 ng/mL. The mean terminal half-life (t1/2) following single oral doses ranged from 169 to 183 hours (~7 days) and was independent of dose. Following multiple oral doses 9 to 45 mg once daily of rolapitant; accumulation of rolapitant was approximately 5-fold.

In the human ADME study following administration of a single oral 200 mg dose of [14C]-rolapitant, the mean terminal half-life (t1/2) was 186 hours and apparent total clearance was 1.74 L/hr. The terminal half-life (t1/2) is consistent with the intended single oral dose application when used in combination with a 5-HT3 receptor antagonist and dexamethasone.

The PK of rolapitant is approximately linear across the dose range of 5 to 200 mg with exposures increased in a dose-proportional manner. Exposure to rolapitant (Cmax and area under the concentration - time curve [AUC]) following single or multiple oral doses was dose-proportional. Rolapitant is slowly eliminated with mean terminal half-life of approximately 7 days. Rolapitant is eliminated mainly through the hepatic/biliary route, with minor contributions from renal elimination. Rolapitant is metabolised primarily by CYP3A4 to form a major active metabolite, M19. *In vitro* studies suggest that rolapitant is not an inhibitor of CYP2E1.

Rolapitant was highly protein bound to human plasma (99.8%). The apparent volume of distribution (Vd/F) was 460 L in healthy subjects, indicating an extensive tissue distribution of rolapitant. In a population pharmacokinetic analysis of rolapitant, the Vd/F was 387 L in cancer patients.

Following multiple oral dose administration of 10 to 50 mg once daily, accumulation of rolapitant was approximately 5-fold, consistent with its long t1/2. Given the 7-day half-life of rolapitant, the accumulation is expected to be minimal following either once every two weeks or once every three weeks dosing.

Following single oral doses (4.5 to 180 mg) of rolapitant, the mean terminal half-life ($t_{1/2}$) of rolapitant ranged from 169 to 183 hours (approximately 7 days) and was independent of dose. In a population pharmacokinetic analysis the apparent total clearance (CL/F) of rolapitant was 0.96 L/hour in cancer patients.

Rolapitant is eliminated primarily through the hepatic/biliary route. Following administration of a single oral 180-mg dose of [^{14}C]-rolapitant, on average 14.2% (range 9% to 20%) and 73% (range 52% to 89%) of the dose was recovered in the urine and feces, respectively over 6 weeks. In pooled samples collected over 2 weeks, 8.3% of the dose was recovered in the urine primarily as metabolites and 37.8% of the dose was recovered in the feces primarily as unchanged rolapitant. Unchanged rolapitant or M19 were not found in pooled urine sample.

The systemic exposures (C_{max} and AUC) to rolapitant increased in a dose-proportional manner when the dose of rolapitant increased from 4.5 mg to 180 mg. With an increase in dose by 4 times from the recommended clinical dose of 180 mg, the C_{max} and AUC of rolapitant increased by 3.1 fold and 3.7 fold, respectively.

The absolute bioavailability of rolapitant is approximately 100%, indicating minimal first pass effect. The apparent volume of distribution (Vd) is high (~ 460 L). Given the nearly 100% absolute bioavailability observed, the apparent Vd would be representative of true Vd, indicating extensive tissue distribution of rolapitant.

Concomitant administration of a high fat meal did not significantly affect the pharmacokinetics of rolapitant, had minimal effects on the rate or extent of absorption of rolapitant when administered as 50 mg capsules, 100 mg tablets, or 2 × 100 mg high shear tablets

Rolapitant is metabolised primarily by CYP3A4 to form a major active metabolite, M19 (C4-pyrrolidine-hydroxylated rolapitant). In a mass balance study, the metabolite M19 was the major circulating metabolite. The formation of M19 was significantly delayed with the median T_{max} of 120 hours (range: 24-168 hours) and the mean half-life of M19 was 158 hours. The exposure ratio of M19 to rolapitant was approximately 50% in plasma.

No specific clinical pharmacology studies have been performed to qualify the suggested mechanism of action of rolapitant.
In a study examining NK1 receptor occupancy, the PK profile of oral rolapitant was similar to that observed in other studies and the study described the relationship of the plasma concentration of rolapitant and brain NK1 receptor occupancy using sigmoid Emax model. Based on model predictions, plasma rolapitant concentrations above 348 ng/mL correspond to >90% NK1 receptor occupancy. At rolapitant dose of 200 mg, mean NK1 receptor occupancy was over 90% for at least 120 hours.

A separate study looking at QTc, rolapitant was well tolerated at single doses up to 800 mg administered as a single oral dose, and confirmed that QTc was evaluated at the Cmax of rolapitant. Administration of rolapitant at doses up to 800 mg does not prolong the QT interval compared to the administration of placebo control, based on QTcF analysis. Results of the other QT analyses (ie, QTcB, QTcI, and uncorrected QT interval) were consistent with the results of the QTcF analysis. In addition, categorical summaries of numbers of subjects with changes in QT/QTc interval of <0, 0 to 30, 31 to 60, and >60 msec and/or with a QT/QTc interval >480 msec were concordant with the above conclusions.

The thorough QT Study fulfilled the requirements to conclude that rolapitant meets the ICH E14 criteria of a negative TQT. However, even though the M19 metabolite is said to be a weaker blocker of hERG (higher IC50) it takes time to appear, possibly way after 24 hours of rolapitant intake. Therefore, caution should be taken and surveillance exerted on lay patients prone to vomiting (or with other causes of electrolyte disturbancies/hypokaliemia) at distance from rolapitant intake.

Population pharmacokinetic analyses indicated that age, sex and race had no significant impact on the pharmacokinetics of Varuby. There are limited data in patients aged 75 years and older.

Following administration of a single dose of 180 mg rolapitant to patients with mild hepatic impairment (Child-Pugh Class A), the pharmacokinetics of rolapitant were comparable with those of healthy subjects. In patients with moderate hepatic impairment (Child-Pugh Class B), the mean C_{max} was 25% lower while mean AUC of rolapitant was similar compared to those of healthy subjects. The median T_{max} for M19 was delayed to 204 hours in patients with mild or moderate hepatic impairment compared to 168 hours in healthy subjects. The pharmacokinetics of Varuby was not studied in patients with severe hepatic impairment (Child-Pugh Class C).

In population pharmacokinetic analyses, creatinine clearance (CLcr) at baseline did not show a significant effect on rolapitant pharmacokinetics in cancer patients with mild (CLcr: 60 to 90 mL/min) or moderate (CLcr: 30 to 60 mL/min) renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal impairment. The pharmacokinetics of Varuby was not studied in patients with end-stage renal disease requiring haemodialysis.

A human Positron Emission Tomography (PET) study with rolapitant demonstrated that rolapitant crosses the blood brain barrier and occupies brain NK_1 receptors. A dose-dependent increase in mean NK_1 receptor occupancy was observed in the dose range from 4.5 mg to 180 mg of rolapitant. At rolapitant plasma concentrations of >15 ng/mL and 348 ng/mL, the NK_1 receptor occupancies in the cortical regions were approximately >50% and 90% respectively. At the 180 mg dose of rolapitant, the mean NK_1 receptor occupancy in the cortical regions was greater than 90% for at least 120 hours.

The clinical pharmacology data with Varuby have been reflected in the SmPC (see section 5.2).

Rolapitant is a moderate CYP2D6 inhibitor. Increased plasma concentration of CYP2D6 substrates may result in potential adverse reactions. A 3-fold increase in the exposure of dextromethorphan, a CYP2D6 substrate, was observed 7 days after a single oral dose of rolapitant and may last longer.

In the SmPC section 4.5 caution is advised when rolapitant is combined with a medicinal product metabolised by CYP2D6, notably those having a narrow therapeutic margin (e.g. propafenone, tamoxifen, metoprolol used in heart failure, thioridazine, pimozide).

Rolapitant is an inhibitor of Breast-Cancer-Resistance Protein (BCRP). Increased plasma concentrations of BCRP substrates (e.g. methotrexate, irinotecan, topotecan, mitoxantrone, rosuvastatin, sulfasalazine, doxorubicin, bendamustine) may result in potential adverse reactions. Co-administration of a single dose of 180 mg rolapitant with sulfasalazine, a BCRP substrate, resulted in an approximately 2-fold increase in C_{max} and AUC of sulfasalazine. Close monitoring is advised In the SmPC if the combination cannot be avoided; the lowest effective dose of rosuvastatin is to be used.

Rolapitant is an inhibitor of P-glycoprotein (P-gp). A 70% increase in C_{max} and 30% increase in AUC of digoxin, a P-gp substrate, were observed when administered with a single dose of 180 mg rolapitant. Therefore, clinical monitoring of adverse reactions is recommended in section 4.5 of the SmPC when rolapitant is combined with digoxin or with other P-gp substrates (e.g. dabigatran or colchicine), and in particular in patients with renal impairment.

In vitro studies suggest that rolapitant is not expected to inhibit OATP1B1 at clinically relevant concentrations, whereas it is unknown whether it inhibits OATP1B3. Therefore, caution should be observed when rolapitant is combined with an OATP1B3 substrate (e.g. statins, bosentan, fexofenadine).

In vivo, rolapitant is not expected to exhibit any inhibitory or inducing effect on CYP3A4. A single dose of 180 mg rolapitant had no significant effects on the pharmacokinetics of midazolam compared to oral midazolam 3 mg alone on Day 1, Day 8 and Day 11.

Rolapitant had no significant effects on the pharmacokinetics of intravenous ondansetron when concomitantly administered with a single 180 mg dose of rolapitant on the same day.

Rolapitant had no significant effects on the pharmacokinetics of dexamethasone when oral dexamethasone was administered on Days 1 to 3 after a single 180 mg dose of rolapitant was co-administered on Day 1.

No clinically significant interaction is expected with the following medicinal products when administered with a single dose of 180 mg rolapitant on Day 1 and without rolapitant on Day 8: repaglinide 0.25 mg (a CYP2C8 substrate), efavirenz 600 mg (a CYP2B6 substrate), tolbutamide 500 mg (a CYP2C9 substrate) or omeprazole 40 mg (a CYP2C19 substrate).

Concomitant administration of rifampicin, a strong enzyme inducer significantly decreased the systemic exposure to rolapitant and to its active metabolite. When 600 mg rifampicin was administered once daily for 7 days before and 7 days after administration of a single dose of 180 mg rolapitant, the mean AUC was reduced by 87% and its active metabolite by 89% compared to administration of rolapitant alone. Varuby in patients who require chronic administration of strong inducers (e.g. rifampicin, carbamazepine, enzalutamide, phenytoin) is not recommended (see SmPC section 4.4 and 4.5).

The effect of moderate inducers (e.g. efavirenz, rifabutin) is not established; therefore, the use of rolapitant in patients already given a moderate inducer is not recommended (see section 4.4).

Due to its strong inducing effect, St John's wort is contraindicated with rolapitant (see SmPC section 4.3).

No clinically significant effect was seen on the pharmacokinetics of rolapitant when ketoconazole, a strong CYP3A4 inhibitor was administered with rolapitant. Concurrent administration of 400 mg ketoconazole once daily for 21 days following a single 90 mg dose of rolapitant, did not significantly affect the C_{max} of rolapitant while the AUC increased by 21%. This is not expected to be clinically relevant. Therefore, no dose adjustment is recommended when rolapitant is combined with a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, posaconazole, ritonavir, cobicistat, clarithromycin).

The efficacy and safety of rolapitant with concurrent use of another NK_1 receptor antagonist is not established and therefore not recommended (see section 4.4).

Further pharmacology studies are requested (see RMP) and the Applicant agreed to perform:

- a DDI study assessing the effect of rolapitant on CYP1A2 substrate as caffeine or theophylline, and taking into account the half-life of rolapitant (dosage of the tested substrate should be made, at least, at day 7 and 14 after rolapitant administration).
- an in vitro study assessing the ability for rolapitant to be a BSEP and MRPs substrate.
- in vitro studies to clarify uncertainties on enzymes or transporters in order to anticipate potential DDI.
- an in vitro study assessing the effect of rolapitant as an inhibitor of OCT1 and OATP1B3 at 20µM
- an in vitro study assessing the effect of rolapitant as an inhibitor of UGTs

2.4.5. Conclusions on clinical pharmacology

Pharmacodynamics data collected are considered adcequate. The Pharmacokinetic of rolapitant has been sufficiently characterized in healthy volunteers and cancer patients. A number of pharmacology studies described in the RMP will be submitted post authorisation.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Study P04351

This was a Phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel-group, dose range-finding study of rolapitant 200mg in subjects receiving HEC (≥70 mg/m2 cisplatin-based chemotherapy). The study was conducted at 75 sites in 21 countries, across Asia, Europe (CZ, PL, and EE), Central and South America, South Africa and Canada. The study was conducted between 13 October 2006 to 27 March 2008.

Doses from 10 to 200 mg were evaluated. The primary objective of the study was to determine if administration of rolapitant in combination with ondansetron and dexamethasone prevented CINV in the overall phase (0 to 120 hours) compared to administration of placebo in combination with ondansetron and dexamethasone.

Rolapitant 10, 25, 100, and 200 mg was administered orally as 2.5, 10, or 50 mg capsules. It was administered approximately 2 hours prior to the administration of the first chemotherapeutic agent on Day 1 of Cycle 1. Ondansetron 32mg IV and dexamethasone 20mg PO were administered concurrently with Rolapitant 0.5 hour before initiation of chemotherapy on Day 1. Dexamethasone 8 mg PO was administered twice daily on Days 2, 3, and 4. Treatment could be administered for up to six chemotherapy cycles. Subjects recorded nausea, emesis, and use of rescue therapy in the SP Nausea and Vomiting (SPNV) Subject Diary daily from Days 1 to 6.

Study population

Patients were cisplatin treatment naïve and about to receive their first course of cisplatin-based chemotherapy (≥70 mg/m2). Tumour type is not specified. Karnofsky performance score of ≥60.

The primary analysis was based on all randomized subjects who received cisplatin-based chemotherapy and a dose of study medication and had at least one posttreatment efficacy assessment in Cycle 1 recorded. Safety was evaluated in all randomized subjects who received at least one dose of study treatment. Symptoms of nausea were self-reported by the study subjects in the Nausea Vomiting (NV) Subject Daily Diary through Day 6 of Cycle 1.

Concomitant medications

Prior and concomitant medications that may have influenced the assessment of efficacy were restricted. 5-HT3 receptor antagonists, phenothiazines, benzamides, domperidone, cannabinoids, NK1 receptor antagonists and benzodiazepines were prohibited within 48 hours prior to the start of study treatment. Subjects who experienced intolerable nausea and/or vomiting during the study were permitted to take rescue medication. A subject who required rescue medication was allowed to continue participating in the study however, this subject was considered to have failed the primary endpoint of complete response.

Primary and key secondary efficacy endpoints

The primary endpoint was the overall complete response rate (no emesis and no use of rescue medication 0 through 120 hours following initiation of cisplatin-based chemotherapy).

Across cycles 2-6 a different primary endpoint was used. Subject's response to questions regarding episodes of emesis/retching or nausea (based on subject recall) on Days 6, 7, or 8 in Cycles 2 to 6 was assessed.

The key secondary endpoint was CR for the acute (0 through 24 hours) and delayed (>24 through 120 hours) phases of CINV.

Table 31: Definitions of Efficacy Endpoints in Study P04351

Endpoint	Definition
Complete response (CR)	No emesis, no use of rescue medication
No emesis	No vomiting, retching, or dry heaves (includes subjects who receive rescue medication)
No nausea	Maximum VAS <5 mm
No significant nausea	Maximum VAS <25 mm
Complete protection	No emesis, no rescue medication, and maximum VAS <25 mm
Total control	No emesis, no rescue medication, and maximum VAS <5 mm

Secondary Endpoints

Secondary efficacy endpoints included no emesis, no nausea, no significant nausea, total control, and complete protection overall and each assessed in the acute and delayed phases. In addition, the time to first emesis or use of rescue medication was assessed along with impact of CINV on daily life using the FLIE Questionnaire.

Statistical approach

The primary endpoint of overall CR rate was evaluated using a logistic regression model with treatment, gender, and use of CEC (yes/no). The key secondary endpoints of CR for the acute (0 through 24 hours) and delayed (>24 through 120 hours) phases of CINV were evaluated using the same logistic regression model. To control for the type I error rate, testing for the primary and key secondary endpoints was conducted in a stepwise fashion. Sequential lower dose comparison against placebo was to be carried out only if the previous comparison was statistically significant ($p < 0.049$).

Methodology

Cycle 1

Approximately 450 subjects were planned. A total of 533 subjects were screened, and 454 were randomized in a 1:1:1:1:1 ratio to one of the five treatment arms: doses of 10, 25, 100, and 200 mg or matching placebo. Randomization occurred centrally using an interactive voice response system. Treatment was stratified according to the following factors:

- Gender
- Use of concomitant emetogenic chemotherapy (CEC) (yes/no).

An interim analysis was carried out after approximately the first 50% of randomized subjects (n≈225) had completed Cycle 1.

Subjects recorded nausea, emesis, and use of rescue therapy in the SP Nausea and Vomiting (SPNV) Subject Diary daily from Days 1 to 6. The duration of each cycle was 29 days (median duration of 24-27 days.). In Cycle 2-6 subjects were questioned about their symptoms of vomiting/retching and nausea on day 6, or 8.

Exposure and patient disposition

A total of 454 subjects were randomised into the study including 91 subjects who were randomised to placebo or 10, 25 or 100 mg rolapitant and 90 subjects who were randomised to 200 mg rolapitant. Participants were distributed across the various regions as follows Asia/South Africa 8.65%, Central South America 53. % Europe 33.5% Canada 4.4%).Two subjects (one in the placebo group and one subject in the 200 mg rolapitant group) were randomised but did not receive study medication.

A total of 416 (91.6%) completed Cycle 1. Thirty-eight (8.4%) subjects discontinued from the Cycle 1 treatment phase. More subjects discontinued during the Cycle 1 treatment phase in the 25-mg dose group (12/91, 13%) compared with the other treatment groups (5%-8%). The primary reason for discontinuation across all groups was adverse events. Median duration of each treatment cycle across all subjects ranged from 24 to 27 days.

All Cycles (Cycles 1 to 6)

Overall, 61% to 65% of subjects administered placebo or SCH 619734 10, 25, or 200 mg continued from the Cycle 1 through 6 treatment phase. The lowest overall discontinuation rate was observed at 100 mg (50/91, 55%).In all treatment groups across all cycles, the primary reason for discontinuation was that subjects did not wish to continue for reasons unrelated to treatment. Across all treatment groups 8% to 12% discontinued because of adverse events.

Demographic and Baseline Characteristics

In Cycle 1, 244 (54%) were male, 256 (56%) were white, and 251 (55%) were Hispanic or Latino. The median age was 55 years (range, 18 to 86 years). Demographics (weight, concomitant emetogenic therapy and Karnofsky Performance Status were comparable across treatment groups in cycle 1 and all treatment cycles. The study enrolled a broad cancer population. A total of 389 (86%) subjects were receiving CEC at Baseline. Median cisplatin dose was 78.5 mg/m2 in Cycle 1.

Efficacy

Primary efficacy endpoint was the overall complete response rate (no emesis and no use of rescue medication from 0 through 120 hours following initiation of cisplatin-based chemotherapy);

The Rolapitant 200-mg dose group had significantly greater complete response rates overall than the placebo group. The overall complete response rate was 62.5% compared with 46.7% for placebo (odds ratio [OR] = 1.94; P = 0.032).

Rolapitant 200mg was statistically superior to control for the key secondary endpoints complete response rates for the acute (0 through 24 hours) and delayed (>24 through 120 hours) phases of CINV. For the acute phase, the response was 87.6% vs 66.7% (OR = 3.60; P = 0.001); for the delayed phase, the response was 63.6% vs 48.9% (OR = 1.86; P = 0.045). Complete response rates for the other Rolapitant dose groups (10, 25 and 100 mg) did not achieve statistical significance when compared with placebo. A positive trend across doses was noted.

Secondary endpoints were also supportive of an effect of rolapitant 200 mg. The 200-mg dose group had significantly greater rates of no emesis overall and in the acute and delayed phases than the placebo group. (Acute: 91.0% versus 67.8%, respectively, p <0.001), (delayed: 68.2% versus 48.9%, respectively, p =0.008) and (overall 67.0% versus 46.7%, respectively, p =0.006). A dose-response trend for no emesis was generally observed for each time interval; the 200-mg dose had the highest response, and the 10-mg dose had the lowest response.

No emesis.

200-mg dose group had significantly greater rates of no emesis overall and in the acute and delayed phases than the placebo group. (Acute: 86.5% versus 73.3% p = 0.029), (delayed 64.4% versus 47.8%, p = 0.026) and (overall 63.2% versus 42.2%p = 0.005)

No significant nausea

The SCH 619734 200-mg dose group had significantly greater rates of no significant nausea overall and in the acute and delayed phases, than the placebo group. Significant nausea was significantly higher in the rolapitant 200 mg dose group compared to control during the acute (86.5% versus 73.3%, respectively, p = 0.029), delayed (64.4% versus 47.8%, respectively, p = 0.026) and overall (63.2% versus 42.2%, respectively, p = 0.005) phases.

Total control overall and no nausea

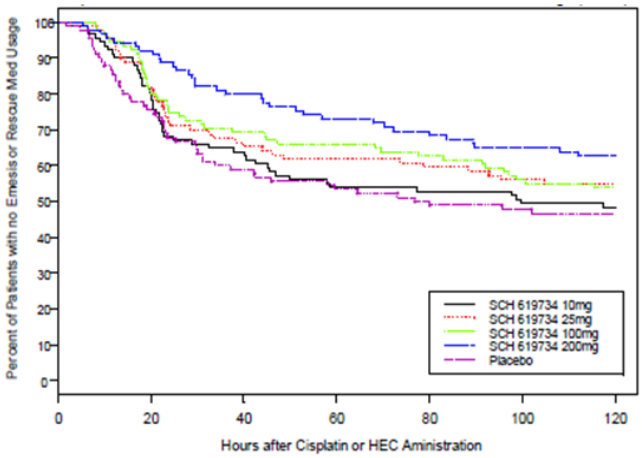
Response rates for total control overall (no emesis, no rescue medication, and a maximum nausea VAS score of <5 mm on a 0- to 100-mm scale) and for no nausea overall and in the acute and delayed phases did not achieve statistical significance for any SCH 619734 dose group when compared with placebo. Longer time to first emesis or need for rescue medication was reported by patients taking 200mg (p=0.011) but not for the other dose groups.

Complete protection (no emesis, no rescue medication, and a maximum nausea VAS score of <25 mm on a 0- to 100-mm scale.)

A significantly greater rate of complete protection was observed for the SCH 619734 200-mg dose group in the acute phase (p=0.009), but not in the delayed phase or overall.

Time to first emesis or to rescue medication use was significantly longer during Cycle 1 for subjects administered rolapitant 200 mg compared to control (p = 0.011), but not for the other dose groups.

Kaplan-Meier Plot for Time to First Emesis or Rescue Medication Use: Cycle 1 (Efficacy Population, Study P04351)



Note: SCH 619734 = rolapitant
Source: CSR P04351, In-text Figure 3

Functional Living Index–Emesis Questionnaire (18 questions on how nausea and vomiting affected their QoL over the last 5 days using a 7-point VAS scale.)

The 100- and 200-mg doses achieved statistically significantly better vomiting- and nausea-related QoL scores than those of the placebo group. QoL scores increased as the dose increased. A higher proportion of subjects treated with 200 mg rolapitant reported no impact on daily life (FLIE total score > 108) compared with subjects who were treated with control (p = 0.005)

Table 32: Overview of Efficacy Analysis: Statistical Significance for Between Group Comparisons (Efficacy Population, Study P04351

Efficacy Variable	CINV Phase	Rolapitant Dose										P-Value 200 mg vs. Control
		Placebo		10 mg		25 mg		100 mg		200 mg		
		n	%	n	%	n	%	n	%	n	%	
Primary												
Complete Response [a]	Overall	90	46.7	91	48.4	88	53.4	91	53.8	88	62.5 *	0.032
Key Secondary												
Complete Response [a]	Acute	90	66.7	90	66.7	89	70.8	91	74.7	89	87.6 *	0.001
	Delayed	90	48.9	91	50.5	88	54.5	91	58.2	88	63.6 *	0.045
Secondary												
No Emesis [b]	Overall	90	46.7	91	54.9	88	58.0	91	61.5	88	67.0 **	0.006
	Acute	90	67.8	91	74.7	90	77.8	91	76.9	89	91.0 ***	<0.001
	Delayed	90	48.9	91	58.2	88	59.1	91	67.0	88	68.2 **	0.008
No Significant Nausea	Overall	90	42.2	91	49.5	89	57.3 *	91	56.0	87	63.2 **	0.005
	Acute	90	73.3	91	74.7	90	77.8	91	74.7	89	86.5 *	0.029

[c]	Delayed	90	47.8	91	52.7	89	59.6	91	60.4	87	64.4*	0.026
No Nausea [d]	Overall	90	24.4	91	20.9	89	21.3	91	27.5	89	30.3	0.386
	Acute	90	52.2	91	48.4	90	55.6	91	47.3	89	51.7	0.927
	Delayed	90	25.6	91	23.1	89	23.6	91	28.6	89	32.6	0.308
Complete Protection [e]	Overall	90	38.9	91	39.6	88	46.6	91	44.0	87	52.9	0.058
	Acute	90	63.3	90	63.3	89	64.0	91	61.5	89	80.9**	0.009
	Delayed	90	42.2	91	41.8	88	47.7	91	48.4	87	52.9	0.151
Total Control [f]	Overall	90	23.3	91	18.7	88	19.3	91	25.3	89	30.3	0.297
	Acute	90	48.9	90	40.0	89	44.9	91	42.9	89	51.7	0.722
	Delayed	90	24.4	91	20.9	88	21.6	91	26.4	89	32.6	0.233
Median Time (hours) to 1st emesis or use of rescue medication [g]	Overall	90	78.5	91	99.8	90	NE	91	NE	89	NE	0.011

Abbreviations: CEC = concomitant emetogenic therapy; CINV = chemotherapy-induced nausea and vomiting; N/C = not calculated; N/A = not applicable; NE =not estimable; VAS = visual analogue scale

Across cycles 2-6 the 200-mg dose maintained the treatment effect of 200 mg vs placebo for no emesis seen in Cycle 1. In each of Cycles 2-6, a higher proportion of rolapitant-treated subjects reported no emesis or nausea compared with subjects who received placebo.

2.5.2. Main studies

HEC Studies P04832 and P04833

Methods

The two studies were efficacy studies of identical design and shared the following common design features. Both protocols included the same methodological approach for the inclusion and exclusion criteria, rolapitant dosing regimen, comparator regimen, primary and secondary efficacy variables and assessments and statistical methodology.

Study Participants

The studies included outpatients, aged ≥18 years with a wide range of solid tumours, who had never been treated with cisplatin and were scheduled to receive the first course of cisplatin-based chemotherapy (≥60 mg/m2). They had to have a Karnofsky performance score of ≥60 and a predicted life expectancy of ≥4 months. Patients with significant bone marrow suppression and renal and liver impairment were excluded.

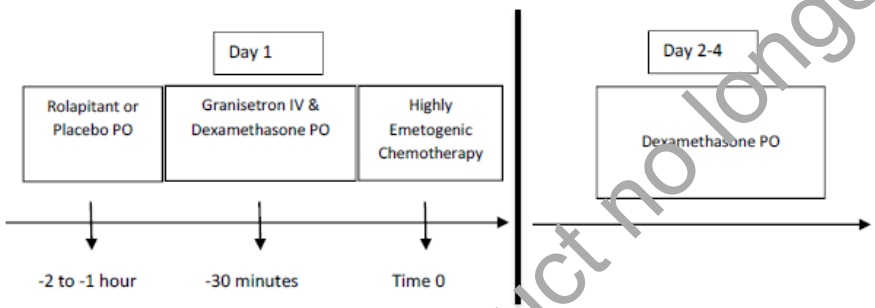
Treatment within 48 hours prior to commencing study drug with the following agents was restricted. Agents that could impact on the anti-emetogenic efficacy of 5-HT3 antagonists e.g. phenothiazines, benzamides, domperidone, cannabinoids, NK1 antagonist (aprepitant) and benzodiazepines (e.g., lorazepam, alprazolam) were prohibited. Palonosetron was not permitted within 7 days prior to the start of study treatment. Systemic

corticosteroids or sedative antihistamines (e.g. dimenhydrinate, diphenhydramine) were prohibited within 72 hours of Day 1 except as premedication for chemotherapy (e.g., taxanes).

Treatments

A single dose of study drug (4 × 50 mg capsules of rolapitant or matching placebo) was administered 1 to 2 hours prior to administration of the first chemotherapeutic agent on Day 1 Granisetron (10 μg/kg IV) plus dexamethasone (20 mg PO) was administered approximately 30 minutes before administration of the first chemotherapeutic agent. It is generally recommended that cisplatin-based chemotherapy be administered over approximately 3 hours on Day 1. Dexamethasone (8 mg PO) was administered PO BID on Days 2, 3, and 4. Inclusion of an aprepitant comparator arm would have been very useful to demonstrate the comparative clinical relevance of this new NK-1 antagonist. There is general agreement that there are no differences in efficacy between the 5HT3 antagonists dolasetron, granisetron, ondansetron and tropisetron (Roila 2010) so efficacy data using a regimen containing granisetron should be generalizable to antiemetic regimens containing these other agents.

Figure 4: Flow Chart for Drug Administration – Days 1-4



Because of the potential for hypersensitivity reactions to taxanes, subjects receiving taxanes received doses of dexamethasone according to the respective taxane package insert, in lieu of the 20 mg PO dose of dexamethasone on Day 1.

Objectives

Primary Objective

The primary objective of this study was to determine whether administration of rolapitant with granisetron and dexamethasone improved CINV in the delayed phase (>24 to 120 hours) during the first cycle of chemotherapy compared with administration of placebo with granisetron and dexamethasone in subjects receiving HEC. The primary outcome was based on the CR, defined as no emetic episodes and no use of rescue medication in the delayed phase.

Key Secondary Objectives

- Determine the effect of rolapitant on CR rates in the acute (0 to 24 hours) and overall (0 to 120 hours) phases of CINV
- Determine if rolapitant is safe and well tolerated in subjects receiving HEC.

- *Other secondary objectives included the following:*
- Determine the effect of rolapitant treatment on the incidences of no emesis in the acute, delayed, and overall phases of CINV.
- Determine the effect of rolapitant treatment on the incidence of no significant nausea in the overall phase of CINV.
- Determine the effect of rolapitant treatment on the time to first emesis or use of rescue medication.

Tertiary study objectives included the following:

- To determine the effect of rolapitant treatment on the incidences of no significant nausea in the acute and delayed phases of CINV
- To determine the effect of rolapitant treatment on the incidences of no nausea and complete protection in the acute, delayed, and overall combined phases of CINV
- To evaluate the effect of rolapitant treatment on health-related quality of life as assessed by the FLIE

Pharmacokinetic Objective

Another study objective was to evaluate the population PK of rolapitant and its primary metabolite M19 in subjects receiving chemotherapy.

Outcomes/endpoints

Primary Endpoint

The primary efficacy endpoint for this study was the complete response rate in the delayed phase of CINV, from >24 through 120 hours following initiation of cisplatin-based chemotherapy. Complete response is defined as no emesis and no use of rescue medication.

Key Secondary Endpoint

The key secondary endpoints are the complete response rates for the acute (0 through ≤24 hours) and overall (0 through ≤120 hours) phases of CINV.

Secondary Endpoints and Tertiary Endpoints

The secondary efficacy endpoints for this study included:

- No emesis (no vomiting, retching, or dry heaves) in the acute, delayed, and overall phases of CINV.
- No significant nausea (maximum VAS <25 mm) in the overall phase of CINV.
- Time to first emesis or to use of rescue medication.

The tertiary efficacy endpoints for this study included:

- No significant nausea in the acute and delayed phases of CINV.
- No nausea (maximum VAS <5 mm) and Complete protection (no emesis, no rescue medication, and maximum nausea VAS <25 mm on a 0 to 100 mm scale) in the acute, delayed, and overall phases of CINV.
- No impact on daily life (total score >108) as assessed by the FLIE Questionnaire.

A summary of the response criteria used in this study is provided inTable

Table 33: Summary of the Response Criteria for Chemotherapy-Induced Nausea and Vomiting

Endpoint	Definition	Duration
Complete response	No emesis, no use of rescue medication	Overall, acute (0 through ≤24 hours) and delayed (>24 through 120 hours) phases
No emesis	No vomiting, retching, or dry heaves (includes subjects who receive rescue medication)	Overall, acute (0 through ≤24 hours), and delayed (>24 through 120 hours) phases
No nausea	Maximum VAS <5 mm	Overall, acute (0 through ≤24 hours), and delayed (>24 through 120 hours) phases
No significant nausea	Maximum VAS <25 mm	Overall, acute (0 through ≤24 hours), and delayed (>24 through 120 hours) phases
Complete protection	No emesis, no rescue medication, and maximum VAS <25 mm	Overall, acute (0 through ≤24 hours), and delayed (>24 through 120 hours) phases

Assessment in Subsequent Cycles (up to 5 Additional Cycles for up to 6 Cycles Total)

Subjects were asked the following CINV assessment questions on Days 6, 7, or 8 in each subsequent cycle (Cycles 2 to 6):

- Have you had any episode of vomiting or retching since your chemotherapy started in this cycle?
- Have you had any nausea since your chemotherapy started in this cycle that interfered with normal daily life?

Randomisation

Randomization of subjects occurred centrally using an interactive web-based randomization system (IWRS) at Cycle 1. Randomization was stratified by gender. In each stratum, subjects were randomized in a 1:1 ratio to 1 of 2 study drug treatment arms.

Blinding (masking)

A double-blind technique was used.

Sample size

Sample size calculations and statistical methods were acceptable It was estimated that with 257 subjects per group, an absolute difference of 15% in the delayed phase CR rates between the rolapitant and control groups could be detected at an α = 0.05 level of significance (2-sided) with 93% power, assuming a control group CR rate of 50%. The 50% control response rate estimate was based on the results of a Phase 3 aprepitant trial with a similar study design. Using this same sample size, the study had 90% power to detect an absolute difference of 12% in the key secondary endpoint of CR in the acute phase of CINV assuming a control response rate of 71%. The sample size assumptions used for CR in the overall phase of CINV were the same as those used for the delayed phase, resulting in 93% power for this key secondary endpoint. Therefore, a minimum of 530 subjects was planned for randomization to 1 of 2 treatment groups (rolapitant group or control group) in a 1:1 ratio to ensure 257 evaluable subjects per group.

Statistical methods

Continuous data were summarized using n (number of subjects with non-missing observations), mean, median, standard deviation (SD), minimum value, and maximum value. Categorical data were summarized using the frequency count and percentage of subjects in each category. Unless otherwise specified, all statistical hypothesis tests were 2-sided with a significance level of α = 0.05.

Adverse events and medical histories were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0. All medications were coded using the World Health Organization (WHO) Drug Dictionary (March 2012 version).

Statistical analyses for the primary, secondary, and tertiary endpoints were performed on the Modified Intent-to-Treat (MITT) Population. Analyses for the primary, key secondary, and secondary endpoints were repeated on the As-Treated (AT) and PP Populations. All safety analyses were performed on the Safety Population. The primary analysis population (MITT) should be further justified .

The *MITT population* consisted of all randomized subjects who received at least 1 dose of study drug. Subjects were analyzed in the treatment group into which they were randomized. The following criteria were used to exclude subjects from the MITT population:

- Subject was enrolled at a noncompliant site with major GCP violations
- Subject did not provide informed consent
- Subject did not receive at least one dose of study drug (olapitant or placebo)

As-Treated Population (Cycle 1)

The AT population consisted of all randomized subjects who received at least 1 dose of study drug. Subjects were analyzed in the group in which they actually received treatment in Cycle 1.

Per Protocol Population (Cycle 1)

The PP population consisted of all randomized subjects who received at least 1 dose of study drug, received emetogenic chemotherapy (Hesketh Level 5), and did not have protocol deviations significantly affecting the interpretation of the study results. In addition, if a subject had missing diary data and the determination of CR could not be made from the remaining data, this subject was excluded from the respective phase of the efficacy analysis. Subjects were analyzed based on actual treatment received in Cycle 1. Criteria used to further exclude subjects from the PP population can be found in the SAP.

Safety Population

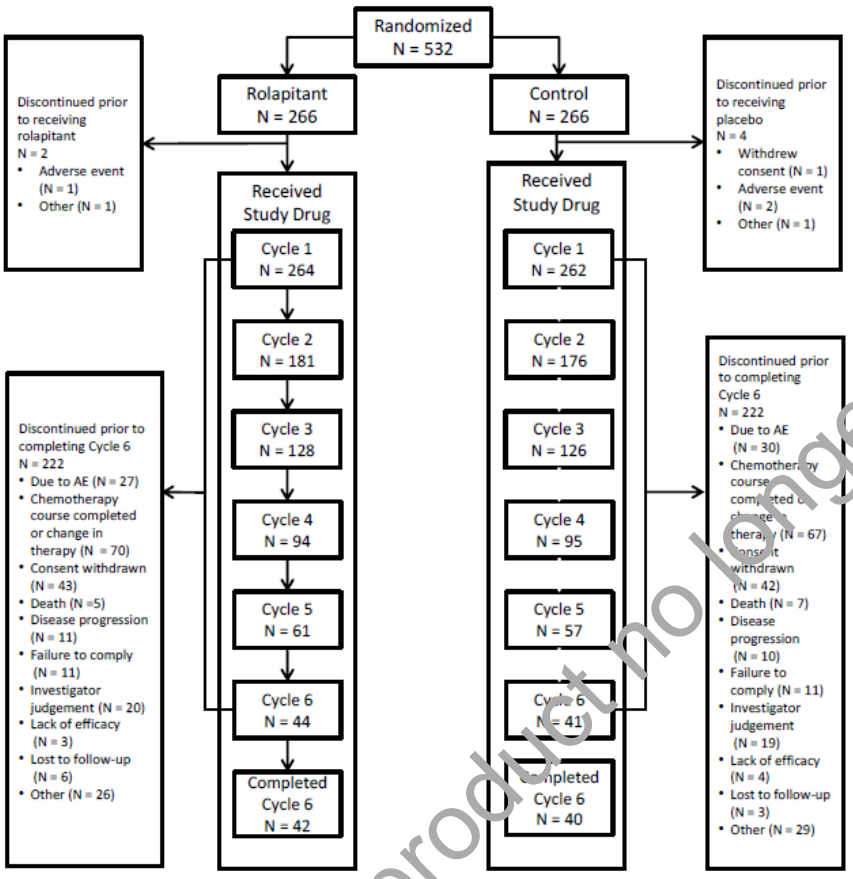
The Safety population consisted of all subjects who were randomized to treatment groups and who received at least 1 dose of study drug. Safety analysis was based on actual treatment received in Cycle 1.

The safety population for subsequent cycles consisted of Safety subjects who received at least 1 dose of study drug for the respective subsequent cycle.

Results

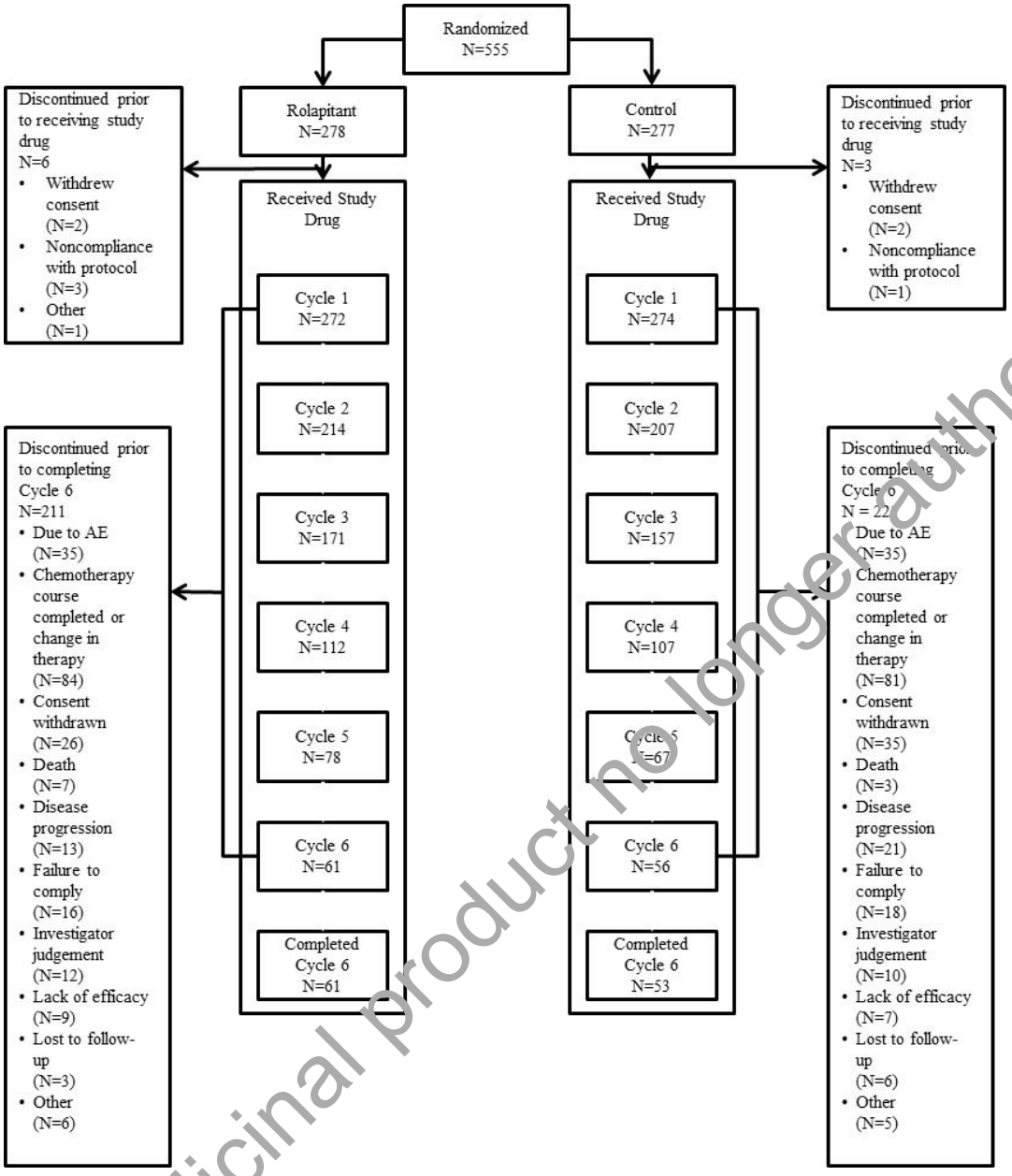
Participant flow

Figure. 5: participant flow from randomization through cycle 6 in study PO4832



Note: This figure displays discontinuations that occurred prior to receiving study drug separately from those that occurred after receiving study drug. For rolapitant, discontinuation due to: AE=28 (1 before dosing and 27 after); other=27 (1 before dosing; 26 after). For control discontinuation due to: withdrawal of consent=43 (1 before dosing and 42 after); AE =32 (2 before dosing and 30 after).

Figure 6:. participant flow from randomization through cycle 6 in study PO4833



Recruitment

A total of 532 subjects were randomised into study P04832 at 76 sites, including 266 subjects randomised to receive rolapitant with granisetron and dexamethasone and 266 randomised to receive placebo with granisetron and dexamethasone (control).

First subject enrolled (date consent signed): 25 April 2012; Last subject completed (date of last assessment): 03 April 2014; Release date of report: 11 August 2014

A total of 555 subjects were randomised into study P04833 at 79 sites, including 278 subjects randomised to receive rolapitant with granisetron and dexamethasone and 277 randomised to receive placebo with granisetron and dexamethasone (control).

First subject enrolled: 20 February 2012; Last subject completed: 24 January 2014; Release date of report: 04 August 2014

Conduct of the study

There were no major amendments to the original study protocols of both studies..

Baseline data

Table 34: Demographics and Baseline Characteristics (MITT Population)

Characteristic	HEC (P04832)		HEC (P04833)		HECs Pooled	
	Rolapitant 200 mg (N=264)	Control (N=262)	Rolapitant 200 mg (N=271)	Control (N=273)	Rolapitant 200 mg (N=535)	Control (N=535)
Age (yrs)						
Mean (SD)	57.0 (10.08)	57.7 (11.15)	58.5 (10.05)	58.5 (9.45)	57.8 (10.09)	58.1 (10.22)
Median	58.0	58.0	59.0	59.0	59.0	59.0
Range	27,86	20,90	21,80	18,83	21,86	18,90
Age (yrs),n (%)						
<45	33 (12.5)	27 (10.3)	23 (8.5)	18 (6.6)	56 (10.5)	45 (8.4)
≥45 - <65	166 (62.9)	166 (63.4)	175 (64.6)	182 (66.7)	341 (63.7)	348 (65.0)
≥65 - <75	60 (22.7)	56 (21.4)	62 (22.9)	66 (24.2)	122 (22.8)	122 (22.8)
≥75	5 (1.9)	13 (5.0)	11 (4.1)	7 (2.6)	16 (3.0)	20 (3.7)
Sex,n (%)						
Female	110 (41.7)	112 (42.7)	88 (32.5)	87 (31.9)	198 (37.0)	199 (37.2)
Male	154 (58.3)	150 (57.3)	183 (67.5)	186 (68.1)	337 (63.0)	336 (62.8)
Race,n (%)						
White	178 (67.4)	179 (68.3)	226 (83.4)	212 (77.7)	404 (75.5)	391 (73.1)
Asian	61 (23.1)	56 (21.4)	34 (12.5)	41 (15.0)	95 (17.8)	97 (18.1)
Black/African-American	2 (0.8)	3 (1.1)	2 (0.7)	3 (1.1)	4 (0.7)	6 (1.1)
American Indian or Alaska Native	2 (0.8)	0	2 (0.7)	8 (2.9)	4 (0.7)	8 (1.5)
Other[a]	21 (8.0)	24 (9.2)	7 (2.6)	9 (3.3)	28 (5.2)	33 (6.2)

Demographics and Baseline Characteristics (MITT Population) (Continued)

Characteristic	HEC (P04832)		HEC (P04833)		HECs Pooled	
	Rolapitant 200 mg (N=264)	Control (N=262)	Rolapitant 200 mg (N=271)	Control (N=273)	Rolapitant 200 mg (N=535)	Control (N=535)
Ethnicity,n (%)						
Hispanic or Latino	33 (12.5)	34 (13.0)	36 (13.3)	38 (13.9)	69 (12.9)	72 (13.5)
Not Hispanic or Latino	231 (87.5)	228 (87.0)	235 (86.7)	235 (86.1)	466 (87.1)	463 (86.5)
BSA (m^2)						
Mean (SD)	1.77 (0.224)	1.78 (0.259)	1.80 (0.227)	1.81 (0.211)	1.78 (0.226)	1.79 (0.236)
Median	1.75	1.76	1.80	1.79	1.77	1.76
Primary Tumor Site ,n (%)[b]						
Breast	7 (2.7)	9 (3.4)	5 (1.8)	17 (6.2)	12 (2.2)	26 (4.9)
Lung	106 (40.2)	98 (37.4)	129 (47.6)	134 (49.1)	235 (43.9)	232 (43.4)
Head & Neck	52 (19.7)	55 (21.0)	45 (16.6)	45 (16.5)	97 (18.1)	100 (18.7)
Stomach	11 (4.2)	9 (3.4)	23 (8.5)	25 (9.2)	34 (6.4)	34 (6.4)
Colon/Rectum	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
Ovary	23 (8.7)	25 (9.5)	10 (3.7)	6 (2.2)	33 (6.2)	31 (5.8)
Alcohol Consumption,n (%)[c]						
0 drinks/wk	225 (85.9)	197 (75.5)	209 (78.0)	217 (79.8)	434 (81.9)	414 (77.7)
>0 to ≤5 drinks/wk	26 (9.9)	35 (13.4)	33 (12.3)	34 (12.5)	59 (11.1)	69 (12.9)
>5 to ≤10 drinks/wk	5 (1.9)	15 (5.7)	7 (2.6)	8 (2.9)	12 (2.3)	23 (4.3)
>10 drinks/wk	6 (2.3)	14 (5.4)	19 (7.1)	13 (4.8)	25 (4.7)	27 (5.1)

Mean age in the MITT Population in P04833 was 58.5 years and ranged from 18 to 83; most subjects were <65 years of age (73.2%), male (57.8%), white (80.5%), and did not consume alcohol (self-reported) (78.9%). The MITT Population included subjects from Europe (62.1%), North America (NA) (United States of America) (6.6%), Asia/South Africa (16.5%) and Central/South America (14.7%).

Numbers analysed

Overall a total of 1087 subjects were included in the MITT population, including 544 subjects who received rolapitant.

Discontinuation during Cycle 1 was uncommon, reported in 4.9% and 6.9% of subjects in the rolapitant and control groups, respectively, in the pooled HEC studies.

The most common reason for discontinuation in Cycle 1 in all studies was withdrawal of consent. Compliance with rolapitant dosing was high (>99%) across both studies as was compliance with adjunct antiemetic therapy (>99%).

Across both studies (>99%) rolapitant and control subjects received at least one dose of cisplatin-based chemotherapy during Cycle 1. The mean and median dose of cisplatin across both studies was >75mg/m^2. Compliance with administration of HEC agents was high in both studies; >99% of subjects in the HEC studies received at least one HEC agent in Cycle 1.

The minimum duration per cycle was 14 days .The median cycle duration across both studies was approximately 22 days. The dosing interval proposed in section 4.2 is 14 days.

Outcomes and estimation

CR delayed phase (primary endpoint)

The rolapitant group achieved a statistically significantly higher CR rate in the delayed phase compared to the control group in study P0483 2 (72.7% vs 58.4%, respectively; p < 0.001) and in study P04833 (70.1% vs 61.9%, respectively; p = 0.043). This higher CR rate in the rolapitant group corresponds to a 34% relative reduction in failure rate with respect to the incidence of emesis or rescue medication use during the delayed phase of CINV.

Table 35 : Complete Response in the Delayed Phase of CINV: Summary and Between Group Comparison (MITT Population, Study P04832 Study P04833 and pooled analysis)

Endpoint[a] Study	Rolapitant 200 mg n / N (%)	Control n / N (%)	Rolapitant 200 mg vs. Control	
			Odds Ratio (95% CI)[b]	P-value[b]
Complete Response – Delayed Phase				
HEC (P04832)	192/ 264 (72.7)	153/ 262 (58.4)	1.9 (1.3, 2.7)	<0.001
HEC (P04833)	190/ 271 (70.1)	169/ 273 (61.9)	1.4 (1.0, 2.1)	0.043
HECs Pooled (P04832/P04833)	382/ 535 (71.4)	322/ 535 (60.2)	1.6 (1.3, 2.1)	<0.001

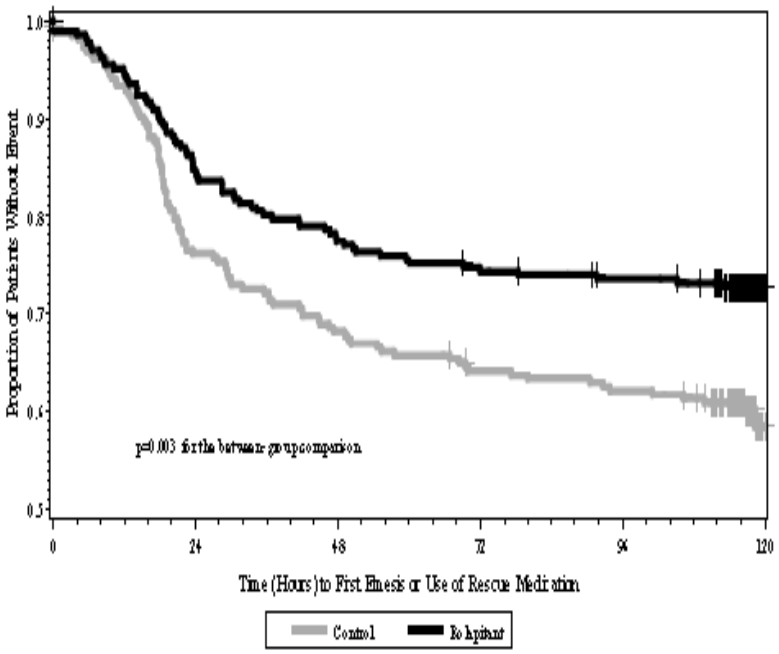
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel Haenszel; HEC = highly emetogenic chemotherapy; Analysis Populations: MITT for P04832, P04833, and a complete response is defined as no emesis or use of rescue medication.

Key secondary endpoint; Time to First Emesis or Use of Rescue Medication

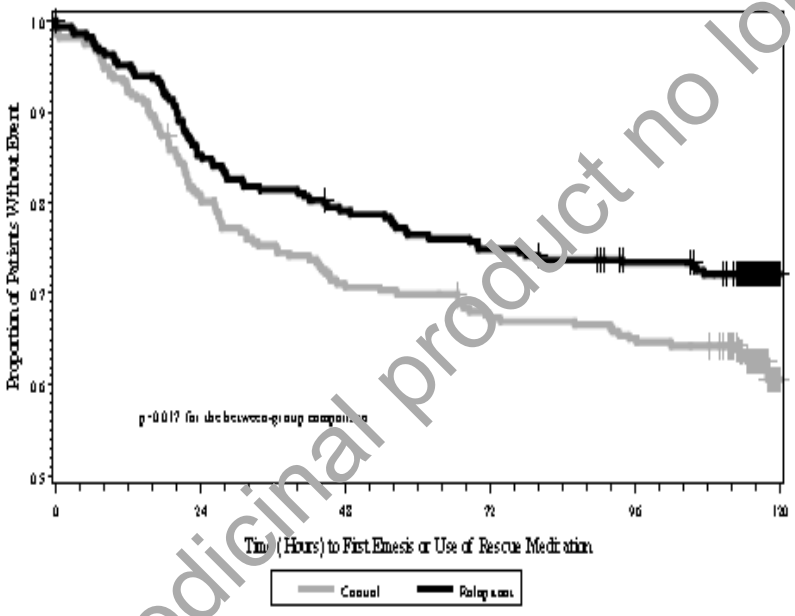
The proportion of subjects with a complete response in the acute and overall phase (no emesis and no use of rescue medication due to nausea) during the initial chemotherapy cycle (key secondary endpoints) was statistically significantly higher in the rolapitant group compared to the standard therapy group in Study P08342 but not Study P08433. CR Acute phase: HEC (Study P04832 (83.7 vs 73.7) OR (95% CI).8 (1.2, 2.8) p=0.005) and (P04833 HEC (83.4% vs 79.5) OR (95% CI) 1.3 (0.8, 2.0) p=0.233). As statistical significance was not achieved for CR (acute phase) in study P04833, based on the statistical hierarchy specified in the SAP, formal statistical significance of subsequent endpoints within the hierarchy could not be assigned. However, for completeness, the unadjusted p-values are reported but no inference can be made from them, other than that the comparison was non-significant for those endpoints.

Kaplan-Meier Plot of Proportions of Subjects without Emesis or Use of Rescue Medication (MITT Population P04832 and P04833)

Study P04832



Study P04833



For the overall phase statistical significance was achieved for Study P04832 but not Study P04833. (Study P04832 (rolapitant 70.1% vs control 56.5%) OR (95% CI) 1.8 (1.3, 2.6) p=0.001) and (P04833 HEC (67.5% vs 60.4) OR (95% CI) 1.4 (1.0, 1.9) p=0.084).

Other secondary endpoints evaluated included no emesis during the acute, delayed, and overall phases of CINV, and no significant nausea during the overall phase and time to first emesis or use of rescue medication. Tertiary endpoints (not formally tested for significance) included no significant nausea during acute and delayed phases, no acute, delayed and overall phase nausea, complete protection across all three phases and impact on daily life (FLIE). The results for the secondary and tertiary endpoints are generally

concordant with the results for the primary and key secondary endpoints across both for HEC study P04832. Statistically significant differences in favour of rolapitant were seen for all endpoints for HEC P08432 but not HEC P08433.

Nausea

The proportion of subjects with a no significant nausea in the delayed, acute and overall phase during the initial chemotherapy cycle was statistically significantly higher in the rolapitant group compared to the standard therapy group in Study P08342 but not Study P08433. When the studies were pooled statistical significance was achieved across all three time points.

Time to First Emesis or Use of Rescue Medication During the First 120 Hours

In both studies P08432 and P08433 and the pooled analysis, the time to first emesis or use of rescue medication was longer for rolapitant compared to control. A separation in the Kaplan Meier curves is visually apparent early during the acute phase of CINV by 12 hours after administration of study drug. This separation continues to increase during the acute phase (0-24hrs). At 24hrs the separation of the curves increases considerably and from 48hrs the effect is maintained in the rolapitant arm and is sustained throughout the delayed phase of CINV. Subjects achieving CR at 48hrs maintained their control up to 120 hrs. For both Study P04832 and P04833 the incidence of subjects requiring ≥1 rescue medication during Cycle 1 was lower in the rolapitant group than in the control group (13.3% and 21.0%, vs 13.3% and 22.0%, respectively).

Effect on daily life

Effect on daily life (using FLIE) was the only QoL endpoint evaluated across these studies. It was included as a tertiary endpoint that was not subject to formal statistical testing. No inference can be made from unadjusted p values calculated for these endpoints, other than that the comparison was non-significant for those endpoints. A higher proportion of subjects treated with rolapitant reported no impact on daily life with respect to both the vomiting and nausea domains of the FLIE compared to control; unadjusted P=0.027.

Table 36: Efficacy variables in HEC studies

Efficacy Variable	CINV Phase	Rolapitant (N=666)[a] Rate (%)	Control (N=666) Rate (%)	Unadjusted P-Value[b]
No Significant Nausea[d]	Acute Phase n (%)	547 (82.1) (79.0, 85.0)	564 (84.7) (81.7, 87.3)	0.193
No Significant Nausea	Delayed phase n (%)	484 (72.7) (69.1, 76.0)	462 (69.4) (65.7, 72.9)	0.194
No Nausea[e]	Acute Phase n (%)	433 (65.0) (61.3, 68.6)	439 (65.9) (62.2, 69.5)	0.693

No Nausea	Delayed Phase n (%)	323 (48.5) (44.6, 52.4)	299 (44.9) (41.1, 48.8)	0.201
No Nausea	Overall n (%)	303 (45.5) (41.7, 49.4)	280 (42.0) (38.3, 45.9)	0.219
Complete Protection[f]	Acute Phase n (%)	514 (77.2) (73.8, 80.3)	508 (76.3) (72.9, 79.5)	0.726
Complete Protection	Delayed Phase n (%)	428 (64.3) (60.5, 67.9)	379 (56.9) (53.0, 60.7)	0.006
Complete Protection	Overall n (%)	413 (62.0) (58.2, 65.7)	354 (53.2) (49.3, 57.0)	0.001
No Impact on Daily Life[g]	Overall n (%)	443 (73.2) (69.5, 76.7)	409 (67.4) (63.5, 71.1)	0.027

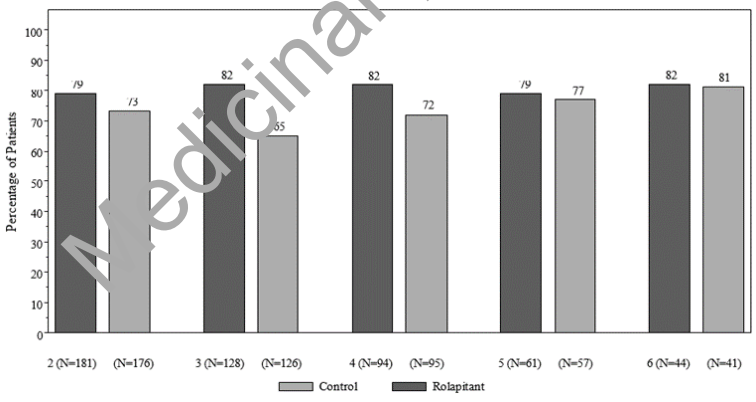
Abbreviations: CINV = chemotherapy-induced nausea and vomiting; FLIE = Functional Living Index-Emesis; N/C=not calculated; N/A= not applicable; NE=not estimable; VAS = visual analogue scale

Repeat efficacy

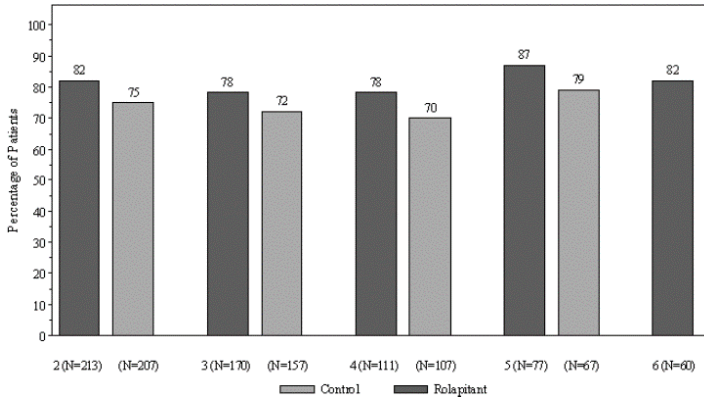
The effect of rolapitant over repeat courses of HEC was evaluated by measuring subject incidences of no emesis or nausea, no emesis, and no nausea from Day 1 to Day 6 of each cycle for additional Cycles 2-6 . Unlike cycle 1 where daily diary entries were used to record events of emesis and nausea, subject recall at day 6-8 (Visit 2) was used to evaluate sustained benefit of rolapitant over multi-cycle use.

Figure 7 Subject Response of No Emesis or Nausea by Cycle (MITT Population)

Study P04832 Cycle 2-6



Study P04833 Cycle 2-6



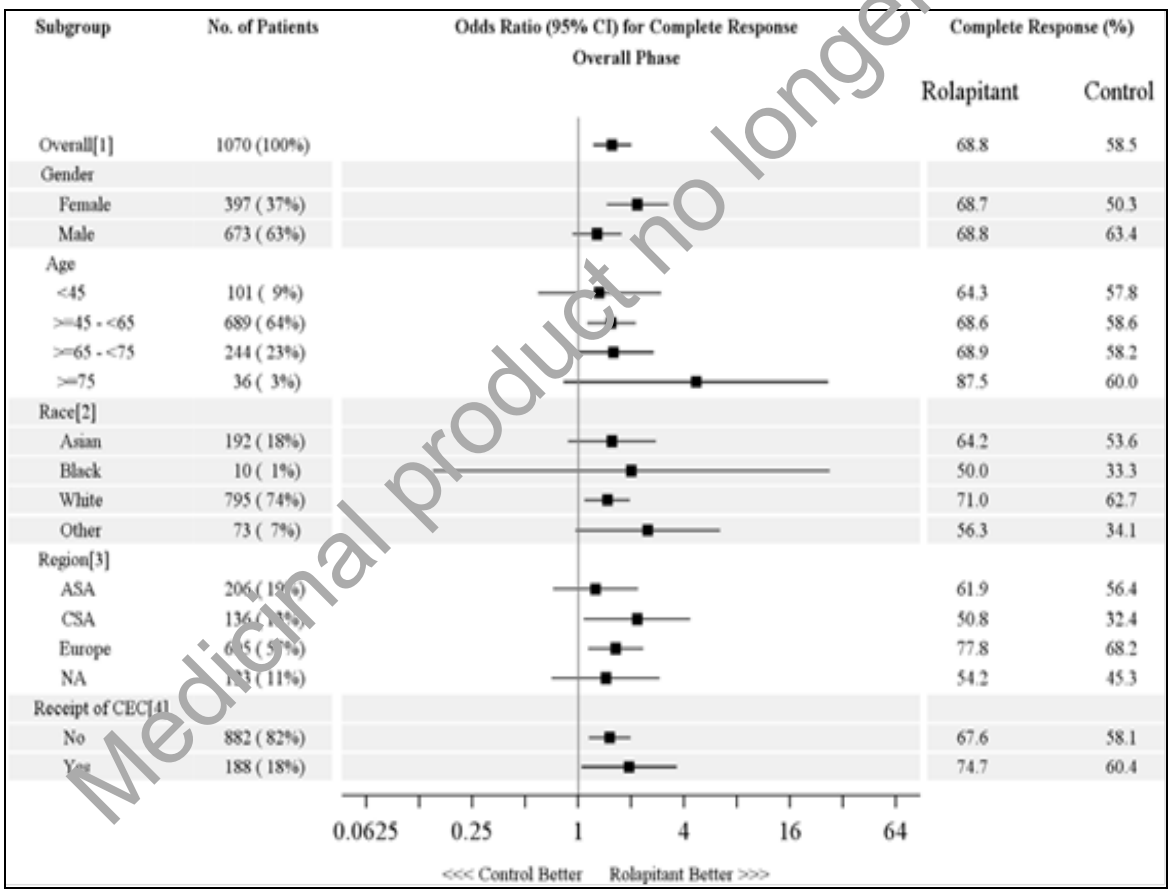
Ancillary analyses

Subgroup analyses

Exploratory analyses of the primary, key secondary were conducted for subject subgroups, according to gender, age, race, region, and receipt of CEC. During the delayed and overall phases of CINV, the CR rate favoured rolapitant across all subgroups for the pooled HEC studies. There was some variability across subgroups in the acute phase responses.

Efficacy outcomes by gender were variable across the two HEC studies. Response rates for females were consistently higher compared to males receiving rolapitant versus control across all CINV phases (pooled analysis). (e.g. CR delayed phase females 71.2% vs control 52.3% OR 2.3 (1.5, 3.4) vs males 71.5% vs 64.9% OR 1.4 (1.0, 1.9) respectively. The magnitude of the treatment effect (CR delayed phase)for males was much smaller than that for females (e.g 18.9% difference vs 6.6%. A Gail-Simon test conducted by the applicant indicated that there were no qualitative interactions between treatment and subgroup regardless of gender across all of these endpoints.

Figure 8: Complete Response for the Overall Phase by Subgroup (MITT Population) HEC Studies Pooled



Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37 : Summary of efficacy for pivotal HEC trial P04832

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy- Induced Nausea and Vomiting (CINV) in Subjects Receiving Highly Emetogenic Chemotherapy (HEC)			
Study identifier	TS-P04832		
Design	Multicenter, Randomized, Parallel-group, Double-Blind, Active Controlled Study in Patients Receiving Cisplatin Based HEC		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Acute phase (0 to 24 hours) delayed phase (>24 to 120 hours) over all phase (0 to 120 hours) phases of CINV not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Rolapitant		Rolapitant 200 mg (50 mg×4)PO on Day 1 + granisetron IV (10 µg/kg on Day 1) + dexamethasone PO (20 mg on Day 1 and 8 mg BID from Day 2 to Day 4) n=264
	Placebo		Placebo on Day 1 + granisetron IV (10 µg/kg on Day 1) + dexamethasone PO (20 mg on Day 1 and 8 mg BID from Day 2 to Day 4) n=262
Endpoints and definitions	Primary endpoint	CR delayed phase	Complete response rate (defined as no emetic episodes, no rescue medication) from >24 through 120 hours after the start of the highly emetogenic chemotherapy administration (delayed phase)
	Key Secondary endpoint	CR acute phase	Complete response rate (defined as no emetic episodes, no rescue medication) from 0 through ≤ 24 hours after the start of the highly emetogenic chemotherapy administration (acute phase)
	Key Secondary endpoint	CR overall phase	Complete response rate (defined as no emetic episodes, no rescue medication) from 0 through ≤ 120 hours after the start of the highly emetogenic chemotherapy administration (overall phase)
	Secondary endpoint	No emesis Acute	No emesis (no vomiting, retching or dry heaves) during the acute phase (0 through ≤ 24 hours)
	Secondary endpoint	No emesis delayed	No emesis (no vomiting, retching or dry heaves) during the delayed phase (>24 through 120 hours)
	Secondary endpoint	No emesis overall	No emesis (no vomiting, retching or dry heaves) during the overall phase (0 through 120 hours)

	Secondary endpoint	No significant nausea	No significant nausea (nausea <25 mm on VAS) during the overall phase (0 through 120 hours)
	Secondary endpoint	TTF	Time to the first emetic episode or time to the first rescue medication
Database lock	03 April 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent to treat		
Descriptive statistics and estimate variability	Treatment group	rolapitant	control
	Number of subject	264	262
	CR delayed n (% patients)	192 (72.7)	153 (58.4)
	95% IC[a]	[66.9;78.0]	[52.2;64.4]
	p-value[b]	< 0.001	
	CR acute* n (% patients)	221 (83.7)	193 (73.7)
	95% IC[a]	[78.4;88.0]	[67.9;78.9]
	p-value[c]	0.005	
	CR overall* n (% patients)	185 (70.1)	148 (56.5)
	95% IC[a]	[64.2;75.5]	[50.2;62.6]
	p-value[c]	0.001	
	Other secondary analyses		
	No emesis Delayed phase	206/ 264 (78.0)	162/ 262 (61.8)
	Mean difference to control	16.2%	
	Odds Ratio (95% CI) P-value	2.0 (1.5, 3.2) 0.002	
	No emesis acute phase	228/ 264 (86.4)	199/ 262 (76.0)
	Mean difference to control	10.4%	
	Odds Ratio (95% CI) P-value	2.0 (1.3, 3.2) 0.002	
	No Emesis – Overall Phase	199/ 264 (75.4)	155/ 262 (59.2)
	Mean difference to control	16.2%	

	Odds Ratio (95% CI) P-value	2.1 (1.5, 3.1) <0.001	
	Significant tertiary analysis		
	FLIE No Impact on Daily Life FLIE total score >108. Denominator was based on the number of subjects with valid questionnaire	72.8	67.8
	Odds Ratio (95% CI) P-value	1.3 (0.9, 1.9) 0.231	
Notes	[a]p-value from Cochran-Mantel-Haenszel test, stratified by gender [b]Exact 95% confidence interval (CI) for response rate c Unadjusted p-values are *The key secondary endpoints of CR rate in the acute and overall phases of CINV were analyzed in a stepwise fashion using the same methodology as the primary endpoint. To control for multiplicity within the prespecified secondary endpoints, the Bonferroni-Holm multiple comparison procedure was used.		

Table 38: Summary of efficacy for trial P04833

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy- Induced Nausea and Vomiting (CINV) in Subjects Receiving Highly Emetogenic Chemotherapy (HEC)		
Study identifier	TS-P04833	
Design	Multicenter, Randomized, Parallel-group, Double-Blind, Active-Controlled Study in Patients Receiving Cisplatin Based HEC	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Acute phase (0 to 24 hours) delayed phase (>24 to 120 hours) over all phase (0 to 120 hours) phases of CINV not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Rolapitant	Rolapitant 200 mg (50 mg×4)PO on Day 1 + granisetron IV (10 µg/kg on Day 1) + dexamethasone PO (20 mg on Day 1 and 8 mg BID from Day 2 to Day 4) n=264
	Placebo	Placebo on Day 1 + granisetron IV (10 µg/kg on Day 1) + dexamethasone PO (20 mg on Day 1 and 8 mg BID from Day 2 to Day 4) n=262

Endpoints and definitions	Primary endpoint	CR delayed phase	Complete response rate (defined as no emetic episodes, no rescue medication) from >24 through 120 hours after the start of the highly emetogenic chemotherapy administration (delayed phase)
	Key Secondary endpoint	CR acute phase	Complete response rate (defined as no emetic episodes, no rescue medication) from 0 through ≤ 24 hours after the start of the highly emetogenic chemotherapy administration (acute phase)
	Key Secondary endpoint	CR overall phase	Complete response rate (defined as no emetic episodes, no rescue medication) from 0 through ≤ 120 hours after the start of the highly emetogenic chemotherapy administration (overall phase)
	Secondary endpoint	No emesis Acute	No emesis (no vomiting, retching or dry heaves) during the acute phase (0 through ≤ 24 hours)
	Secondary endpoint	No emesis delayed	No emesis (no vomiting, retching or dry heaves) during the delayed phase (>24 through 120 hours)
	Secondary endpoint	No emesis overall	No emesis (no vomiting, retching or dry heaves) during the overall phase (0 through 120 hours)
	Secondary endpoint	No significant nausea	No significant nausea (nausea <25 mm on VAS) during the overall phase (0 through 120 hours)
	Secondary endpoint	TTF	Time to the first emetic episode or time to the first rescue medication
Database lock	03 April 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent to treat		
Descriptive statistics and estimate variability	Treatment group	rolapitant	control
	Number of subject	271	273
	CR delayed n (% patients)	190 (70.1)	169 (61.9)
	95% IC[a]	[64.3;75.5]	[55.6;67.7]
	p-value[b]	0.043	
	CR acute* n (% patients)	226 (83.4)	217 (79.5)
	95% IC[a]	[78.4;87.6]	[74.2;84.1]
	p-value[c]	0.233	
	CR overall* n (% patients)	183 (67.5)	165 (60.4)
	95% IC[a]	[61.6;73.1]	[54.4;66.3]

	p-value[c]	0.084	
	Other secondary analyses		
		Rolapitant 200 mg n / N (%)	Control n / N (%)
	No emesis Delayed phase	198/ 271 (73.1)	198/ 271 (73.1)
	Mean difference to control	7.9%	
	Odds Ratio (95% CI) P-value	1.4 (1.0, 2.1) 0.046	
	No emesis acute phase	232/ 271 (85.6)	223/ 273 (81.7)
	Mean difference to control	3.9%	
	Odds Ratio (95% CI) P-value	1.3 (0.8, 2.1) 0.208	
	No Emesis – Overall Phase	192/ 271 (70.8)	175/ 273 (64.1)
	Mean difference to control	6.7%	
	Odds Ratio (95% CI) P-value	1.4 (1.0, 1.9) 0.091	
	Significant tertiary analysis		
	FLIE No Impact on Daily Life FLIE total score >108. Denominator was based on the number of subjects with valid questionnaire	194/ 248 (78.2)	183/ 249 (73.5)
	Odds Ratio (95% CI) P-value	1.3 (0.9,2.0) 0.206	
Notes	[a]p-value from Cochran-Mantel-Haenszel test, stratified by gender [b]Exact 95% confidence interval (CI) for response rate c Unadjusted p-values are *The key secondary endpoints of CR rate in the acute and overall phases of CINV were analyzed in a stepwise fashion using the same methodology as the primary endpoint. To control for multiplicity within the prespecified secondary endpoints, the Bonferroni-Holm multiple comparison procedure was used.		

MEC Study P04834

Methods

This was a Phase 3, multicenter, randomized, parallel-group, double-blind, active-controlled study of rolapitant in subjects receiving MEC. Rolapitant or placebo was administered orally 1-2 hours prior to the initiation of chemotherapy on Day 1. Granisetron (2 mg PO) and dexamethasone (20 mg PO) were

administered approximately 30 minutes before initiation of chemotherapy on Day 1, except in subjects receiving taxanes as part of MEC.

Study participants

Approximately 1300 evaluable subjects were required to evaluate the primary objective of the study. It was expected that 1350 subjects would be enrolled at approximately 150 investigational sites.

In this study unlike the HEC studies (cisplatin but not chemotherapy naïve subjects were included in HEC studies) participants were naive to MEC and HEC, and were scheduled to receive a first course of MEC. Cyclophosphamide IV (<1500 mg/m2), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine IV (>1 g/m^2) were the required chemotherapies included in the MEC protocol. The protocol also specified that at least 50% of the study subjects would receive anthracycline in combination with cyclophosphamide (AC) as the MEC regimen. Since 2010 (Roila et al) it has been recognised that CINV associated with the commonly used combination of the MEC agents cyclophosphamide and anthracycline should be treated the same as for HEC.

Rolapitant 200 mg (50mgx4) or placebo was administered orally 1 to 2 hours prior to the initiation of chemotherapy on Day 1. Granisetron (2 mg PO) and dexamethasone (20 mg PO) were administered approximately 30 minutes before initiation of chemotherapy as standard therapy (i.e., 1-2 hours prior to the initiation of chemotherapy on Day 1). In this study, all subjects continued to receive granisetron (2 mg daily) on Days 2 and 3.

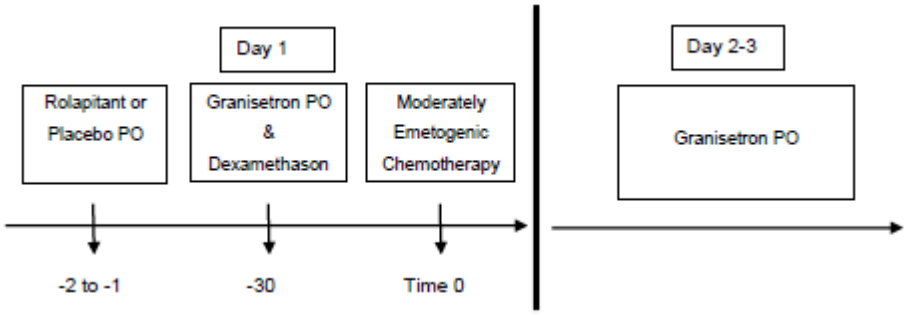
Treatments

Rolapitant (4 × 50 mg capsules) or matching placebo was administered orally 1-2 hours prior to the initiation of chemotherapy on Day 1.

Granisetron (2 mg [PO]) and dexamethasone (20 mg oral [PO]) were administered approximately 30 minutes before initiation of chemotherapy on Day 1, except in subjects receiving taxanes as part of MEC. All subjects continued to receive granisetron (2 mg daily) on Days 2 and 3.

All subjects were expected to complete Cycle 1; at the end of Cycle 1, eligible subjects, as determined by the site investigator, were offered the opportunity to continue with the same study medication administered in the same manner as in Cycle 1 for up to five additional cycles (a total of 6 cycles).

Figure 9 Flow Chart for Drug Administration – Days 1-3 P04834



The control treatment regime is not in line with the recommended prophylaxis for AC or non AC MEC in CINV (MASCC /ESMO 2010) that was current the time this study was commenced (2012) or the most recent 2016 guidance. The administration of 5HT-3RA from day 2 to day 3 post chemotherapy was not and is not recommended as part of the EU (MASCC/ESMO) consensus guidelines.

The comparator regime recommended in EU consensus guidelines (MASCC/ESMO 2010) from that time for non- AC MEC or AC are different. In the 2010 guidance it was established that for patients receiving non-AC MEC a combination of a 5HT-3RA and dexamethasone was considered standard antiemetic prophylaxis whereas patient receiving AC should be treated more like HEC. Study P04834 was conducted between March 5, 2012, and Sept 6, 2013 so it is unclear why such a high proportion of the study population for the MEC study comprised subjects treated with AC and why the comparator regime was chosen (i.e. choice of granisetron, dosing on day 2,3 of cycle). Subjects in the AC arm were potentially undertreated. Control of CINV in the acute phase has a direct relationship with control of CINV in the delayed phase. The comparator regime in the MEC study should be further justified.

Objectives

The primary objective of this study was to determine whether administration of rolapitant with granisetron and dexamethasone improved CINV in the delayed phase (>24 to 120 hours) of CINV compared with administration of placebo with granisetron and dexamethasone in subjects receiving MEC. The primary outcome was based on the CR (defined as no emetic episodes and no rescue medication) in the delayed phase.

Key Secondary Objectives

- To determine the effect of rolapitant treatment on the incidence of CR in the acute (0- ≤24 hours) and overall (0-≤120 hours) phases of CINV.
- To determine if rolapitant was safe and well tolerated in subjects receiving MEC.

Secondary Objectives

- To determine the effect of rolapitant treatment on the incidences of no emesis (no vomiting, retching, or dry heaves; included subjects who received rescue medication) in the acute, delayed and overall phases of CINV.
- To determine the effect of rolapitant treatment on the incidence of no significant nausea in the overall phase of CINV.

- To determine the effect of rolapitant treatment on the time to first emesis or use of rescue medication.

Tertiary Objectives

- To determine the effect of rolapitant treatment on the incidences of no significant nausea in the acute and delayed phases of CINV.
- To determine the effect of rolapitant treatment on the incidences of no nausea and complete protection in the acute, delayed and overall combined phases of CINV.
- To evaluate the effect of rolapitant treatment on health-related quality of life as assessed by the FLIE.

- **Outcomes/endpoints**

The efficacy of rolapitant was assessed through approximately 120 hours following initiation of MEC. The primary assessment of efficacy was based on the responses recorded in the NVSD Diary for Cycle 1.

The primary efficacy endpoint for this study was the complete response rate in the delayed phase of CINV, from >24 through 120 hours following initiation of MEC. Complete response is defined in as no emesis and no rescue medication.

The key secondary efficacy endpoints were

- the incidence of CR during the acute (0-≤24 hours) and overall (0-≤120 hours) phases of CINV following the initiation of MEC.

The secondary efficacy endpoints for this study included:

- No emesis (no vomiting, retching, or dry heaves) in the acute, delayed, and overall phases of CINV.
- No significant nausea (maximum VAS <25 mm) in the overall phase of CINV.
- Time to first emesis or to use of rescue medication.

The tertiary efficacy endpoints for this study included:

- No significant nausea in the acute and delayed phases of CINV.
- No nausea (maximum VAS <5 mm) and Complete protection (no emesis, no rescue medication, and maximum nausea VAS <25 mm on a 0 to 100 mm scale) in the acute, delayed, and overall phases of CINV.
- No impact on daily life (total score >108) as assessed by the FLIE Questionnaire.

Sample size

Approximately 1350 subjects were to be randomized to one of two treatment groups (rolapitant group or control group) in a 1:1 ratio to ensure 650 evaluable subjects per group. With 650 subjects per group, the study was able to detect an absolute difference of 9% in the delayed phase CR rates between the rolapitant and control groups at an $\alpha = 0.05$ level of significance (2-sided) with 90% power, assuming a control group

complete response rate of 49%. The sample size assumptions were based on the results of two Phase 3 aprepitant studies performed in a similar patient population receiving MEC.

Using this same sample size, the study had 91% power to detect an absolute difference of 8% in the key secondary endpoint of complete response in the acute phase assuming a control response rate of 70%. The study had 90% power to detect an absolute difference of 9% in the key secondary endpoint of CR in the overall phase assuming a control response rate of 42%.

Efficacy data and additional analyses Study P04834

Baseline characteristics

A broad population of cancer subjects was enrolled across both studies based on age, gender, type of underlying malignancy, and geographic region. Mean age in the MITT population was 56.7 years. Most subjects were <65 years of age (72.4%), female (80.1%), white (77.0%), and did not consume alcohol (self-reported) (80.6%). Cancer diagnosis was similar between the treatment groups; the most common types of cancer overall were breast cancer (63.4%) and lung cancer (16.5%). All other cancer types were reported in <5% of subjects overall. Greater than 50% of subjects in both the rolapitant and control groups received an anthracycline-cyclophosphamide (AC) chemotherapy.

A total of 1369 subjects were randomised into this study at 170 sites, including 684 subjects randomised to receive rolapitant with granisetron and dexamethasone and 685 randomised to receive placebo with granisetron and dexamethasone (control). Twenty five subjects randomised did not receive study medication. A further 12 subjects were excluded due to GCP noncompliance at site 181.This data was considered to be unusable and was excluded from the dataset. The MITT Population (primary analysis population) for Cycle 1 comprised a total of 1332 subjects (666 subjects in each treatment group).

Discontinuation during Cycle 1 was uncommon, reported in 7% and 6.6% of subjects in the rolapitant and control groups, respectively. The most common reason for discontinuation from Cycle 1 in both rolapitant and control subjects was withdrawal of consent (7.0% and 8.8%, respectively). Compliance with rolapitant dosing was high (>99%) across both studies as was compliance with adjunct antiemetic therapy (>99%). Mean and median numbers of chemotherapy cycles administered in the MITT population were 3.7 and 4.0, respectively, in both the rolapitant and control groups. Median duration of each treatment cycle was 21 days in both groups

Efficacy results

Table 39 : Complete Response in the Delayed Phase of CINV: Summary and Between Group Comparison (MITT Population, Study P04834)

Efficacy Variable	CINV Phase	Rolapitant (N^a=666) Rate (%)	Control (N^a=666) Rate (%)	Unadjusted P-Value
Complete Response	Delayed Phase (>24-120 hours) n (%)	475 71.3% (67.7, 74.7)	410 61.6% (57.7, 65.3)	<0.001

Key secondary endpoints

Table 40 : Complete Response in the Acute and Overall Phases of CINV: Summary and Between-Group Comparisons (MITT Population MEC Study P04834)

Efficacy Variable	CINV Phase	Rolapitant (N=666) Rate (%)	Control (N=666) Rate (%)	Unadjusted P-Value
Complete Response	Acute Phase (0-≤24 hours) (%) (95% CI for %)c	556 (83.5) (80.4, 86.2)	535 (80.3) (77.1, 83.3)	0.143
Complete Response	Overall Phase (0-≤120 hours) n (%) (95% CI for %)c	457 (68.6) (64.9, 72.1)	385 (57.8) (54.0, 61.6)	<0.001

A pre-specified subgroup analysis was performed for the endpoint of complete response in each CINV phase for subjects who received Non-AC MEC (MEC according to recent guidelines) vs. AC based chemotherapy.

Table 41: Proportion of Patients Receiving AC or non AC Chemotherapy Achieving Complete Response

Complete Response	Rolapitant	Control	P-Value[a]
Non-AC	**N=322**	**N=307**	
Delayed	76.1	63.8	<0.001
Acute	90.7	84.4	0.016
Overall	74.8	61.2	<0.001
AC	**N=344**	**N=359**	
Delayed	66.9	59.6	0.047
Acute	76.7	76.9	N.S.
Overall	62.8	54.9	0.033

[a] Unadjusted P-values are obtained from Cochran-Mantel-Haenszel test.

N.S.=Not significant (p>0.05)

Nausea

The proportion of subjects with no significant nausea (maximum VAS of <25 mm) and no nausea (maximum VAS of <5mm) did not achieve statistical significance for the rolapitant group compared to the standard therapy group in any of the phases. In fact in the acute phase the control group were numerically higher than the rolapitant group for the no significant nausea endpoint. Rolapitant has very little impact on the treatment of nausea across any of the phases of MEC induced CINV. The results of the other secondary and tertiary

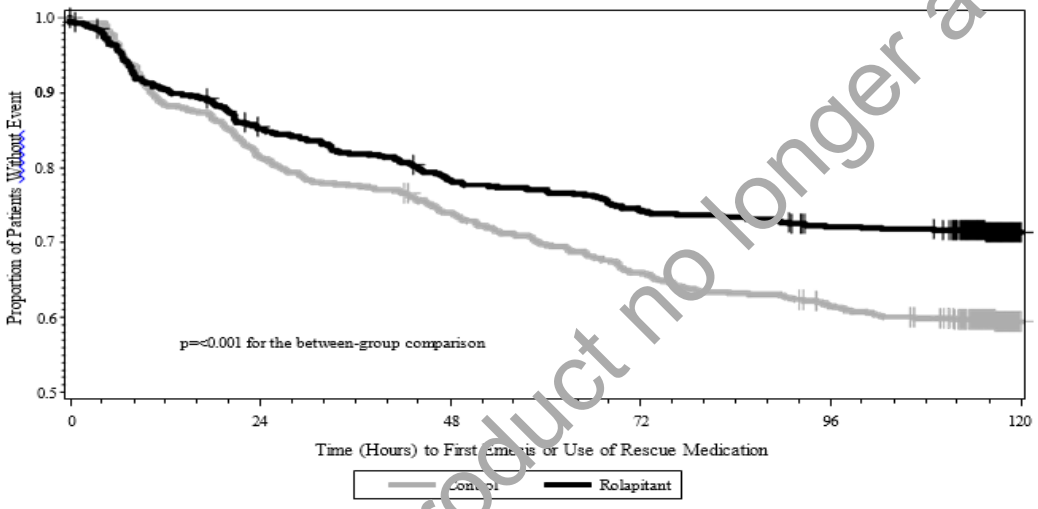
endpoints were generally in line with those of the primary and key secondary endpoints for the delayed, and overall phases for (no emesis and complete protection).

A higher proportion of subjects treated with rolapitant reported no impact on daily life (FLIE total score >108) compared with subjects who were treated with control (73.2% and 67.4%, respectively; unadjusted p = 0.027).

Time to First Emesis or Use of Rescue Medication During the First 120 Hours

A separation in the Kaplan-Meier curves is visually apparent early during the acute phase of CINV by 12 hours after administration of study drug. This separation continues to increase during the acute phase (0-24hrs) is sustained in the delayed phase of CINV(>24hrs). For Study P04834 the incidence of subjects requiring ≥1 rescue medication during Cycle 1 was lower in the rolapitant group than in the control group). (18.3% and 26.3%, respectively).

Figure 10: Kaplan-Meier Plot of Proportions of Subjects without Emesis or Use of Rescue Medication (MITT Population, Study P04834)



Source: CSR P04834, Figure 14.2.2

Overall the statistically significant and clinically relevant changes in CR in favour of rolapitant was seen across the delayed phase of CINV in subjects receiving MEC. The treatment effect was more pronounced in subjects receiving g non-AC MEC 12.3% compared with AC MEC 7.3%.

Subgroup analyses

Exploratory analyses of the primaryand key secondary were conducted for subject subgroups, according to gender, age, race, region, and receipt of CEC. During the delayed and overall phases of CINV, the CR rate favoured rolapitant across all subgroups for the MEC studies. There was some variability across subgroups in the acute phase responses.

Similar to the HEC studies efficacy outcomes by gender were variable across the MEC studies however opposite to the HEC studies response rates for males were consistently higher compared to females receiving rolapitant versus control across all CINV phases. (e.g. CR delayed phase females 68.4% vs control 59.3% OR 1.5 (1.2, 1.9) vs males 83.0% vs 70.8% OR 2.0 (1.1, 3.6) respectively. The magnitude of the treatment effect (CR delayed phase)for males was higher than that for females (e.g 12.2% difference vs 9.1%. Response rates for males receiving rolapitant were consistently higher than response rates in females

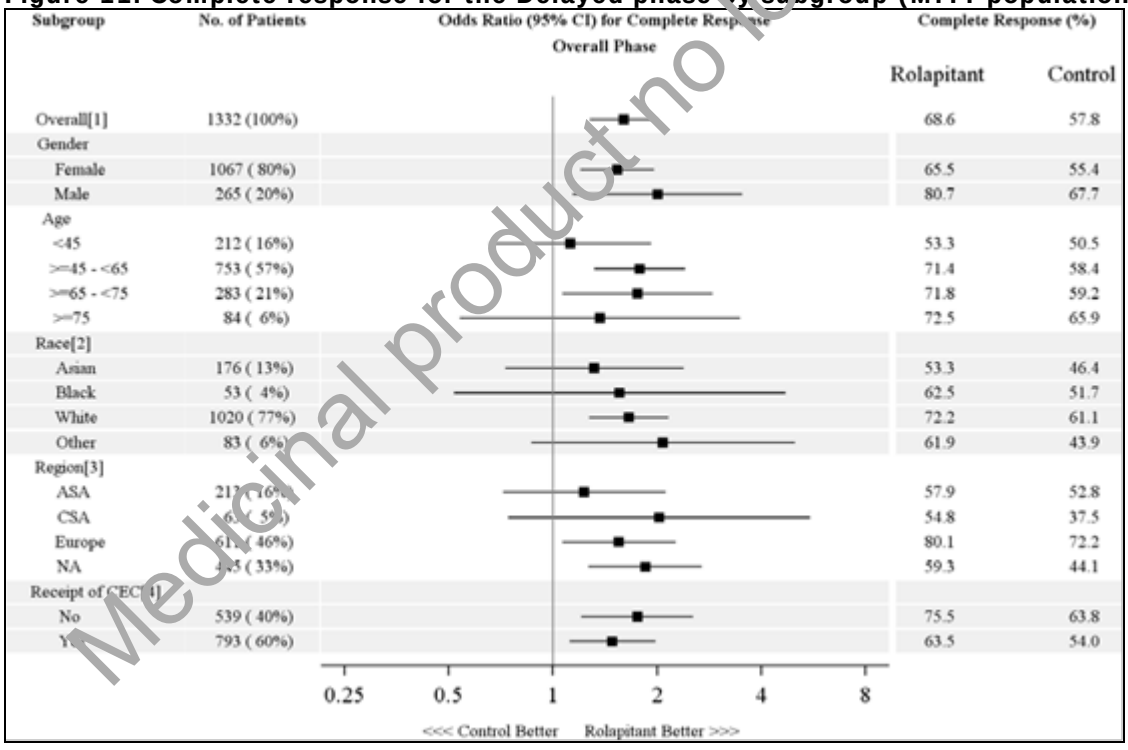
across all CINV phases . A Gail-Simon test conducted by the applicant indicated that there were no qualitative interactions between treatment and subgroup regardless of gender across all of these endpoints. The variability in response across gender within studies and across the HEC and MEC studies has not been fully explained.

Approximately 16% of the study population were under 45 years (age <45 is a risk factor for CINV) and just 6% of the study population were over 75 years. The CR rate was consistently higher in the rolapitant group compared to control in the age subgroups in the 45 -65 age group. Rolapitant was least effective in <45yrs and >75 yrs age group across all three phases.

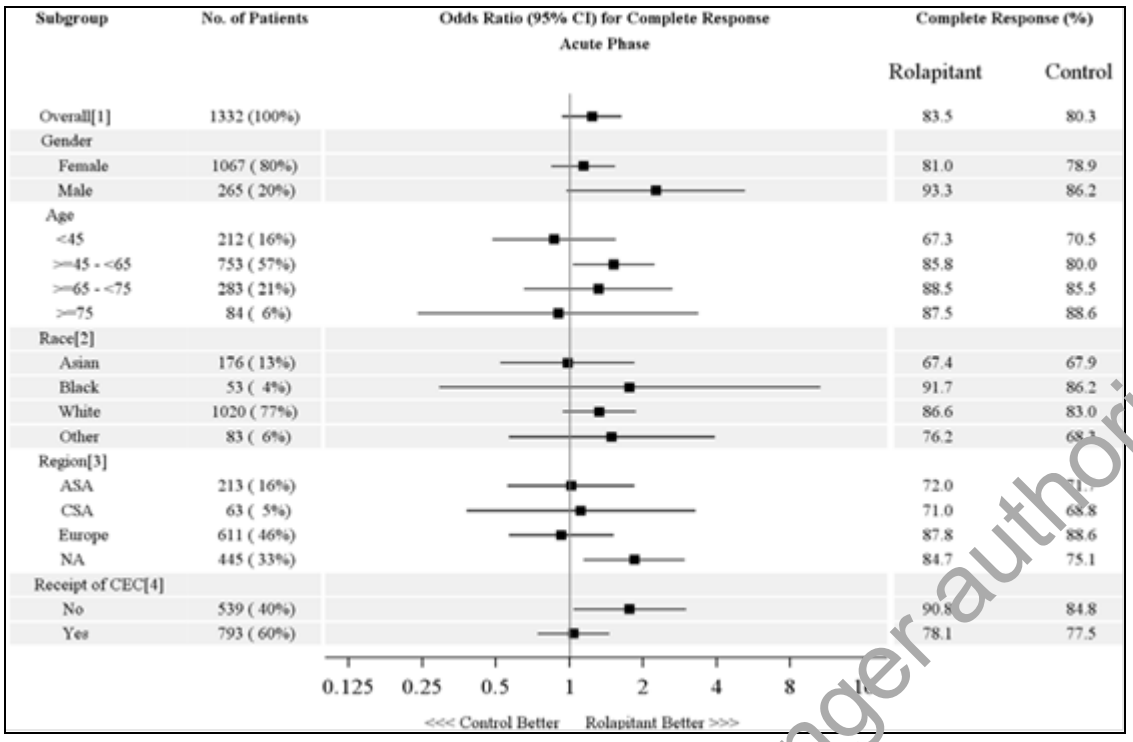
The CR rate was higher (OR>1) in the rolapitant group compared to the control group for all of the race categories in the MEC studies for all phases in the CR analyses except in the acute phase for the Asian population(OR=1).

The CR rate was higher in the rolapitant group compared to control in the majority of regions in the pooled analyses across all three phases of CINV.A further subgroup analysis was conducted for the three regions within Europe(Western, Central and Eastern Europe). Across all three phases the odds ratio for CR rate in Western Europe was less than zero (OR 0.9 delayed phase; OR 0.6 Acute phase; OR 0.8 Overall phase. The CR rate across all phases in Central Europe was consistently higher than the other regions. The reason for this variability across Europe is unclear.

Figure 11: Complete response for the Delayed phase by subgroup (MITT population) MEC study



Complete response for the Acute phase by subgroup (MITT population) MEC study



Repeat Efficacy

Similar to the HEC studies this study offered an optional multiple-cycle extension of up to 5 additional cycles for MEC.

Subjects response of no emesis or nausea based on duration of Cycle 1 (analysis over cycle duration <21 days versus ≥21 days also conducted for study P04834) for the MITT population was assessed to evaluate whether repeat dosing demonstrated sustained benefit of the use of rolapitant over multi-cycle use. Note that subjects evaluation of no emesis or nausea was based on subject recall on day 6, 7 or 8 rather than daily diary entries. Similar percentages of patients reported no emesis or nausea across cycles regardless of Cycle 1 duration and the treatment effect for rolapitant between Cycles 2 and 6 appears to be maintained.

Figure 12: Subject Response of No Emesis or Nausea by Cycle (MITT Population) P04834

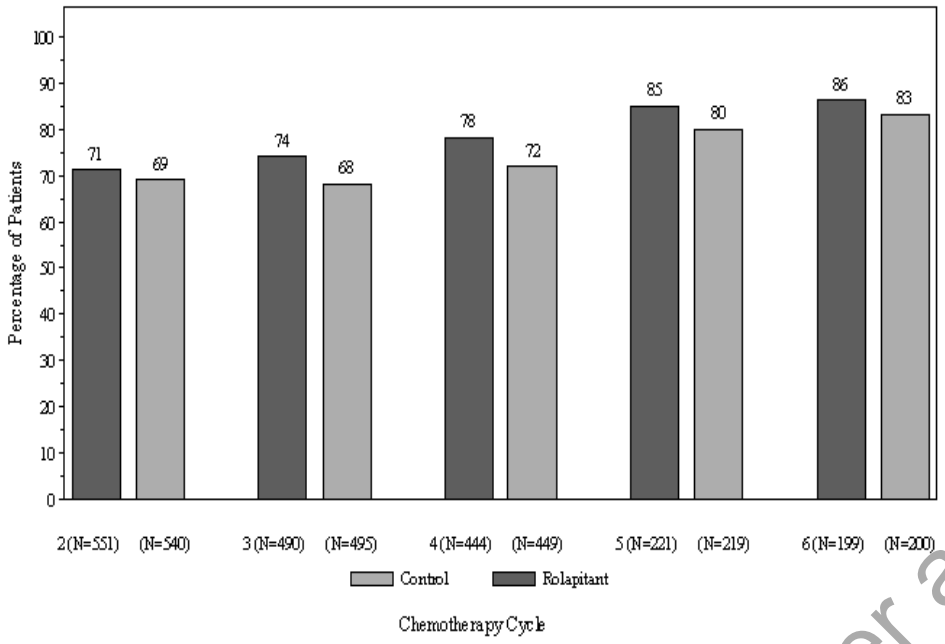


Table 42: Summary of efficacy for trial P04834

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy- Induced Nausea and Vomiting (CINV) in Subjects Receiving Moderatly Emetogenic Chemotherapy (MEC)		
Study identifier	TS-P04834	
Design	Multicenter, Randomized, Parallel-group, Double-Blind, Active-Controlled Study in Patients Receiving MEC MEC includes the following agents: cyclophosphamide IV (<1500 mg/m2), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine IV (>1 g/m2). These were the required chemotherapies included in the MEC protocol. For this study, the protocol specified that at least 50% of the study subjects would receive anthracycline in combination with cyclophosphamide as the MEC regimen	
	Duration of main phase:	Acute phase (0 to 24 hours) delayed phase (>24 to 120 hours) overall (0 to 120 hours) phases of CINV.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	Rolapitant	Rolapitant 200 mg on Day 1 + granisetron PO (2 mg from Day 1 to Day 3) + dexamethasone PO (20 mg on Day 1) n=666

	Placebo		Placebo on Day 1 + granisetron IV (10 µg/kg on Day 1) + dexamethasone PO (20 mg on Day 1 and 8 mg BID from Day 2 to Day 4) n=666
Endpoints and definitions	Primary endpoint	CR delayed phase	Complete response rate (defined as no emetic episodes, no rescue medication) from >24 through 120 hours after the start of the highly emetogenic chemotherapy administration (delayed phase)
	Key Secondary endpoint	CR acute phase	Complete response rate (defined as no emetic episodes, no rescue medication) from 0 through ≤ 24 hours after the start of the highly emetogenic chemotherapy administration (acute phase)
	Key Secondary endpoint	CR overall phase	Complete response rate (defined as no emetic episodes, no rescue medication) from 0 through ≤ 120 hours after the start of the highly emetogenic chemotherapy administration (overall phase)
	Secondary endpoint	No emesis Acute	No emesis (no vomiting, retching or dyr heaves) during the acute phase (0 through ≤ 24 hours)
	Secondary endpoint	No emesis delayed	No emesis (no vomiting, retching or dyr heaves) during the delayed phase (>24 through 120 hours)
	Secondary endpoint	No emesis overall	No emesis (no vomiting, retching or dyr heaves) during the overall phase (0 through 120 hours)
	Secondary endpoint	No significant nausea	No significant nausea (nausea <25 mm on VAS) during the overall phase (0 through 120 hours)
	Secondary endpoint	TTF	Time to the first emetic episode or time to the first rescue medication
Database lock	Last subject completed: 22 January 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent to treat		
	Overall patients		

Descriptive statistics and estimate variability	Treatment group	rolapitant	placebo
	Number of subject	666	666
	Primary endpoint CR delayed n (% patients)	475 (71.3)	410 (61.6)
	95% ICa	[67.7;74.7]	[57.7;65.3]
	p-valueb	<0.001	
	Key secondary endpoint CR acute n (% patients)	556 (83.5)	535 (80.3)
	95% ICa	[80.4;86.2]	[77.7;82.8]
	p-valuec	0.143	
	As per the SAP, with the hierarchical testing, as statistical significance was not achieved for this endpoint, formal statistical significance of subsequent endpoints within the hierarchy could not be established. The applicant acknowledges this however for completeness the unadjusted p-values are presented here		
	Key secondary endpoint CR overall n (% patients)	457 (68.6)	385 (57.8)
	95% ICa	[64.9;72.1]	[54.0;61.6]
	p-valuec	<0.001	
	Secondary endpoints No significant nausea during the overall phase of CINV	470 (70.6)	443 (66.5)
	p-valuec	0.118	
	Secondary endpoints No Emesis – Delayed Phase	536 (80.5)	465 (69.8)

	p-value[c]	<0.001	
	Secondary endpoints No Emesis – Acute Phase	585/666 (87.8)	563/666 (84.5)
	p-value[c]	0.085	
	Secondary endpoints No Emesis – Overall Phase	524/666 (78.7)	435/666 (65.3)
	p-value[c]	<0.001	

	Tertiary endpoints No Significant Nausea – delayed Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.2
		95% CI	(0.9, 1.5)
		P-value	0.194

	Tertiary endpoints No Significant Nausea – Acute Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.2
		95% CI	(0.9, 1.5)
		P-value	0.194

	Tertiary endpoints No Nausea – delayed Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.2
		95% CI	(0.9, 1.4)
		P-value	0.201

	Tertiary endpoints No Nausea – acute Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.0
		95% CI	(0.8, 1.2)
		P-value	0.693

	Tertiary endpoints No Nausea – overall Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.1
		95% CI	(0.9, 1.4)
		P-value	0.219
	Tertiary endpoints Complete Protection – Delayed Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.5
		95% CI	(1.2, 2.0)
		P-value	<0.001
	Tertiary endpoints Complete Protection – Acute Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	
		95% CI	
		P-value	
	Tertiary endpoints Complete Protection – overall Phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.4
		95% CI	(1.2, 1.8)
		P-value	0.001
	Tertiary endpoints No Impact on Daily Life Overall phase	Comparison groups	Rolapitant 200mg vs control
		Odds ratio	1.3
		95% CI	(1.0, 1.7)
		P-value	0.027
	Subgroup analysis Non-AC MEC Group		
Descriptive statistics and estimate variability	Treatment group	rolapitant	placebo
	Number of subject	322	307
	CR delayed n (% patients)	245 (76.1)	196 (63.8)
	Odds Ratio (IC95%) p-value[b]	1.8 (1.27,2.55) <0.001	
	CR acute n (% patients)	292 (90.7)	259 (84.4)

	Odds Ratio (IC95%) p-value[b]	1.80 (1.11,2.63) P=0.016	
	CR overall n (% patients)	241 (74.8)	188 (61.2)
	Odds Ratio (IC95%) p-value[b]	1.88 (1.34,2.65) P<0.001	
	Subgroup analysis AC Group		
Descriptive statistics and estimate variability	Treatment group	rolapitant	placebo
	Number of subject	344	359
	CR delayed n (% patients)	230 (66.9)	214 (59.6)
	Odds Ratio (IC95%) p-value[b]	1.37 (1.00,1.86) 0.047	
	CR acute n (% patients)	264 (76.7)	276 (76.9)
	Odds Ratio (IC95%) p-value[b]	0.99 (0.70,1.41) 0.966	
	CR overall n (% patients)	216 (62.8)	197 (54.9)
	Odds Ratio (IC95%) p-value[b]	1.39 (1.03,1.88) 0.033	
Notes	[a]p value from Cochran-Mantel-Haenszel test, stratified by gender [b]Exact 95% confidence interval (CI) for response rate c Unadjusted p-values		

Analysis performed across trials (pooled analyses and meta-analysis)

Table 43: Pooled results from HEC studies.

Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase (Studies 1 and 2 – HEC Individual Results)									
Efficacy Endpoints[a]	**HEC Study 1**			**HEC Study 2**			**Study 1 and 2 Combined**		
	Rolapitant (N=264) Rate (%)	**Control (N=262) Rate (%)**	**P-Value[b]**	**Rolapitant (N=271) Rate (%)**	**Control (N=273) Rate (%)**	**P-Value[b]**	**Rolapitant (N=535) Rate (%)**	**Control (N=535) Rate (%)**	**P-Value[c]**

Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase (Studies 1 and 2 – HEC Individual Results)									
	HEC Study 1			HEC Study 2			Study 1 and 2 Combined		
Complete Response									
Delayed	72.7	58.4	<0.001	70.1	61.9	0.043	71.4	60.2	<0.001
Acute	83.7	73.7	0.005	83.4	79.5	N.S.	83.6	76.6	0.004
Overall	70.1	56.5	0.001	67.5	60.4	N.S.	68.8	58.5	<0.001
No Emesis									
Acute	86.4	76.0	0.002	85.6	81.7	N.S.	86.0	78.9	0.002
Delayed	78.0	61.8	<0.001	73.1	65.2	0.046*	75.5	63.6	<0.001
Overall	75.4	59.2	<0.001	70.8	64.1	N.S.	73.1	61.7	<0.001
No Significant Nausea									
Acute	86.4	79.4	0.035	90.0	85.7	N.S.	88.2	82.6	0.009
Delayed	73.5	64.9	0.034	74.5	68.9	N.S.	74.0	66.9	0.011
Overall	71.6	63.0	0.037	72.7	67.8	N.S.	72.1	65.4	0.017

[a] Primary endpoint was complete response in the delayed phase. Delayed phase: 24 to 120 hours post-cisplatin treatment; Acute phase: 0 to 24 hours post-cisplatin treatment; Overall phase: 0 to 120 hours post-cisplatin treatment
[b] Unadjusted P-values are obtained from Cochran-Mantel Haenszel test, stratified for sex.
[c] Unadjusted P-values are obtained from Cochran-Mantel-Haenszel test, stratified by study and sex.
N.S.=Not significant (p>0.05)
*Not significant after applying pre-specified multiplicity adjustment.

Efficacy in repeat cycles

In order to address the potential concern that the numerical improvements observed with rolapitant over multiple cycles were due to control in Cycle 1, an exploratory analysis of time to emesis for those patients who had no emesis in Cycle 1 was performed. By limiting the analysis to patients with no emesis in Cycle 1, the two treatment groups are comparable for the assessment of effect in subsequent cycles. This analysis accounts for patient drop outs via censoring. Data from the HEC studies were pooled to provide a more robust sample size for this subset analysis. For the subset of patients without emesis in Cycle 1, the time to emesis in subsequent cycles was significantly extended (pooled HECs: p=0.0167; P04834: p=0.0027).

Discontinuation across cycles due to 'lack of efficacy' was analysed. Across all six cycles in the 3 Phase 3 clinical studies, discontinuation rates due to lack of efficacy were as follows (rolapitant vs. control): 4832: 1.1% vs. 1.5%; 4833: 3.2% vs. 2.5%; 4834: 2.0% vs. 4.4%.

Clinical studies in special populations

Table 44: Number of older patients in clinical efficacy studies.

	Age < 65 n/N (%)	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials				
P04832	392/526 (74.5%)	116/526 (22.1%)	16/526 (3.0%)	2/526 (0.4%)

	Age < 65 n/N (%)	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
P04833	398/544 (73.2%)	128/544 (23.5%)	18/544 (3.3%)	0/544 (0%)
P04834	965/1332 (72.4%)	283/1332 (21.2%)	81/1332 (6.1%)	3/1332 (0.2%)
Total	**1755/2402 (73.1%)**	**527/2402 (21.9%)**	**115/2402 (4.8%)**	**5/2402(0.2%)**

Supportive study(ies)

No additional studies were assessed as supportive. A phase II study was initiated in 2006 while phases III were initiated in 2012 where only 91 patients were included in the 200 mg rolapitant group. Considering the difference of sample size between the phase II and the 3 phases III and the possible changes in standard of care, the assessment has focused on results from the 3 phase III studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

All 3 phase III studies were multicentre, randomised, parallel-group, double-blind, and placebo-controlled studies with objective to determine whether the administration of rolapitant on add-on therapy with a 5-HT3 receptor antagonist and dexamethasone improves protection from CINV in the delayed phase (>24 to 120 hours) compared to administration of placebo on add-on with a 5-HT3 receptor antagonist and dexamethasone, in cycle 1, in subjects receiving highly or moderately emetogenic chemotherapy.

Two phase III HEC studies (P04832 and P04833) were conducted in subjects receiving for treatment of their underlying malignancy ≥ 60 mg/m2 of cisplatin-based chemotherapy which is generally regarded as a relevant model of highly emetogenic chemotherapy (HEC). Since 2010 consensus clinical guidelines (MASCC/ESMO) recommend a combination of aprepitant plus a 5HT3 receptor antagonist and dexamethasone to prevent acute nausea and vomiting in subjects receiving cisplatin based chemotherapy. Data comparing the longer-acting NK-1 receptor antagonist rolapitant with first-generation NK-1 receptor antagonists such as aprepitant would have helped clarify rolapitant's place in antiemetic management for CINV associated with HEC.

The study design chosen for MEC study was add-on of NK-1 RA to dexamethasone and 5HT3 receptor antagonist with further doses of 5HT3 receptor antagonist on days 2, 3. The protocol specified that at least 50% of the study subjects would receive anthracycline in combination with cyclophosphamide as the MEC regimen. Since this study was designed anthracycline in combination with cyclophosphamide has been designated as HEC. However since 2010 antiemetic prophylaxsis for AC and non-AC MEC have been different recognising the higher emetogenicity of AC. The administration of oral granisetron from day 2 to day 3 post chemotherapy is not recommended as part of the MASCC/ESMO consensus guidelines for the prevention of CINV with non- AC MEC. In subjects treated with AC chemotherapy, the guidelines recommend use of a 5-HT3 receptor antagonist plus a corticosteroid Plus an NK-1 RA on day 1 followed by NK-1 RA on day 2 and 3. The comparator regimen is not in line with the recommended prophylaxis for AC or non-AC MEC in CINV (MASCC /ESMO 2010) but reflects treatment guidelines that were available at the time of the study design.

The decision to include more than 50% of subjects on AC chemotherapy in both the rolapitant and control groups was based on the study designs conducted for other earlier NK-1 RAs.

The subjects recruited to the MEC study were chemotherapy naïve. The HEC study participants were not required to be chemotherapy naïve. The current EMA guidance on CINV recommends that subjects should be stratified at baseline according to prior chemotherapy. Subjects were stratified according to gender only in the pivotal efficacy studies. The primary endpoint for those studies was the rate of complete response (CR) defined as no emesis and no use of rescue medication during the delayed phase (> 24 through 120 hours). This endpoint is considered to be appropriate Indeed, the NK1 receptor antagonists are expected to be mainly effective in the delayed phase of emesis, while 5-HT3 antagonists have been proven to be mainly effective in the acute phase. The primary analysis was conducted using the MITT.

In all phase III studies, patients had the possibility to participate up to 5 additional cycle (a total of 6 cycles). However, the primary endpoint differed for the subsequent cycles. Indeed, instead of CR in the delayed phase subjects were recall and asked if they had no vomiting/retching and no nausea that interfered with quality of life. Furthermore, the data was not collected in a diary as in cycle 1 but via a telephone call around 7 days after chemotherapy which less rigorous.

No re-randomization was planned after cycle 1 and patients continued with the same study medication administered in the same manner as in cycle 1. In these three studies, subjects were randomised 1:1 to receive rolapitant 200 mg administered orally or placebo, randomization was stratified by gender but not by age.

Efficacy data and additional analyses

In both HEC Studies, the demographics were generally well-balanced between the treatment groups in this study. However, there were some differences in demographic characteristics noted across the two pivotal studies. Study P04832 had more females, more subjects of Asian origin, more non-drinkers and more subjects with ovarian cancer than study P04833.There were more white subjects more subjects with lung and stomach cancer, more subjects from Europe included in study P04833. Although the differences across the populations in the two HEC studies are small, they occur across a diverse range of variables. Onset of CINV can be impacted by a number of variables (age, sex , level of alcohol consumption, history of pregnancy-related nausea and vomiting, prior response to CINV with previous cycles of chemotherapy, susceptibility to motion sickness, and cisplatin dose) and there is some evidence that this effect can be cumulative (Warr et al 2014). The impact of this variability may account for the difference in outcomes for the pivotal studies. The demographic differences that were noted reflect the broad patient population recruited in terms of location, tumour type, chemotherapy regimen etc. A number of the variables that are recognised as risk factors for onset of CINV are missing from the baseline characteristics presented for the pivotal studies, in particular prior response to CINV with previous cycles of chemotherapy, for subjects in the HEC studies. A similar picture was seen for patients who had received medication or pre-medication for nausea and vomiting during previous chemotherapy or a history of nausea or vomiting during the previous chemotherapy. However, overall the proportion of patients involved was relatively small and the distribution of patients in the three subgroups was well balanced across treatment groups.

Less than 9% of the study population were under 45 years (age <45 is a risk factor for CINV) and just 3% of the study population were over 75 years. A sufficient number of young (<45yrs) and elderly subjects >75yrs have not been included in the confirmatory studies to provide a firm basis for the assessment of safety and efficacy in these age groups. The majority of participants were white (approx.75% across HEC and MEC

studies). Low numbers in the other race categories make it difficult to draw clear conclusion on efficacy in these subgroups.

In the MEC study, the demographics were generally well-balanced between the treatment groups in this study. However there was a preponderance of female participants reflecting the fact that breast cancer was the commonest cancer subtype. Other baseline characteristics previously identified as risk factors for CINV such as alcohol consumption (self-reported), and age were well balanced across treatment groups. Clinical experience with NK-1 RA in clinical practice and this has not resulted in differential clinical guidelines for males being treated with MEC (MASCC ESMO 2016, NCCN2016) and the findings in the MEC study are generalizable to men.

Results of the studies showed a statistical superiority of rolapitant (plus granisetron and dexamethasone) over placebo (plus granisetron and dexamethasone PO) in terms of complete response (CR), defined by the absence of emesis and use of rescue medication, during the delayed phase (i.e. > 24h -120h) following initiation of chemotherapy. CR in the delayed phase for each clinical study were: 72.7% vs 58.4% (△=14.3%) p < 0.001in P04832 HEC; 70.1% vs 61.9% (△=8.2%) p 0.043 in P04833 HEC; 71.3% vs 61.6% (△= 9.7%) p < 0.001 in P04834 MEC as defined by the applicant; 66.9% vs 59.6 (△= 7.3%) p= 0.047 P04834 AC regimen; 76.1% vs 63.8% (△=12.3%) p< 0.001 in P04834 MEC (AC regimen excluded).
The proportion of subjects, who had no emesis and no use of rescue medication was significantly higher in the rolapitant group versus the placebo group, in both studies in patients receiving highly emetogenic chemotherapy regimen (HEC) including cisplatin and the study in patients receiving moderately emetogenic chemotherapy (MEC) regimen or a combination of anthracycline plus cyclophosphamide regimen (AC).

The results in key secondary endpoints in P04832 HEC study were clinically and statistically significant, however in the P04833 HEC and P04834 MEC studies, key secondary endpoints did not achieved statistical significance. In the HEC studies, Kaplan-Meier curves for time to first emesis or use of rescue medication for both pooled HEC studies the separation was widest from 24hs and plateaued at 48hrs. If CR was achieved at 48hrs complete response was maintained throughout the 120 hour period.

In the MEC study, Kaplan-Meier curves for time to first emesis or use of rescue medication for both studies separated for the rolapitant and the control curves around the 10 hour mark (in the acute phase) and was maintained throughout the 24 to 120 hour period. The incidence of subjects requiring ≥1 rescue medication during Cycle 1 was lower in the rolapitant group than in the control group (18.3% and 26.3%, respectively) but was higher than that seen for the HEC studies.

No impact was seen in terms of reduction or prevention of nausea across any of the phases in the MEC study. The proportion of subjects who experienced no significant nausea and no nausea in the acute and delayed phase were not significantly higher in the rolapitant group compared to the control group.

In the HEC studies, subgroup analyses showed some variability in response rates between men and women. Women had a consistently more favourable response than men across all phases of CINV. The magnitude of the treatment effect (CR delayed phase) for males was much smaller than that for females (e.g 18.9% difference vs 6.6%. The less favourable results in the HEC setting for males has not been fully explained. Less than 9% of the study population were under 45 years (age <45 is a risk factor for CINV) and just 3% of the study population were over 75 years. The CR rate was higher in the rolapitant group compared to control in the majority of age subgroups in the pooled HEC analyses and the treatment effect is consistently in favour of rolapitant across age groups tending to increase with age. However subject <45yrs and >75 are not adequately represented in these studies.

In the MEC Study, a further subgroup analysis by region in Europe indicated that there was considerable regional variation across Western Eastern and Central Europe. In particular the CR response rate was lower in Western Europe across all phases of treatment compared with the other regions.

In this study, at least 50% of the study subjects would receive anthracycline in combination with cyclophosphamide IV which is considered to be a highly emetogenic regimen. The comparator control regimen is not in line with current standard of care as outlined in the MASCC/ESMO consensus guidelines current at the time the study or the most recent version for AC chemotherapy.

The efficacy of rolapitant compared with control in the delayed phase (71.3% vs, 61.6%) OR 95% CI 1.6 (1.2, 2.0) p<0.001 is slightly less than that seen in the HEC studies pooled. The treatment effect (rolapitant compared to control) for CR delayed phase was 9.7% in the MEC study for the combined AC and non AC MEC populations compared with 11.2% in the pooled HEC studies. Rolapitant was less effective in AC MEC subgroup compared with non-AC MEC. Non-AC MEC Delayed phase: 76.1%vs 63.8% OR 1.8 95%CI (1.27, 2.55) p<0.001 compared with AC Delayed phase: 66.9% vs 59.6 OR 1.37 95% CI (1.00, 1.86) p= 0.047.

Across both HEC and MEC studies efficacy data from subsequent cycles were a very fluctuating with a low amplitudes regarding benefit of the use of rolapitant over multi-cycle use. This analysis is difficult to interpret because different endpoints were used in the repeat cycles and the methodology for collection the nausea and vomiting data was different. Furthermore subjects are not re-randomised prior to subsequent cycle of chemotherapy.

The choice of a different endpoint for subsequent endpoint (compared to first cycle) in order to limit patient burden indeed completing comprehensive diaries over 6 cycles can be demanding for patients with cancer is justified. An analysis of efficacy over multiple cycles in patients without emesis in cycle 1 was presented. The time-to-emesis or rescue med across cycles in patients with no emesis at cycle 1 show a statistically significant benefit in rolapitant patients compared to the control group suggesting that efficacy in subsequent cycles was maintained. This differentiation in the KM curves for the time to emesis analysis in patients who had no emesis in cycle 1 across following repeat treatment, the lack of differential drop-outs across treatment groups and the low levels of discontinuation due to lack of efficacy gives support to the claim for efficacy over repeat cycles of chemotherapy. The maintenance of efficacy over multiple cycles is considered useful clinical information and is included in section 5.1.of the SmPC.

As recommended by current guidelines in combination NK1 inhibitors should be used in combination with a 5-HT3 inhibitor and dexamethasone in order to prevent emesis and nausea in both acute and delayed phase.

The CR treatment effect in the acute phase achieved statistical significance in only one of the 2 HEC studies but not the MEC study. The treatment effect of rolapitant in the acute phase as demonstrated by the CR, no emesis, no nausea and no significant nausea endpoints was modest, therefore the clinical significance of the treatment effect for rolapitant in the acute phase has not been (only historical comparisons) up to the level of other KN1 antagonists aprepitant and netupitant - in association with palonosetron.

Key secondary endpoints (complete response in acute and overall CINV phases) were numerically in favour of rolapitant arm but not statistically significant in study P048033in subject receiving HEC regimen.

Regarding repeat course, due to the change of primary end point and the way it is collected, to the absence of re randomisation after cycle 1, weaknesses in methodology are considered however the effect of rolapitant in repeat course is sufficiently shown and is described in section 5.1.

The only measure of impact of rolapitant on quality of life used in all three studies was the FLIE questionnaire. This was only evaluated as an exploratory tertiary endpoint. An inconsistent response was

seen across studies. The MEC study subjects reported experiencing less interference with normal daily life. A higher proportion of subjects treated with rolapitant reported no impact on daily life compared with subjects who were treated with control. Unlike the HEC studies where there was no difference across the treatment groups in the proportion of subjects reporting no impact on daily life.

No direct comparative data with any of the currently approved NK1RA are available. Indirect comparison of CR rates in delayed phase with aprepitant suggest that the treatment effect with rolapitant is smaller than that seen with aprepitant but exceeds the >10% difference considered to be clinically relevant.

2.5.4. Conclusions on the clinical efficacy

Results from clinical studies showed efficacy of rolapitant as add on to a standard therapy compared to standard therapy plus placebo in the prevention of chemotherapy induced delayed nausea and vomiting in adults receiving initial course of highly and moderately emetogenic chemotherapy regimen. The primary endpoint CR for the treatment effect in the acute phase achieved statistical significance in one of the HEC studies but was numerically higher (although modest) vs control across studies.

As recommended by current guidelines in combination NK1 inhibitors should be used in combination with a 5-HT3 inhibitor and dexamethasone in order to prevent emesis and nausea in both acute and delayed phase.

2.6. Clinical safety

The oral rolapitant clinical development program consists of 20 completed studies, including 13 Phase 1 studies in healthy adults and one Phase 1 study in adults with mild or moderate hepatic impairment; two Phase 2 studies, one each in subjects at risk for chronic idiopathic cough (CIC), and Post-Operative Nausea and Vomiting (PONV); and four studies in subjects at risk for CINV.

In order to review the data, pooling groups were constructed:

Pooling Group 1 consists of the four clinical studies supporting the proposed indication in CINV.

Pooling Group 2 represents a second integrated analysis on safety data from healthy subjects receiving a single dose (doses ranged from 5 mg to 800 mg) of rolapitant as monotherapy.

Other Phase 1 studies and Phase 1 study cohorts with potential confounding effects (eg, co-administration of concomitant medications, hepatic impairment), and Phase 2 studies that studied indications other than the target indication, were not included in the pooled analyses.

Patient exposure

Pooling Group 1 (CINV studies)

A total of 2868 subjects received at least one dose of study drug in the CINV studies, of which 1567 subjects received rolapitant at any dose and 1301 received control. Among rolapitant-treated subjects, 1294 were assigned to receive the proposed dose of 200 mg across these studies.

A high percentage of subjects completed Cycle 1 of the studies (95.1%, 94.9%, and 94.2% in the 200 mg rolapitant, all rolapitant dose, and control groups, respectively).

Participation in Cycles 2 to 6 was voluntary. A similar percentage of subjects in the control group (76.9%), rolapitant 200 mg group (78.4%), and rolapitant overall group (76.7%) continued to Cycle 2. The most common reason for not continuing into Cycle 2 was study completion in the overall rolapitant group (7.0%), and withdrawn consent in the rolapitant 200 mg group (4.3%) and control group (5.4%). Within the HEC group, 22.3% of subjects receiving <200 mg rolapitant completed Cycle 1 but did not continue to the next cycle because of study completion, compared with 4.8% and 6.4% in the control and rolapitant 200 mg groups, respectively. Overall only 367 subjects in the CINV trials completed 6 cycles of therapy and 319 completed 6 cycles at the proposed dose of 200mg.

Pooling Group 2 (single dose in healthy subjects)

A total of 606 healthy subjects were enrolled in the Phase 1 studies included in Pooling Group 2 and randomized to receive a single dose of rolapitant (n = 550) or placebo (n = 56)

Overall, a high percentage of subjects completed the studies (rolapitant, 97.3%, placebo, 96.4%) in Pooling Group 2. The most common reason for premature discontinuation in the overall rolapitant group was withdrawn consent (0.7%). No subjects discontinued from study treatment due to AEs.

Individual Studies or Study Cohorts not Included in Pooling Group 1 or 2

Phase 1 Studies

A total of 268 subjects were enrolled in Phase 1 studies or study cohorts during the rolapitant oral development that were not included in Pooling Group 1 or Pooling Group 2 and they received rolapitant (n = 258) or control (n = 10). The reasons for discontinuation were AEs unrelated to study treatment (n = 2), loss to follow-up (n = 1), protocol noncompliance (n = 1), and withdrawn consent (n = 1).

Phase 2 Studies

A total of 644 subjects were enrolled in Phase 2 studies not included in Pooling Group 1 or Pooling Group 2 and received rolapitant (n = 423) and/or placebo (n = 135) or active control (n = 104). Due to the crossover design of Study P04888, 27 subjects received both rolapitant and placebo. Most subjects completed the Phase 2 studies with data described individually. There was no relationship between discontinuations and increasing dose. The most common reasons for discontinuation were subject decision and loss to follow-up.

Table 45 : Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	1568	1567	1294	367
Active controlled				
Other studies^		1231	730	-
Post marketing	0	0	0	0
Compassionate use	0	0	0	0

Adverse events

POOLING GROUP 1 (CINV patients)

Pooling Group 1 is the primary analysis set that allows for a comparison of rolapitant to control in subjects in the CINV studies. It includes all subjects from the controlled, double-blind, randomized, parallel comparison studies conducted in subjects at risk for CINV.

The safety assessment included analysis of AEs, clinical laboratory parameters, vital signs, ECGs, neurological parameters, and concomitant medications. The effect of intrinsic factors (age, gender, body weight, race, and ethnicity) and extrinsic factors (geographic region and cycle length) were evaluated. Potential drug interactions with substrates of CYP2D6 and BCRP were assessed.

The overall incidence of TEAEs across subjects in the CINV studies who received rolapitant 200 mg or rolapitant at any dose in Cycle 1 was 64.0% and 65.2%, respectively, which was similar to the overall incidence in subjects who received control (64.6%). Across all cycles combined, the overall incidence of TEAEs for subjects with CINV who received rolapitant 200 mg or rolapitant at any dose was 81.5% and 82.3%, respectively, similar to the incidence reported in subjects who received control (80.9%).

Table 46: Summary adverse events in CINV studies P04832 (HEC), P04833 (HEC) and P04834 (MEC)

	HEC (P04832 and P04833)		MEC (P04834)		ALL CINV	
	Control	Rolapitant 200mg	Control	Rolapitant 200mg	Control	Rolapitant 200mg
N	537	535	674	670	1211	1205
≥ 1 TEAE	427 (79.5%)	428 (80%)	551 (81.8%)	547 (81.6%)	978 (80.8%)	975 (80.9%)
≥ 1 TRTEAE	27 (5%)	26 (4.9%)	92 (13.6%)	80 (11.9%)	119 (9.8%)	106 (8.8%)
≥ 1 Grade 3 TEAE	178 (33.1%)	179 (33.5%)	174 (25.8%)	179 (26.7%)	352 (29.1%)	358 (29.7%)
≥ 1 TESAE	119 (22.2%)	117 (21.9%)	103 (18.7%)	89 (13.3%)	222 (18.3%)	206 (17.1%)
≥ 1 TRTESAE	0	1 (0.2%)	0	0	0	1 (0.1%)
TEAE DC	65 (12.1%)	61 (11.4%)	37 (5.5%)	34 (5.1%)	102 (8.4%)	95 (7.9%
Death	21 (3.9%)	20 (3.7%)	7 (1%)	13 (1.9%)	28 (2.3%)	33 (2.7%)

The most common TEAEs in cycle 1 in subjects receiving 200 mg rolapitant were fatigue (11.8%), constipation (9.0%), neutropenia (8.2%), decreased appetite (7.8%), and alopecia (7.6%). The incidence of these common TEAEs was similar in the rolapitant 200 mg group, all rolapitant and control groups.

For all cycles combined, the most common TEAEs in subjects receiving 200 mg rolapitant were fatigue (19.8%), alopecia (15.8%), and neutropenia (15.2%). The incidence of these common TEAEs was similar in the rolapitant 200 mg, all rolapitant dose, and control groups.

Within the HEC group in Cycle 1 and across all cycles combined, the incidence of the most common TEAEs was similar to or slightly higher in the <200 mg rolapitant group compared with the 200 mg rolapitant and control groups.

In Cycle 1, the incidence of treatment-related TEAEs was comparable in the 200 mg rolapitant group, the all rolapitant doses group, and the control group. The most commonly reported treatment-related events in the overall rolapitant 200 mg group were fatigue (1.9%), constipation (1.5%), and headache (1.5%); the incidence of these events was similar in the all rolapitant doses group (1.8%, 2.0%, and 1.8%, respectively) and the control group (1.4%, 1.5% and 1.4%, respectively). In all cycles combined, the incidence of treatment-related TEAEs was comparable in the 200 mg rolapitant group, the all rolapitant doses group, and the control group.

Table 47 : TEAEs by MedDRA Preferred Term with Incidence of ≥ 3% of Subjects in the Overall Rolapitant 200mg group or ≥ 10% of subjects in any group. Cycle 1 all subjects in CINV trials

	Overall CINV		
	Control N =1301	Rolipant 200mg N =1294	All Rolipant N =1567
Subjects ≥ 1 incidence	840 (64.6%)	828 (64%)	1021 (65.2%)
Fatigue	146 (11.2%)	153 (11.8%)	187 (11.9%)
Constipation	151 (11.6%)	117 (9%)	149 (9.5%)
Neutropenia	88 (6.8%)	106 (8.2%)	122 (7.8%)
Decreased appetite	100 (7.7%)	101 (7.8%)	122 (7.8%)
Alopecia	112 (8.6%)	98 (7.6%)	111 (7.1%)
Diarrhoea	89 (6.8%)	87 (6.7%)	116 (7.4%)
Headache	101 (7.8%)	81 (6.3%)	108 (6.9%)
Asthenia	100 (7.7%)	76 (5.9%)	99 (6.3%)
Nausea	104 (8%)	72 (5.6%)	127 (8.1%)
Dizziness	41 (3.2%)	61 (4.7%)	79 (5%)
Dyspepsia	35 (2.7%)	52 (4%)	67 (4.3%)
Mucosal inflammation	43 (3.3%)	48 (3.7%)	60 (3.8%)
Stomatitis	29 (2.2%)	42 (3.3%)	49 (3.1%)
Hiccups	32 (2.5%)	41 (3.2%)	49 (3.1%)
Anaemia	35 (2.7%)	40 (3.1%)	50 (3.2%)
UTI	33 (2.5%)	39 (3%)	42 (2.7%)
Vomiting	61 (4.7%)	19 (1.5%)	51 93.3%)

Table 48 : TEAEs by MedDRA Preferred Term with Incidence of ≥ 3% of Subjects in the Overall Rolapitant 200mg group or ≥ 10% of subjects in any group all cycles combined, all subjects in CINV trials

	Overall CINV		
	Control N =1301	Rolipant 200mg N =1294	All Rolipant N =1567
Subjects ≥ 1 incidence	1053 (80.9%)	1055 (81.5%)	1289 (82.3%)
Fatigue	253 (19.4%)	256 (19.8%)	310 (19.8%)
Alopecia	227 (17.4%)	204 (15.8%)	227 (14.5%)
Neutropenia	173 (13.3%)	197 (15.2%)	240 (15.3%)
Constipation	215 (16.5%)	186 (14.4%)	234 (14.9%)
Asthenia	190 (14.6%)	182 (14.1%)	217 (13.8%)
Decreased appetite	172 (13.2%)	174 (13.4%)	215 (13.7%)
Diarrhoea	160 (12.3%)	164 (12.7%)	207 (13.2%)
Nausea	201 (15.4%)	151 (11.7%)	246 (15.7%)
Anaemia	113 (8.7%)	136 (10.5%)	168 (10.7%)
Headache	143 (11%)	115 (8.9%)	152 (9.7%)
Dizziness	91 (7%)	97 (7.5%)	120 (7.7%)
Mucosal inflammation	74 (5.7%)	86 (6.6%)	106 (6.8%)
Dyspepsia	71 (5.5%)	79 (6.1%)	98 (6.3%)
UTI	69 (5.3%)	76 (5.9%)	85 (5.4%)
Leukopenia	72 (5.5%)	75 (5.8%)	108 (6.9%)
Hypomagnesaemia	54 (4.2%)	70 (5.4%)	71 (4.5%)
Stomatitis	76 (5.8%)	69 (5.3%)	77 (4.9%)
Abdominal pain	56 (4.3%)	64 (4.9%)	83 (5.3%)
Cough	66 (5.1%)	59 (4.6%)	81 (5.2%)
Dyspnoea	46 (3.5%)	58 (4.5%)	69 (4.4%)
Dehydration	76 (5.8%)	57 (4.4%)	70 (4.5%)
Pyrexia	58 (4.5%)	55 (4.3%)	69 (4.4%)
Hiccups	32 (2.5%)	53 (4.1%)	63 (4%)
Dysgeusia	51 (3.9%)	50 (3.9%)	58 (3.7%)

Vomiting	117 (9%)	50 (3.9%)	113 (7.2%)
Insomnia	82 (6.3%)	49 (3.8%)	62 (4%)
Bone pain	52 (4%)	46 (3.6%)	49 (3.1%)
Back pain	36 (2.8%)	45 (3.5%)	54 (3.4%)
Thrombocytopenia	39 (3%)	43 (3.3%)	55 (3.5%)
Febrile neutropenia	49 (3.8%)	42 (3.2%)	52 (3.3%)
Hypokalaemia	47 (3.6%)	40 (3.1%)	53 (3.4%)
Pain in extremity	30 (2.3%)	40 (3.1%)	49 (3.1%)
Peripheral oedema	42 (3.2%)	39 (3%)	45 (2.9%)

Nervous System Events

The incidence of TEAEs in the *Nervous system disorders* SOC in Cycle 1 was similar in the rolapitant 200 mg group the all rolapitant doses group and the control group (14.7%, 15.6%, and 14.6%, respectively). Results were also similar for the all cycles combined analysis (25.1%, 25.4% and 24.5%, respectively). The most common TEAEs in the *Nervous system disorders* SOC in both Cycle 1 and all cycles combined were headache, dizziness, and dysgeusia. Across all cycles combined, the incidence of headache was 8.9%, 9.7%, and 11.0% in the rolapitant 200 mg, all rolapitant doses, and control groups, respectively; dizziness was reported in 7.5%, 7.7%, and 7.0% of subjects, respectively; and dysgeusia in 3.9%, 3.7%, and 3.9%, respectively.

Across all cycles combined, convulsion occurred at a similar frequency in the rolapitant 200 mg and control groups (0.2% each); one additional subject in the rolapitant 200 mg group experienced partial seizures. Two subjects who received <200 mg rolapitant experienced convulsions. In 4 of 8 subjects, seizures occurred during Cycle 1 of treatment. All cases were reported as recovered/resolved and 3 events were associated with discontinuation. All subjects who experienced events of convulsion/partial seizure had multiple confounding factors. For the rolapitant subjects, four subjects had metastatic disease to the central nervous system that was not known to be present prior to the event.

Haematopoietic Leukopenia Events

Overall across all cycles combined, 21.6% of subjects in the 200 mg rolapitant group and 21.8% of subjects in the all rolapitant doses group experienced at least one TEAE derived from the SMQ for Haematopoietic leukopenia, compared with 19.7% of subjects in the control group. Most of these events were assessed as unrelated to study treatment

Anemia Events

Across all cycles combined, the incidence of anemia was 10.5%, 10.7%, and 8.7% in the 200 mg rolapitant, all rolapitant, and control groups, respectively. All other TEAEs related to anemia were reported in <0.5% of subjects who received rolapitant 200 mg with similar incidence, in both Cycle 1 and all cycles combined, as that reported in the control group. Most of these events were assessed as unrelated to study treatment

Acute Renal Failure

Overall across all cycles combined, 3.5% of subjects in the 200 mg rolapitant group and 3.9% of subjects in the all rolapitant doses group experienced at least one TEAE derived from the SMQ for acute renal failure, compared with 4.0% of subjects in the control group. Most of these events were assessed as unrelated to study treatment

Hepatic Dysfunction

Overall across all cycles combined, 2.3% of subjects in the 200 mg rolapitant group and 2.6% of subjects in the all rolapitant doses group experienced at least one TEAE derived from the SMQ for hepatic dysfunction, compared with 2.5% of subjects in the control group.

5 cases met Hy's law criteria. One case occurred in a subject in the 10 mg dose group in Study P04351. In this subject, mild to moderate elevations in ALT (4.9 x ULN) and bilirubin (2.9 x ULN) with AST and ALP within normal limits observed at Cycle 1 Visit 2; these elevations resolved spontaneously to within normal limits by the next visit. This subject received a total of 4 cycles of therapy with no further elevations in liver function tests that met Hy's law laboratory criteria. The remaining 4 cases occurred in the control group in HEC studies

Cardiac Arrhythmias

Overall across all cycles combined, the incidence of cardiac arrhythmia events was similar in the rolapitant 200 mg group (4.6%), the all rolapitant doses group (4.5%), and the control group (4.5%). The most common TEAEs in this analysis were syncope, with an overall incidence across all cycles of 1.3%, 1.1%, and 1.1% in the 200 mg rolapitant, all rolapitant, and control groups, respectively, and tachycardia (1.1%, 1.0%, and 0.7%, respectively). The incidence of all other events in Cycle 1 and across all cycles combined was <1% and did not differ remarkably across all treatment groups.

Rhabdomyolysis/Myopathy Events

Overall across all cycles combined, the incidence of rhabdomyolysis/myopathy events was 7.7% in the rolapitant 200 mg group and 7.8% in the all rolapitant doses group compared with 9.3% and the control group. The most common TEAEs in this analysis were myalgia. Most of these events were assessed as unrelated to study treatment; the only treatment-related TEAEs related to rhabdomyolysis/myopathy events reported in more than 1 subject in the rolapitant 200 mg group were blood creatinine increased (0.2% of subjects each in the 200 mg rolapitant and control groups), and myalgia and muscular weakness (0.2% and <0.1% in the rolapitant 200 mg and control groups, respectively).

POOLING 2 (healthy subjects who received single doses of rolapitant.)

The overall incidence of TEAEs across the 550 healthy subjects who received single-dose rolapitant was 30.7%; the incidence was highest among subjects who received >200 mg rolapitant (54.2%) compared with those who received 200 mg (28.7%) or <200 mg (23.2%) doses. Among the 56 subjects who received placebo in these studies, the incidence of TEAEs was 51.8%.

The most commonly reported TEAEs in Pooling Group 2 were in the SOC *Nervous system disorders* and occurred with increasing incidence across rolapitant dose. The most commonly reported TEAEs were headache (8.9%, 4.3%, 5.7%, and 6.8% of subjects in the placebo and <200, 200 and >200 mg rolapitant groups, respectively), somnolence (1.8%, 5.8%, 5.5%, and 3.4%, respectively), and dizziness (1.8%, 0, 3.3%, and 16.9%, respectively.

The most common SOCs in which treatment-related TEAEs were reported in subjects receiving 200 mg rolapitant and placebo were Nervous system disorders (11.8% and 8.9%), Gastrointestinal disorders (3.3% and 3.6%), and General disorders and administration site conditions (1.2% and 5.4%), respectively.

The incidence of some treatment-related TEAEs possibly increased with rolapitant dose, particularly dizziness and nausea. The incidence of these events in the rolapitant < 200 mg, 200 mg, and > 200 mg dose groups compared with placebo was as follows: dizziness (0, 2.8%, 15.3% and 1.8%, respectively) and nausea (0, 0.5%, 6.8% and 0, respectively)

Serious adverse event/deaths/other significant events

Deaths

Pooling 1 (CINV population)

Overall a total of 79 patients had a TEAEs leading to death including 48 (3.1%) patients who received rolapitant at any dose, 38 (2.9%) of whom received 200 mg of rolapitant and 31 (2.4%) patients who received control. None of these events were considered to be related to study drug.

Pooling 2 (healthy subjects who received single doses of rolapitant)

No deaths were reported in any of the Phase 1 studies included in Pooling Group 2.

Serious adverse events

In all cycles combined, the most common SOCs in which TESAEs were reported in the overall 200 mg rolapitant group were Blood and lymphatic system disorders (4.6%), Infections and infestations (3.6%), and Respiratory, thoracic and mediastinal disorders (2.6%). In general, the incidence of TESAEs was similar in the 200 mg rolapitant group, the all rolapitant doses group, and the control group. Within each PT, the overall incidence of TESAEs was ≤ 3.0%. The most commonly reported TESAEs in the overall rolapitant 200 mg group with corresponding incidence in the overall control group were febrile neutropenia (2.6% and 3.0%, respectively) and neutropenia (1.2% and 2.0%, respectively); all other TESAEs were reported in <1% of rolapitant subjects. Across cycles, the incidence of febrile neutropenia was highest in Cycles 1 and 2 in all groups, with lower incidence in individual subsequent cycles; for neutropenia the incidence varied across cycles with no apparent trend

POOLING 2 (healthy subjects who received single doses of rolapitant.)

Three TESAEs were reported in 2 subjects, both of whom received rolapitant 200 mg in Study PR-10-5014-. Subject 001045 experienced an SAE of rhabdomyolysis and Subject 001068 experienced SAEs of moderate syncope and bradycardia.

Table 49: Pooled data on SAEs from PO4351 (HEC), PO4832(HEC) and PO4834 (MEC)

System Organ Class Preferred Term	Control N =1301	Rolipant 200mg N =1294	All Rolipant N =1567
All	***244 (18.8%)***	***227 (17.5%)***	***290 (18.5%)***

Blood and lymphatic system disorders	**73 (5.6%)**	**59 (4.6%)**	**83 (5.3%)**
Febrile neutropenia	39 (3%)	32 (2.6%)	42 (2.7%)
Neutropenia	26 (2%)	16 (1.2%)	27 (1.7%)
Anaemia	8 (0.6%)	8 (0.6%)	10 (0.6%)
Thrombocytopenia	3 (0.2%)	5 (0.4%)	8 (0.5%)
Infections and infestations	**45 (3.5)**	**47 (3.6%)**	**60 (3.8%)**
Pneumonia	14 (1.1%)	11 (0.9%)	14 (0.9%)
Respiratory, thoracic and mediastinal disorders	**25 (1.9%)**	**33 (2.6%)**	**40 (2.6%)**
Pulmonary embolism	10 (0.8%)	10 (0.8%)	11 (0.7%)
Gastrointestinal disorders	**34 (2.6%)**	**27 (2.1%)**	**41 (2.6%)**
Vomiting	9 (0.7%)	2 (0.2%)	7 (0.4%)
Dysphagia	1 (< 0.1%)	1 (<0.1%)	4 (0.3%)
Nausea	6 (0.5%)	1 (<0.1%)	5 (0.3)
General disorders and administration site conditions	**27 (2.1%)**	**25 (1.9%)**	**32 (2%)**
Asthenia	6 (0.5%)	6 (0.5%)	7 (0.4%)
Nervous system disorders	**8 (0.6%)**	**21 (1.6%)**	**26 (1.7%)**
Metabolism and nutrition disorders	**20 (1.5%)**	**19 (1.5%)**	**27 (1.7%)**
Dehydration	14 (1.1%)	12 (0.9%)	17 (1.1%)
Vascular disorders	**16 (1.2%)**	**18 (1.4%)**	**25 (1.6%)**
Cardiac disorders	**11 (0.8%)**	**15 (1.2%)**	**19 (1.2%)**
Renal and urinary disorders	**11 (0.8%)**	**7 (0.5%)**	**13 (0.8%)**
Renal failure acute	6 (0.5%)	3 (0.2%)	6 (0.4%)
Investigations	**11 (0.8%)**	**5 (0.4%)**	**6 (0.4%)**

Laboratory findings

Hematology results (actual and change from baseline/predose) were collected for Pooling Group 1

Mean red cell parameters, including hemoglobin, hematocrit, and red blood cell count decreased between Visit 1 and Visit 3 of each cycle; the mean changes were similar in the overall rolapitant 200 mg and control groups.Mean WBC count decreased from baseline to Visit 2 and to Visit 3 in Cycle 1 and the mean changes were similar in the overall rolapitant 200 mg and control groups. No notable differences were noted between the groups at any cycle.

Serum chemistry results (actual and change from baseline/predose) were collected for Pooling Group 1.

Small increases from baseline in mean creatinine values were observed in all treatment groups across cycles, with comparable (or smaller) increases seen in the rolapitant 200 mg group compared with the control and rolapitant <200 mg groups. Mean changes in glucose values were small and comparable across treatment groups and cycles. In general, mean total bilirubin, AST, and ALT levels increased from baseline to Visit 2, then returned toward (or below) baseline levels at Visit 3. Similar changes were observed in all treatment groups.

Table 26 : Post baseline PCS abnormal laboratory results, all cycles combined all CINV studies

	Overall CINV		
	Control N = 1301	**Rolapitant 200 mg** N = 1294	All Rolapitant N = 1567
Subjects with ≥ 1 incidence	562 (43.2%)	569 (44%)	689 (44%)
ALP > 1.5 X ULN	205 (15.8%)	214 (16.5%)	242 (15.4%)
ALT >3 X ULN	70 (5.4%)	75 (5.8%)	99 (6.3%)
AST > 3 X ULN	32 (2.5%)	29 (2.2%)	35 (2.2%)
Total bilirubin > 1.5 X ULN	78 (6%)	93 (7.2%)	121 (7.1%)
BUN > 3 X ULN	26 (2%)	18 (1.4%)	22 (1.4%)
Creatinine > 1.5 X ULN	22 (1.7%)	12 (0.9%)	17 (1.1%)
HgB < 8.0 G/L	35 (2.7%)	44 (3.4%)	60 (3.8%)
WBC < 2.0 X 10^9/L	167 (12.8%)	163 (12.6%)	193 (12.3%)
Neutrophils < 1.0 X 10^9/L	278 (21.4%)	260 (20.1%)	322 (20.5%)

Electrocardiogram

The percentage of subjects with postdose QTcF >450 msec in Cycle 1 was approximately 6% across all treatment groups. This decreased to between 2.2% and 2.7% of subjects at Visit 2. No subjects in the 200 mg rolapitant group or the all rolapitant doses group had QTcF >500 msec postdose or at Visit 2.

Overall in all cycles combined at the post-dose assessment, 35.6% of subjects of subjects in the 200 mg rolapitant group and 32.3% of subjects in the all rolapitant doses group had a QTcB >450 msec, compared with 37.8% of subjects in the control group. The percentage of subjects QTcB >500 msec ranged from 1.0% to 1.4% across treatment groups.

Safety in special populations

Table 51: Safety according to age.

MedDRA Terms	**Age <65** **number (percentage)** N =971	**Age 65-74** **number (percentage)** N = 265	**Age 75-84** **number (percentage)** N = 58 aged > 75	**Age 85+** **number (percentage)**
Total AEs	781(80.4%)	228 (86%)	46 (79.3)	
Serious AEs – Total				
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders	75 (7.7%)	19 (7.2%)	7 (12.1%)	
Nervous system disorders	233 (24%)	77 (29.1%)	15 (25.9%)	
Accidents and injuries				
Cardiac disorders	35 (4.6%)	12 (4.5%)	6 (10.3%)	
Vascular disorders	93 (9.6%)	30 (11.3%)	9 (15.5%)	
Cerebrovascular disorders	0	3 (1.1%)	0	
Infections and infestations	225 (23.2%)	54 (20.4%)	16 (27.6%)	
Anticholinergic syndrome				

Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

The incidence of TEAEs in Cycle 1 were generally similar between rolapitant and control for all age groups. The exception was in the >75 y population where dizziness was higher in the rolapitant compared to control group (10.3% and 1.5%, respectively) as was alopecia (10.3% and 3.0%, respectively).

Individual TEAEs reported in subjects ≥ 75 years of age at higher incidence (>5% difference) in the rolapitant group compared with control included diarrhea (20.7% and 13.6%), peripheral edema (10.3% and 3.0%), anemia (17.2% and 6.1%), leukopenia (10.3% and 4.5%), dizziness (12.1% and 4.5%), alopecia (15.5% and 7.6%), dyspnea (12.1% and 4.5%) and hypotension (10.3% and 0). Generally, across all cycles, in both treatment groups, the elderly population experienced a higher rate of TEAEs than those subjects <75 y, driven largely by fatigue and asthenia.

Gender

During Cycle 1, the overall incidence of TEAEs was similar between rolapitant and control subjects in Pooling Group 1, regardless of gender. Within the SOC of *Nervous system disorders*, the incidence of headache in control and rolapitant groups was higher in female subjects (10.4% and 7.6%) than in male subjects (3.9% and 4.2%).Similarly, the incidence of alopecia was higher in female subjects (11.5% and 10.3%) than in male subjects (4.2% and 3.5%) in both control and rolapitant subjects, respectively

Similar to Cycle 1, evaluations of TEAEs across all cycles combined revealed no significant differences between the rolapitant and control groups for either gender.

Race

The number of non-white participants in the CINV studies was small, making up just over 25% of participants, of which about 14% were categorised as Asian. This is a broad category that could cover a number of ethnic groups. Only 2.3% were Black or African American.

Geographic Region

During Cycle 1 and across all cycles combined the overall incidence of TEAEs was higher in North America and Asia/South Africa compared with Central/South America and Europe in both the rolapitant and control groups. This was generally the case across the SOCs, particularly for North America. However, there was no difference in the overall incidence of TEAEs in the rolapitant group compared with the control group in any of the geographic regions for Pooling Group 1

Cycle Length

The overall incidence of TEAEs in Cycle 6 for subjects who received chemotherapy at intervals <21 days, 21 to <28 days, and ≥ 28 days at Cycle 1 was higher in control subjects than in subjects who received rolapitant; however the subgroups <21 days and to >28 days contained few subjects for the Cycle 6 analysis.

The Cycles 2-6 analysis showed that the incidence of TEAEs was similar in the 200 mg rolapitant and control group for subjects who received chemotherapy at intervals <21 days, 21 to <28 days, and ≥ 28 days.

Pregnancy and lactation:

The use of rolapitant in pregnant or lacting women has not been studied.

Safety related to drug-drug interactions and other interactions

Rolapitant is a mild to moderate inhibitor of CYP2D6 and a mild inhibitor of BCRP. TEAEs and select TESAEs for subjects who did and did not receive CYP2D6 and BCRP substrates during the same treatment cycle as the study drug were reported.

The overall incidence of TEAEs and TESAEs in Cycle 1 was higher among subjects who received concomitant treatment with CYP2D6 and BCRP substrates compared with those who did not; however, the rates were generally similar between the respective rolapitant and control groups.

There were no remarkable differences in the incidence of TESAEs in subjects who received rolapitant or control concomitantly with a BCRP substrate compared with subjects who did not. This analysis was done for all individual cycles and no significant differences were observed between rolapitant and control.

Discontinuation due to AES

In Cycle 1, the overall incidence of TEAEs leading to treatment discontinuation was reported in 3.1% of subjects who received 200 mg rolapitant, 3.1% of subjects who received any dose of rolapitant and 3.7% of subjects in the control group.

Overall, in all cycles combined, 8.1% of subjects who received 200 mg rolapitant experienced at least 1 TEAE that lead to study discontinuation, compared with 8.2% of subjects who received any dose of rolapitant and 8.7% of subjects in the control group.

The most common SOCs in which TEAEs leading to study discontinuation were in the overall 200 mg rolapitant group were Gastrointestinal disorders (1.6%) and Blood and lymphatic system disorders (1.1%) they were similar in the 200 mg rolapitant group, the all rolapitant doses group, and the control group. The incidence of TEAEs leading to study discontinuation was similar in the 200 mg rolapitant group, the all rolapitant doses group, and the control group. Within each PT, the overall incidence of TEAEs leading to study discontinuation was <1%. TEAEs leading to discontinuation in more than 2 subjects in any treatment group across Cycles 1-6 in the 200 mg rolapitant, all rolapitant, and control groups were nausea (0.5%, 0.6%, and 0.2%, respectively), stomatitis (0.4%, 0.3%, and 0, respectively), vomiting (0.2%, 0.3%, and 0.5%, respectively), dysphagia (0.2%, 0.2%, and 0, respectively), anaemia (0.4%, 0.3%, and 0.3%, respectively), febrile neutropenia (0.2%, 0.3%, and 0.5%, respectively), leukopenia (0.2%, 0.4%, and <0.1%, respectively), neutropenia (0.2%, 0.1%, and 0.3%, respectively), disease progression (0.2%, 0.1%, and 0.2%, respectively), respiratory tract infection (0.2%, 0.2%, and 0, respectively), pneumonia (0.2%, 0.2%,

and 0.3%, respectively), blood creatinine increased (0.3%, 0.3%, and 0.6%, respectively), and drug hypersensitivity (0.3%, 0.3%, and <0.1%, respectively).

Post marketing experience

Rolapitant was launched into the US market in November 2015. As of the cutoff date of 01 December 2015 approximately 331 patients have been exposed based on the number of doses distributed by 01 December 2015.

2.6.1. Discussion on clinical safety

Clinical safety was assessed through the 4 studies that were performed in the target population: prevention of CINV in patient receiving HEC and MEC but also in post-operative nausea and vomiting population and in healthy volunteers as recommended in European guideline. However the data is difficult to interpret given that the study populations may have differed and the number of placebo subjects in the pooled group was only 56 out of a total of 550. Three case of presyncope and one of rhabdomyolysis were noted in those exposed to rolapitant. However specific analysis conducted across the CINV studies failed to show any signal for rhabdomyolysis/myopathic events or cardiac arrhythmias.

Overall a total of 2798 subjects were exposed to oral rolapitant at any dose, including 1567 subjects at risk for CINV among them 1294 received the recommended dose of 200 mg.

The overall incidence of TEAEs in subjects at risk for CINV receiving rolapitant 200 mg was around 65 % (n=828) in cycle 1 and 80% (n=1055) in all cycles and was similar in all groups. The most commonly reported events were as expected for a cancer population with underlying comorbidities undergoing myelosuppressive chemotherapy.

Across cycles, the most commonly reported TEAEs in the CINV studies were fatigue, alopecia, and neutropenia with similar incidence in the rolapitant 200 mg and control groups. The most common treatment related TEAEs in the 200 mg group were fatigue (2.4%), constipation (2.2%) and headache (1.9%).

Serious TEAEs rates were similar in CINV patient groups. In all cycles combined, 17.5% (n=227) of subjects who received 200 mg rolapitant experienced at least 1 serious TEAE, compared with 18.8% (n=244) of subjects in the control group. The most common SOCs in which Serious TEAEs in 200 mg rolapitant group were observed were Blood and lymphatic disorders (4.6% n= 59), infectious and infestations (3.6% n=47) and respiratory, thoracic and mediastinal disorders (2.6% n= 21). Most of serious TEAEs were considered to be unrelated to study drug.

In all cycles combined, the overall incidence of TEAEs leading to treatment discontinuation were reported in 8.1% of subjects who received 200 mg rolapitant, and 8.7% of subjects in the control group. The most common SOCs leading to discontinuation were gastrointestinal disorder (1.6% n= 21) and Blood and lymphatic disorders (1.1% n=14).

Of the 2868 subjects treated in CINV studies, 79 died: 48 (3.1%) in the rolapitant group and 31 (2.9%) in the placebo group. None of the deaths were considered to be related to treatment with study drug.

A research on the following TEAEs was realised: hematopoietic leucopenia, anemia, acute renale failure hepatic dysfunction, cardiac arrhythmia, embolic and thrombotic events and rhabdomyolysis/myopathy events.

Regarding adverse events related to the central nervous system, the most common TEAEs in CINV studies were headache (8.9%), dizziness (7.5%) and dysgeusia (3.9%). Rates were similar between rolapitant, and control groups. Review by cycle did not show an increase in the incidence or severity with repeated dose.

Pre-clinical data raised a potential proconvulsivant effect of rolapitant. In CINV studies, the TEAEs of seizure/convulsions were reported at the same incidence (0.2%) in the rolapitant 200 mg (n=4) and control groups (n=2) and occurred in subjects with known risk factors (mostly unknown brain metastasis). Two others subjects receiving lower dose of rolapitant experienced convulsion. None were reported in healthy volunteers.

Analyses of haematologic events (leukopenia, anemia), acute renal failure, cardiac arrhythmia, thrombothic events and rhabdomyolysis/myopathy events did not show a signal for rolapitant compared to placebo over multiple cycles of chemotherapy.

Regarding hepatic toxicity, overall, 5 patients met the Hy's law criteria. One case occurred in a patient taking 10 mg of rolapitant and 4 in patients taking placebo.

In CINV studies, there were no patterns of changes for hematology, blood chemistry, and vital signs in Cycle 1 and across multiple cycles they were comparable between rolapitant and control groups across all time points. Most changes were expected in cancer patients receiving myelosuppressive chemotherapy. There was no evidence of a treatment-related effect on clinical laboratory or ECG parameters.

In studies in healthy volunteers, 550 subjects received single doses of rolapitant, including 69, 422, and 59 subjects who received <200 mg rolapitant, 200 mg rolapitant, and >200 mg rolapitant, respectively.

The overall incidence of TEAEs was 30.7% (n=169) in patients receiving rolapitant and 51.8% (n=29) in placebo groups. The incidence raised with rolapitant doses (8.7%,16.6% and 30.5% respectively). In placebo group the incidence was 21.4%.

At 200 mg dose, the most commonly reported treatment-related TEAEs (rates in rolatipant and placebo groups) were somnolence (5.2%, 1.8%), headache (4.3%, 4.6%), dizziness (2.8%, 1.8%) and diarrhoea (1.4%,0%). Only dizziness seems to occur at an increasing frequency with dose.

In patients receiving rolapitant dose > 200mg , the most common treatment-related TEAEs were dizziness (15.3% and 1.8%), nausea (6.8% and 0), headache (5.1% and 3.6%), somnolence (3.4% and 1.8%), fatigue (3.4% and 5.4%), and polyuria (3.4% and 0) in the rolapitant and control groups, respectively.

A case of rhabdomyolysis reported as a TESAE in Pool 2 was judged to be related to rolapitant or not and if not what alternative explanations might account for this episode of rhabdomyolysis. Following assessmsnt of D120 Applicant's response, the Applicant cannot exclude the possibility that the incident of rhabdomyolyis in a healthy volunteer participating in a bioequivalence study was related to rolapitant. As rhabdomyolyis is at least possibly related to rolapitant in this incident, rhabdomyolysis should be included in section 4.8 of the SmPC.

No convulsions were reported in healthy subjects. No death and no TEAES leading to treatment discontinuation occurred.

There are no adequate and well-controlled studies on the use of rolapitant in pregnant or lactating women: no clinical studies has been conducted in these subpopulations, and it is not known whether rolapitant is excreted in human milk. Overall, given the claimed indication, and the preclinical data, rolapitant should should not be used during pregnancy unless clearly necessary, and lactation is not recommended during treatment. (See SmPC section 4.6.)

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of rolapitant used in prevention of CINV appears sufficiently investigated. No major safety issues have been identified in the course of the CINV trials with most of adverse events appearing manageable, and in line with the adverse events usually observed with anti-emetic products.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Interaction with CYP2D6 substrates with narrow therapeutic index e.g. thioridazine, pimozide Neutropenia
Important potential risks	Seizures Other than CYP2D6 related drug interaction
Missing information	Use in pregnancy Use in patients <18 years old Use in patients with severe hepatic impairment Use in patients with severe renal impairment and patients with end stage of renal diseases undergoing haemodialysis

Having considered the data in the safety specification the CHMP agrees that the safety concerns listed by the applicant are appropriate and has added one important identified risk, which is the interaction with CYP2D6 substrates with narrow therapeutic index e.g. thioridazine, pimozide.

Pharmacovigilance plan

Table of ongoing and planned additional PhV studies/activities in the Pharmacovigilance Plan:

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PIP Study3: Multicenter, open-label single dose study to evaluate the safety/tolerability and pharmacokinetic of rolapitant (part 1) followed by a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of rolapitant compared to placebo as adjunct treatment to 5-HT3 receptor antagonists and dexamethasone in the prevention of nausea and vomiting (part 2) in paediatric patients from 12 to less than 18 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment., 3	The Objectives of this study are to: Evaluate the safety/tolerability and pharmacokinetic of rolapitant (part 1) Evaluate the efficacy and safety of rolapitant compared to placebo as adjunct treatment to 5-HT3 receptor antagonists and dexamethasone in the prevention of nausea and vomiting (part 2)	Use in patients <18 years old	Planned start Part 1: April 2017 Part 2: August 2018	Dec 2025
PIP Study 4: Multicenter, open-label dose-ranging multi-cohort study to evaluate the safety/tolerability and pharmacokinetic of rolapitant in paediatric patients from 6 months to less than 12 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment., 3	The objective of this study is to evaluate the safety/tolerability and pharmacokinetic of rolapitant in paediatric patients from 6 months to less than 12 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment.	Use in patients <18 years old	Planned to start After the age appropriate formulation is developed and the results of Part 1 of Study 3 available. Not earlier than April 2017	Dec 2025
PIP Study 5: Randomised, double-	The objective of this study is to evaluate the	Use in patients	Planned To be initiated only	Dec 2025

blind, placebo-controlled study to evaluate the efficacy and safety of rolapitant compared to placebo as adjunct treatment to 5-HT3 receptor antagonists and dexamethasone in the prevention of nausea and vomiting in paediatric patients from 6 months to less than 12 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment., 3	efficacy and safety of rolapitant compared to placebo as adjunct treatment to 5-HT3 receptor antagonists and dexamethasone in the prevention of nausea and vomiting in paediatric patients from 6 months to less than 12 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment.	<18 years old	after the completion of formulation development, results available from Study 6, PK results from Study 4, and modelling and simulation Study 7. Not earlier than April 2017	
PIP Study 6: Single dose study comparing rolapitant tablets (reference) and age-appropriate oral liquid formulation (test) to evaluate the bioavailability between the two formulations in healthy adult subjects., 3	The objective of this study is to evaluate the bioavailability between the two formulations in healthy adult subjects.	Use in patients <18 years old	Planned to start after the age appropriate formulation is developed.	Dec 2025
PIP Study 7: Modelling and simulations study to evaluate the use and support dosing regimen of rolapitant in the prevention of nausea and vomiting in paediatric patients from 6 months to less than 18 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment., 3	The objective of this study is to evaluate the use and support dosing regimen of rolapitant in the prevention of nausea and vomiting in paediatric patients from 6 months to less than 18 years of age receiving highly emetogenic chemotherapy and moderately emetogenic chemotherapy treatment	Use in patients <18 years old	Planned to start After the completion of the PK phase of Study 3.	Dec 2025
In vitro study assessing the effect of rolapitant as an inhibitor of OATP1B3 at 20 µM., 3	The objective of this study is to evaluate the potential interaction of rolapitant with OATP1B3 substrates, e.g. statins, fexofenadine, and bosentan	Other than CYP2D6 drug interactions	Planned to start in Q1 2017	Q3 2017
In vitro study assessing the effect of rolapitant as an inhibitor of OCT1 at	The objective of this study is to evaluate the potential interaction of	Other than CYP2D6 drug	Planned to start in Q1 2017	Q3 2017

20 µM., 3	rolapitant with OCT1 substrates e.g. oxaliplating, metformin, and aciclovir	interactions		
In vivo study assessing the ability for rolapitant on CYP1A2 substrate., 3	The objective of this study is to assess the ability for rolapitant on CYP1A2 substrate in vivo	Other than CYP2D6 drug interactions	Planned to start in Q2 2017	Q1 2018
In vitro study assessing the effect of rolapitant as an inhibitor of UGT., 3	The objective of this study is to evaluate the potential interaction of rolapitant with UGT substrates	Other than CYP2D6 drug interactions	Planned to start in Q1 2017	Q3 2017
In vitro study assessing the ability for rolapitant to be interacted with inhibitors or inducers of BSEP, MRPs, or UGT enzyme., 3	The objective of this study is to assess the ability for rolapitant to be interacted with inhibitors or inducers of BSEP, MRPs, or UGT enzyme	Other than CYP2D6 drug interactions	Planned to start in Q1 2017	Q3 2017

The safety profile of rolapitant in the prevention of nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy in adults will be evaluated through the routine pharmacovigilance system of TESARO UK Ltd. Routine pharmacovigilance activities are fully described in the Pharmacovigilance System Master File (PSMF). The Applicant has updated Part III regarding all safety concerns.

Risk minimisation measures

V.3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk 1. Interaction with CYP 2D6	(Proposed) text in SmPC (Section 4.5)	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
substrates with narrow therapeutic index e.g. thioridazine, pimozide	Prescription only medicine use restricted to physicians experienced in oncology	
2. Neutropenia	List in SmPC table of ADRs (Section 4.8) Prescription only medicine use restricted to physicians experienced in oncology	None
Important potential risk 3. Seizures	None proposed	None
4. Other than CYP2D6 related drugs interactions	(Proposed) text in SmPC (Section 4.5) Prescription only medicine use restricted to physicians experienced in oncology	None
Missing information 5. Use in Pregnancy	(Proposed) text in SmPC (Section 4.6) Prescription only medicine use restricted to physicians experienced in oncology	None
6. Use in patients <18 years old	(Proposed) text in SmPC (section 4.2) Prescription only medicine use restricted to physicians experienced in oncology	None
7. Use in patients with severe hepatic impairment	(Proposed) text in SmPC (Section 4.4) Prescription only medicine use restricted to physicians experienced in oncology	None
8. Use in patients with severe renal impairment: end stage renal disease undergoing haemodialysis	(Proposed) text in SmPC (section 4.4): Prescription only medicine use restricted to physicians experienced in oncology	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.7 (28 Feb 2017) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant compared the structure of rolapitant with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Varuby (rolapitant) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chemotherapy-induced nausea and vomiting (CINV) can interfere with treatment adherence, functional activity and quality of life in patients treated with cytotoxic chemotherapy. It is defined as acute and delayed emesis, both phases being mediated by neurotransmitter- driven mechanisms.

The acute phase, which represents the first 24 hours following chemotherapy, is mediated in part by chemotherapy-induced increases in serotonin (5-HT) release and activation of 5-HT3 receptors on vagal afferent neurons located primarily in the gastrointestinal tract. The delayed phase of CINV, which occurs 2 to 5 days following the initiation of chemotherapy involves the production of substance P, which binds to NK1 receptors in the vomiting centre of the brain, leading to nausea and vomiting. Although NK-1 signalling has some role in acute chemotherapy-induced nausea and vomiting (≤24 h), delayed emesis has primarily been

linked with substance P mediated stimulation of neurokinin 1 receptors within the central and peripheral nervous systems.

3.1.2. Available therapies and unmet medical need

Three categories of drugs are routinely used for the management of CINV: type three 5-hydroxytryptamine (5-HT3) receptor antagonists, the neurokinin-1 receptor antagonists (NK1 RA), and glucocorticoids to prevent acute nausea and vomiting following chemotherapy of high emetic risk.

A three-drug regimen including single doses of a 5-HT3 receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. A number of agents are licensed for the prevention of CINV including the first- and second generation 5HT3 receptor antagonists ondansetron, granisetron and palonosetron and NK1 receptor antagonists aprepitant, fosaprepitant, and netupitant.

Evidence-based guidelines for CINV prophylaxis have been published by different contemporary sources, (ESMO/MASCC 2010; NCCN 2016;ASCO0 generally recommending a 5HT3 receptor antagonists plus corticosteroid for patients receiving moderately emetogenic chemotherapy (MEC), and combination treatment with an NK-1RA and 5HT3 receptor antagonist plus a corticosteroid for patients receiving HEC. No differences between the 5-HT3 receptor antagonists, dolasetron, granisetron, ondansetron, tropisetron have been shown in terms of efficacy. There is no consensus on the dose of dexamethasone to be used in delayed emesis. A single 20-mg dose before chemotherapy is recommended based on the observations that the 20-mg dose had the highest numerical efficacy.

NK1 receptor antagonists, aprepitant and netupitant are inhibitors of cytochrome P450 (CYP) 3A4, with aprepitant also having CYP3A4 and CYP2C9 induction potential and inhibition of other CYP enzymes induction potential. Dosage adjustment of concomitantly administered drugs is required including dexamethasone.

Although antiemetic prophylaxis has been improving continuously, significant numbers of patients still continue to experience CINV. Compliance with current emetic guidelines can be suboptimal. Treatment of nausea remains a challenge.

3.1.3. Main clinical studies

The efficacy of rolapitant for the prevention of CINV was initially evaluated in one phase 2 dose ranging study and 3 pivotal studies in subjects at risk for CINV including:

- *Study P04351*: multicentre, randomised, double-blind, parallel-group study evaluated rolapitant doses ranging from 10 to 200 mg, in patient receiving HEC chemotherapy.

- *Studies P04832 and P04833 :* multicentre, randomised, parallel-group, double-blind studies designed to evaluate the efficacy of a single dose of rolapitant 200 mg administered PO with a 5-HT3 receptor antagonist and dexamethasone compared to placebo administered with a 5-HT3 receptor antagonist and dexamethasone for the prevention of delayed phase CINV (>24 to 120 hours) in patient receiving HEC chemotherapy.

- *Study P04834 :* multicentre, randomised, parallel-group, double-blind study designed to evaluate the efficacy of a single dose of rolapitant 200 mg administered PO with a 5-HT3 receptor antagonist and dexamethasone compared to placebo administered with a 5-HT3 receptor antagonist and dexamethasone for the prevention of delayed phase CINV (>24 to 120 hours) in patient receiving MEC chemotherapy.

3.2. Favourable effects

All three studies enrolled a broad population of subjects based on age, gender, race and region with considerable comorbidities who were undergoing myelosuppressive chemotherapy for a variety of cancers.

HEC phase III studies (Study P04832 and Study P04833)

In both studies, the primary efficacy endpoint was reached, the rolapitant in combination with a 5-HT3 inhibitor and dexamethasone group achieved a statistically significantly higher Complete Response CR (no emesis and no rescue medication) rate in the delayed phase compared to the in placebo combination with a 5-HT3 inhibitor and dexamethasone group (72.7% versus 58.4%, respectively; $p < 0.001$ in the first study and 70.1 versus 61.9% $p=0.43$ in the second study).

Statistical significance was reached in both key secondary endpoints (CR in acute and overall phases) in only one of the HEC study P04832: Acute phase: OR 1.8 95%CI (1.2, 2.8) p=0.005) and Overall phase: OR 1.8 95%CI (1.3, 2.8) p=0.001.

MEC study (Study P04834)

This study included patients naive to moderately or highly emetogenic chemotherapy and were scheduled to receive a first course of MEC. At least 50% of the study subjects would receive anthracycline in combination with cyclophosphamide IV (AC MEC).

In the MEC study, a pre-specified subgroup analysis was performed for the endpoint of complete response in each CINV phase for subjects who received Non-AC MEC (MEC according to recent guidelines) vs. AC based chemotherapy (considered HEC according to recent guidelines).

The primary efficacy endpoint of complete response in the delayed phase of CINV (>24 through 120 hours following initiation of MEC) was achieved; specifically, a statistically significant higher complete response rate was observed in the rolapitant group compared to the control group (71.3% versus 61.6% OR 1.6 95% CI (1.2,2.0) p<0.001 respectively). The treatment effect for rolapitant compared to placebo was 9.7%.

Complete response in acute and overall CINV phases were numerically in favour of rolapitant arm but not statistically significant in one of the studies in subject receiving HEC regimen (P048033). Complete response over the overall phase (0-120 hat-risk period) was demonstrated in favour of the rolapitant treatment arm in Study P04834 (Overall phase OR 1.6 95%CI (1.3, 2.0) p<0.001) but not for the acute phase OR 1.2 95%CI (0.9,1.6 =p 0.143)

In this study the rates of CR in the delayed phase were significantly higher for rolapitant group compared with subjects who received control in the overall population (71.3%, 61.6% respectively), in the non-AC MEC population (76.1%, 63.8% respectively) and in the AC population (66.9%, 59.6% respectively).

Efficacy in repeat phases across studies has been shown and is reflected in the SmPC.

3.3. Uncertainties and limitations about favourable effects

The CR treatment effect in the delayed phase has been demonstrated as discussed above whereas in the acute phase there was a numerical effect that achieved statistical significance in only one of the 2 HEC and in the pooled analysis HEC studies compared with control is 7%. In the MEC study however complete protection (a composite score defined as no emesis, no rescue medication and maximum nausea VAS<25mm) was in favour of rolapitant in both the delayed and overall phases of CINV. Therefore the indication was revised to

state the benefit of the product is on the prevetion of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults.

3.4. Unfavourable effects

Clinical safety was assessed through the 4 studies that were performed in the target population: prevention of CINV in patient receiving HEC and MEC but also in post-operative nausea and vomiting population and in healthy volunteers as recommended in European guideline.

Overall 2798 individuals have been exposed to rolapitant at any dose in a variety of clinical trials. In CINV trials 1657 patients have been exposed to rolapitant and 1294 have been exposed to the proposed dose, of whom 319 have been exposed to 6 cycles of treatment.

TEAEs across CINV trials (P04832, P04833, P04834) were reported in 80.9% of the rolapitant 200mg group and 80.8% of the control group. TEAEs occurred at a similar rate in the HEC and MEC populations and there were no differences between the rolapitant 200 mg and control groups.

The most commonly reported types of events in the CINV studies were gastrointestinal disturbances (constipation, diarrhoea and nausea). Other commonly reported events were fatigue, asthenia, neutropenia, anaemia, alopecia and decreased appetite.

A slightly higher frequency of occurrence was recorded for a number of TEAES in the rolapitant group compared to the control group in Cycle 1: neutropenia (6.8% control, 8.2% rolapitant); dizziness (3.2% control, 4.7% rolapitant); dyspepsia (2.7% control, 4% rolapitant), stomatitis (2.2% control, 3.3% rolapitant); hiccups 2.5% control, 3.2% rolapitant) and anaemia (2.7% control, 3.1% rolapitant). For cycles 1 to 6 a difference in frequency was maintained for neutropenia, anaemia, dyspepsia, hiccups and mucosal inflammation. There were also small excesses noted for hypomagnesaemia, abdominal pain, dyspnoea and thrombocytopenia across the 6 cycles of treatment.

In all cycles combined, 17.5% (n=227) of subjects who received 200 mg rolapitant experienced at least 1 serious TEAE, compared with 18.8% (n=244) of subjects in the control group. The most commons SOCs in which Serious TEASs in 200 mg rolapitant group were Blood and lymphatic disorders (4.6% n= 59), infectious and infestations (3.6% n=47) and respiratory, thoracic and mediastinal disorders (2.6% n= 21).

There were 79 deaths during the CINV studies, including 48 (3.1%) in rolapitant group and 31 (2.4%) in control group but none of the deaths were considered to be related to treatment with study drug.

In healthy subjects, the most commonly reported treatment-related TEAEs (rates in rolatipant and placebo groups) were somnolence (5.2%, 1.8%), headache (4.3%, 4.6%), dizziness (2.8%, 1.8%) and diarrhoea (1.4%, 0%)

3.5. Uncertainties and limitations about unfavourable effects

The vast majority (75%) of those participating in the pivotal CINV studies were aged under 65, just over 20% were aged between 65 and 74 and only 4.5% were aged over 75 and ony 5 many patients were aged over 85. Overall the proportion of those in the under 65 age-group experiencing TEAEs across all 6 cycles combined was similar to that in the over 75 population. No patients in the studies have been exposed to greater than 6 cycles of treatment so there is no data on longer term treatment. Limited data are available in patients who were aged over 75 and in non-white populations other racial/ethnic groups in the studies,

however additional safety data are expected from studies included in the RMP and from post-marketing phase (see RMP).

Further drug – drug interaction studies are to be provided post authorisation and are described in the RMP.

3.6. Effects Table

Table 52: Effects Table for Varuby in CINV

Effect	Short Description	Unit	Rolapitant 200 mg	placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Prevention of nausea and vomiting following HEC regimen	% of patients with no emesis, no rescue medication during: 25-120h	%	72.7[a] 70.1[b]	58.4 [a] 61.9 [b]	P<0.001 P=0.043	Studies P04832 P04833
Prevention of nausea and vomiting following HEC regimen	0-24h		83.7 [a]	73.7 [a]	Key secondary endpoint	Studies P04832
Prevention of nausea and vomiting following HEC regimen	0-120h	%	70.1 [a]	56.5 [a]	Key secondary endpoint Significant difference between treatment and placebo could be observed only in study P04832	Studies P04832
Prevention of nausea and vomiting following MEC +AC regimen	% of patients with no emesis, no rescue medication during 25-120h	%	71.3	61.6	Primary endpoint Statistically significant superior to placebo 50% of subjects did not receive MEC regimen as currently defined.	Study P04834
Prevention of nausea and vomiting following HEC regimen	% of patients with no emesis, no rescue medication during: 0-24h	%	83.4 [b]	79.5[b]	Key secondary endpoint not statistically significant vs placebo	Studies P04833
	0-120h	%	67.5 [b]	60.4 [b]	Improvement not statistically significant vs control	

Effect	Short Description	Unit	Rolapitant 200 mg	placebo	Uncertainties / Strength of evidence	References
Prevention of nausea and vomiting following HEC regimen Studies P04833	% of patients with no emesis, no rescue medication during: 0-24h	%	83.5	80.3	Key secondary endpoint not statistically significant vs placebo	
	0-120h	%	68.6	57.8		
Unfavourable Effects						
	Headache					See Clinical Safety section
	Fatigue					
	Dizzines					

Notes:

[a] Study P04832

[b] Study P04833

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from clinical studies showed statistically significant efficacy of rolapitant in combination with a 5-HT3 inhibitor and dexamethasone over placebo in combination with a 5-HT3 inhibitor and dexamethasone in the prevention of chemotherapy induced in delayed nausea and vomiting in adults receiving initial course of highly and moderately emetogenic chemotherapy regimen.

The most important effects observed are 14.3% and 8.2% improvement in CR in the delayed phase in the both HEC studies and 9.7% improvement in the MEC study. This represents a clinically relevant improvement in the number subjects who did not experience emesis or use rescue medications during the delayed phase. A 10% difference has been described in the literature as clinically relevant (Olver 2004, Roila 2010) for the HEC studies. The CR rate in MEC was further analysed for subjects who received non-AC MEC vs. AC chemotherapy across all phases of CINV. Although the complete response rates were significantly higher for both the AC and non AC chemotherapy populations, the treatment effect in the delayed phase was more pronounced for the Non AC MEC group compared to the AC group (treatment effect 12.3% and 7.3% respectively).

Rolapitant reduces emesis and the requirement for rescue medication in the delayed phase for patients experiencing CINV following an initial cycle of cisplatin based chemotherapy. Similarly an improvement in nausea was seen across the pooled studies in the delayed phase.

Persistence of effect over repeat treatments is considered satisfactory with the accepted limitations identified such as use of different endpoints, use of 6 day recall for nausea and vomiting data and lack of re randomisation following cycle 1, and clinically relevant information has been described in the SmPC.

Side effects are in line with what is expected from this type of products in this indication. Overall the safety profile of rolapitant appears favourable and no significant safety issue has been identified.

3.7.2. Balance of benefits and risks

Prevention of vomiting and reduction in the use of rescue medication in the delayed phase has been clearly established for initial courses of highly emetogenic cisplatin based chemotherapy and non-AC moderately emetogenic chemotherapy in adults. Improvement in nausea was less consistent across the two study populations. There was a clinically meaningful improvement in nausea for the delayed phase of CINV for the HEC population and in the non-AC MEC or AC subgroup.

Overall rolapitant appears to have been well tolerated in the CINV population and there were no clinically meaningful differences in the incidence of commonly reported events between the rolapitant group and the control group in the CINV studies and there was no evidence for cumulative toxicity over multiple cycles for any TEAE and most of the common TEAEs reported were as expected based on a population of subjects with cancer undergoing chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

Collectively, data show that rolapitant is active in prevention of chemotherapy-induced delayed nausea and vomiting following cisplatin based HEC and non-AC MEC. The treatment effect associated with rolapitant in terms of controlling symptoms of nausea and vomiting in the acute phase of CINV following treatment with HEC is modest in one of the HEC studies and non statistically significant in the other HEC study. Rolapitant has shown adequate efficacy in terms of reducing rates of emesis and use of rescue medicine in patients treated with MEC in the delayed and overall phases but not the acute phase and the treatment effect in favour of rolapitant was inconsistent across the non-AC MEC and AC subgroups. Data on repeat efficacy over chemotherapy cycles have been considered adequate and described in section 5.1 of the SmPC.

The originally applied indication Prevention of nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy in adults was revised as follows:

Prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults. Varuby is given as part of combination therapy.

3.8. Conclusions

The overall B/R of Varuby is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Varuby is favourable in the following indication:

Prevention of delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy in adults

Varuby is given as part of combination therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rolapitant is considered to be a new active substance.