EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2012
EMA/CHMP/169525/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BindRen

International non-proprietary name: colestilan

Procedure No. EMEA/H/C/002377

Note

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

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List of abbreviations

ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APD	Ambulatory peritoneal dialysis
AST	Aspartate aminotransferase
AUC0-∞	Area under the curve from time 0 to infinity
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMS	Bristol Myers Squibb
Ca × P	Calcium × phosphorus ion product
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence interval
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-mineral bone disorder
Cmax	Maximum concentration after dosing
CNS	Central nervous system
CP	Completers population
CPMP	Committee for Proprietary Medicinal Products
DOPPS	Dialysis Outcome and Practice Pattern Study
ECG	Electrocardiogram
EMA	European Medicines Agency
FAMHP	Federal Agency for Medicines and Health Products
FGF-23	Fibroblast growth factor-23
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HbA1c	Glycosylated haemoglobin
HD	Haemodialysis
HDL-C	High-density lipoprotein-cholesterol
HP	Hyperphosphataemia
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcome Quality Initiative
LDL-C	Low-density lipoprotein-cholesterol
LOCF	Last observation carried forward
LSM	Least squares mean
MAA	Marketing Authority Application
MTPC	Mitsubishi Tanabe Pharma Corporation
MEB	Medicines Evaluation Board
1,25(OH)2D	1,25-dihydroxyvitamin D
P	Phosphorus
PD	Peritoneal dialysis
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PTH	Parathyroid hormone

SAWG	Scientific Advice Working Group
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
tmax	Time of maximum concentration
TEAE	Treatment-emergent adverse event
t.i.d	Three times per day

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mitsubishi Pharma Europe Ltd. submitted on 30 August 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for BindRen, 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 28 September 2010.

The applicant applied for the following indication:

> *BindRen is indicated for the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis.*

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

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 studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) (P\207\2011) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/207/2011 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 colestilan contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on the following different dates: 16 September 2005, 19 March 2008 and 19 November 2009. The Scientific Advice pertained to Clinical aspects (EMEA/H/SA/617/1/2005/II), Environmental Risk Assessment aspects (EMEA/H/SA/1026/1/2008/II) and paediatric aspects (EMEA/H/SA/1026/2/2009/PED/II) of the dossier.

Licensing status

Colestilan has been authorised in Japan since 1999 to treat hypercholesterolemia.

1.2. Manufacturers

Manufacturer responsible for batch release

Allphamed PHARBIL Arzneimittel GmbH
Hildebrandstrasse 12
D-37081 Göttingen
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Romaldas Maciulaitis**

CHMP Peer reviewer: Philippe Lechat

- The application was received by the EMA on 30 August 2011.
- The procedure started on 21 September 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 December 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 December 2011.
- During the meeting on 19 January 2012, 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 23 January 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 June 2012.
- During the CHMP meeting on 19 July 2012, 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 15 August 2012.
- The CHMP, in the light of the overall data submitted, issued a positive opinion for granting a Marketing Authorisation via written procedure to BindRen on 26 September 2012.
- The European Commission sent a letter to the CHMP on 12 October 2012 requesting some clarifications regarding the opinion.
- During the CHMP meeting on 15 November 2012, the CHMP adopted a revised opinion and assessment report to address the EC's request.

2. Scientific discussion

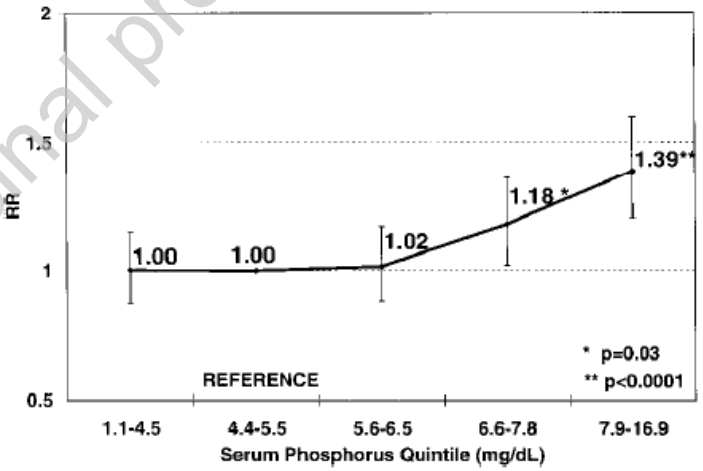
2.1. Introduction

Problem statement

Hyperphosphataemia develops from an imbalance between the dietary phosphate intake and the amounts excreted in the urine. Increased serum phosphorus levels result in stimulation of parathyroid hormone (PTH) secretion and parathyroid gland hyperplasia, and secondary hyperparathyroidism develops. Hyperphosphataemia also has an effect on the overall calcium/phosphorus balance in the body and increases the calcium × phosphorus ion product (Ca×P), with an increased risk of extra-skeletal phosphorous-calcium precipitation.

With renal function deterioration, progressive disturbances of mineral homoeostasis occurs, affecting calcium, phosphorus, vitamin D, and PTH. At chronic kidney disease (CKD) stage 3, the reduction in glomerular filtration rate (GFR) impairs phosphorus excretion, resulting in hyperphosphataemia, decreased 1,25-dihydroxyvitamin D levels, and elevated PTH and fibroblast growth factor-23 levels. The kidneys can no longer respond adequately to FGF-23 (which promotes phosphorus excretion and reduces 1,25(OH)2D synthesis) or PTH (which would normally stimulate phosphorus excretion and calcium reabsorption). This leads to a vicious cycle in which phosphorus-stimulated secretion of PTH also stimulates the release of calcium and phosphorus from bone, and inhibits bone formation and mineralisation. Consequently, the mineral disturbances seen in CKD have adverse effects on bone modelling, remodelling and growth. High serum calcium and phosphorus levels can also lead to extraskeletal calcification. Serum phosphorus levels generally become abnormal when GFR falls below 40 mL/min/1.73 m^2 (CKD stage 3). When GFR has fallen to <20 mL/min/1.73 m^2 (CKD stages 4 and 5), around 40% of patients have elevated phosphorus levels. Almost all patients with CKD Stage 5 have hyperphosphataemia unless steps are taken to control phosphorus levels. A direct relationship between serum phosphorus levels and mortality in patients with CKD has been known for many years.

Figure 1 Relative mortality risk by serum phosphate



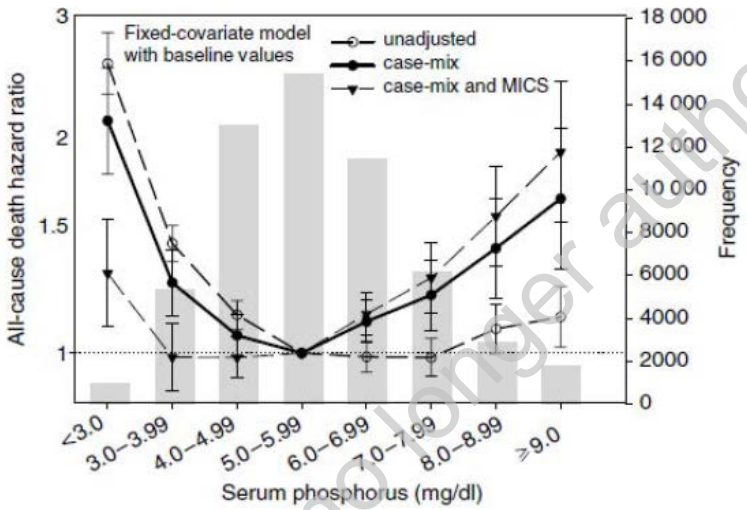
(*Data source: Block GA et al, 1998)*

Epidemiological data suggests that the phosphate level of 6.0 mg/dL (1.95 mmol/L) is a value that falls on the nadir of a U-shaped curve where changes in serum phosphorus levels by 1 mg/dL (0.3 mmol/L) are related to mortality. Dialysis outcome and practice pattern study (DOPPS) also suggested that a 1

mg/dL (0.3mmol/L) lower plasma phosphorous level was significantly associated with lower all-cause mortality and cardiovascular mortality (figure 2).

Increased phosphorous and high calcium levels are associated with vascular calcification, which can increase cardiovascular mortality. This can be exacerbated by long-term use of high doses of calcium based phosphate binders. Cardiovascular disease is the leading cause of morbidity and mortality in patients with CKD Stage 5 on dialysis.

Figure 2 All-cause death hazard ratio by serum phosphorous level categories in maintenance haemodialyis patients over a 2-year period



Data source: Kalantar-Zadeh K et al, 2006

Current treatments for hyperphosphataemia: At present, hyperphosphataemia is generally managed using the following strategies:

a) Dialysis

b) Dietary phosphate restriction**.** A low phosphate diet can however be difficult to maintain and is usually not sufficient for phosphorous control.

c) Phosphate binding agents:

- *Aluminium-based binders* are effective but cause many severe AEs, especially in the CNS.

- *Calcium salts* are used extensively to bind phosphate in the GI tract. Calcium salts control hyperphosphataemia and also suppress secretion of PTH via calcium receptors. Large amounts of calcium salts can cause hypercalcaemia and arterial calcifications.

- *Lanthanum carbonate* is well tolerated and as effective as calcium carbonate.

- *Sevelamer hydrochloride/carbonate* is a non-absorbed phosphate binding polymer, free of metal and calcium. It reduces serum phosphorous levels effectively without increasing serum calcium levels. The most frequently occurring adverse reactions related to sevelamer are GI disorders.

- *Calcium/phosphate metabolism modifiers:* These include agents aimed at correcting PTH levels, which will have an effect on calcium and phosphate levels. Vitamin D sterols, such as calcitriol and alfacalcidol, are effective at suppressing PTH levels but increase intestinal absorption of phosphate and calcium and can be associated with hypercalcaemia. Selective vitamin D analogues, such as

paricalcitol, may be less likely to cause hypercalcaemia. Cinacalcet, a calcimimetic which increases the sensitivity of the calcium-sensing receptor, is effective at reducing PTH, calcium, and phosphate levels in adult dialysis patients, although reduction of plasma calcium levels can cause symptomatic hypocalcaemia.

Other risk factors: Hyperlipidaemia is also known to increase mortality in the general population and is common in the CKD population. A reduction in low-density lipoprotein-cholesterol (LDL-C) has been shown to also benefit the CKD population. Diabetes is another common co-morbidity in the CKD population and diabetic patients are known to be at high cardiovascular risk.

About the product

Colestilan is an anion exchange resin developed by Mitsubishi Tanabe Pharma Corporation (MTPC). It is a long-chain polymer synthesised by cross-linking oligomers. It is not absorbed from the human gastrointestinal (GI) tract and is not metabolised during transit of the GI tract. In the treatment of hyperphosphataemia, it acts in the GI tract as a non-calcium, non-metallic phosphate binder.

The product was originally developed in Japan for the treatment of hypercholesterolaemia (the name of the product during the development was MCI-196), and was registered in 1999 in Japan for the indication “Treatment of hypercholesterolaemia and familial hypercholesterolaemia”. The recommended dose in Japan is 3 g (maximum dose 4 g) daily, given as a divided dose before breakfast and supper.

The clinical development program was designed to demonstrate the safety and efficacy of colestilan in the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis. The program included 5 phase II studies and 6 phase III studies.

There is at present no CHMP guideline on the development of phosphate binders. Scientific advice was provided by the CHMP in September 2005. Subsequently in October 2009, scientific advice was given for the Paediatric Investigational Plan (PIP) and written advice on ERA was given on March 2008.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets and granules. The film coated tablets contain 1g of colestilan and the granules contain 2g and 3g.The composition is described in section 6.1 of the SmPC.

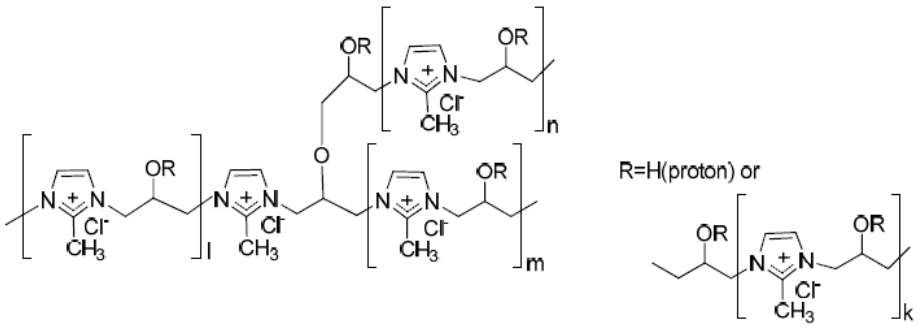
The film coated tablets are available in high density polyethylene bottles and in blisters of PVC/Aclar with Aluminium foil lid. The granules are packed in laminated foil sachets (Polyethylene terephthalate/polyethylene/aluminium foil/polyethylene/polyvinylidene chloride) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Colestilan is a cross-linked polymeric anion exchange resin, is a white to pale yellowish white powder, practically insoluble in water and common organic solvents. It is reversibly hygroscopic.

Colestilan has two chemical names and the following structural formula:

- 2-Methylimidazole polymer with 1-chloro-2,3-epoxypropane
- 2-Methylimidazole-epichlorohydrin copolymer



The molecule does not contain any chiral centres and polymorphism has not been observed. Colestilan is not described in any pharmacopoeial monograph.

Manufacture

Colestilan is synthesised in two main steps, polymerization and purification, using commercially available and well defined starting materials.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Batch analysis data are provided on a number of batches produced with the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

Specification

The active substance specification includes tests for visual description, identification(IR, KCl disk), swelling volume, heavy metals (visual), related substances(HPLC), residual solvents(GC),residual reagents (GC-MS), residual processing aid (HPLC), water content (KF), residue on ignition, particle size, chloride assay (potentiometric titration) and phosphate exchange capacity assay (HPLC).

Batch analysis data on a number of batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in double PE bag with desiccant (between bags) inside steel drums from the proposed manufacturer were put on stability testing as per ICH conditions for up 36 months under long term (25°C/60%RH) and for up to six months at accelerated (40°C/75%RH) conditions.

One batch packed in an open glass bottle and propylene tube was put on stability testing at accelerated conditions for 6 months. For the same batch photostability test results, following ICH guidelines Q1B, and stress testing at 60°C were provided.

The parameters tested were identification, swelling volume, related substances, residual solvents, water content, residue on ignition, particle size, chloride assay and phosphate exchange capacity.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Different strength tablets and granules, colestilan film coated tablets 500mg and film coated compressed granules 83%, have been used in Japan since 1999 and 2003 respectively, to treat hypercholesterolemia. The proposed indication for BindRen is the treatment of hyperphosphatemia for which a higher dose regime of up to 15g/day and larger tablets are needed. The aim of the pharmaceutical development was to develop tablets and granules more appropriate for this increase in the dose regime using the same excipients as the currently marketed products in Japan.

The main physicochemical characteristics of colestilan drug substance that were taken into consideration for the pharmaceutical development of both tablets and granules were solubility, particle size, water content and powder properties. To fulfil its role as an anionic ion exchange resin, colestilan needs to remain insoluble in water through the intestinal tract.

The excipients used were qualitative the same as those used for the Japanese formulations but with different quantities and different grade. These excipients are standard ingredients in compliance with the Ph. Eur. The concentration of each excipient is within usual ranges of application.

A bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation.

The primary packaging proposed for the tablets is high density polyethylene bottles and blisters of PVC/polychlorotrifluoroethylene with Aluminium foil lid. The granules are packed in laminated foil sachets (Polyethylene terephthalate/polyethylene/aluminium) foil/polyethylene/polyvinylidene chloride) as described in section 6.5 of the SmPC.

The material complies with Ph. Eur. requirements and it is adequate to support the stability and use of the product.

Adventitious agents

Not applicable.

Manufacture of the product

The manufacturing process for BindRen tablets and granules uses standard pharmaceutical techniques: granulation, screening, blending, compression and coating. There are no intermediates in the manufacturing process.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. The in-process controls are adequate for the tablets and granules formulations.

The available batch analysis data on pilot scale validation batches shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of these oral preparations.

Product specification

The finished product specifications include methods for description, identification(IR), uniformity of dosage units, disintegration, related substances (HPLC), related substances (HPLC),water content (KF), microbial limits (pour plate) and phosphate assay capacity assay(HPLC).

The finished product specifications have been justified and all methods of analysis have been described and adequately validated.

Batch analysis results on a number of batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

For the tablets the following stability data were provided:

- plain tablets: 17 production scale batches ,3 of them packed in aluminium blisters were tested for 36 months at long term conditions (25°C ± 2°C/60% RH ± 5°C and the other 14 packed in HDPE bottles were tested for 24 months at long term conditions (25°C ± 2°C/60% RH ± 5°C) and 6 months under accelerated conditions (40°C ± 2°C/75% RH ± 5°C).

- printed tablets: 2 production scale batches and 4 pilot scale batches packed in HDPE bottles were tested for 24 months at long term conditions (25°C ± 2°C/60% RH ± 5°C) and 6 months under accelerated conditions (40°C ± 2°C/75% RH ± 5°C).

The parameters tested were the same as those tested for release of the finished product.

In addition, 2 batches were exposed to light following ICH guidelines Q1B and the results show that the finished product is not sensitive to light as no significant changes were observed.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

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 the clinic.

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.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant conducted a comprehensive non-clinical development programme to support the use of colestilan in humans. The main part of the program was performed prior to its marketing in Japan, which dates back to 1999, thus prior to implementation of most of relevant non-clinical ICH guidelines. None of the submitted pharmacology, safety pharmacology and pharmacokinetics studies were

performed according to GLP. However, the studies submitted and presented in this assessment report were extensively described in study reports and are of acceptable quality. All pivotal toxicology studies were conducted according to GLP.

2.3.2. Pharmacology

The pharmacology programme was considered to be adequate. The overall results of these studies are reported below.

Primary pharmacodynamic studies

The primary pharmacodynamic data originates both from *in vitro* and *in vivo* studies.

Primary pharmacodynamic *in vitro*

The phosphate binding properties of MCI-196/colestilan has been studied *in vitro* in different fluids.

The experiments performed *in vitro* show that MCI-196 bind phosphate *in vitro*. The phosphate binding was weaker than the cholic acid binding and was not affected by pH in the range 4-9 (a slight decrease in binding was seen at pH 2-3 and at pH 10-11).

Primary pharmacodynamics *in vivo*

In vivo the effects of MCI-196/colestilan on phosphorous levels has been studied in rats, both normal rats and in disease models where rats were nephrectomised or pre-treated with adenine or adriamycin to induce renal failure.

In normal rats, oral administration of 500 mg/kg MCI-196 twice a day (b.i.d.) for 2 days increased faecal phosphorus excretion ratio (amount of phosphorus excreted in faeces/amount of phosphorus ingested), decreased urinary phosphorus excretion ratio (amount of phosphorus excreted in urine/amount of phosphorus ingested), but had no effect on plasma phosphorus concentrations. After 7 days of b.i.d. oral administration of 500 mg/kg MCI-196, urinary phosphorus excretion ratio decreased and urinary calcium excretion ratio increased; there were no changes in faecal phosphorus excretion ratio or plasma concentrations of phosphorus or calcium. After administration of a 2% of MCI-196 in the diet for 7 days in rats, urinary phosphorus excretion ratio decreased and urinary calcium excretion ratio and faecal phosphorus excretion ratio increased slightly while no effects on faecal calcium were seen.

Nephrectomisation and adenine- or adriamycin-induced renal failure were used as models to study the effects of MCI-196 in conditions of hyperphosphataemia and chronic renal failure:

In nephrectomised rats fed a phosphorus enriched diet for 5 weeks, 4 and 8% of MCI-196 in the diet for 5 weeks did not suppress the increase in plasma phosphorous concentration induced by nephrectomy but did induce a decreased urinary phosphorous excretion ratio and also an increased fecal phosphorous excretion ratio at high concentration. PTH was also decreased in MCI-196 treated animals and as expected plasma total cholesterol was decreased dose dependently in MCI-196 treated animals (see secondary pharmacodynamics).

In adenine-induced renal failure rats, treatment with a 2% of MCI-196 in the diet for 2 weeks decreased plasma inorganic phosphorus concentrations. Plasma PTH concentrations also decreased in MCI-196 treated rats and a decrease in the severity of diffuse hyperplasia in the parathyroid gland was also detected. There were no changes in urinary or faecal excretion of phosphorus or calcium with MCI-196 while an increase in plasma calcium levels was observed. In another study, 2% of MCI-196 in the

diet for 2 weeks was also shown to decrease thoracic aorta calcification and to decrease aorta calcium content in adenine-induced renal failure rats, as well as to decrease the calcium and inorganic phosphorus contents of heart. The calcium content in the left kidney increased in MCI-196 treated rats (while no effect was seen in the right kidney) and the inorganic phosphorus content in the kidneys decreased. In MCI-196-treated rats a decreased severity of diffuse hyperplasia in the left side of the parathyroid gland was seen but there were no significant decreases in plasma inorganic phosphorus levels or plasma PTH levels. In adriamycin-induced renal failure rats, treatment with a 1 and 3% of MCI-196 in the diet for 111 days had no significant effect on serum levels of inorganic phosphorus, calcium, creatinine, or urea nitrogen. Plasma PTH levels were decreased in rats given 3% of MCI-196 in the diet.

Secondary pharmacodynamic studies

Secondary pharmacodynamics *in vitro*

MCI-196 binds to bile acids and long chain fatty acids *in vitro*. Results obtained also indicate that MCI-196 does not adsorb glucose, sucrose, or starch. A weak binding affinity to ascorbic acid was also observed.

Secondary pharmacodynamics *in vivo*

In vivo studies in rats and rabbits showed that MCI-196 increased bile acid excretion in faeces. Results suggest that MCI-196 trap bile acid in the intestinal tracts during at least 6 hr after a single administration in rats. MCI-196 decreased levels of bile acids in portal blood in rats, decreased total and free cholesterol levels in lymph fluid, increased bile acid excretion in feces and HMG-CoA reductase activity and microsomal cholesterol 7α-hydroxylase activity in liver in treated rats. MCI-196 also decreased the elevation of serum cholesterol induced by a high cholesterol diet in rats.

MCI-196 had an inhibitory effect on dietary triglyceride absorption but had no effect on triglyceride synthesis in isolated hepatocytes from treated rats or fatty acid mobilization induced by nor-epinephrine.

MCI-196 treatment also decreased plasma LDL- and total cholesterol and increased liver LDL-clearance in hamster and induced a dose dependent decrease in the elevation of total cholesterol, as well as VLDL- and LDL-cholesterol, caused by cholesterol diet in rabbits. (The VLDL-cholesterol secretion rate decreased in MCI-196 treated rabbits (3.7±0.25 mg/dL/3hr *vs* 6.6±0.67 in control).) Significant decrease in total plasma cholesterol was seen in rabbits after 8 and 12 weeks of treatment with MCI-196. After 12 weeks of treatment significant decreases in the cholesterol levels in the arch and thoracic aorta were detected together with a decreased cholesterol deposition. MCI-196 increased faecal concentrations of bile acids and cholesterol in rabbits fed a normal diet as well as in rabbits fed a cholesterol diet and increased LDL receptor mRNA in liver of rabbits fed a high cholesterol diet. MCI-196 had a cholesterol-lowering effect in rabbits fed a high cholesterol diet and also in rabbits fed a normal diet. MCI-196 also decreased total cholesterol levels in LDL-receptor deficient rabbits.

Fasting plasma glucose and insulin levels, as well as glucose AUC after glucose loading decreased in KK-Ay mice after administration of MCI-196 containing diet. The hypoglycemic effect of MCI-196 was accompanied by a decreased insulin level.

Safety pharmacology programme

Central Nervous system

Two non-GLP safety pharmacology studies were conducted to evaluate the effects of MCI-196 on the central nervous system (CNS), cardiovascular (CV) system, respiratory system, urinary system, autonomic nervous system, and gastrointestinal (GI) system. These studies were conducted in the early 1990's prior to implementation of the ICH S7A and S7B guidelines. A hERG study was not conducted as per the recommendations of ICH S7B as this assay was not available when the safety pharmacology package was undertaken. The applicant states that as MCI-196 is orally administered and no absorption of MCI-196 into whole blood was observed in pharmacokinetic studies after 21 days repeat dosing in the rat at 200 mg/kg and after a single 200 mg/kg dose in the dog, the results of the study in concious dogs are considered to be an adequate examination of the CV system. This conclusion is endorsed by the CHMP.

Doses of MCI-196 up to 1500 mg/kg did not affect general symptoms or normal body temperature in rat, central nervous system in mice (spontaneous motor activity, traction test, synergy effect on anesthesia, anti-convulsive effect, analgesic effect (acetic acid writhing method)), or spontaneous electroencephalogram in rabbit, suggesting that MCI-196 did not show any effect on the central nervous system.

Possible effects on the autonomic nervous system or smooth muscles were analysed using effects on pupils of mice, where MCI-196 was found not to have an effect at doses up to 1500 mg/kg. In additional studies *in vitro*, MCI-196 did not show any effect at concentrations up to 10-3 g/mL on nor-adrenaline-induced contraction in rat isolated vas deferens. Spontaneous motility of isolated rabbit ileum and agonist-induced contraction of isolated guinea pig isolated ileum were neither affected by MCI-196 at concentrations up to 10-4 g/mL. At 10-3 g/mL MCI-196 reduced the amplitude of contraction and sporadically raised isotonic tension (since foaming was found at the time of treatment with MCI-196 at 10-3 g/mL, this effect was suggested to be attributed to a physical effect and not to the test compound).

Cardiovascular and respiratory system

Effect of MCI-196 on the cardiovascular system was examined using isolated guinea-pig atria. No effect was found at concentrations up to 10^{-4} g/mL. At 10^{-3} g/mL a slight positive chronotropic effect in the beating rate was observed. This change was also suggested to be attributed a physical effect due to foaming rather than the compound. MCI-196 had no effect on the cardiovascular or respiratory systems in Beagle dogs *in vivo* at oral doses up to 1500 mg/kg.

Gastrointestinal system

Possible effects on the gastrointestinal system were also investigated and MCI-196 was found not to affect charcoal transportation in mice or to cause irritation of gastric mucosa in rats at doses up to 1500 mg/kg. However it should be noted that cholestyramine (which was used as a reference drug) did not show the expected effect on charcoal transportation in the present study. MCI-196 decreased gastric secretion and total acid output, and raised pH by intraduodenal administration in rats at a dose of 1500 mg/kg. Cholestyramine, a reference drug, did not show any effect.

MCI-196 at a dose of 500 mg/kg and above tended to increase urinary excretion of Na^+, K^+ and Cl^-.

Pharmacodynamic drug interactions

A pharmacodynamic study was performed to evaluate the combined effects of MCI-196 and pravastatin on serum cholesterol in rabbits fed a high cholesterol-diet. MCI-196 and pravastatin synergistically decreased the level of plasma total cholesterol in rabbits.

2.3.3. Pharmacokinetics

The pharmacokinetics properties of MCI-196 were studied in rats and dogs after single and repeated oral administration with a dose of 200 mg/kg. The detection methods used in the studies were radioactive labelled [14C]-MCI-196 measured by liquid scintillation counter or whole body autoradiography. The limit of detection (LOD) of radioactivity, using liquid scintillation counting, was defined as twice the background radioactivity. Liquid scintillation counting method is considered adequate for such type of study but was not validated for measurements in animal tissues. However, liquid scintillation counting efficacy was corrected using external radioactive standards and the absence of matrix interference was confirmed from the raw data. Liquid scintillation counting is thus considered to be appropriate and to accurately reflect colestilan concentrations in the non-clinical studies performed.

Absorption

Colestilan is not absorbed from the gastrointestinal tract, and is claimed not to be metabolised during GI transit. Due to the low solubility of colestilan, it has also not been possible to develop a non-radioactive chemical assay for biological media, and conventional PK studies have not been performed. Due to the anion binding properties of colestilan, there is, however, a potential to alter the oral bioavailability of co-administered drugs, and thus, a number of non-clinical as well as clinical studies have been performed to investigate the drug-drug interaction potential of colestilan.

The systemic absorption of MCI-196 is very low or negligible in the results from the submitted data. The relevant parameters were adequately studied in two species, rat and dog, after single and repeated oral administration of the substance at a dose of 200 mg/kg.

Distribution

No tissue distribution of [14C]-MCI-196 was observed after oral administration in the rat. No radioactivity was detected by whole body autoradiography in the tissues investigated or in tissues containing melanin. Furthermore, MCI-196 potential to bind to proteins or transfer through the placenta was not studied in the present MAA. However, taken into consideration the low or negligible absorption and distribution of the substance, these parameters are not considered necessary to be addressed.

Metabolism

The possibility of MCI-196 to be metabolized in the intestine was investigated by dialysis in vitro after incubation for 24 hours at 37° C. No low-molecular compounds were detected in this assay concluding that there is no metabolic activity in the intestine of MCI-196. The low-molecular weight impurity substances in the samples after incubation with the upper and lower digestive tract contents were 0.15% and 0.14% of the dose, respectively, which was comparable to the control and background values. In addition *in vitro* forced degradation studies showed that colestilan was only degraded to any significant extent in an alkaline suspension at high temperature (0.1 mol/L NaOH, 80°C), which is not considered relevant for *in vivo* conditions.

The low or negligible absorption, distribution, metabolism and the almost exclusive excretion of unchanged colestilan in the faeces together with the results from the in vitro degradation studies strongly suggest that no appreciable depletion of colestilan, or formation of degradation products, occurs in the GI tract following administration of colestilan in clinical use. No experimental data are available regarding possible interaction between colestilan and gut flora. However, in the series of toxicology studies conducted in mice, rats, rabbits and dogs, administration of large quantities of

colestilan did not induce any clinically relevant GI toxicity, indicating that colestilan has no significant impact on the GI environment, including the status of gut flora.

An *in vivo* study to investigate MCI-196 effect on liver microsomal drug-metabolizing enzymes after 21 days oral administration in rat was submitted by the applicant. No indication of any influence of MCI-196 on the liver enzymes examined was found.

Excretion

In rat and dog and after oral administration (200 mg/kg), MCI-196 is only excreted via faeces. More than 97% of the dose was excreted within 120 hours in both species.

Pharmacokinetic drug interactions

Since MCI-196 is an anion exchanger, the molecule demonstrates a high affinity to substances with a certain size of hydrophobic portion. There are fat-soluble vitamins presented in the intestinal tract that are suspected to be adsorbed by MCI-196. The applicant has investigated *in vivo* the effect of MCI-196 on the absorption of vitamin D_3 and *in vitro* the adsorption capacity of MCI-196 on fat-soluble vitamins, A, D_3, E and K_1, studied in bile acid-lipid-vitamin mixed micelles solution. In conclusion, there are statistically significant decreases in Cmax and AUC0-48 of 1α(OH)-cholecalciferol (active D_3 vitamin) serum concentration of 32% and 29%, after co-administration of 1α(OH)-cholecalciferol (1 µg) at 0.5 hours after MCI-196 respectively, compared to endogenous levels after a single oral dose co-administered of MCI-196 and 1α(OH)-cholecalciferol (1 µg). No change was observed after that 1α(OH)-cholecalciferol was co-administered 4 hours after MCI-196. The fat-soluble vitamins A, D_3, E and K_1 have an *in vitro* adsorption rate (%) to MCI-196 of 57.9%, 54.0%, 62.2% and 78.4%, respectively. In the rat, effects of MCI-196 on coagulation parameters at high doses led to mortalities. These effects are considered associated with MCI-196 lowering lipid effect which leads to vitamin K deficiency. No obvious observations of increased bleeding tendency with colestilan were done in clinical studies of up to one year. A warning regarding malabsorption and vitamin deficiencies has been included in the SmPC in section 4.4. No evidence of vitamin K deficiency was observed in the dog studies.

Generally, no female animals were included in the pharmacokinetic studies. However, it is not likely that the absorption in females should be different than that in males. The two species used in the studies, rat and dog, are relevant animal models. In conclusion, no or negligible systemic exposure is expected after MCI-196 administration.

2.3.4. Toxicology

Single-dose Toxicity

Two GLP compliant single dose oral toxicity studies were performed in the mouse, rat, and dog at doses up to 1000 mg/kg and 5000 mg/kg, respectively. There were no MCI-196 related deaths and the only clinical signs observed were yellow faeces and vomiting after dosing.

There were no MCI-196-related deaths in mice and rats following a single oral dose of 1000 mg/kg of MCI-196. The only clinical signs noted with MCI-196 were soft stool and dirty perineum in the rats. No MCI-196-related effects on body weight or food consumption were noted, and there were no macroscopic findings. The LD50 was >1000 mg/kg in mice and rats.

There were no deaths in dogs following a single oral dose of 1000, 3000, or 5000 mg/kg of MCI-196. The only clinical signs noted with MCI-196 were vomiting at doses ≥3000 mg/kg and yellow faeces at doses ≥1000 mg/kg. The cause of these effects is unclear, but these GI findings may be due to a physical effect of the presence of a large volume or bulk of MCI-196 powder in the GI tract. These

findings were not associated with any macroscopic or microscopic changes and have little if any toxicological significance. There were no MCI-196-related effects on body weight, food consumption, vital signs, haematology, serum chemistry, urinalysis, macroscopic findings, organ weights, or microscopic findings. The non-emetic dose of MCI-196 was identified as 1000 mg/kg, and the LD50 was >5000 mg/kg.

Repeat-dose Toxicity

A number of GLP compliant repeat dose toxicity studies were conducted in the mouse (3 months only), rat (up to 12 months + 3 months recovery) and the dog (up to 12 months + 3 months recovery).

The main effects observed following repeat dosing can be ascribed to the pharmacology, i.e. bile acid sequestration potential of MCI-196 resulting in lipid lowering. Cholesterol, fatty acids and triglycerides levels were decreased in both rats and dogs. These effects were seen from 4 weeks of dosing through to 12 months but were minimal at all time-points.

Increased coagulation parameters, PT and APTT, were evident in rats from 4000(M) - 6000 (F) mg/kg/day and from 3000 (M) – 4000 (F) in the 3 months study and at 1200mg/kg/day in the 12 months study. In the 12 month study this increase was accompanied by internal haemorrhage leading to death. This effect is considered to be associated with the lipid lowering effect of MCI-196 which results in a reduction of fat and fat-soluble vitamins leading to Vitamin K deficiency. The NOAEL for this effect in the 12 month rat study is 500 mg/kg/day which is only 2-fold to the clinical dose. There was no evidence of vitamin K deficiency in dogs and there was no consistent increase in PT and APTT in any of the dog studies. Coagulation parameters and vitamin K levels are easily monitored in the clinic and deficiencies are easily manageable by supplementation. Very slightly decreased vitamin K, and increased PT and APTT was observed in the clinical studies of up to one year, however this did not translate into an obviously increased bleeding incidence. A warning regarding malabsorption and vitamin deficiencies has been included in the SmPC in section 4.4.

Increased serum chloride (noted only in the 12 month dog study) and increased urine chloride levels were noted in both rats and dogs. This is considered to be related to the exchange of phosphate ions for chloride ions from the MCI-196 resin. These chloride ions are then absorbed from the GI-tract and excreted via the urine. This increase in urine chloride levels results in decreased urine pH which causes uric acid to precipitate resulting in uric acid crystals (noted in the urine of both rats and dogs). There was no evidence that the increase in serum chloride levels had any effect on blood pH and no evidence of any associated lesions.

Abnormally (yellow/white) coloured faeces in both rats and dogs at high dose levels were observed and this is considered to be the excretion of the test compound. In dogs, mucus was also occasionally observed in the faeces of dogs receiving 2000 mg/kg/day during the 12 month study, but there was no evidence of any adverse effect on the GI-tract.

Decreased body weight gain (ranging from 2 to 12%) was noted in rats during the 1, 3, 6 and 12 month study. Decreased body weight gain was not observed during the dietary 3 month study, the oral gavage 3 month study, or in the 3 month oral gavage study investigating hepatic toxicity. The decreased bodyweight gain was also noted in mice during the 3 month oral gavage study. The reason for the observed decrease is uncertain but as it is inconsistent it does not seem to be directly related to MCI-196 exposure.

MCI-196 is not systemically absorbed and toxicokinetic data from the toxicity studies has not been provided. This is acceptable. Therefore it is accepted to estimate the safety margins based on comparison of the mg/kg/day dose instead of plasma concentrations. The safety margins to the NOAELs are low, from nearly 2-fold, but considering the nature of the findings in the toxicity studies

(emesis, abnormally coloured stools and effects ascribed mainly to secondary pharmacological effects) this is not considered as a concern.

Table 1 Comparison of Dose levels of MCI-196 in Human, Mouse, Rat and Dog

Species	Treatment Duration	NOAEL (mg/kg/day)	Safety cover over human dose of 250mg/kg/day
Mouse	3 months	7000	28
Rat	3 months	400 (highest dose)	1.6
	6 months	400	1.6
	12 months	500	2
Dog	3 months	1000 (highest dose)	4
	12 months	2000 (highest dose)	8

An attempt to evaluate the observed increase in liver enzymes was made, however the mechanism by which AST and ALT levels are increased still remains uncertain. The applicant offered a hypothetical but although plausible mechanism involving the sequestration of bile acids leading to a decreased direct absorption of lipids into the systemic circulation and disturbing the homeostasis of enterohepatic circulation of bile acids. Such an effect would promote increased production of bile acids in the liver and an increased catabolism of cholesterol in the liver. Since MCI-196 is not absorbed from the gastrointestinal tract, the indirect impact on the liver via increasing metabolic activity in the liver (an adaptive effect on liver function) is presumed to be an explanation for the elevation of hepatic enzymes.

Genotoxicity

MCI-196 was not mutagenic in the bacterial reverse mutation assay and CHO/HGPRT forward gene mutation test, was negative for the induction of structural and numerical chromosome aberrations in CHO cells with and without metabolic activation, and was negative for micronucleus induction in the mouse micro nucleated erythrocyte assay.

Carcinogenicity

Carcinogenicity studies were conducted in the mouse and in the rat. In the mouse no carcinogenic, pre-neoplastic, or non-neoplastic finding was observed. In the rat, a slightly increased incidence of pancreatic cell adenomas was observed in males only at 2000 mg/kg/day (highest dose). This increase was not statistically significant when compared with either of the control groups, but only when compared with the pooled control group. The increase was also significant when compared against pooled historical controls from four 24-month rat carcinogenicity studies. There was no drug-related increase in the incidence of pancreatic cell carcinoma, pancreatic cell hyperplasia, or non-neoplastic microscopic findings in the pancreas. The applicant argues that “MCI-196 is chemically and biologically inert, it is not orally bioavailable, produces no systemic exposure, and is not metabolized. MCI-196 remains in the gastrointestinal (GI) tract after oral administration until excreted unchanged in the feces along with the bound phosphate (or bile acids). No drug-related macroscopic or microscopic findings of any type were observed in the pancreas in any repeated dose toxicity study of MCI-196 in mice (up to 3 months in duration), rats (up to 12 months in duration), or in dogs (up to 12 months in duration). No drug-related neoplastic or non-neoplastic microscopic findings of any type were observed in the pancreas in the mouse carcinogenicity study. In addition, no evidence of a mutagenic or

clastogenic potential was observed in *in vitro* and *in vivo* genotoxicity studies with MCI-196." Taken together, the CHMP agrees that these are strong evidences that MCI-196 should not be considered as carcinogenic. A sustained increase in serum cholecystokinin (CCK) is suggested as a possible indirect epigenetic mechanism that may enhance pancreatic acinar cell foci and hyperplasia with the eventual formation of adenomas and it is pointed out by the applicant that changes in bile salt components were manifested in rats in a 12-week repeated dose study in rats (although effects on CCK levels in bloodstream were not measured). However, an increase of acinar cell foci or hyperplasia was not observed in the repeated dose toxicity studies or the carcinogenicity study in rats. As such the absence of acinar cell foci or hyperplasia indicates that colestilan does not have any potency to stimulate proliferation of exocrine pancreatic cells. The pancreatic acinar cell adenoma, observed at very low incidence in the high dose male rats of the carcinogenicity study, is therefore considered to be incidental and not related to the treatment with colestilan and that these findings does not have any clinical relevance.

Reproductive and developmental toxicity

Studies of male and female fertility, early embryonic development, embryo-foetal development, and peri-postnatal development in the rat and the rabbit did not reveal any effects on any of the reproductive parameters. NOAELs in all studies were the highest doses tested. It should be noted that maternal toxicity was not observed in any of the studies, and that margins to the human dose on a mg/kg basis is about 2.5 fold. This is accepted because MCI-196 is not systemically absorbed and was found to be of very low toxicity in the repeat-dose studies.

Fertility and early embryonic development

The reproductive toxicity of oral MCI-196 was studied in rats and rabbits. Daily oral doses of 100, 240, or 600 mg/kg/day of MCI-196 to rats had no parental toxicity or adverse effects on fertility and reproductive performance of the F0 generation. There were no treatment-related effects on the subsequent development and reproductive capacity of the untreated F1 and F2 offspring. The NOAEL for the general condition and reproductive capacity of the parents and for the development of their offspring was considered to be 600 mg/kg/day.

Embryo-fœtal development

There was no teratogenicity, mortality, or maternal or embryofoetal toxicity with oral doses up to 800 mg/kg/day of MCI-196 administered to rats during organogenesis. There were no effects on growth or physical, functional, or reproductive development in the F1 generation of MCI-196-treated dams. The F2 generation pre-weaning growth and necropsy findings were similar among groups. The NOAEL for the general condition and reproductive capacity of the F0 generation dams and for the development of their offspring was considered to be 800 mg/kg/day.

Daily oral doses of 100, 250, or 600 mg/kg/day of MCI-196 to rabbits during organogenesis had no adverse effects on reproductive parameters and there was no teratogenicity. The NOAEL for the general condition and reproductive capacity of the mothers and for the development of their offspring was considered to be 600 mg/kg/day.

Prenatal and postnatal development, including maternal function

There was no treatment-related mortality, or maternal toxicity with oral doses up to 800 mg/kg/day of MCI-196 administered to rats during the peri- and postnatal period. There were no effects on growth or physical, functional, or reproductive development in the F1 generation of MCI-196-treated dams. The F2 generation pre-weaning growth and necropsy findings were similar among groups. The NOAEL

for the general condition and reproductive capacity of the F0 generation dams and for the development of their offspring was considered to be 800 mg/kg/day.

There is a risk that pregnant patients with malabsorption will experience vitamin K deficiency that could lead to embryotoxicity. This could be prevented by adequate vitamin supplementation. This is adequately reflected in the SmPC, section 4.6.

Local Tolerance

No specific study was conducted.

Other toxicity studies

To evaluate the hepatic toxicity of MCI-196, female rats were administered MCI-196 orally by gavage at doses of 0 and 800 mg/kg/day over a 12 week treatment period. There were no changes in lipid content or fluidity of hepatocyte membrane. Serum vitamin E and hyodeoxycholic acid were decreased whereas chenodeoxycholic acid and lithocholic acid were increased. However, total bile acid content in liver as well as the levels of the bile acids with the greatest known hepatotoxicity, were unchanged. The NOAEL was judged to be 800 mg/kg/day and the mechanism by which AST and ALT levels are increased remains uncertain.

The palatability of MCI-196 was evaluated in mice and rats in Study No. 41546-302-90-91.

In mice given 0, 7000, or 14000 mg/kg/day MCI-196 in the diet for 12 weeks, decreased body weight was noted in males at ≥7000 mg/kg/day. Daily doses of 7000 or 14000 mg/kg/day were palatable.

In rats given MCI-196 in the diet for 3 months, daily doses of 1000, 2000, or 5000 mg/kg/day were palatable. One male at 2000 mg/kg/day and four males at 5000 mg/kg/day died or were sacrificed due to moribund conditions; the death at 2000 mg/kg/day was due to unknown causes and the deaths at 5000 mg/kg/day were due to haemorrhage. For the animals that survived to the end of the dosing period, gross and microscopic evidence of haemorrhage was seen in males at ≥2000 mg/kg/day. Dose-related increases in PT and APTT in males at 2000 mg/kg/day and in males and females at 5000 mg/kg/day were noted. A toxicologically significant decrease in body weight was observed in males at 5000 mg/kg/day, although the reason is unclear and food consumption was increased in females at 2000 mg/kg/day probably due to compensatory reasons due to the large volume of non-nutritional compound in the diet. The NOAEL was judged to be 1000 mg/kg/day due to the death, haemorrhage, and increases in PT and APTT at 2000 mg/kg/day.

2.3.5. Ecotoxicity / environmental risk assessment

The environmental risk assessment was performed in accordance with the obtained Central Scientific Advice. Colestilan is a highly cross linked polymer substance and is insoluble in a range of standard solvents, including water and octanol. Therefore, the octanol-water partition coefficient cannot be determined. Colestilan is non-absorbable and it is agreed that bioaccumulation in aquatic species is highly unlikely. Colestilan was found not to be readily biodegradable. It can however be concluded that colestilan should not be considered as a PBT substance, even when considering its stability and probable persistence in the environment.

The colestilan resin particles are expected to be retained in the sewage treatment plants and could reach the terrestrial compartment by spreading of sludge on agricultural land or used as landfill. No effects were observed on activated sludge microorganisms or on the process of nitrogen transformation in aerobic soil. Due to the poor solubility, high molecular weight, and inertness of the

molecule this is not considered as a concern and it is not likely that colestilan will pose a risk to the sewage treatment plant microorganisms or to the terrestrial compartment.

A $PEC_{SURFACE\ WATER}$ of 0.00525 µg/L was calculated for the colestilan aqueous leachable related substance using a refined Fpen taking into account the prevalence of end-stage renal disease. The Fpen refinement is acceptable and no further studies are warranted.

Calculation of the Predicted Environmental Concentration (PEC)

The market penetration factor (Fpen) default value of 1% that can be employed for the Phase I assessment of $PEC_{SURFACE\ WATER}$ is not appropriate for BindRen 1000 mg film-coated tablets and BindRen 2000 mg/3000 mg granules containing colestilan, owing to the nature of the intended indication, i.e. treatment of hyperphosphataemia in adults receiving haemodialysis and peritoneal dialysis. Hyperphosphataemia develops in the majority of patients with end-stage renal disease (ESRD) (equivalent to Chronic Kidney Disease (CKD) stage 5). The prevalence of treated ESRD in the EU was reported as being in the range 500-900 patients per one million population(Hall et al, 2002) and ESRD affects 0.05-0.07% of the population (Kaitelidouet al, 2005). Consequently, 0.07% is a worst-case assumption for ESRD prevalence.

After entering the sewage system, colestilan is expected to be retained in the sewage treatment plant. It will be just one of the many insoluble materials present, many of which are of unknown composition.

Since there is the potential for very low concentrations of the aqueous leachable water soluble component of colestilan to enter the aqueous compartments, a $PEC_{SURFACE\ WATER}$ calculation has been performed for this aqueous leachable component.

The maximum daily dose ($DOSE_{ai}$) of the aqueous leachable water soluble component is calculated as 15.0 mg/patient/day (15,000 mg x 0.1%) which could in theory enter the environment, assuming no metabolism in humans. The 0.1% represents the aqueous leachable component of a 15,000 mg maximum dose of colestilan, based on batch analysis data presented on the water soluble related substance, oligomer.

• DOSEai = maximum aqueous leachable water soluble component (= 15.0 mg) from maximum daily dose of active ingredient (15 g).

• Fpen = percentage of market penetration = 0.07% = 0.0007

• WASTEWinhab = Amount of wastewater per inhabitant per day (= 200 L/inh/day)

• Dilution = dilution factor (= 10)

Hence, $PEC_{SURFACE\ WATER}$ = (15.0 x 0.0007)/(200 x 10)= 5.25 x 10-3 µg/L **= 0.00525 µg/L**

The EU guideline on environmental risk assessment applies a threshold $PEC_{SURFACE\ WATER}$ of 0.01 µg/L in respect of triggering an assessment of environmental effects. The above worst case predicted surface water concentration for colestilan aqueous leachables is <53% of this default threshold value (action limit) for considering a Phase II environmental effects analysis.

Retention of Colestilan in the Sewage Treatment Plant

Colestilan resin is formulated as a tablet or granule for oral use containing practically insoluble resin particles. The average particle size ranges between 80-130 µm. Colestilan is very poorly soluble/highly insoluble in a wide range of solvents.

It is possible that on occasion, sewage sludge containing colestilan could be used for spreading on agricultural land. In such a case, colestilan is expected to pose a minimal risk to terrestrial organisms in view of its high level of insolubility and inertness. Many components of sewage sludge such as

transition metals have marked toxic potential, especially if industrial effluents enter the particular sewage treatment works. By comparison, colestilan is innocuous.

Colestilan will be excreted into the sewage system with patient stools as saturated granular polymeric gel. After entering the sewage system, colestilan is expected to be retained in the sewage treatment plant by filtering and sedimentation and disposed of in landfill or incineration. If disposed of in landfill, the stability and the very poor solubility of colestilan will cause it to remain localised.

Table 2 Summary of main study results

Substance (INN/Invented Name): Colestilan					
CAS-number (if available): 95522-45-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Not feasible			Potential PBT (NO)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				not B
	BCF				not B
Persistence	DT50 or ready biodegradability				not P
Toxicity	NOEC or CMR				not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	0.00525	µg/L			> 0.01 threshold NO
Other concerns (e.g. chemical class)					NO
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Ready Biodegradability Test	OECD 301	0.8% (after 28 days)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	8.94	µg/L	
Phase IIb Studies					
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	42% effect	1000	mg/kg	

Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100	mg/ kg	L.Perenne, C. Sativa, A.Ceoa, B.Rapa, L.Sativa, L.Esculentum
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/ kg	Eisenia Fetida

It can be concluded that the proposed use of colestilan is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

MCI-196 is an anion exchange resin and the primary pharmacodynamic effect of MCI 196 in the treatment of hyperphosphataemia is due exclusively to its binding and excretion of phosphate. The same mechanism of action (i.e. the ability of MCI-196 to bind anions) is also the basis for the secondary pharmacodynamic effect of MCI-196, the binding and excretion of bile acids.

Phosphate binding characteristics of MCI-196 have been studied *in vitro* and the results obtained indicate that MCI-196 would be expected to bind phosphates within the GI tract after oral administration. In phosphate solution a lower affinity for phosphate was seen in artificial intestinal fluid and in presence of cholate. Results of *in vivo* phosphorus mass balance studies in normal rats and in rat models of hyperphosphataemia and chronic renal failure suggest that MCI-196 increases inorganic phosphorus excretion and thereby might improve hyperphosphataemia.

MCI-196 is registered in Japan as a hypolipidemic drug since 1999 and secondary pharmacological effects presented in the present application showed a hypocholesterolemic effect of MCI-196, including the binding of bile acids and a decrease in blood total as well as LDL-cholesterol. A possible effect on plasma glucose and insulin levels was also indicated in one experiment. The binding of bile acids in the GI tract has been suggested to reduce absorption of fat soluble vitamins and thus to possibly produce vitamin K deficiency with subsequent effects on coagulation parameters.

In safety pharmacology studies, MCI-196 was found not to affect general symptoms or central nervous system at up to 1500 mg/kg. No effect on the autonomic system, measured as effects on pupil diameter, isolated smooth muscle and isolated atria, was either seen at these doses. Gastric secretion and stress ulceration was suppressed by MCI-196 at the highest dose (1500 mg/kg), while it did not show any effect on the charcoal transportation and gastrointestinal motility. In addition, MCI-196 tended to increase secretion of urinary electrolytes. None of the effects of MCI-196 seen in the safety pharmacology studies performed thus indicate risk for serious acute adverse reactions in the clinic.

In phosphate solution a lower affinity for phosphate was seen in artificial intestinal fluid and in presence of cholate. The phosphate binding of MCI-196 was shown to be weaker than the cholic acid binding. Results of *in vivo* phosphorus mass balance studies in normal rats and in rat models of hyperphosphataemia and chronic renal failure suggest that MCI-196 increases inorganic phosphorus excretion and thereby might improve hyperphosphataemia. Secondary pharmacological effects include binding of bile acids which has been suggested to reduce absorption of fat soluble vitamins and thus to possibly produce vitamin K deficiency and a subsequently impaired coagulation. Data from safety pharmacology studies does not indicate any risk for serious acute adverse reactions in the clinic.

The pharmacokinetic rat and dog studies showed that no or negligible systemic exposure is expected after MCI-196 administration. The possibility of MCI-196 to be metabolized in the intestine was investigated by dialysis in vitro after incubation for 24 hours at 37º C. No low-molecular compounds

were detected in this assay concluding that there is no metabolic activity in the intestine of MCI-196. MCI-196 is only excreted via faeces. No female animals were included in the pharmacokinetic studies. However, it is not likely that the absorption in females should be different that in males. No effect of colestilan on the gut flora is anticipated.

Relevant findings in the non-clinical toxicity studies relate to secondary effects to the pharmacological effects. Of most importance are the effects on coagulation parameters, vitamin K deficiency, and internal haemorrhage. Coagulation parameters and vitamin K levels are easily monitored in the clinic and deficiencies are easily manageable by supplementation. Very slightly decreased vitamin K, and increased PT and APTT was observed in the clinical studies of up to one year, however this did not translate into an obvious increased bleeding incidence. In any case, a warning regarding malabsorption and vitamin deficiencies has been included in the SmPC in section 4.4. There is a risk that pregnant patients with malabsorption will experience vitamin K deficiency that could lead to embryotoxicity. This could be prevented by adequate vitamin supplementation. This is adequately reflected in the SmPC, section 4.6.

MCI-196 remains in the gastrointestinal (GI) tract after oral administration until excreted unchanged in the feces along with the bound phosphate (or bile acids). No drug-related macroscopic or microscopic findings of any type were observed in the pancreas in any repeated dose toxicity study of MCI-196 in mice (up to 3 months in duration), rats (up to 12 months in duration), or in dogs (up to 12 months in duration). No drug-related neoplastic or non-neoplastic microscopic findings of any type were observed in the pancreas in the mouse carcinogenicity study. In addition, no evidence of a mutagenic or clastogenic potential was observed in in vitro and in vivo genotoxicity studies with MCI-196. The CHMP agrees that these are strong evidences that MCI-196 should not be considered as carcinogenic. The pancreatic acinar cell adenoma, observed at very low incidence in the high dose male rats of the carcinogenicity study, is considered to be incidental and not related to the treatment with colestilan and thus not to have any clinical relevance.

The toxicity of colestilan has thus been adequately studied in non-clinical species. Colestilan was found to be of low toxicity with observed adverse effects secondary to the pharmacological action. The finding of most concern is the effects on coagulation parameters, vitamin K deficiency and internal haemorrhage. This was only observed in the rat, but relevant warnings have been included in the SmPC. No effects on fertility or reproduction parameters were observed at doses close to the clinical dose. Colestilan was not mutagenic or carcinogenic.

It is also concluded that the proposed use of colestilan is not expected to pose a risk to the environment.

2.3.7. Conclusions on non-clinical aspects

The overall non-clinical development programme was considered adequate to support the marketing authorisation application for colestilan and the concerns identified by the CHMP during its evaluation are considered resolved.

2.4. Clinical aspects

2.4.1. Introduction

The applicant is seeking a Marketing Authorisation for colestilan for the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis. Colestilan is an anion exchange resin developed by Mitsubishi Tanabe Pharma Corporation (MTPC). It is a long-chain polymer synthesised by cross-linking oligomers

resulting from the copolymerisation of 2-methylimidazole and epichlorohydrin. It is not absorbed from the human gastrointestinal (GI) tract and is not metabolised during transit of the GI tract. In the treatment of hyperphosphataemia, it acts in the GI tract as a non-calcium, non-metallic phosphate binder.

The product was originally developed in Japan for the treatment of hypercholesterolaemia (the name of the product during the development was MCI-196), and was registered in 1999 in Japan for the indication "Treatment of hypercholesterolaemia and familial hypercholesterolaemia". The recommended dose in Japan is 3 g (maximum dose 4 g) daily, given as a divided dose before breakfast and supper. This application is supported by an extensive clinical program to establish the therapeutic dose and to assess the efficacy and safety of colestilan in the treatment of hyperphosphataemia have been performed by the applicant.

Table 3 Clinical studies conducted to evaluate the use of MCI-196 in hyperphosphataemia

Study Number	Location of study	Number of subjects/patients	Study Description
Phase 1 studies			
MCI-196-E01	UK	44 healthy subjects	Single and multiple dose high dose safety and tolerance/phosphorus mass balance study
MCI-196-E02	UK	12 healthy subjects	Absorption and excretion study using radiolabelled MCI-196
MCI-196-E03	Belgium	14 healthy subjects	Drug interaction study with warfarin
MCI-196-E04	Germany	24 healthy subjects	Drug interaction study with digoxin
MCI-196-E05	Germany	32 healthy subjects	Drug interaction study with enalapril maleate
MCI-196-E12	Germany	16 healthy subjects	Drug interaction study with ciprofloxacin
36,210-06	USA	23 healthy subjects	Drug interaction study with propranolol
MCI-196-A13	USA	20 healthy subjects	Swallowability assessment of granules
MCI-196-J18	Japan	46 haemodialysis patients with HP	Double-blind, Placebo-controlled clinical pharmacology
Phase 2 studies			
MCI-196-E06	Europe	119 haemodialysis patients with HP	Double-blind, placebo-controlled study
MCI-196-A01	USA	75 haemodialysis patients with HP	Comparative forced titration study versus calcium acetate
MCI-196-A02	USA	41 haemodialysis patients with HP	Comparative long-term extension study of MCI-196-A01 study versus calcium acetate
MCI-196-A03	USA	59 haemodialysis patients with HP and type 2 diabetes	Comparative forced titration study versus calcium acetate
MCI-196-A04	USA	38 haemodialysis patients with HP and type 2 diabetes	Comparative long-term extension study of MCI-196-A03 study versus calcium acetate
Phase 3 studies			
MCI-196-E08	Europe, Russia, Asia	639 dialysis patients with HP and dyslipidaemia	Double-blind, placebo-controlled study
MCI-196-A05	USA	245 dialysis patients with HP	Double-blind, placebo-controlled withdrawal study
MCI-196-E07	Europe, Australia, South Africa	331 dialysis patients with HP	Double-blind, comparator study versus sevelamer, plus placebo-controlled withdrawal phase

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. All the clinical studies

included in this Marketing Authority Application (MAA) are declared by the applicant to have been conducted according to Good Clinical Practice (GCP), with the exception of study 36, 201-03. This study was carried out under license to Bristol Myers Squibb (BMS) and was conducted prior to 1997 when ICH GCP became effective. A low dose (4g/day) was administered in this study, and the study was conducted with a tablet formulation different to the product intended to be marketed

- **Tabular overview of clinical studies**

Table 4 Clinical studies conducted to evaluate the use of MCI-196 in hyperphosphataemia

Study Number	Location of study	Number of subjects/patients	Study Description
Phase 1 studies			
MCI-196-E01	UK	44 healthy subjects	Single and multiple dose high dose safety and tolerance/phosphorus mass balance study
MCI-196-E02	UK	12 healthy subjects	Absorption and excretion study using radiolabelled MCI-196
MCI-196-E03	Belgium	14 healthy subjects	Drug interaction study with warfarin
MCI-196-E04	Germany	24 healthy subjects	Drug interaction study with digoxin
MCI-196-E05	Germany	32 healthy subjects	Drug interaction study with enalapril maleate
MCI-196-E12	Germany	16 healthy subjects	Drug interaction study with ciprofloxacin
36,210-06	USA	23 healthy subjects	Drug interaction study with propranolol
MCI-196-A13	USA	20 healthy subjects	Swallowability assessment of granules
MCI-196-J18	Japan	46 haemodialysis patients with HP	Double-blind, Placebo-controlled clinical pharmacology
Phase 2 studies			
MCI-196-E06	Europe	119 haemodialysis patients with HP	Double-blind, placebo-controlled study
MCI-196-A01	USA	75 haemodialysis patients with HP	Comparative forced titration study versus calcium acetate
MCI-196-A02	USA	41 haemodialysis patients with HP	Comparative long-term extension study of MCI-196-A01 study versus calcium acetate
MCI-196-A03	USA	59 haemodialysis patients with HP and type 2 diabetes	Comparative forced titration study versus calcium acetate
MCI-196-A04	USA	38 haemodialysis patients with HP and type 2 diabetes	Comparative long-term extension study of MCI-196-A03 study versus calcium acetate
Phase 3 studies			
MCI-196-E08	Europe, Russia, Asia	639 dialysis patients with HP and dyslipidaemia	Double-blind, placebo-controlled study
MCI-196-A05	USA	245 dialysis patients with HP	Double-blind, placebo-controlled withdrawal study
MCI-196-E07	Europe, Australia, South Africa	331 dialysis patients with HP	Double-blind, comparator study versus sevelamer, plus placebo-controlled withdrawal phase
MCI-196-E10	Europe, Russia, Asia, South Africa	556 dialysis patients with HP	Long-term, open-label, extension study of MCI-196-E07 (versus sevelamer), MCI-196-E08 and MCI-196-E09
MCI-196-A06	USA, Canada	116 dialysis patients with HP	Long-term, open-label, safety study
MCI-196-E11	Europe, Asia	259 dialysis patients with dyslipidaemia	Double-blind, comparator study versus simvastatin, plus placebo-controlled withdrawal phase
MCI-196-E09	Europe	6 dialysis patients with HP (study prematurely terminated)	Double-blind, placebo-controlled study in combination with a calcium-based phosphate binder

HP = hyperphosphataemia

2.4.2. Pharmacokinetics

Colestilan is not absorbed from the gastrointestinal tract, and is claimed not to be metabolised during GI transit. Due to the low solubility of colestilan, it has also not been possible to develop a non-radioactive chemical assay for biological media, and conventional PK studies have not been performed. Due to the anion binding properties of colestilan, there is, however, a potential to alter the oral bioavailability of co-administered drugs, and thus, a number of non-clinical as well as clinical studies have been performed to investigate the drug-drug interaction potential of colestilan.

Absorption

Colestilan is not absorbed from the gastrointestinal tract; in a study with radiolabelled colestilan 99.7% of the radioactivity was found in faeces. The insolubility of the molecule precluded the development of a bioanalysis method, and no characterization of systemic pharmacokinetics has been made. This is acceptable. Different formulations have not been possible to compare using conventional bioequivalence studies.

The systemic absorption of MCI-196 was studied following single and repeated (21 days) oral administration of [14C]MCI-196 at a dose of 200 mg/kg to rats or dogs. The radioactivity concentration was analysed in blood or plasma. The animals, with the exception of rats in the repeat-dose study, were fasted prior to the administration and feeding was resumed 4 or 6 hours after administration. Only male animals were included in the studies. Furthermore, none of the submitted studies were performed according to GLP.

Low concentration of radioactivity was detected in blood at 30 minutes after single oral administration of [14C]MCI-196 in male rats (study AE-836 April). No radioactivity was observed in blood at other sampling points in this study or in any other study submitted.

Distribution

The tissue distribution of radioactive labelled [14-C]MCI-196 was studied in three studies after oral administration of 200 mg/kg. Tissue distribution was studied both after single and repeated administration in male rats with whole body autoradiography. In addition, the distribution in tissues containing melanin was studied after a single oral dose in pigmented rats.

With the exception of the gastro-intestinal contents, no radioactivity was detected in any other tissue after a single administration. At 168 hours, no radioactivity was observed in any tissue. The same results were observed after a 21 day period of daily oral administration.

Metabolism

To study the metabolism of MCI-196 in the digestive tract after oral administration of the substance, an *in vitro* decomposition study was performed. The upper digestive tract (duodenum and upper small intestine) and lower digestive tract (middle to lower small intestine) were collected and washed. Part of the mixture was incubated for 24 hours at 37 °C in anaerobic conditions. In order to examine the stability and ratios of metabolites (decomposition products), intestinal contents were passed through a dialysis membrane to separate low- and high-molecular compounds. A control without addition of intestinal contents was included in the assay. The results shown that the radioactivity concentrations detected in the external solution of the dialysis membrane from the mixture of [14C]-MCI-196 after incubation was comparable with the control and background values. In addition, no metabolites or degradation products [14C]-MCI-196 were detected in the faeces of rats or dogs.

Elimination

The mass balance study showed that >99% of the dose was excreted in faeces. A small amount of radioactivity was found in urine, but the applicant claims that this probably results from absorption of some water soluble impurity of the 14C-labeled colestilan. No *in vitro* metabolism studies have been performed, and the applicant claims that colestilan is excreted unchanged in faeces, which seems probable considering the high chemical stability of colestilan.

After oral administration of [14C]-MCI-196 to male rats and dogs, the excretion radioactivity in the urine and faeces within 12 hours was <0.1% and around 25% of the dose, respectively. After 12 hours, no excretion of radioactivity in the urine was within 120 hours post-dose. In addition, no radioactivity was detected in expired air in rats within the same period of time. The cumulative excretion of radioactivity in the faeces after 120 hours was > 97% of the dose in both rats and dogs.

Dose proportionality and time dependencies

BindRen can be administered in doses of 6 up to 15 g/day. No formal assessment of pharmacokinetic dose proportionality or time dependency has been made which is considered acceptable considering the lack of systemic drug absorption.

Special populations

The target population, for which efficacy and safety has been determined, is in patients with severe renal impairment. The dosing is adjusted according to drug efficacy (serum phosphorous levels). The mass balance and interaction studies have been performed in healthy volunteers. No studies in special populations are available, but caution is recommended in patients with severe gastrointestinal disorders as well as in patients with hepatic insufficiency. The lack of studies in special populations is considered acceptable in view of the pharmacokinetic properties of the substance.

Pharmacokinetic interaction studies

Colestilan has the ability to bind other agents in the gastrointestinal tract, leading to a potential for drug-drug interactions. The interaction potential has been studied both *in vitro* and *in vivo*.

Several in vitro studies have been performed to study the binding of drugs and other agents to colestilan in simulated intestinal fluids. Comparisons have also been made to established bile acid or phosphate binding compounds.

Data from these studies show a high binding capacity of colestilan for several substances, but the clinical relevance of these experiments is not fully clear, and the applicant has not discussed this in depth. *In vivo*, a number of compounds, including phosphate, will compete with drug binding to colestilan and drug-drug interactions seem to be a smaller clinical problem for the established agents sevelamer and colesevelam than could be expected from in vitro binding data.

In most experiments, colestilan showed a similar binding capacity to that of the clinically used agents sevelamer and colesevelam, and somewhat lower than that of colestyramine. For sevelamer and colesevelam, generally small or no effects on the bioavailability were observed for the drugs tested in drug-drug interaction studies *in vivo.* In addition five clinical drug-drug interaction studies were performed in healthy subjects. Digoxin, warfarin, enalapril, ciprofloxacin and propranolol were studied. The studies had a similar design, cross-over studies in healthy volunteers where the victim drugs were administered together with colestilan, and additional colestilan doses were administered over the

following 1-2 days. In general the colestilan doses used were low compared with the maximum recommended colestilan dose.

In general, no large effects on drug absorption were observed. Using the conventional bioequivalence limits for the ratio between drug AUC or Cmax when administered alone or together with colestilan (0.8-1.25), the only significant differences seen were a decreased AUC of digoxin (-16%) and decreased Cmax of digoxin (-17%) and enalapril (-27%). Notably, a decreased bioavailability of propranolol (-32%) was observed when propranolol was administered 1 hour before colestilan. This was based on complementary statistical analysis performed on an older (1993) non-GCP-study. These results are not mentioned in the SmPC and their relevance for dosing instructions in relation to concomitantly administered medicinal products have to be discussed further.

The *in vivo* interaction studies were performed with a 2-3 g colestilan dose 2-3 times daily, whereas the maximum dose applied for is 5 g three times daily. This is a clear deficiency since the majority of patients in the clinical studies needed doses of 12-15 g/day to control their phosphorous levels. In addition, the first colestilan dose is given together with the test drug, and no pre-treatment is investigated. This could not be considered a worst-case scenario. The SmPC clearly indicates in section 4.5 that interactions have not been studied at higher doses than 9 g daily and that greater interaction effects at higher doses of BindRen cannot be excluded.

The proposed dosing recommendation in section 4.5 in the SmPC for drugs where a reduction in bioavailability could have a clinically relevant effect on safety or efficacy is that the medicinal product should be administered at least one hour before, or three hours after BindRen. In addition, close monitoring of plasma concentrations and effects/adverse effects is recommended for drugs with narrow therapeutic index when initiated or dose-adjusted when the patient is on BindRen, or when BindRen is initiated or dose-adjusted during treatment with the other medicinal agent.

To conclude, the choice of drugs for the interaction studies as well as the study design and dose of colestilan used need to be discussed further by the applicant, as well as the clinical implications, to be able to fully assess the risk of drug-drug interactions with colestilan. A post-approval drug-drug interaction study designed to mirror a worst-case scenario has been agreed by the applicant.

2.4.3. Pharmacodynamics

Colestilan is an anion exchange resin. It is a long-chain polymer synthesised by cross-linking oligomers that are the result of copolymerisation of 2-methylimidazole and epichlorohydrin. It is not absorbed from the human gastrointestinal tract and is not metabolised during transit of the GI tract. In the context of treatments for hyperphosphataemia, it can be considered as a non-calcium, non-metallic phosphate binder. The mechanism of action resembles that of sevelamer.

Pharmacologically, bile acids in the GI tract bind to the product and are excreted in the faeces, leading to increased cholesterol catabolism and a decrease in blood low-density lipoprotein (LDL)-cholesterol. Colestilan (MCI-196) also binds dietary phosphate leading to increased MCI-196 bound phosphate excretion in the faeces, limiting the availability of phosphate for absorption into the blood. Another pharmacological effect is the reduction of elevated blood glucose and glycosylated haemoglobin (HbA1c) levels in patients with diabetes mellitus. In a mouse model, the hypoglycemic effect of MCI-196 was accompanied by a decrease in insulin level, suggesting that the hypoglycemic effect resulted from an improvement in insulin resistance. The applicant suggests that lowering of plasma glucose levels observed in the mouse insulin-resistant mice following administration of colestilan may be a class effect that is common to bile acid sequestrants (BAS).

Primary pharmacology: In short, the phosphate binding characteristics were found consistent over a pH range of 3 to 11. The phosphate binding capacity of the drug increased according to the drug concentration up to 30 mg/ml in artificial intestinal fluid. In normal rats, the drug caused a decrease in urinary phosphorous excretion and increased faecal phosphorous excretion.

In rats with renal failure, colestilan decreased thoracic aorta calcification and in one experimental model also decreased plasma PTH.

Colestilan binds to bile acids *in vitro*, and a weak binding affinity to ascorbic acid was also observed. *In vivo* studies showed that it increased bile acid excretion in faeces and decreased bile acid reabsorption.

It also accelerated catabolism of cholesterol in the liver and increased LDL-receptor messenger mRNA in the liver, resulting in decreases in blood total cholesterol. The drug lowered total blood cholesterol in several animal models of hypercholesterolaemia.

Secondary pharmacology: Beneficial secondary pharmacological effects mentioned above (in particular lowering of serum glucose and HbA1c, lowering of LDL cholesterol and total serum cholesterol) will be discussed in the context of clinical studies under Clinical Efficacy and Safety.

Harmful secondary pharmacological effects are particularly gastrointestinal. The most frequent treatment emergent adverse events related to colestilan during every time period in the phase 2 and phase 3 clinical trials were GI disorders and the most frequent Preferred Terms were nausea, vomiting, dyspepsia, diarrhoea, constipation and abdominal pain.

Pharmacokinetic drug interactions

Interactions with fat-soluble vitamins

MCI-196 effect on absorption of fat-soluble vitamins (A, D_3, E, K_1) was investigated in two studies (Study No 2435 and 710404).

In vivo (Study 2435), activated vitamin D_3 (1α(OH)-cholecalciferol) was orally co-administered with MCI-196 (300 mg) to male Beagle dogs (3M/group). 30 minutes and 4 hours after gavage administration of MCI-196, the animals were treated with 1µg activated vitamin D_3. Serum 1α,25$(OH)_2$ vitamin D_3 concentration was measured in serum at 2, 4, 8, 12, 24, and 48 h after active vitamin D_3 administration. One placebo group/time without MCI-196 treatment was included in the study. In addition, the endogenous values 1α,25$(OH)_2$ vitamin D_3 concentration of serum was subtracted from the test sample results at each time point of blood collection. The pharmacokinetic parameters, Cmax and AUC, were presented in the study.

The results shown that there are significant decreases in Cmax and AUC_{0-48} of 1α(OH)-cholecalciferol serum concentration of 32% and 29% after co-administration of 1α(OH)-cholecalciferol (1 µg) at 0.5 hours after MCI-196, respectively, compared to endogenous levels after a single oral dose co-administered of MCI-196 and 1α(OH)-cholecalciferol (1 µg). No statistically significant change in Cmax and AUC was observed when 1α(OH)-cholecalciferol was co-administered 4 hours after MCI-196.

In vitro (Study 710404), MCI-196 capacity to adsorb fat-soluble vitamins (A, D_3, E and K_1) was investigated in a bile acid-lipid-vitamin mixed micelles solution. The fat-soluble vitamin concentrations were determined by UV method. Under the conditions of the study, the adsorption rate (%) to MCI-196 for A, D_3, E and K_1 were 57.9%, 54.0%, 62.2% and 78.4%, respectively.

Mechanism of action

Colestilan is a non-calcium, non-metallic phosphate binder. The mechanism of action resembles that for sevelamer. It is not absorbed from the gastrointestinal tract, as demonstrated in a clinical mass balance study. It is an anion exchange resin not metabolised during transit of the GI tract. Colestilan has pH-consistent phosphate lowering effects and also lowers serum glucose and HbA1c, as well as cholesterol and LDL in serum.

Primary and Secondary pharmacology

Primary pharmacology

The phosphate binding characteristics were found consistent over a pH range of 3 to 11. The phosphate binding capacity of the drug increased according to the drug concentration up to 30 mg/ml in artificial intestinal fluid. In normal rats, the drug caused a decrease in urinary phosphorous excretion and increased faecal phosphorous excretion.

In rats with renal failure, colestilan decreased thoracic aorta calcification and in one experimental model also decreased plasma PTH.

Colestilan binds to bile acids *in vitro*, and a weak binding affinity to ascorbic acid was also observed. *In vivo* studies showed that it increased bile acid excretion in faeces and decreased bile acid reabsorption.

It also accelerated catabolism of cholesterol in the liver and increased LDL-receptor messenger mRNA in the liver, resulting in decreases in blood total cholesterol. The drug lowered total blood cholesterol in several animal models of hypercholesterolaemia.

Secondary pharmacology

Beneficial secondary pharmacological effects mentioned above (in particular lowering of serum glucose and HbA1c, lowering of LDL cholesterol and total serum cholesterol) will be discussed in the context of clinical studies under Clinical Efficacy and Safety.

Harmful secondary pharmacological effects are particularly gastrointestinal. The most frequent treatment emergent adverse events related to colestilan during every time period in the phase 2 and phase 3 clinical trials were GI disorders and the most frequent Preferred Terms were nausea, vomiting, dyspepsia, diarrhoea, constipation and abdominal pain. They correspond to what can be expected from a drug that is not absorbed and exerts its effect locally in the GI tract and resembles those of sevelamer, which has a similar mechanism of action.

From a pharmacokinetic point of view, the risk for interactions between BindRen and other drugs with high binding affinity to colestilan has been further discussed. A post-approval drug-drug interaction study designed to mirror a worst-case scenario has been agreed by the applicant, however, there are some comments on the proposed study design.

2.4.4. Discussion on clinical pharmacology

Colestilan is a non-absorbable, non-calcium, non-metallic phosphate binder. The mechanism of action resembles that for sevelamer. It is not absorbed from the gastrointestinal tract, as demonstrated in a clinical mass balance study. It is an anion exchange resin not metabolised during transit of the GI tract. Colestilan has pH-consistent phosphate lowering effects and also lowers serum glucose and HbA1c, as well as cholesterol and LDL in serum. Minor questions related to the potential for colestilan to interact with other medicinal products were issued to the applicant during the assessment.

The conclusion on the risk for interactions between BindRen and other drugs with high binding affinity to colestilan should be further addressed in a post-approval drug-drug interaction study. The CHMP has requested the applicant to suggest a worst-case design of such a study. The candidate drug should have high in vitro binding affinity to colestilan and preferably low gastrointestinal permeability. The maximum recommended dose of BindRen should be used, and pre-treatment with BindRen should be tested to obtain a worst-case exposure. Simultaneous dosing as well as 1 h before and 3 hours after BindRen administration, as recommended in the SmPC, should be evaluated.

Harmful secondary pharmacological effects are particularly gastrointestinal (e.g. nausea, vomiting, dyspepsia, diarrhoea, constipation and abdominal pain) and were dose dependent. The type of effects correspond to what can be expected from a drug that is not absorbed and exerts its effect locally in the GI tract and resembles those of sevelamer, which has a similar mechanism of action.

2.4.5. Conclusions on clinical pharmacology

Colestilan is a non-calcium, non-metallic phosphate binder. The mechanism of action resembles that for sevelamer. It is not absorbed from the gastrointestinal tract, as demonstrated in a clinical mass balance study. It is an anion exchange resin not metabolised during transit of the GI tract. Colestilan has pH-consistent phosphate lowering effects and also lowers serum glucose and HbA1c, as well as cholesterol and LDL in serum. The effect on blood uric acid reduction is not very well explained and should be further elaborated by the applicant, with respect to magnitude, mechanism of action and possible importance.

Harmful secondary pharmacological effects are particularly gastrointestinal (e.g. nausea, vomiting, dyspepsia, diarrhoea, constipation and abdominal pain) and were dose dependent. The type of effects correspond to what can be expected from a drug that is not absorbed and exerts its effect locally in the GI tract and resembles those of sevelamer, which has a similar mechanism of action.

Clinical pharmacodynamic studies showed that MCI-196 reduces phosphorus in plasma in CKT Stage V population. The non-clinically proven mechanism of action is relevant to clinical setting as this is shown clinically: MCI-196 increases faecal excretion of phosphorus. Two pharmacodynamic interaction studies were carried out – one with warfarin and another one with propranolol. The pharmacodynamic interaction studies did not show respective changes expected from PK changes.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

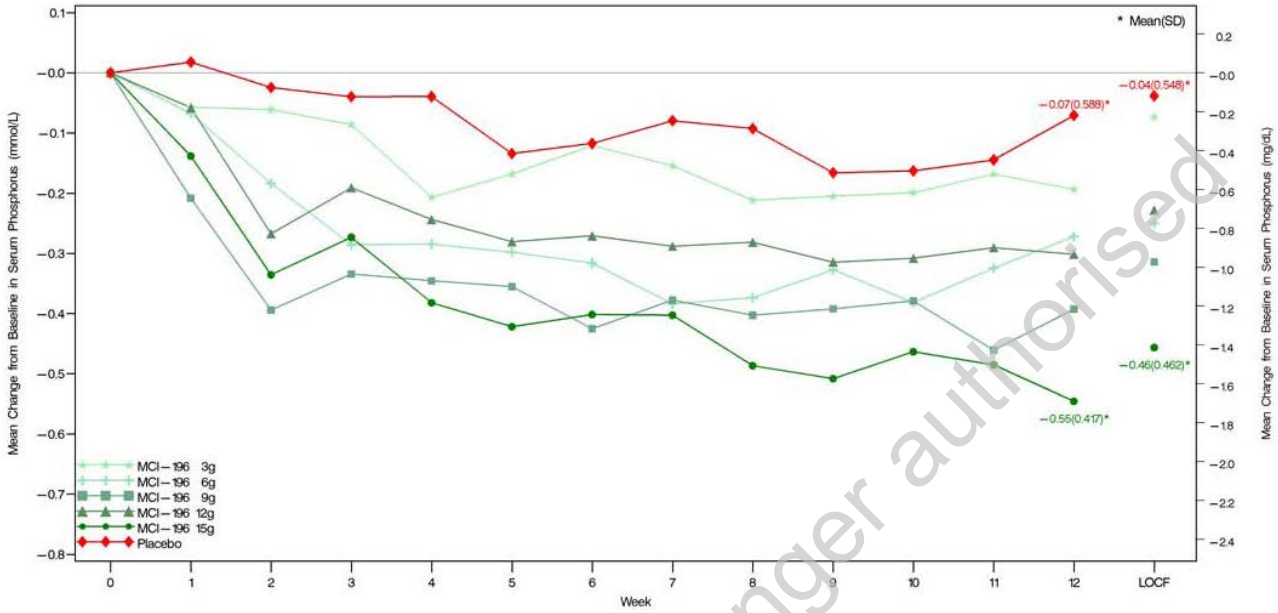
Dose-response studies and main clinical studies

Dose finding elements were included in the following phase 2 studies: E06, A01, and A03. Dose finding was also undertaken in the double blind placebo-controlled phase 3 studies, with fixed dose (study E08) and with dose titration (studies A05 and E07). Long-term open label phase 3 studies E10 and A06 used flexible dosing.

2.5.2. Main study(ies)

Dose response studies

Figure 3 Study E08: Mean change from baseline in serum phosphorous over time, ITT



The doses indicated in the figure above are, from lower to higher right of the curves: 15g, 9g, 12g, 6g, 3g, and placebo. To be noted, the baseline phosphorous level in the 12 g dose group was lower than that in the other dose groups.

Main clinical studies

During the drug development, colestilan was called MCI-196. The 3 phase 3 studies MCI-196-A05, MCI-196-E07, and MCI-196-E08 are considered to be the pivotal studies in this application. Parts of study designs are similar for these three studies, namely *Phosphate restricted diet, Study drug*, and *Definition of study drug noncompliance*.

Phosphate restricted diet: Study subjects were advised to maintain a stable low phosphate diet as prescribed. They were not allowed to receive phosphate binders or drugs that influenced phosphate (P) metabolism during the study.

Study drug: Study drug/placebo, as 1 g yellow film-coated tablets, was to be taken orally 3 times daily with breakfast, lunch, and dinner at regular times. 1000 mg yellow film-coated tablets and matching placebo/comparator was used.

Study drug noncompliance: In study MCI-196-A05, study drug noncompliance was defined as taking < 70% or > 130% of study medication during an evaluation period. In studies MCI-196-E07 and MCI-196-E08, study drug noncompliance was defined as taking less than 80% of study medication during any evaluation period. In the latter study, there was also an upper limit of 120 % for compliance.

Table 5 Description of clinical efficacy studies

Study ID	Number of Centres Location(s)	Study Start Enrolment status, date Total treated/ treated goal	Design Control type	Study & Control Drugs: Total dose/day, route[a] and regimen[b]	Study Objective	Number of Subjects by arm entered/ completed	Duration	Gender M/F mean age (range)	Diagnosis Inclusion Criteria	Primary Efficacy Variables
Phase 1 Patient Volunteer Clinical Pharmacology Study										
MCI-196-J18	Multicentre 2 centres in Japan	Start Jul 2002, completed Jan 2003 46/48	DB, random-ised, PC, repeated, clinical pharmacolog y study	MCI-196 6 g/day Placebo	Efficacy and safety.	46 patients: MCI-196: 29/20 Placebo: 17/12	2 weeks	FAS: (n=45) 36M/9F Age: 55.7 (30 to 84)	Hyperphos-phataemia on haemodial-ysis	Serum phosphorus (P) level from baseline to end of Week 2
Phase 2 Double-Blind, Placebo-Controlled Study										
MCI-196-E06	Multicentre 19 centres in Italy, Macedonia, Poland, Serbia and Montenegro	Start Apr 2003, completed Jul 2003 119/100	DB, random-ised, PC, multiple fixed dose	MCI-196 3, 6 or 9 g/day Placebo	Effect on serum levels of phosphorus. Safety and tolerability.	119/111 patients MCI-196: 90/82 Placebo: 29/29	3 weeks	74M/45F Age: 51.4 (22 to 78)	ESRD with hyperphos-phataemia on haemo-dialysis	Change baseline to endpoint in serum P level
Phase 2 Open-Label Active-Controlled Studies										
MCI-196-A01	Multicentre 30 centres in the USA	Start Dec 2002, completed Jun 2004 75/75	OL, random-ised, PG, forced dose titration	MCI-196 3, 6, 9 or 12 g/day MCI-196 3, 6, 9 or 12 g/day + Ca acetate (pre-study dose) Ca acetate alone (pre-study dose)	Safety and efficacy.	75/57 patients MCI-196: 23/17 MCI-196+ Ca acetate: 27/21 Ca acetate: 25/19	8 weeks	51M/24F Age: 50.2 (20 to 84)	Non-diabetic, ESRD with hyperphos-phataemia on haemo-dialysis	Change from baseline to endpoint and change from last run-in value to endpoint, in serum P level
MCI-196-A02	Multicentre 18 centres in the USA	Start Apr 2003, completed Nov 2004 41/max. 75	OL, PG extension of MCI-196-A01	MCI-196 3, 6, 9 or 12 g/day MCI-196 3, 6, 9 or 12 g/day+ Ca acetate (pre-study dose) Ca acetate alone (pre-study dose)	Long-term safety and efficacy.	41/26 patients MCI-196: 11/4 MCI-196+ Ca acetate: 14/9 Ca acetate: 16/13	24 weeks	29M/12F Age: 51.8 (22 to 85)	ESRD with hyperphos-phataemia on haemo-dialysis. Patients who completed study MCI-196-A01	Change from baseline (MCI-196-A01 study) to endpoint (MCI-196-A02 final visit) in serum P level
MCI-196-A03	Multicentre 30 centres in the USA	Start Dec 2002, completed Jul 2004 59/75	OL, Random-ised, PG, forced dose titration	MCI-196 3, 6, 9 or 12 g/day) MCI-196 3, 6, 9 or 12 g/day+ Ca acetate (pre-study dose) Ca acetate alone (pre-study dose)	Safety and efficacy.	59/48 patients MCI-196: 22/17 MCI-196+ Ca acetate: 16/13 Ca acetate: 21/18	8 weeks	30M/29F Age: 58.1 (28 to 77)	ESRD with hyperphos-phataemia and type II diabetes on haemodial-ysis	Change from baseline to endpoint, and change from last run-in value to endpoint, in serum P level
MCI-196-A04	Multicentre 30 centres in the USA	Start Apr 2003, completed Nov 2004 38/max 75	OL, PG extension of study MCI-196-A03	MCI-196 3, 6, 9 or 12 g/day MCI-196 3, 6, 9 or 12 g/day+ Ca acetate (pre-study dose) Ca acetate alone (pre-study dose)	Long-term safety and efficacy.	38/20 patients MCI-196: 14/6 MCI-196+ Ca acetate: 10/6 Ca acetate: 14/8	24 weeks	22M/16F Age: 56.3 (29 to 77)	ESRD with hyperphos-phataemia and type II diabetes on haemodial-ysis. Patients who completed study MCI-196-A03	Change from baseline (MCI-196-A03) to endpoint (MCI-196-A04 final visit) in serum P level

Phase 3 Double-Blind, Placebo-Controlled Studies										
MCI-196-E08	Multicentre 100 centres in Hungary, Italy, Poland, Serbia, Macedonia, Ukraine, Russia and Malaysia	Start Dec 2007, completed Nov 2009 639/625	DB, randomised, PC, multiple fixed-dose	MCI-196 3, 6, 9, 12 or 15 g/day Placebo	Efficacy, safety and tolerability	MCI-196 510/328 Placebo 132/82	12 weeks	340M/299F Age: 49.1 (19 to 80)	CKD Stage 5 with hyperphosphataemia and hypercholesterolaemia on dialysis	Co-primary endpoints: 1) mean change in serum P 2) mean % change in serum LDL-C; both from baseline (Week 0) to end of Week12 or LOCF
MCI-196-A05	Multicentre 45 centres in the USA	Start Sep 2007, completed Sep 2009 245/200	DB, randomised, PC, withdrawal study with an initial OL, dose titration period with MCI-196	Flexible dose period: MCI-196 3, 6, 9, 12 or 15 g/day Withdrawal period: MCI-196 same dose as at the end of flexible dose period Placebo	Effect on serum levels of phosphorus. Safety and tolerability	Flexible dose period: 245/169 patients Withdrawal period: MCI-196: 85/82 Placebo: 84/79	Flexible dose period: 12 weeks Withdrawal period: 4 weeks	ITT population: (n=241) 144M/97F Age: 55.9 (22 to 84)	CKD Stage 5 with hyperphosphataemia on dialysis	Change from Week 12 to Week 16 (or last observation post Week 12) in serum P levels
MCI-196-E07	Multicentre 69 centres in Australia, Austria, Czech Republic, France, Germany, Hungary, Italy, Poland, South Africa, Spain, and UK.	Start Jul 2007, completed Nov 2009 336/320	DB, randomised, PC, withdrawal study with an initial OL, randomised, dose titration with MCI-196 or sevelamer HCl	Flexible dose period: MCI-196 3, 6, 9, 12 or 15 g/day Sevelamer HCl 2.4, 4.8, 7.2, 9.6 or 12 g/day Withdrawal period: MCI-196 same dose as at the end of flexible dose period Placebo	Effect on serum levels of phosphorus. Comparison with sevelamer. Safety and tolerability	Flexible dose period: MCI-196 165/105 patients Sevelamer 171/139 Withdrawal period: MCI-196: 50/49 Placebo: 54/49	Flexible dose period: 12 weeks Withdrawal period: 4 weeks	Safety population: (n=331) 205M/126F Age: 58.0 (19 to 89)	CKD Stage 5 with hyperphosphataemia on dialysis	Change from Week 12 to Week 16 in serum P levels for placebo versus MCI-196
Phase 3 Open-Label Long-Term Safety Studies										
MCI-196-E10	Multicentre 128 centres in Europe, Russian Federation, Ukraine, Malaysia and South Africa	Start Oct 2007, completed Aug 2010 556/700	OL, flexible dose, long-term safety of MCI-196 or sevelamer HCl Extension of studies MCI-196-E07, MCI-196-E08 and MCI-196-E09	MCI-196 3, 6, 9, 12 or 15 g/day) Sevelamer HCl 2.4, 4.8, 7.2, 9.6 or 12 g/day	Long-term safety and tolerability	MCI-196 432/326 Sevelamer 124/92	40 weeks	300M/256F Age: 52.3 (19 to 88)	CKD Stage 5 with hyperphosphataemia on dialysis Patients who completed studies MCI-196-E07, MCI-196-E08 or MCI-196-E09	Change from baseline to end of study for: serum P, Ca, Ca x P, intact PTH, CRP, uric acid; lipid parameters, proportion of responders; HbA1c, glucose, serum iron, UIBC, transferrin saturation
MCI-196-A06	Multicentre 23 centres in the USA and Canada	Start Jan 2009, completed Aug 2010 116/100	OL, flexible dose, long-term safety study	MCI-196 3, 6, 9, 12 or 15 g/day	Long-term safety and tolerability	116/61	52 weeks	76M/40F Age: 57.3 (18-85)	CKD Stage 5 with hyperphosphataemia on dialysis	Mean or % change from baseline to Week 52 or LOCF for: serum P, Ca, Ca x P, PTH; lipid parameters; LDL particle size; bone metabolism markers; uric acid, CRP, HbA1c, and proportion of responders

AE=adverse event; Ca=calcium; Ca x P=calcium-phosphorus ion product; CKD=chronic kidney disease; CRP=C-reactive protein; DB=double-blind; ESRD=end stage renal disease; F=female; FAS=full analysis set; HbA1c=glycosylated haemoglobin; ITT=intent-to-treat; LDL=low density lipoprotein; LDL-C=low density lipoprotein-cholesterol; LOCF=last observation carried forward; M=male; OL=open-label; P=phosphorus; PC=placebo-controlled; PG=parallel group; PTH=parathyroid hormone; t.i.d=three times daily; UIBC=unsaturated iron binding capacity

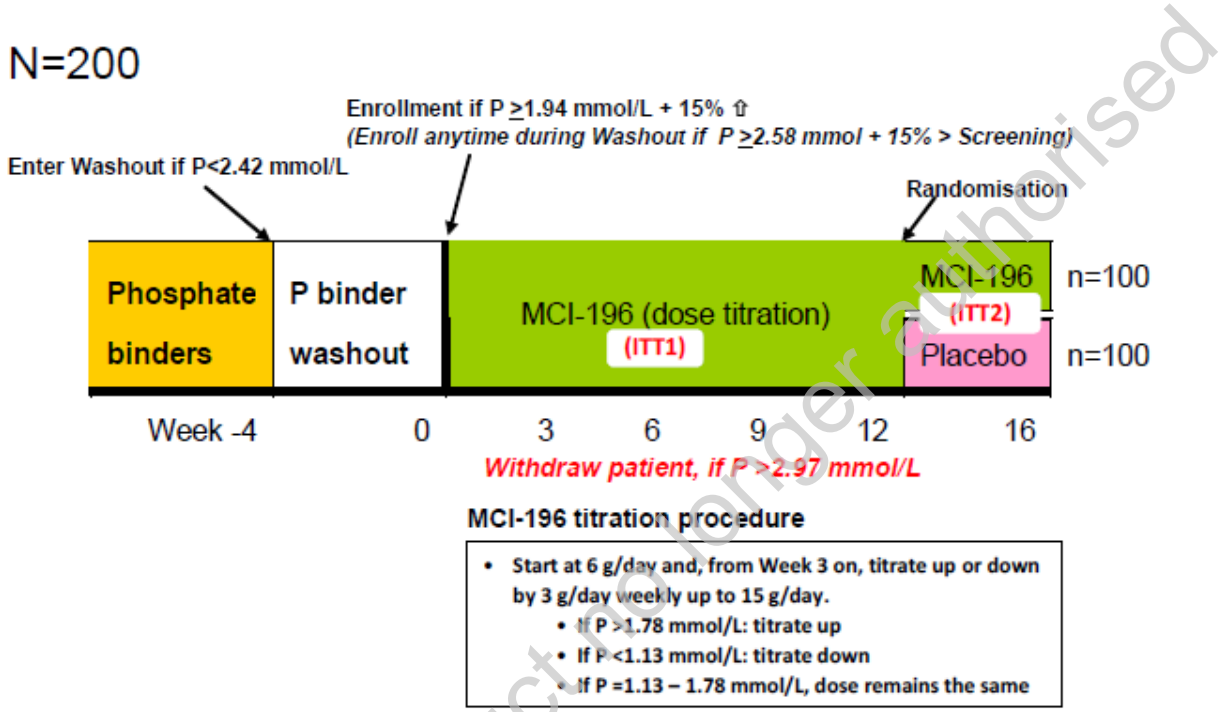
[a] All treatments were administered orally

[b] MCI-196 (and matching placebo where appropriate) was administered three times daily in all studies; comparators sevelamer and calcium acetate were also administered three times daily

A. Study MCI-196-A05

This was a phase 3, randomised double-blind placebo-controlled multicenter withdrawal study comparing MCI-196 to placebo following a 12-week dose titration period with MCI-196 in chronic kidney disease (CKD) stage 5 subjects on dialysis (hemodialysis or peritoneal dialysis) with hyperphosphatemia.

Figure 4 MCI-196-A05: Study design overview



Methods

The study consisted of a 12-week open-label flexible dose titration period (after a 4 - 5 week washout period for current phosphate binders) followed by a 4-week randomised, double-blind, placebo-controlled withdrawal period.

Study Participants

The planned enrolment was 200 subjects. There were 245 subjects enrolled in the open-label period, and 169 subjects randomised to the double-blind period. For the open-label period, 241 subjects were analysed (intent-to-treat, ITT1, population) and for the double-blind period, 168 subjects were analysed (ITT2 population).

Sixty-two US centers conducted the study. Study duration was between September 2007 and September 2009.

Table 6. Subject disposition: Summary of discontinuations, all subjects in study MCI-196-A05

	Open-label Period	Double-blind Period		
	MCI-196 (N=245)	MCI-196 (N=85)	Placebo (N=84)	Overall (N=169)
Parameter	N (%)	N (%)	N (%)	N (%)
Number of subjects withdrawn	76 (31.0)	3 (3.5)	5 (6.0)	8 (4.7)
Primary reason for withdrawal:				
Adverse event(s), including abnormal lab tests	21 (8.6)	0	1 (1.2)	1 (0.6)
Protocol violation	9 (3.7)	0	0	0
Lost to follow-up	2 (0.8)	0	0	0
Withdrawal of consent	13 (5.3)	1 (1.2)	0	1 (0.6)
Lack of efficacy	0	0	0	0
Pregnancy	0	0	0	0
High phosphorus levels	13 (5.3)	0	2 (2.4)	2 (1.2)
Withdrawal at Investigator's request	5 (2.0)	1 (1.2)	1 (1.2)	2 (1.2)
Death	0	0	0	0
Other	13 (5.3)	1 (1.2)	1 (1.2)	2 (1.2)
Number of subjects completing the study		82 (96.5)	79 (94.0)	161 (95.3)

In the open-label period, most discontinuations due to AEs (16/21), withdrawal of consent (8/13), high P levels (12/13), and other (9/13) occurred before week 6; most discontinuations due to protocol violation (7/9) occurred before week 3. In contrast, all incidences of discontinuations due to lost to follow up and withdraw by investigator's request occurred after week 6. The withdrawal rates during the double blind period were considerably lower compared to the open label period.

Objectives

Main objectives

The **primary objective** was to demonstrate superior efficacy of MCI-196 over placebo in the control of serum phosphorous (P) in subjects with chronic kidney disease (CKD) stage 5 on dialysis.

The **secondary objectives** were:

- To demonstrate superiority of MCI-196 over placebo in the control of other efficacy parameters (e.g. low-density lipoprotein LDL cholesterol [LDL-c], other lipid parameters, parathyroid hormone [PTH], calcium [Ca], calcium x phosphorous [Ca x P] ion product) in subjects with CKD stage 5 on dialysis.
- To demonstrate efficacy of MCI-196 during the treatment period in the control of all efficacy parameters (e.g., serum P, LDL-c, other lipid parameters, PTH, Ca, Ca x P ion product) in subjects with CKD stage 5 on dialysis.
- To assess the safety and tolerability of flexible-dose MCI-196.

Responders were defined as subjects who achieved any of the following: serum P level of ≤ 5.5 mg/dL; LDL-c < 100 mg/dL; LDL-c < 70 mg/d; all 4 parameters of mineral metabolism within the required target ranges, as recommended by the KDOQI guidelines (Serum P: 3.5 - 5.5 mg/dL, serum Ca 8.4 -

9.5 mg/dL, Ca x P ion product: < 55 mg^2/dL^2, Serum PTH: 150 - 300 pg/mL), or ≥ 3 parameters of mineral metabolism (1 of which must be P) within the required target ranges, as specified in definition 4 above.

Outcomes

Serum P levels at pre-washout were 1.67 mmol/L (5.14 mg/dL ,SD: 1.04) and increased to 2.44 mmol/L (7.55 mg/dL SD: 1.67) at baseline after the washout period.

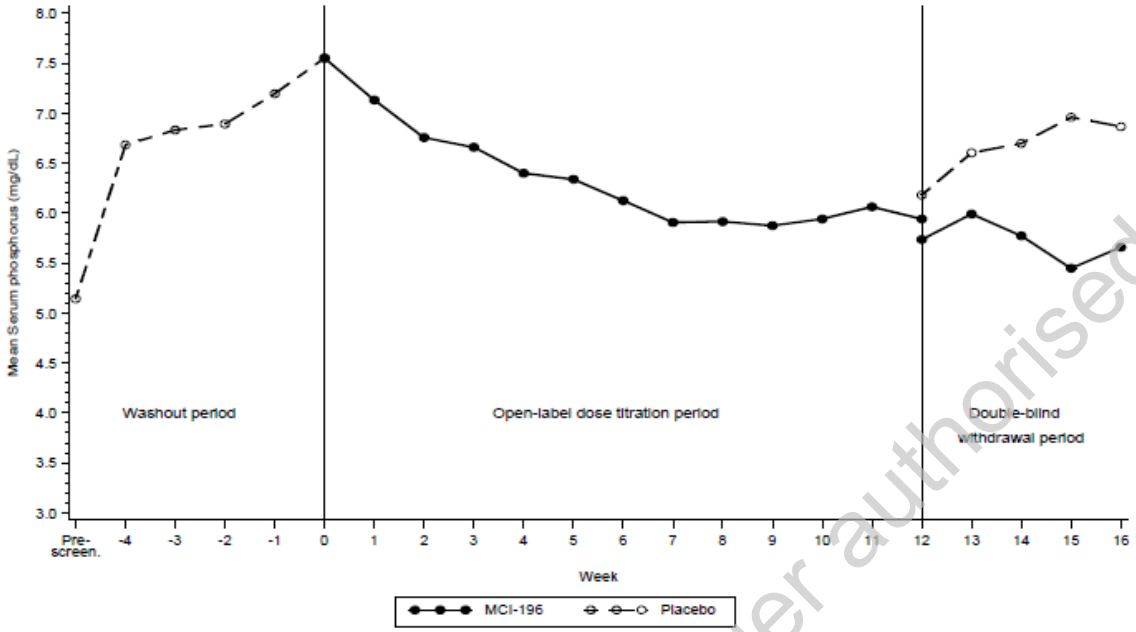
Open-label period: For the open-label period, there were statistically significant decreases from baseline to week 12 (LOCF) for the following: serum P levels (mean change -1.54 mg/dL (0.5 mmol/L); p < 0.001), Ca x P ion product (mean change -12.99 mg2/dL2; p < 0.001), PTH (mean change -33.63 pg/mL; p = 0.006), LDL-c (mean % change -30.14 %; p < 0.001), TC (mean % change -18.73 %; p < 0.001), oxidized LDL-c (mean % change – 14.70 %; p < 0.001), LDL particle size (mean % change -1.77 %; p = 0.004), HbA1c (mean % change – 0.23 %; p < 0.001), uric acid (mean change – 0.72 mg/dL; p < 0.001), serum Fe (mean change – 5.68 µg/d; p = 0.030), and transferrin (mean change mean % change – 2.57 %; p = 0.008). There were significant increases from baseline to week 12 for UIBC (mean change 7-91 µg/L; p = 0.005) and BAP (mean change 2.72 µg/L p = 0.003).

There were no significant differences from baseline to week 12 by t-test analysis for Ca, HDL-c, triglycerides, VLDL-c, lipoprotein(a), CRP, or the bone metabolism markers CTX, OC and PINP.

Double-blind period: The primary objective of the study was met, as superior efficacy of MCI-196 over placebo in the control of serum P levels for subjects with CKD stage 5 on dialysis was demonstrated. See figure 5 (Mean change from week 12 to week 16; -0.19mg/dl versus 0.82mg/dl for colestilan and placebo, difference -1.01 mg/dl [0.33 mmol/L], 95%CI -1.45 to -0.57, p<0.001).

There were significant differences in the LS means of changes or percent changes from week 12 to week 16 (LOCF) with favourable changes in the MCI-196 group compared to placebo for the following secondary endpoints: Ca x P ion product (difference in LS means – 7.91 mg2/dL2; p < 0.001); PTH (difference in LS means -66.58 pg/mL; p = 0.014), LDL-cholesterol (difference in LS means of % change –51.9 %: p < 0.001), oxidised LDL-cholesterol (difference in the LS means of % changes -40.62 %; p < 0.001), HbA1c; (difference in LS means –0.28 %; p = 0.002), and uric acid (difference in LS means -0.45 mg/dL; p = 0.014). There were no significant differences from week 12 to week 16 (LOCF) for calcium, HDL-c, triglycerides, VLDL-c, lipoprotein(a), LDL particle size, CRP, serum Fe, UIBC, transferrin, BAP (by ANCOVA), or the bone metabolism markers CTX, osteocalcin (OC), and PINP.

Figure 5 Serum phosphorous levels (mg/dL), ITT1 and ITT2 populations, study MCI-196-A05



Responder analysis: The proportion of responders in the MCI-196 treatment group was 45.2% at week 12 and 51.2%, at week 16; however, in the placebo group, the proportion of responders decreased from the highest at 42.2% at week 12 to the lowest at 20.3% at week 16 (20.5% by week 16 [LOCF]). In the open-label period, the proportion of responders in the ITT1 population increased from 14.5% to 43.6% (weeks 1 - 12 [LOCF], respectively).

Serum phosphorus subgroup analyses: The overall change from baseline to week 12 (LOCF) for mean serum P levels was greater for the baseline serum P ≥ 7.5 mg/dL (2.44 mmol/L) subgroup than for the baseline serum P < 7.5 mg/dL subgroup. From week 12 to week 16 (LOCF), MCI-196-treated subjects with higher baseline serum P levels (≥ 7.5 mg/dL) had a greater decrease from week 12 overall than those with lower (< 7.5 mg/dL) baseline serum P levels. Placebo treated subjects with higher (≥ 7.5 mg/dL) baseline serum P levels had a greater increase from week 12 (i.e., greater difference from MCI-196) than those with lower baseline serum P levels (< 7.5 mg/dL).

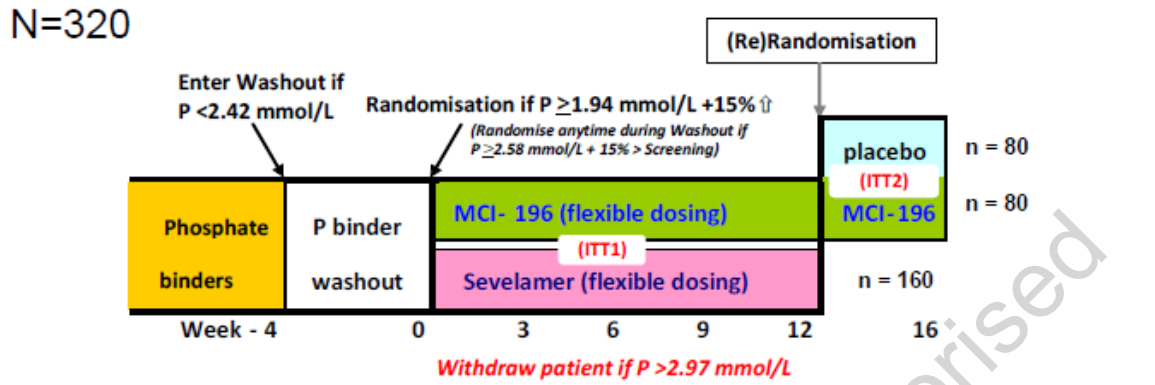
The withdrawal rate during the open label period was 31%, but considerably lower during the double blind period (colestilan 3.5%, placebo 6.0%). The most common reasons for withdrawal during the open label period was adverse events (8.6%), withdrawal of consent (5.3%) and high phosphorus levels (5.3%).

Thus, this study showed a clinically significant phosphate lowering effect during the open label phase and a clinically and statistically significant difference in comparison to placebo during the double blind period, and also significant lowering of the Ca x P product, LDL-cholesterol, and oxidised LDL-cholesterol compared to placebo.

B. Study MCI-196-E07

This was a phase 3 randomised double-blind multicentre withdrawal study comparing MCI-196 versus placebo in chronic kidney disease stage 5 subjects on dialysis with hyperphosphataemia (incorporating a randomised 12-week open-label dose titration period with MCI-196 or sevelamer).

Figure 6 MCI-196-E07: Study design overview



Methods

The study consisted of 3 consecutive periods: an initial 1-4-week phosphate binder washout period; a 12-week open-label, randomised, parallel group, flexible-dose period dose comparison of MCI-196 and sevelamer; and a 4-week double-blind placebo-controlled withdrawal period comparing MCI-196 with placebo. During the 1-4-week washout period, all phosphate binder medication was withdrawn and no study medication was administered. Following the washout period, eligible subjects were randomised in a 1:1 ratio to receive open-label active 12-week treatment with either MCI-196 or sevelamer. Subjects in the MCI-196 group who completed the open-label period were re-randomised to either continue MCI-196 or switch to placebo for a subsequent 4 weeks placebo-controlled withdrawal period. After completion of the study, eligible subjects could enter the long-term safety study MCI-196-E10.

Study Participants

The study was conducted at 69 active sites in Australia, Austria, Czech Republic, France, Germany, Hungary, Italy, Poland, South Africa, Spain, and United Kingdom. Study duration was between July 2007 and November 2009.

The total target enrolment was approximately 320 subjects allocated to MCI-196 or sevelamer in a 1:1 ratio for the 12-week open-label period.

Open-label, active controlled period: total (MCI-196, sevelamer)
– Randomised: 336 (165, 171)
– Safety 1 (SAF1): 331 (162, 169)
– Intent-to-treat 1 (ITT1): 327 (160, 167)
– Per-protocol 1 (PP1): 213 (95, 118)

Placebo-controlled withdrawal period: total (MCI-196, placebo)
– Randomised: 104 (50, 54)
– SAF2: 103 (50, 53)

– ITT2: 103 (50, 53)

– PP2: 63 (26, 37)

Subject disposition, study MCI-196-E07

Table 7 Subject disposition Reasons for withdrawal, open-label period, study MCI-196-E07

Reasons for Withdrawal n (%)	MCI-196 N=165	Sevelamer N=171	Overall N=336
Adverse event(s) including abnormal laboratory tests	28 (17.0)	10 (5.8)	38 (11.3)
Withdrawal of consent	16 (9.7)	5 (2.9)	21 (6.3)
High phosphorus levels	8 (4.8)	1 (0.6)	9 (2.7)
Protocol violation	3 (1.8)	3 (1.8)	6 (1.8)
Death	2 (1.2)	1 (0.6)	3 (0.9)
Randomised in error [a]	0	3 (1.8)	3 (0.9)
Other	3 (1.8)	9 (5.3)	12 (3.6)
Total	**60 (36.4)**	**32 (18.7)**	**92 (27.4)**

Table 8 Reasons for withdrawal, placebo-controlled withdrawal period, study MCI-196-E07

Reasons for Withdrawal n (%)	MCI-196 N=50	Placebo N=54	Overall N=104
High phosphorus levels	0	3 (5.6)	3 (2.9)
Protocol violation	1 (2.0)	1 (1.9)	2 (1.9)
Adverse event(s) including abnormal laboratory tests	0	1 (1.9)	1 (1.0)
Total	1 (2.0)	5 (9.3)	6 (5.8)

Main objectives

The **primary objective** of this study was to demonstrate that MCI-196 is superior to placebo in the control of serum phosphorous in subjects with chronic kidney disease (CKD) on dialysis.

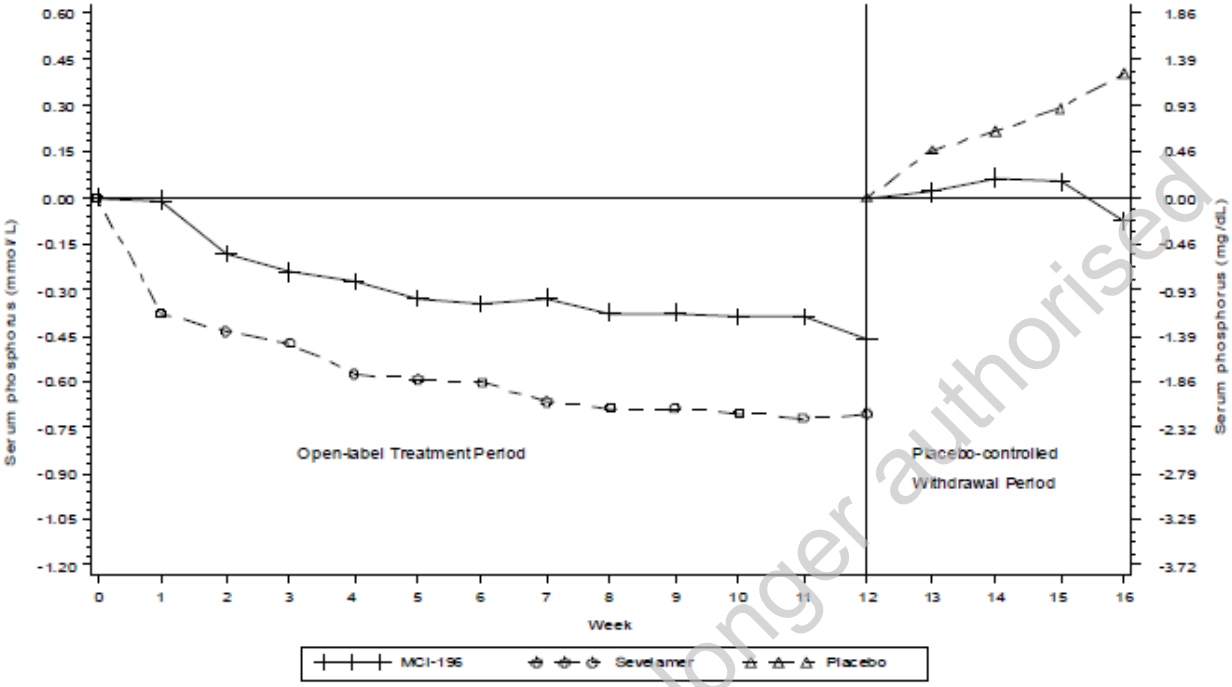
The **secondary objectives** of this study were:

- To demonstrate superiority of MCI-196 over placebo in the control of other efficacy parameters (e.g. LDL-cholesterol [LDL-C], other lipid parameters (total cholesterol [TC], high density lipoprotein cholesterol [HDL-C], triglycerides [TG]), intact parathyroid hormone [iPTH], calcium, calcium x phosphorus ion product [Ca x P]) in subjects with stage 5 CKD on dialysis.
- To assess the safety and tolerability of flexible-dose MCI-196 compared to sevelamer
- To assess the efficacy of flexible-dose MCI-196 compared to sevelamer
- To assess the mean daily dose of MCI-196 compared to sevelamer

N= total number of subjects analysed; n=subset of subjects with available data, based on N; AE=adverse event; WC= withdrawal of consent.

Outcomes

Figure 7 Mean serum phosphorous levels (mg/dL and mmol/L) during study MCI-196-E07, ITT1 and ITT2



Colestilan was superior to placebo with respect to serum phosphorous in the placebo-controlled withdrawal period: The difference between LS means for colestilan and placebo was 0.36 mmol/L (1.11 mg/dL, p< 0.001) at week 16.

In the open-label period, non-inferiority of MCI-196 to sevelamer could not be concluded according to the pre-specified criteria (LS mean change from Baseline during the open-label period was -0,42 mmol/L [-1.30 mg/dL] for the colestilan group and -0.72 mmol/L [– 2.22 mg/dL] for the sevelamer group).

Subgroup analyses indicated that there was an effect of Baseline serum phosphorus levels on the phosphorous-lowering effect of study medication (greater decrease in serum phosphorus with baseline phosphorus level ≥2.42 mmol/L. i.e. 7.5 mg/dL).

The Ca x P product LS mean change from Baseline was -0.90 $mmol^2/L^2$ for colestilan and -1.44 $mmol^2/L^2$ for sevelamer (p <0.001); serum L-cholesterol LS mean % change from Baseline was – 35.49 % for colestilan and – 30.42 % for sevelamer (p = 0.023), and serum total cholesterol LS mean % change from Baseline was -24.34 % for colestilan and -17.52 % for sevelamer (p< 0.001). There were no clinically relevant differences between the treatment groups with regards to CRP, serum Fe levels, transferrin saturation or UIBC.

There was no notable difference in uric acid or HbA1c between colestilan and sevelamer groups. Both MCI-196 and sevelamer produced a decrease in uric acid (LS mean -38.87 mcmol/l for colestilan, and -27.77 mcmol/l for sevelamer (p =0.075)). Mean HbA1c at week 12 (LOCF) was 5.80 % in the colestilan group and 5.80 % in the sevelamer group, with a mean change from Baseline of -0.24 % in the colestilan group and -0.32 % in the sevelamer group.

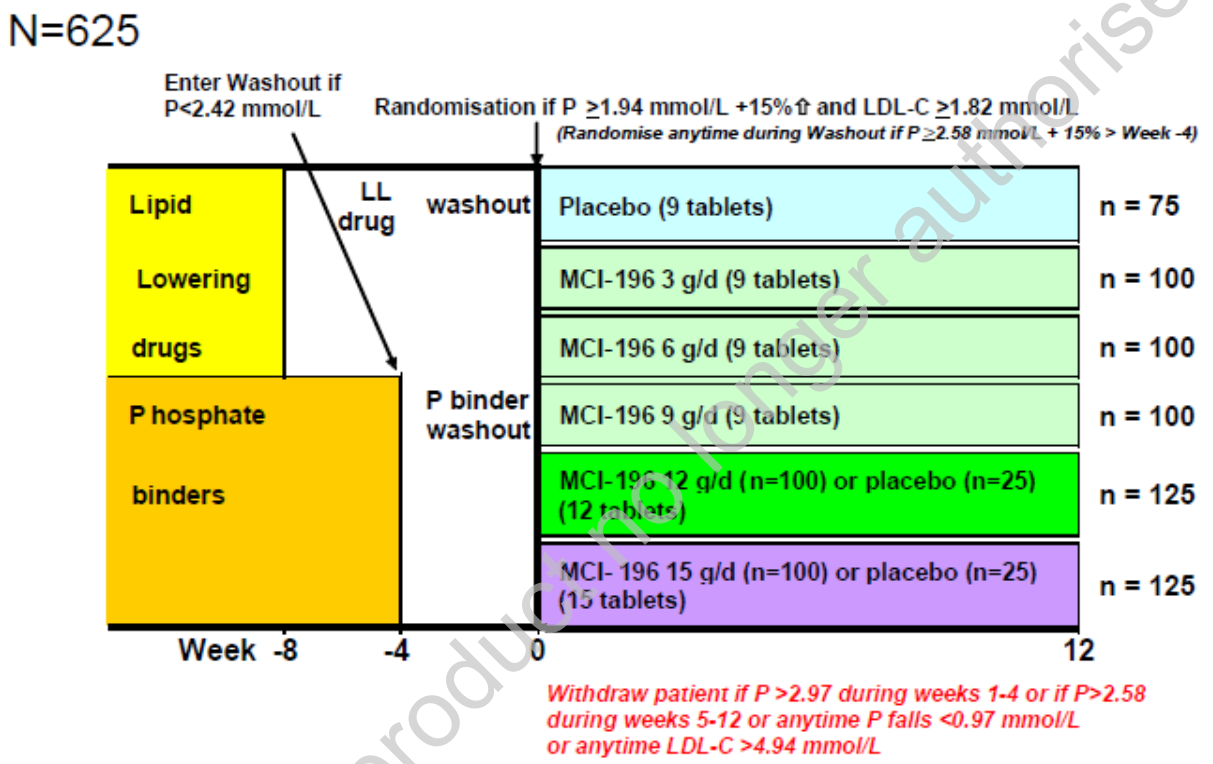
Thus, sevelamer had a greater phosphate reducing capacity than colestilan in this study, while the Ca x P product was lowered more by sevelamer than by colestilan. Serum total cholesterol was lowered

more by colestilan than by sevelamer while the lowering of serum LDL-cholesterol was nearly the same for both these drugs.

C. Study MCI-196-E08

This was a phase 3, multi-centre double-blind randomised placebo-controlled multiple fixed-dose study of MCI-196 versus placebo in chronic kidney disease stage V subjects on dialysis with hyperphosphataemia and dyslipidaemia (incorporating two parallel high dose groups).

Figure 8 MCI-196-E08: Study design overview



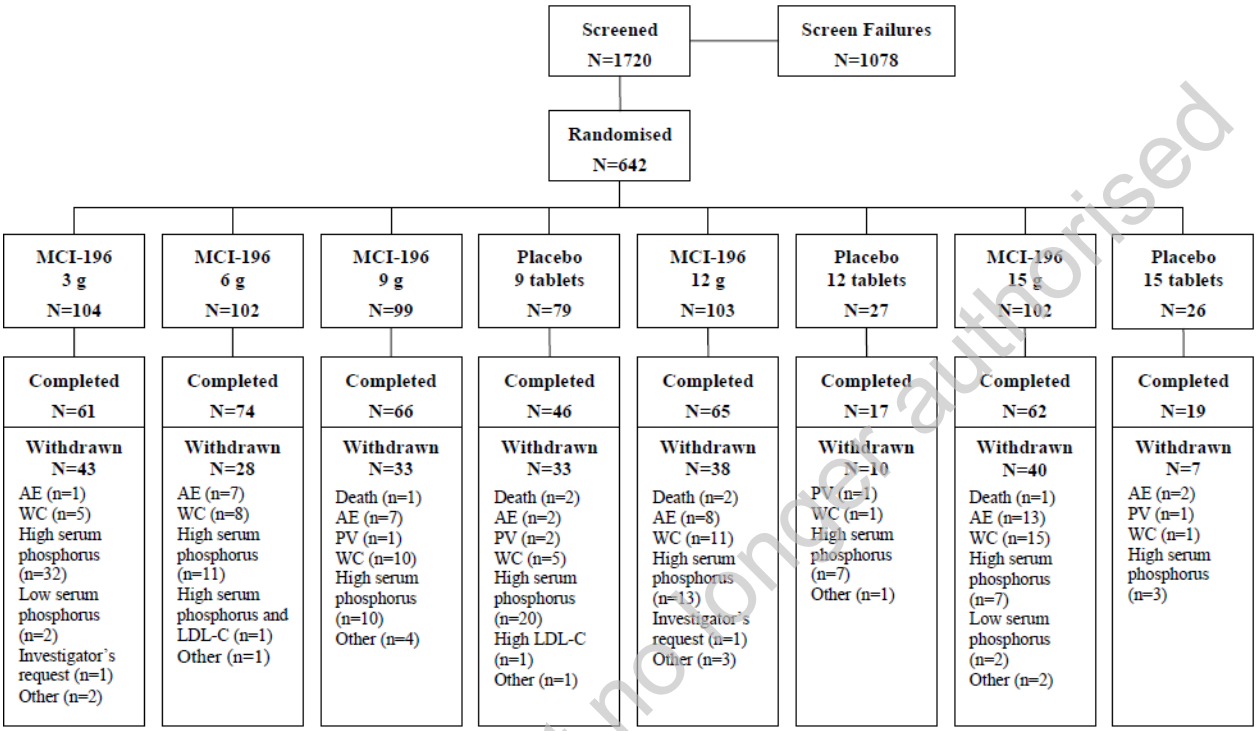
Methods

The study consisted of a washout period (week - 8 to Baseline for lipid lowering drugs, and week -4 to Baseline for phosphate binders), followed by a 12-week fixed-dose, double-blind, placebo-controlled treatment period, and a safety follow-up visit. The subjects could complete the washout period as soon as they met the additional inclusion criteria for randomisation and continue into the treatment period. Randomisation to treatment took place at the Baseline visit. The study included 5 active treatment groups: MCI-196 3 grams (g), 6 g, 9 g, 12 g and 15 g per day. Subjects receiving MCI-196 3 g and 6 g per day also received 6 and 3 matching placebo tablets per day, respectively, so that all subjects in the 3 g, 6 g and 9 g per day groups took 9 tablets per day in total. There were matching placebo groups in which subjects received placebo 9 tablets, 12 tablets or 15 tablets per day. At the end of the double-blind treatment period (week 12), eligible subjects on MCI-196 or placebo were permitted to enter the long term safety study MCI-196-E10. A Data Safety Monitoring Board (DSMB) conducted an independent, objective review of all accumulated data from both blinded and unblinded data sources of this clinical study. Subjects were not allowed to receive lipid lowering drugs.

Study Participants

The study was conducted at 100 active sites in Hungary, Italy, Poland, Serbia, Macedonia, Ukraine, Russia and Malaysia. Study duration was between December 2007 and November 2009.

Figure 9 Disposition of subjects in study MCI-196-E08



N= total number of subjects analysed; n=subset of subjects with available data, based on N; AE=adverse event; LDL-C=low density lipoprotein cholesterol; PV=protocol violation; WC=withdrawal of consent.

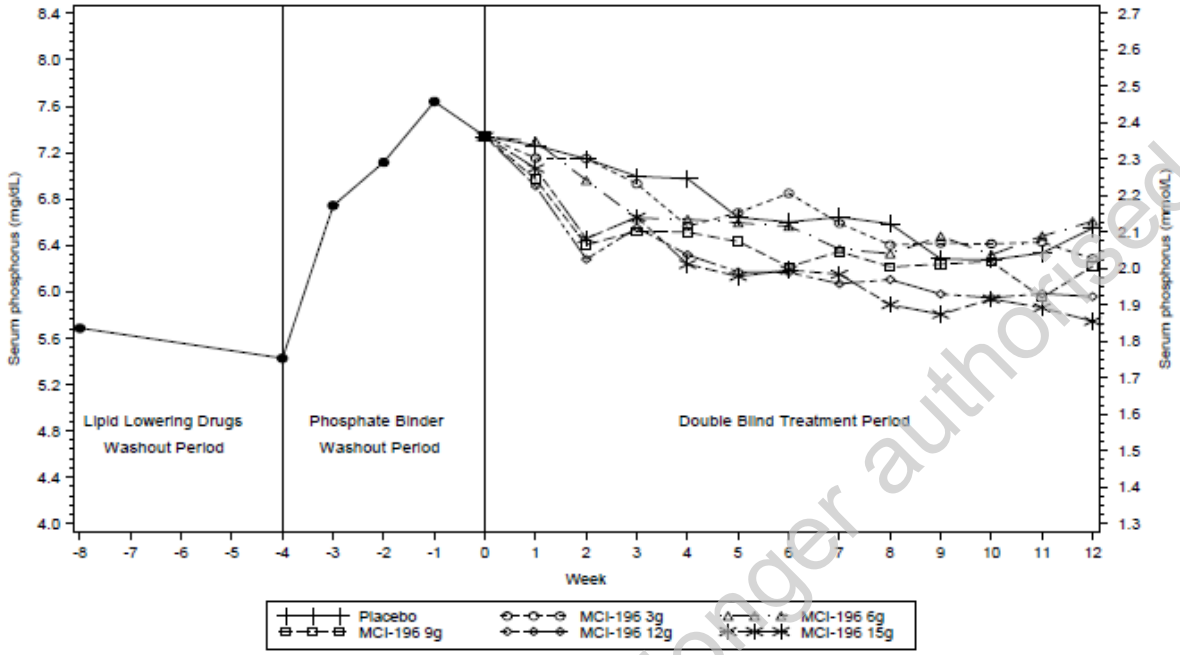
Main objectives

The **primary objective** of this study was to demonstrate the efficacy of a range of fixed doses of MCI-196 compared to placebo in the control of serum phosphorous and serum low density lipoprotein (LDL) cholesterol (LDL-C) in subjects with CKD Stage 5 on dialysis.

The **secondary objectives** included the evaluation of further efficacy comparisons of a range of fixed doses of MCI-196 compared to placebo with regard to both hyperphosphataemia and dyslipidaemia. The safety and tolerability of MCI-196 compared to placebo was also evaluated.

Outcomes

Figure 10 Mean serum phosphorous levels (mg/dL and mmol/L), ITT population, study MCI-196-E08



Placebo includes placebo 9 tablets, 12 tablets and 15 tablets pooled. Single overall mean presented at week 0 (end of washout period). ITT=intent-to-treat.

Table 9 Change in serum phosphorus, ITT population, study MCI-196-E08

	Treatment					
	Placebo 9 tablets (N=77)	MCI-196 9 g (N=97)	MCI-196 6 g (N=101)	MCI-196 3 g (N=104)	Pooled Placebo (N=130)[a]	Pooled MCI-196 (12 g+15 g) (N=199)
Primary[b]						
Serum Phosphorus (mg/dL)[c]						
Baseline	n=77	n=97	n=101	n=104	n=130	n=199
Mean (SD)	7.30 (1.36)	7.61 (1.53)	7.53 (1.38)	7.32 (1.44)	7.20 (1.45)	7.23 (1.46)
Week 12 (LOCF)	n=76	n=87	n=100	n=103	n=129	n=181
Mean (SD)	7.16 (1.67)	6.67 (1.63)	6.75 (1.73)	7.10 (1.96)	7.09 (1.73)	6.23 (1.56)
LS Mean change from Baseline	-0.21	-0.87	-0.72	-0.28	-0.18	-1.06
Difference between LS Means (MCI-196 - placebo) (95% CI)		-0.66 (-1.16, -0.16)	-0.52 (-1.00, -0.03)	-0.07 (-0.54, 0.41)		-0.88 (-1.22, -0.54)
p-value		0.009	0.036	0.785[d]		<0.001
Serum LDL-C (mg/dL)[e]						
Baseline	n=77	n=97	n=101	n=104	n=130	n=199
Mean (SD)	110.4 (26.6)	111.6 (31.9)	108.3 (26.4)	113.9 (29.9)	113.4 (29.6)	111.4 (29.9)
Week 12 (LOCF)	n=74	n=83	n=94	n=96	n=124	n=167
Mean (SD)	111.7 (28.7)	77.7 (25.5)	81.9 (24.7)	93.4 (30.2)	116.1 (33.5)	77.9 (26.6)
LS Mean change from Baseline (%)	1.86	-27.61	-23.60	-15.91	4.09	-27.62
Difference between LS Means (MCI-196 - placebo) (95% CI)		-29.47 (-35.44, -23.51)	-25.46 (-31.25, -19.66)	-17.77 (-23.54, -12.00)		-31.71 (-36.53, -26.89)
p-value		<0.001	<0.001	<0.001		<0.001
Secondary[b,f]						
Serum Calcium (mmol/L)						
Baseline	n=77	n=97	n=101	n=104	n=130	n=199
Mean (SD)	2.234 (0.183)	2.238 (0.163)	2.231 (0.219)	2.244 (0.193)	2.233 (0.198)	2.216 (0.230)
Week 12 (LOCF)	n=76	n=87	n=100	n=103	n=129	n=181
Mean (SD)	2.192	2.190	2.224	2.222	2.209	2.198 (0.211)

Table 10 Change in serum phosphorus, PP population, study MCI-196-E08

	Treatment					
	Placebo 9 tablets (N=63)	**MCI-196 9 g (N=76)**	**MCI-196 6 g (N=83)**	**MCI-196 3 g (N=82)**	**Pooled Placebo (N=106)[a]**	**Pooled MCI-196 (12 g+15 g) (N=140)**
Baseline Mean (SD) (mg/dL)	7.35 (1.39)	7.63 (1.51)	7.56 (1.40)	7.27 (1.48)	7.27 (1.47)	7.26 (1.49)
Week 12 (LOCF) Mean (SD) (mg/dL)	7.22 (1.66)	6.57 (1.64)	6.66 (1.71)	7.01 (2.04)	7.05 (1.74)	6.15 (1.53)
LS Mean[b]	-0.20	-0.98	-0.87	-0.36	-0.30	-1.22
Difference between LS Means (MCI-196 - placebo)[b]		-0.78	-0.67	-0.16		-0.92
95% CI for difference[c]		-1.34, -0.23	-1.21, -0.13	-0.70, 0.38		-1.30, -0.54
p-value[b,c]		0.006	0.015	0.564		<0.001

Source: Tables 14.2.1.1.2 and 14.2.1.1.4.

[a] *Includes placebo 9 tablets, 12 tablets and 15 tablets.*

[b] *ANCOVA on change from Baseline to Week 12 (LOCF) with treatment and pooled country as factors and Baseline value as a covariate. LOCF is the last available on-treatment (i.e. ≤1 day after last dose) value. Any data collected >1 day after the date of last dose were not included.*

[c] *Alpha=0.03 for comparison of MCI-196 3 g, 6 g, 9 g with placebo 9 tablets (closed procedure).*
Alpha=0.01 for comparisons of 12 g, 15 g (pooled) MCI-196 with pooled placebo.

N= total number of subjects analysed.

ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last observation carried forward; LS mean=least squares mean; PP=per protocol; SD=standard deviation.

In study E08, colestilan reduced serum phosphorous levels from baseline compared to placebo, in a dose-dependent manner with statistically significant differences compared to placebo at daily doses of 6g and higher. Results in the ITT population (table 9) was supported by results in the PP population (table 10). The difference compared to placebo in the 12+15g dose group was of clear clinical relevance (i.e. reduction of 0.3 mmol/L). When compared to placebo, colestilan significantly reduced LDL-C from Baseline in a dose-dependent manner, at doses 3 g and higher. Colestilan also significantly lowered the Ca x P product and serum triglycerides compared to placebo. The effect seemed to be dose proportional, up to a daily dose of 15 g.

Subgroup analyses for efficacy: The results of the subgroup analyses showed a greater reduction in serum phosphorus in patients with higher baseline serum phosphorous concentrations (when stratified by serum phosphorous levels >2.44 mmol/L or ≤2.44 mmol/L). There were similar trends for greater reductions in older patients and in female patients. However, this effect in elderly patients and females may be a factor of reduced volume phosphate distribution in these two subgroups compared to younger patients and male patients, since MCI-196 exerts its effect by binding phosphate in the diet. No specific efficacy analysis for elderly patients (≥65 and ≥75 years of age) was presented and discussed. The reductions in diabetic patients were similar to those seen in non-diabetic patients. Although the majority of patients across the studies were Caucasian no a clear effect of race was demonstrated. It was noted a trend towards greater reductions in serum phosphorous in Black or African American patients in those studies where they represented a greater proportion of patients. As the majority of patients were on HD no clear effect of dialysis type could be detected, though those on HD appeared to respond better to MCI-196 than those on PD; this may be related to the lower phosphorous levels in PD patients.

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 11 Summary of Efficacy for trial MCI-196-A05

Title: A Phase 3, Randomised, Double-blind, Placebo-controlled, Multicenter Withdrawal Study Comparing MCI-196 Versus Placebo Following a 12-week Dose Titration Period with MCI-196 in Chronic Kidney Disease (CKD) Stage V Subjects on Dialysis (Hemodialysis or Peritoneal Dialysis) with Hyperphosphatemia.			
Study identifier	MCI-196-A05		
Design	The study consisted of a 12-week, open-label, flexible-dose titration period (after a 4 - 5 week washout period for current phosphate binders) followed by a 4-week randomised, double-blind, placebo-controlled withdrawal period in subjects with CKD (stage V) with hyperphosphatemia on dialysis.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		12 weeks (flexible dose period) 4 weeks (withdrawal period) 1-5 weeks not applicable
Hypothesis	Superiority		
Treatments groups	Flexible dose period		245 subjects treated with MCI-196 only
	Withdrawal period		Randomised to MCI-196; 85 subjects
	Withdrawal period		Randomised to placebo; 84 subjects
Endpoints and definitions	Primary endpoint	Efficacy	Change from Week 12 to Week 16 (or last observation post week 12) in serum P levels for the MCI-196 and placebo treatment groups.
	Secondary	Efficacy	- The change from Week 12 to Week 16 (LOCF) for other efficacy parameters (e.g., LDL-c, other lipid parameters [total cholesterol: TC, triglycerides, VLDL-c and HDL-c], PTH, Ca and Ca x P ion product) and - The change from baseline to Week 12 (LOCF) in serum P and other efficacy parameters (e.g., LDL-c, other lipid parameters [TC, triglycerides, VLDL-c and HDL-c], PTH, Ca and Ca x P ion product).
	Other	Safety	Adverse events (AEs), vital signs, clinical laboratory assessments, 12-lead electrocardiograms (ECG), physical examinations
Database lock	17 February 2010		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Randomised withdrawal MCI-196	Randomised withdrawal Placebo	-
	Number of subject	85	83	-
Change from week 12 - 16 (LOCF) in serum levels Mean (SD)	Phosphorus (mg/dL)	-0.04 (1.49)	0.71 (1.71)	-
	Ca (mg/dL)	0.05 (0.72)	-0.09 (0.54)	-
	Ca x P ion product (mg^2/dL^2)	-0.23 (13.36)	5.73 (14.58)	-
	PTH (pg/mL)	-6.2 (234.5)	61.8 (146.4)	-
	LDL-Cholesterol	4.01 % change (25.02)	56.38 % change (46.14)	-
	Total Cholesterol	2.81 % change (24.68)	26.35 % change (22.73)	-
	HDL-Cholesterol	-0.05 % change (13.75)	2.38 % change (15.91)	-
	Triglycerides	6.94 % change (33.08)	0.70 % change (33.39)	-
	VLDL Cholesterol	5.23 % change (32.81)	-0.75 % change (32.91)	-
	Oxidized LDL Cholesterol	4.45 % change (31.63)	46.02 % change (57.69)	-
	HbA1C (%)	-0.06 (0.53)	0.21 (0.58)	-
	Uric Acid (mg/dL)	0.03 (1.36)	0.46 (1.22)	-
	- Responders - Serum phosphorus level of <=5.5 mg/dL Week 12 (LOCF)	49.4 %	20.5 %	
		Flexible Dose MCI-196	-	-
Change from baseline to Week 12 in serum levels	Phosphorus (mg/dL)	-1.54 (2.05)	-	-

Mean (SD)	Ca (mg/dL)	0.02 (0.75)	-	-
	Ca x P ion product (mg^2/dL^2)	-12.99 (18.01)	-	-
	PTH levels (pg/mL)	-33.6 (187.7)	-	-
	Total Cholesterol	-18.73 % change (17.11)	-	-
	LDL Cholesterol	-30.14 % change (21.61)	-	-
	VLDL Cholesterol	4.61 % change (45.49)	-	-
	HDL Cholesterol	2.51 % change (20.05)	-	-

Change from baseline to Week 12 in serum levels Mean (SD)	Oxidized LDL Cholesterol	-14.7 %change (40.02)	-	-
	Uric Acid (mg/dL)	-0.72 (1.35)	-	-
	HbA1C levels (%)	-0.23 (0.93)	-	-
	- Responders - phosphorus level of <=5.5 mg/dL Week 12 (LOCF)	43.6 %		
Effect estimate per comparison	Primary Week 12 – 16 Phosphorus (mg/dL)	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	-1.01	
		95% CI	-1.45, -0.57	
		P-value	<0.001	
	Secondary Week 12 – 16 PTH (pg/mL)	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	-66.58	
		95% CI	-119.44, -13.72	
		P-value	0.014	
	Secondary Week 12 – 16 Ca (mg/dL)	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	0.13	
		95% CI	-0.04, 0.31	
		P-value	0.136	
	Secondary Week 12 – 16 Ca x P ion product (mg^2/dL^2)	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	-7.91	
		95% CI	-11.81, -4.00	
		P-value	<0.001	
	Secondary Week 12 – 16 LDL-Cholesterol	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	-51.90 % change	
		95% CI	-62.53, -41.28	
		P-value	<0.001	
	Secondary Week 12 – 16 Total Cholesterol	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	-23.04 % change	
		95% CI	-30.05, -16.04	
		P-value	<0.001	
	Secondary Week 12 – 16 HDL-Cholesterol	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	-2.59 % change	
		95% CI	-7.10, 1.91	
		P-value	0.258	
	Secondary Week 12 – 16 Triglycerides	MCI-196 vs Placebo	MCI-196 - Placebo	
		LS Mean	6.39 % change	
		95% CI	-3.82, 16.60	
		P-value	0.218	

Effect estimate per comparison	Secondary Week 12 – 16 VLDL Cholesterol	MCI-196 vs Placebo	MCI-196 – Placebo
		LS Mean	5.00 % change
		95% CI	-4.96, 14.95
		P-value	0.323
	Secondary Week 12 – 16 Oxidized LDL Cholesterol	MCI-196 vs Placebo	MCI-196 - Placebo
		LS Mean	-40.62 % change
		95% CI	-53.35, -27.90
		P-value	<0.001
	Secondary Week 12 – 16 HbA1C (%)	MCI-196 vs Placebo	MCI-196 - Placebo
		LS Mean	-0.28
		95% CI	-0.45, -0.10
		P-value	0.002
	Secondary Week 12 – 16 Uric Acid (mg/dL)	MCI-196 vs Placebo	MCI-196 - Placebo
		LS Mean	-0.45
		95% CI	-0.81, -0.09
		P-value	0.014
Notes	No statistically significant treatment difference seen in CRP, Iron, UIBC, Transferrin saturation, BAP, Lipoprotein (a) and LDL particle size.		
Analysis description			
Primary	The change in serum phosphorus from Week 12 to Week 16 (LOCF) was analyzed using analysis of covariance (ANCOVA) with treatment and centre as factors and Week 12 serum phosphorus as covariant. The analysis was two-sided and conducted at a significance level of 0.05. Least square means and 95% confidence intervals were calculated and presented for the difference of MCI-196 compared to placebo.		
Secondary	For the secondary efficacy parameters such as changes of serum levels of LDL cholesterol calcium (Ca), calcium-phosphorus ion product, PTH, total cholesterol, VLDL, and HDL, triglycerides, uric acid, and CRP from the week 12 to last observation, the analyses were the same ANCOVA model as for primary efficacy. The responders were analysed using logistic regression, taking account of factors for treatment (MCI-196 or placebo) and center. Week 12 values were used as covariates.		

Table 12 Summary of Efficacy for trial MCI-196-A06

Title: A Phase 3, Multi-center, Open-label, Flexible-dose, Long-term Safety Study of MCI-196 in Chronic Kidney Disease Stage V Subjects on Dialysis With Hyperphosphatemia	
Study identifier	MCI-196-A06
Design	This study consisted of a pre-screening visit, 2- to 6-week washout of phosphate-binding medication, 12-week initial active treatment period, and 40-week subsequent active treatment period. During the washout period, subjects discontinued all phosphate-binding medication. In order to qualify for the treatment period, subjects had to have a serum phosphorus level ≥5.6 mg/dL and at least 15% greater than their pre-screening level (prior to washout of phosphate-binding medications) after washout. If at any time during the washout period a subject's serum phosphorus level was ≥8.0 mg/dL and at least 15% greater than their pre-screening level, the subject could proceed immediately to the open-label treatment period given that they met all other inclusion and exclusion criteria.

	All subjects enrolled in the open-label treatment period received 6 g/day of MCI-196 for at least 2 weeks. During the treatment period, the dose of MCI-196 could be titrated up or down at the discretion of the Investigator to achieve and maintain serum phosphorus levels between 3.5 mg/dL and 5.5 mg/dL.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		12 weeks (initial active treatment period) 40 weeks (subsequent active treatment period) 2-6 weeks not applicable
Hypothesis	Long-term safety study		
Treatments groups	Enrolled		116 subjects treated with MCI-196 only
Endpoints and definitions	Primary endpoint	Safety	Adverse events (AEs), vital signs, electrocardiograms (ECG) parameters, clinical laboratory assessments and physical examination
	Secondary endpoint	Efficacy	Change (or Percent Change) from baseline to Week 52 (LOCF) for serum phosphorus, Ca and Ca x P ion, PTH, LDL-c, HDL-c, TC, triglycerides, LDL particle size, bone metabolism markers (e.g. osteocalcin, BAP), uric acid, CRP, HbA1c
Database lock	08 November 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	MCI-196	-
	Number of subject	116	-
Change from baseline – Week 52 (LOCF) in serum levels Mean (SD)	Phosphorus (mg/dL)	-1.18 (2.05)	-
	Ca levels (mg/dL)	0.08 (0.74)	-
	Ca x P ion product (mg^2/dL^2)	-9.99 (17.94)	-
	PTH (pg/mL)	-33.9 (279.4)	-
	Total Cholesterol	-14.25 % change (19.89)	-
	LDL-Cholesterol	-23.95 % change (27.59)	-

	HDL-Cholesterol	7.48 % change (22.56)	-
	Triglycerides	-1.02 % change (51.35)	-

Change from baseline – Week 52 (LOCF) in serum levels Mean (SD)	Oxidized LDL Cholesterol	-24.36 % change (33.25)	-
	Uric Acid (mg/dL)	-0.53 (1.16)	-
	HbA1C (%)	-0.19 (0.91)	-

Effect estimate Change from baseline – Week 52 (LOCF) in serum levels	P levels (mg/dL)	MCI-196	MCI-196
		Mean	-1.18
		95% CI (SD)	-1.56, -0.81 (2.05)
		P-value	<0.001
	Ca levels (mg/dL)	MCI-196	MCI-196
		Mean	0.08
		95% CI (SD)	-0.06, 0.21 (0.74)
		P-value	0.278
	Ca x P ion product (mg^2/dL^2)	MCI-196	MCI-196
		Mean	-9.99
		95% CI (SD)	-13.29, -6.69 (17.94)
		P-value	<0.001
	PTH levels (pg/mL)	MCI-196	MCI-196
		Mean	-33.9
		95% CI (SD)	-85.3, 17.5 (279.4)
		P-value	0.194
	Total Cholesterol	MCI-196	MCI-196
		Mean	-14.2 % change
		95% CI (SD)	-17.9, -10.6 (19.89)
		P-value	<0.001
	LDL-Cholesterol	MCI-196	MCI-196
		Mean	-24.0 % change
		95% CI (SD)	-29.0, -18.9 (27.59)
		P-value	<0.001
	HDL-Cholesterol	MCI-196	MCI-196
		Mean	7.5 % change
		95% CI (SD)	3.3, 11.6 (22.56)
		P-value	<0.001
	Triglycerides	MCI-196	MCI-196
		Mean	-1.0 % change
		95% CI (SD)	-10.5, 8.5 (51.35)
		P-value	0.831
	Oxidized LDL Cholesterol	MCI-196	MCI-196
		Mean	-24.4 % change
		95% CI (SD)	-30.6, -18.1 (33.25)
		P-value	<0.001
		P-value	0.088

Effect estimate Secondary Change from baseline – Week 52 (LOCF) in serum levels	Uric Acid (mg/dL)	MCI-196	MCI-196
		Mean	-0.53
		95% CI (SD)	-0.75, -0.32 (1.16)
		P-value	<0.001
	HbA1C (%)	MCI-196	MCI-196
		Mean	-0.19
		95% CI (SD)	-0.36, -0.02 (0.91)
		P-value	0.026
Notes	No statistically significant treatment difference seen in LDL particle size, CRP, osteocalcin, BAP, PINP, CTX, and lipoprotein.		
Analysis description			
Primary	The number and percentage of subjects with treatment-emergent adverse events, treatment-emergent serious adverse events (SAEs), and treatment-emergent drug-related adverse events were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities for the time periods up to and including Week 12 (the initial active treatment period) and after Week 12 (the subsequent active treatment period). Summary statistics for baseline and post-baseline measurements and changes from baseline are presented by visit for laboratory parameters, vital signs, and ECG parameters.		
Secondary	Summary statistics (n, mean, standard deviation, minimum, maximum, and median) for baseline and post-baseline measurements and changes or percent changes from baseline are presented by visit and at Week 12 with LOCF, Week 24 with LOCF, Week 36 with LOCF, and Week 52 with LOCF for the efficacy parameters. For each efficacy parameter, the change or percent change from baseline to Week 52 with LOCF was assessed for clinical significance using the one-sample t-test. If the data was found to be non-normal in distribution as assessed using the Shapiro-Wilk test, the non-parametric Wilcoxon Signed Rank test was used.		

Table 13 Summary of Efficacy for trial MCI-196-E07

Title: A Phase III, Randomised, Double-blind, Multi-centre, Withdrawal Study Comparing MCI-196 Versus Placebo in Chronic Kidney Disease Stage V Subjects on Dialysis with Hyperphosphataemia (Incorporating a Randomised, 12-week, Open-label Dose Titration Period with MCI-196 or Sevelamer)	
Study identifier	MCI-196-E07
Design	This was a phase III, randomised, multi-centre study. The study consisted of 3 consecutive periods: a 1- to 4-week phosphate binder washout period; a 12-week, open-label, randomised, parallel group, flexible-dose period dose comparison of MCI-196 and sevelamer; a 4-week double-blind placebo-controlled withdrawal period comparing MCI-196 with placebo. During the 1 to 4-week washout period, all phosphate binder medication was withdrawn and no study medication was administered. Following the washout period, eligible subjects were randomised in a 1:1 ratio to receive open-label active 12-week treatment with either MCI-196 or sevelamer. Subjects in the MCI-196 group who completed the open-label period were re-randomised to either continue MCI-196 or switch to placebo for a subsequent 4 weeks (placebo-controlled withdrawal period).

	Duration of main phase: Duration of run-in phase: Duration of extension phase:		12 weeks (flexible dose period) 4 weeks (withdrawal period) 1-5 weeks E10
Hypotheses	Superiority/non-inferiority		
Treatments groups	Flexible dose period		162 subjects treated with MCI-196 169 subjects treated with sevelamer
	Withdrawal period		Randomised to MCI-196; 50 subjects
	Withdrawal period		Randomised to placebo; 54 subjects
Endpoints and definitions	Primary endpoint	Efficacy	Change from week 12 to week 16 (or last observation post week 12) in serum P levels.
	Secondary	Efficacy	Change from Week 12 to Week 16 (LOCF) for other efficacy parameters (lipid profile: serum TC, HDL-C, LDL-C, and TG; serum calcium; serum Ca x P; serum iPTH, uric acid and C-reactive protein [CRP] Change from Baseline to Week 12 (LOCF) in serum phosphorus and other efficacy parameters (as above) for MCI-196 and sevelamer
	Other	Safety	Adverse events (AEs), vital signs, clinical laboratory assessments, 12-lead electrocardiograms (ECG), physical examinations
Database lock	21 May 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Randomised withdrawal MCI-196	Randomised withdrawal Placebo
	Number of subjects (ITT2 population)	50	53
Change from Week 12 - 16 (LOCF) in serum levels Mean (SD)	Phosphorus (mmol/L)	-0.075 (0.471)	0.410 (0.479)
	Ca (mmol/L)	-0.002 (0.110)	-0.023 (0.145)
	Ca x P ($mmol^2/L^{2)}$	-0.191 (1.025)	0.856 (1.079)
	iPTH (pmol/L)	2.59 (18.63)	9.85 (12.21)

	LDL-Cholesterol % change	9.26 (24.62)	81.98 (65.07)
	Total Cholesterol % change	4.84 (17.15)	39.47 (28.90)
	HDL-Cholesterol % change	2.11 (17.90)	2.19 (19.60)
	Triglycerides % change	6.26 (32.95)	11.37 (36.97)
	Uric acid (mcmol/L)	-13.2 (61.9)	44.5 (64.7)
	CRP (mg/L)	4.82 (35.74)	-0.86 (10.88)
	Responders (P levels <= 1.78 mmol/L) at Week 16 (LOCF) Number (%)	23 (46.0%)	12 (23.1%)
	Open label flexible dose period Treatment group	MCI-196	sevelamer
	No. subjects (ITT1 population)	N=160	N=167
Change from baseline to Week 12 (LOCF) in serum levels Mean (SD)	Phosphorus (mg/dL)	-0.363 (0.525)	-0.698 (0.502)
	Ca (mmol/L)	-0.041 (0.142)	0.026 (0.150)
	Ca x P levels ($mmol^2/L^2$)	-0.864 (0.163)	1.465 (1.072)
	iPTH levels (pmol/L)	-3.59 (18.46)	-7.23 (18.54)
	LDL-Cholesterol	-35.34 % (19.54)	-30.51 % (20.31)
	Total Cholesterol	-24.16 % (14.07)	-17.67 % (17.52)
	HDL-Cholesterol	-1.14 % (18.03)	0.94 % (17.19)
	Triglycerides	-1.00 (40.10)	6.24 (37.42)

	Uric acid (mcmol/L)	-43.9 (71.0)	-27.2 (54.3)
	CRP levels (mg/L)	-1.55 (20.94)	-3.91 (10.95)
	Responders (P levels <= 1.78 mmol/L) at Week 12 (LOCF) Number (%)	65 (42.5%)	111 (67.7%)
Effect estimate per comparison Change from Week 12 - 16 (LOCF) in serum levels	Primary endpoint Phosphorus (mmol/L)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -0.43 -0.60, -0.25 <0.001
	Ca (mmol/L)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo 0.03 -0.02, 0.08 0.307

Change from Week 12 - 16 (LOCF) in serum levels	Ca x P ($mmol^2/L^2$)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -0.90 -1.29, -0.52 <0.001
	iPTH (pmol/L)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -7.09 -13.48, -0.71 0.030
	LDL-Cholesterol	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -71.70 % change -90.25, -53.15 <0.001
	Total Cholesterol	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -35.13 % change -44.29, -25.97 <0.001
	HDL-Cholesterol (%)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -0.14 % change -7.06, 6.79 0.969
	Triglycerides (%)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -7.51 % change -21.34, 6.33 0.284
	Uric acid (mcmol/L)	MCI-196 vs Placebo LS Mean 95% CI P-value	MCI-196 - Placebo -54.98 -79.41, -30.54 <0.001
	Secondary Responders (P levels <= 1.78 mmol/L) at Week 16 (LOCF) Number (%)	MCI-196 vs Placebo Odds Ratio 95% CI P-value	MCI-196 vs Placebo 2.95 1.15, 7.57 0.025
Change from baseline - Week 12 (LOCF) in serum levels	Phosphorus (mmol/L)	MCI-196 vs sevelamer LS Mean 90% CI	MCI-196 - Placebo 0.29 0.21, 0.38
	Ca (mmol/L)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 - sevelamer -0.06 -0.09, -0.03 <0.001
	Ca x P ($mmol^2/L^2$)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer 0.53 0.32, 0.75 <0.001

	iPTH (pmol/L)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer 2.45 -1.37, 6.27 0.209

Change from baseline - Week 12 (LOCF) in serum levels	LDL-Cholesterol (%)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer -5.07 % -9.42, -0.71 0.023
	Total Cholesterol (%)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer -6.81 % -10.30, -3.32 <0.001
	HDL-Cholesterol (%)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer -2.60 % -6.53, 1.32 0.193
	Triglycerides (%)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer -6.88 % -15.44, 1.67 0.114
	Uric acid (mcmol/L)	MCI-196 vs sevelamer LS Mean 95% CI P-value	MCI-196 vs sevelamer -11.10 -23.35, 1.14 0.075
	Secondary Responders (P levels <= 1.78 mmol/L) at Week 12 (LOCF)	MCI-196 vs sevelamer Odds Ratio 95% CI P-value	MCI-196 vs sevelamer 0.29 0.17, 0.47 <0.001
Notes			
Analysis description			
Primary	The primary efficacy (change in serum phosphorus from Week 12 to Week 16, last observation carried forward [LOCF]) was analysed using analysis of covariance (ANCOVA) with treatment and centre as factors and serum phosphorus level at Week 12 (actual values) as a covariate at the 2-sided 5% significance level. The least squares (LS) Means, the difference of MCI-196 compared to placebo, the 95% confidence interval (CI) for the difference and the corresponding p-value which was obtained from the ANCOVA model were presented.		

Secondary	For the comparison of MCI-196 and sevelamer, the change in serum phosphorus from Baseline (Week 0) to Week 12 (LOCF) was analysed using the ANCOVA model as described for the primary efficacy analysis with baseline value as covariate (replacing Week 12 value). If the upper limit for the 90% CI for the difference between MCI-196 and sevelamer was less than +0.15 mmol/L (+0.5 mg/dL) then MCI-196 could be regarded as non-inferior to sevelamer. The change (or percent change) in other secondary efficacy endpoints was also analysed using the same ANCOVA model and the LS Means, the difference, the 95% CI for the difference and the corresponding p-value was presented. The proportion of responders at Week 12 (LOCF) and at Week 16 (LOCF) were analysed using logistic regression, with factors for treatment and centre and Baseline value or Week 12 value as a covariate.

Table 14 Summary of Efficacy for trial MCI-196-E08

Title: A Phase III, Multi-centre, Double-blind, Randomised, Placebo-controlled, Multiple Fixed-dose Study of MCI-196 versus Placebo in Chronic Kidney Disease Stage V Subjects on Dialysis with Hyperphosphataemia and Dyslipidaemia (Incorporating Two Parallel High Dose Groups)		
Study identifier	MCI-196-E08	
Design	The study consisted of a washout period (Week -8 to Baseline for lipid lowering drugs, and Week -4 to Baseline for phosphate binders), followed by a 12-week fixed-dose, double-blind, placebo-controlled treatment period, and a safety follow-up visit. The subjects could complete the washout period as soon as they met the additional inclusion criteria for randomisation and continue with the treatment period. Randomisation to treatment took place at the Baseline visit. This parallel-group study included 5 active treatment groups: MCI-196 3 grams (g), 6 g, 9 g, 12 g and 15 g per day. Subjects receiving MCI-196 3 g and 6 g per day also received 6 and 3 matching placebo tablets per day, respectively, so that all subjects in the 3 g, 6 g and 9 g per day groups took 9 tablets per day in total. There were matching placebo groups in which subjects received placebo 9 tablets, 12 tablets or 15 tablets per day. At the end of the double blind treatment period (Week 12), eligible subjects on MCI 196 or placebo were permitted to enter the Long-Term Safety Study MCI-196-E10.	
	Duration of main phase:	12 weeks
	Duration of run-in phase: Duration of extension phase:	4 weeks (phosphate binder washout period) 8 weeks (lipid lowering drug washout period) 40 weeks (MCI-196-E10 study)
Hypothesis	Superiority	
Treatments groups	Double-blind Period	MCI-196 - 3 g/d (9 tablets/day) ; 104
	Double-blind Period	MCI-196 - 6 g/d (9 tablets/day) ; 102
	Double-blind Period	MCI-196 - 9 g/d (9 tablets/day) ; 99
	Double-blind Period	Placebo (9 tablets/day) ; 79
	Double-blind Period	MCI-196 - 12 g/d (12 tablets/day) ; 103
	Double-blind Period	Placebo (12 tablets/day) ; 27

	Double-blind Period		MCI-196 - 15 g/d (15 tablets/day) ; 102
	Double-blind Period		Placebo (15 tablets/day) ; 26
Endpoints and definitions	Co-Primary endpoints	Efficacy	Change in serum phosphorus and the mean percent change in serum LDL-C from Baseline to Week 12 [LOCF]
	Secondary and additional pre-specified endpoint	Efficacy	Change from Baseline to Week 12 [LOCF] in serum levels of calcium (Ca), Ca-P, iPTH and LDL particle size Percent change from Baseline to Week 12 [LOCF] for TC, HDL-C, TG, lipoprotein(a) and oxidised LDL Change from Baseline to Week 12 [LOCF] in C-reactive Protein, HbA1c and Uric Acid
	Other	Safety	Adverse events (AEs), Laboratory assessments, vital signs, 12 lead ECG, Physical examination, prior and concomitant medications
Database lock	11 December 2009		

Results and Analysis

Analysis description	**Primary Analysis**							
Analysis population and time point description	Intent to treat							
Descriptive statistics and estimate variability	Treatment group	3 g	6 g	9 g	Placebo 9 tabs	12 g	15 g	Pooled Placebo

	Number of subject	104	101	97	77	100	99	130
Change from Baseline to Week 12 (LOCF) Mean (SD)	**Serum Phosphorus** (mg/dL)	-0.23 (1.62)	-0.77 (1.97)	-0.97 (1.68)	-0.15 (1.65)	-0.71 (1.84)	-1.41 (1.43)	-0.12 (1.70)
	Serum Phosphorus Based Responders (<= 5.5 mg/dL) At Week 12(LOCF) Number (%)	21 (20.4%)	21 (21.0%)	25 (28.7%)	15 (19.7%)	28 (30.1%)	32 (36.4%)	26 (20.2%)
Descriptive statistics and estimate variability Change from Baseline to Week 12 (LOCF) in serum levels Mean (SD)	LDL cholesterol (%)	-16.66 (20.05)	-23.56 (20.99)	-27.64 (21.45)	1.49 (16.31)	-29.44 (25.28)	-27.46 (24.57)	2.77 (17.44)
	Calcium (mmol/L)	-0.023 (0.130)	-0.006 (0.200)	-0.046 (0.179)	-0.039 (0.147)	-0.022 (0.201)	-0.010 (0.198)	-0.022 (0.152)
	CaxP ($mmol^2/L^2$)	-0.203 (1.239)	-0.577 (1.499)	-0.809 (1.241)	-0.211 (1.234)	-0.534 (1.305)	-0.980 (1.107)	-0.133 (1.277)
	iPTH (pmol/L)	3.57 (38.92)	0.01 (20.59)	-5.07 (42.67)	2.41 (24.84)	0.82 (20.70)	-1.94 (46.23)	2.54 (23.12)
	Total Cholesterol % change (mmol/L)	-10.53 (14.52)	-15.52 (15.08)	-20.80 (14.11)	2.22 (12.79)	-22.24 (16.65)	-20.54 (19.05)	3.22 (12.99)
	HDL-Cholesterol % change (mmol/L)	0.11 (15.35)	2.64 (19.16)	1.84 (22.76)	0.76 (19.88)	1.03 (22.74)	-0.85 (20.54)	1.52 (18.69)
	Triglyceride % change (mmol/L)	9.96 (42.34)	7.51 (42.78)	4.33 (42.98)	9.71 (44.41)	1.27 (40.34)	-0.80 (37.75)	11.03 (44.11)
	LDL particle size	-0.0077 (0.0260)	-0.0042 (0.0261)	-0.0060 (0.0293)	-0.0035 (0.0193)	-0.0087 (0.0279)	-0.0045 (0.0317)	-0.0052 (0.0248)
	Lipoprotein (a) % (nmol/L)	28.71 (208.82)	-4.02 (27.06)	3.00 (53.16)	3.62 (22.49)	-1.25 (39.59)	-0.87 (23.97)	4.25 (24.12)
	Oxidised LDL % (U/L)	-2.71 (27.38)	-10.48 (33.97)	-17.08 (29.44)	8.55 (32.94)	-9.67 (47.95)	-18.79 (36.67)	9.03 (32.17)

	C-reactive Protein (mg/L)	-1.86 (10.75)	-1.68 (7.59)	-1.43 (7.30)	-0.47 (10.33)	-0.21 (12.67)	-1.15 (11.31)	-1.05 (9.33)
	HbA1c (% TL HB)	-0.07 (0.50)	-0.13 (0.67)	-0.13 (0.62)	0.10 (0.44)	-0.19 (0.68)	-0.24 (0.62)	0.06 (0.42)
	Uric Acid (mcmol/L)	-14.6 (60.1)	-29.6 (64.7)	-30.6 (70.3)	4.0 (57.8)	-32.1 (72.5)	-40.8 (72.3)	7.3 (68.8)

Effect estimate per comparison	Co-Primary endpoint **Serum Phosphorus** (mg/dL) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-0.07 (3g - Placebo 9 tabs) -0.52 (6g - Placebo 9 tabs) -0.66 (9g - Placebo 9 tabs) -0.88 (12g/15g - pooled Placebo)
		95% CI	-0.54,0.41 (3g - Placebo 9 tabs) -1.00,-0.03 (6g - Placebo 9 tabs) -1.16,-0.16 (9g - Placebo 9 tabs) -1.22,-0.54 (12g/15g - pooled Placebo)
		P-value	0.785 (3g - Placebo 9 tabs) 0.036 (6g - Placebo 9 tabs) 0.009 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)
	Co-Primary endpoint **Serum LDL** Percent (%) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-17.77 (3g - Placebo 9 tabs) -25.46 (6g - Placebo 9 tabs) -29.47 (9g - Placebo 9 tabs) -31.71 (12g/15g - pooled Placebo)
		95% CI	-23.54,-12.00 (3g - Placebo 9 tabs) -31.25,-19.66 (6g - Placebo 9 tabs) -35.44,-23.51 (9g - Placebo 9 tabs) -36.53,-26.89 (12g/15g - pooled Placebo)
		P-value	<0.001 (3g - Placebo 9 tabs) <0.001 (6g - Placebo 9 tabs) <0.001 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)
	Secondary endpoint **Serum Calcium** (mmol/L) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	0.02 (3g - Placebo 9 tabs) 0.03 (6g - Placebo 9 tabs) -0.01 (9g - Placebo 9 tabs) 0.00 (12g/15g - pooled Placebo)
		95% CI	-0.02,0.07 (3g - Placebo 9 tabs) -0.01,0.08 (6g - Placebo 9 tabs) -0.05,0.04 (9g - Placebo 9 tabs) -0.04,0.03 (12g/15g - pooled Placebo)
		P-value	0.380 (3g - Placebo 9 tabs) 0.174 (6g - Placebo 9 tabs) 0.816 (9g - Placebo 9 tabs) 0.863 (12g/15g - pooled Placebo)
	Secondary **Serum CaxP** ($mmol^2/L^2$) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-0.02 (3g - Placebo 9 tabs) -0.29 (6g - Placebo 9 tabs) -0.48 (9g - Placebo 9 tabs) -0.61 (12g/15g - pooled Placebo)

		95% CI	-0.33,0.38 (3g - Placebo 9 tabs) -0.65,0.07 (6g - Placebo 9 tabs) -0.85,-0.11 (9g - Placebo 9 tabs) -0.86,-0,36 (12g/15g - pooled Placebo)
		P-value	0.891 (3g - Placebo 9 tabs) 0.109 (6g - Placebo 9 tabs) 0.011 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)

Effect estimate per comparison	Secondary **Serum iPTH** (pmol/L) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	1.62 (3g - Placebo 9 tabs) -2.17 (6g - Placebo 9 tabs) -7.07 (9g - Placebo 9 tabs) -3.73 (12g/15g - pooled Placebo)
		95% CI	-7.96,11.20 (3g - Placebo 9 tabs) -11.81,7.46 (6g - Placebo 9 tabs) -17.01,2.88 (9g - Placebo 9 tabs) -10.70,3.23 (12g/15g - pooled Placebo)
		P-value	0.740 (3g - Placebo 9 tabs) 0.658 (6g - Placebo 9 tabs) 0.163 (9g - Placebo 9 tabs) 0.293 (12g/15g - pooled Placebo)
	Secondary **Serum Total Cholesterol** Percent (%) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-12.25 (3g - Placebo 9 tabs) -17.87 (6g - Placebo 9 tabs) -22.73 (9g - Placebo 9 tabs) -24.60 (12g/15g - pooled Placebo)
		95% CI	-16.36,-8.13 (3g - Placebo 9 tabs) -21.99,-13.74 (6g - Placebo 9 tabs) -26.98,-18.48 (9g - Placebo 9 tabs) -28.06,-21.15(12g/15g - pooled Placebo)
		P-value	<0.001 (3g - Placebo 9 tabs) <0.001 (6g - Placebo 9 tabs) <0.001 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)
	Secondary **Serum HDL-Cholesterol** Percent (%) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-1.87 (3g - Placebo 9 tabs) 1.53 (6g - Placebo 9 tabs) 0.25 (9g - Placebo 9 tabs) -2.99 (12g/15g - pooled Placebo)
		95% CI	-7.60,3.86 (3g - Placebo 9 tabs) -4.21,7.27 (6g - Placebo 9 tabs) -5.66,6.17 (9g - Placebo 9 tabs) -7.53,1.54 (12g/15g - pooled Placebo)
		P-value	0.522 (3g - Placebo 9 tabs) 0.600 (6g - Placebo 9 tabs) 0.933 (9g - Placebo 9 tabs) 0.195 (12g/15g - pooled Placebo)
	Secondary **Serum Triglycerides** Percent (%) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	2.55 (3g - Placebo 9 tabs) -0.48 (6g - Placebo 9 tabs) -2.80 (9g - Placebo 9 tabs) -7.12 (12g/15g - pooled Placebo)

		95% CI	-10.06,15.16 (3g - Placebo 9 tabs) -13.13,12.17 (6g - Placebo 9 tabs) -15.82,10.23 (9g - Placebo 9 tabs) -16.27,2.03 (12g/15g - pooled Placebo)
		P-value	0.691 (3g - Placebo 9 tabs) 0.941 (6g - Placebo 9 tabs) 0.673 (9g - Placebo 9 tabs) 0.126 (12g/15g - pooled Placebo)

Effect estimate per comparison	Secondary **Oxidised LDL** (U/L) Percent (%) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-9.72 (3g - Placebo 9 tabs) -18.95 (6g - Placebo 9 tabs) -25.01 (9g - Placebo 9 tabs) -20.54 (12g/15g - pooled Placebo)
		95% CI	-18.72,-0.73 (3g - Placebo 9 tabs) -28.00,-9.90 (6g - Placebo 9 tabs) -34.32,-15.70 (9g - Placebo 9 tabs) -29.34,-11.74(12g/15g - pooled Placebo)
		P-value	0.034 (3g - Placebo 9 tabs) <0.001 (6g - Placebo 9 tabs) <0.001 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)
	Secondary **HbA1c** (% TL HB) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-0.15 (3g - Placebo 9 tabs) -0.21 (6g - Placebo 9 tabs) -0.21 (9g - Placebo 9 tabs) -0.27 (12g/15g - pooled Placebo)
		95% CI	-0.31,0.02 (3g - Placebo 9 tabs) -0.38,-0.05 (6g - Placebo 9 tabs) -0.38,-0.04 (9g - Placebo 9 tabs) -0.40,-0.13 (12g/15g - pooled Placebo)
		P-value	0.078 (3g - Placebo 9 tabs) 0.011 (6g - Placebo 9 tabs) 0.014 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)
	Secondary **Uric Acid** (mcmol/L) Change from Baseline to Week 12 (LOCF)	MCI-196-Placebo	MCI-196-Placebo
		LS Mean	-18.00 (3g - Placebo 9 tabs) -30.91 (6g - Placebo 9 tabs) -37.17 (9g - Placebo 9 tabs) -46.02 (12g/15g - pooled Placebo)
		95% CI	-35.10,-0.89 (3g - Placebo 9 tabs) -48.14,-13.68 (6g - Placebo 9 tabs) -54.93,-19.42 (9g - Placebo 9 tabs) -61.32,-30.73 (12g/15g - pooled Placebo)
		P-value	0.039 (3g - Placebo 9 tabs) <0.001 (6g - Placebo 9 tabs) <0.001 (9g - Placebo 9 tabs) <0.001 (12g/15g - pooled Placebo)
	Serum Phosphorus Based Responders (<= 5.5 mg/dL) At Week 12 (LOCF)	MCI-196 - Placebo	MCI-196 - Placebo
		Odds Ratio	1.03 (3g - Placebo 9 tabs) 1.17 (6g - Placebo 9 tabs) 1.93 (9g - Placebo 9 tabs) 2.15 (12g/15g - pooled Placebo)

		95% CI	0.48, 2.20 (3g - Placebo 9 tabs) 0.55, 2.51 (6g - Placebo 9 tabs) 0.90, 4.12 (9g - Placebo 9 tabs) 1.23, 3.77 (12g/15g - pooled Placebo)
		P-value	0.948 (3g - Placebo 9 tabs) 0.686 (6g - Placebo 9 tabs) 0.090 (9g - Placebo 9 tabs) 0.007 (12g/15g - pooled Placebo)
Notes			
Analysis description	**Co-primary Analysis**		
Co-primary Analysis	Two separate analyses were performed for each co-primary efficacy variable (change in serum phosphorus and the mean percent change in serum LDL-C from Baseline to Week 12 [LOCF]). The first analysis compared MCI-196 3 g, 6 g and 9 g with placebo (9 tablets) using a closed-testing procedure and the second analysis compared pooled MCI-196 (12 g+15 g) with pooled placebo (9, 12 and 15 tablets). For the primary analysis, an overall α=0.05 was divided into α=0.04 for serum phosphorus and α=0.01 for LDL-C. Furthermore, α was divided within serum phosphorus and LDL-C as follows: – Serum phosphorus – α=0.03 for comparisons of 3 g, 6 g and 9 g per day with 9 tablets placebo (closed procedure). – α=0.01 for comparison of 12 g and 15 g per day (pooled) with 9, 12 and 15 tablets (pooled) placebo. – Serum LDL-C – α=0.0075 for comparisons of 3 g, 6 g and 9 g per day with 9 tablets placebo (closed procedure). – α=0.0025 for comparison of 12 g and 15 g per day (pooled) with 9, 12 and 15 tablets (pooled) placebo. The change in serum phosphorus from Baseline to Week 12 (LOCF) and the percentage change in serum LDL-C from Baseline to Week 12 (LOCF) were analysed using an analysis of covariance (ANCOVA) with treatment and pooled country as factors and the Baseline value as a covariate (Baseline serum phosphorus was used for the serum phosphorus analysis, and Baseline serum LDL-C was used for the serum LDL-C analysis).		
Co-primary Analysis	The least squares (LS) means, the difference of MCI-196 compared to placebo, the 95% CI for the difference, and the corresponding p-value were presented. A mixed model repeated measure (MMRM) was used for sensitivity analysis for ITT population. Serum phosphorus and serum LDL-C levels were summarised descriptively using number of subjects (n), mean, standard deviation (SD), median, minimum and maximum by treatment group at each visit. Data were summarised in terms of absolute values at each visit and change from Baseline for serum phosphorus, and percent change from Baseline for serum LDL-C.		

Secondary Analysis	All secondary efficacy analyses were performed using the same ANCOVA model as for the primary efficacy analysis, and were summarised in the same manner as the primary endpoints. All tests of secondary efficacy parameters were 2-sided and performed at the 5% significance level. For secondary parameters, non normal distributions and outliers in iPTH, HDL-C, TG, lipoprotein(a), oxidised LDL, CRP, HbA1c and uric acid were observed. As a result, these parameters were also analysed using non parametric methods. The proportion of responders at Week 12 (LOCF) were analysed using logistic regression, with factors for treatment and pooled country, and Baseline P value as a covariate.

Table 15 Summary of Efficacy for trial MCI-196-E10

Title: A Phase III, Multi-centre, Open-label, Flexible-dose, Long-term Safety Study of MCI-196 in Chronic Kidney Disease Stage V Subjects on Dialysis with Hyperphosphataemia (Incorporating a Comparison with Sevelamer)

Study identifier	MCI-196-E10		
Design	This was a multi-centre, open-label, flexible-dose, long-term safety study that, in conjunction with MCI-196-E07, MCI-196-E08 and MCI-196-E09 (original studies), allowed exposure to MCI-196 for up to either 52 or 56 weeks or sevelamer for up to 52 weeks (subjects in the sevelamer arm of MCI-196-E07 only). For the first 8 weeks of the 40-week study, study visits were every 2 weeks. Dose titration (up or down) was allowed every 2 weeks (except Visit 2 for subjects coming from the MCI-196 arm of MCI-196-E07 and MCI-196-E08, as serum phosphorus values were blinded at Visit 1) to maintain serum phosphorus levels ⩽1.78 millimoles (mmol)/litre (L) (5.5 milligrams [mg]/decilitre [dL]). After 8 weeks, subjects continued flexible dosing with MCI-196 or sevelamer and attended study visits every 4 weeks. Dose titration (up or down) was allowed every 4 weeks to maintain serum phosphorus levels as described above. Subjects ended the study at Week 40.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		40 weeks No applicable No applicable
Hypothesis	Long-term safety study		
Treatments groups	Flexible-dose period		MCI-196 :432
	Flexible-dose period		Sevelamer :124
Endpoints and definitions	Primary endpoint	Safety	Incidence of adverse events (AEs) and change from Baseline (in original study) to End of E10 (i.e. E10 Week 40) in safety parameters (e.g. laboratory values, vital signs, ECG and physical examination).
	Secondary	Efficacy	Change from Baseline to end of MCI-196-E10 to end of MCI-196-E10 for serum phosphorus, serum calcium, serum Ca x P, serum iPTH, serum uric acid and serum CRP; serum LDL-C, TC, HDL-C, TG
Database lock	08 November 2010		

Results and Analysis

Analysis description	**Secondary Analysis**			
Analysis population and time point description	Other: Safety Population			
Descriptive statistics and estimate variability Change from Baseline to Week 40 (LOCF) in serum levels Mean (SD)	Treatment group	MCI-196-E10	MCI-196-E07	Sevelamer
	Number of subject	429	75	124
	Phosphorus (mg/dL)	-1.23 (1.78)	-1.47 (1.68)	-2.26 (1.82)
	Serum Phosphorus based responders (<= 5.5 mg/dL) at Week 40(LOCF) Number (%)	183 (42.7%)	49 (65.3%)	83 (66.9%)
	Calcium (mmol/L)	-0.022 (0.189)	-0.020 (0.201)	0.035 (0.199)
	CaxP ($mmol^2/L^2$)	-0.927 (1.334)	-1.063 (1.150)	-1.538 (1.267)
	iPTH (pmol/L)	9.40 (53.88)	7.08 (27.48)	0.94 (32.32)
	Serum LDL-Cholesterol (mg/dL)	-26.22 % (27.08)	-30.62 % (20.12)	-28.66 % (23.61)
	Serum HDL-Cholesterol (mmol/L)	4.28 % (24.11)	6.68 % (25.68)	6.03 % (25.94)
	HbA1c (% TL HB)	-0.28 (0.69)	-0.41 (0.71)	-0.37 (0.76)
Effect estimate per comparison	Secondary Serum Phosphorus (mg/dL) Change from Baseline to Week 40 (LOCF)	Week 40 (LOCF) vs. Baseline	Week 40 (LOCF) - Baseline	
		95% CI	-1.40,-1.06 (MCI-196-E10) -1.86,-1.08 (MCI-196-E07) -2.58,-1.93 (Sevelamer)	
		P-value	<0.001 (MCI-196-E10) <0.001 (MCI-196-E07) <0.001 (Sevelamer)	
	Secondary Serum calcium (mmol/L) Change from Baseline to Week 40	Week 40 (LOCF) vs. Baseline	Week 40 (LOCF) - Baseline	
		95% CI	-0.04,0.00 (MCI-196-E10) -0.07,0.03 (MCI-196-E07) 0.00,0.07 (Sevelamer)	

	(LOCF) Mean (SD)	P-value	0.015 (MCI-196-E10) 0.392 (MCI-196-E07) 0.053 (Sevelamer)
	CaxP ($mmol^2/L^2$) Change from Baseline to Week 40 (LOCF) Mean (SD)	Week 40 (LOCF) vs. Baseline	Week 40 (LOCF) - Baseline
		95% CI	-1.05,-0.80 (MCI-196-E10) -1.33,-0.80 (MCI-196-E07) -1.76,-1.31 (Sevelamer)
		P-value	<0.001 (MCI-196-E10) <0.001 (MCI-196-E07) <0.001 (Sevelamer)
	iPTH (pmol/L) Change from Baseline to Week 40 (LOCF) Mean (SD)	Week 40 (LOCF) vs. Baseline	Week 40 (LOCF) - Baseline
		95% CI	4.29,14.51 (MCI-196-E10) 0.76,13.40 (MCI-196-E07) -4.81, 6.68 (Sevelamer)
		P-value	<0.001 (MCI-196-E10) 0.029 (MCI-196-E07) 0.747 (Sevelamer)
	Serum LDL-C (mg/dL) Percent Change from Baseline to Week 40 (LOCF) Mean (SD)	Week 40 (LOCF) vs. Baseline	Week 40 (LOCF) - Baseline
		95% CI	-28.80,-23.65 (MCI-196-E10) -35.25,-25.99 (MCI-196-E07) -32.86,-24.47 (Sevelamer)
		P-value	<0.001 (MCI-196-E10) <0.001 (MCI-196-E07) <0.001 (Sevelamer)
	Serum HDL-C Percent Change (%) from Baseline to Week 40 (LOCF) Mean (SD)	Week 40 (LOCF) vs. Baseline	Week 40 (LOCF) - Baseline
		95% CI	1.99,6.58 (MCI-196-E10) -0.19,11.83 (MCI-196-E07) 2.47,10.84 (Sevelamer)
		P-value	<0.001 (MCI-196-E10) 0.058 (MCI-196-E07) 0.002 (Sevelamer)
Notes			
Analysis description	**Secondary analysis**		

	(Secondary) Efficacy Assessment: The observed value and the absolute (or percent) change from Baseline to end of MCI-196-E10 were summarised using descriptive statistics for each efficacy parameter. For the main efficacy parameters (serum phosphorus, serum calcium, serum Ca x P, serum iPTH, serum uric acid and serum CRP; serum LDL-C, TC, HDL-C, TG) the absolute (or percent) change from Baseline was assessed for statistical significance (2-sided at 5%-level) using a paired t-test for the comparison between Baseline and Week 40 (LOCF) of MCI-196-E10.

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

The following tables summarise the efficacy results from the main studies supporting the present application.

Table 16 Change from baseline to endpoint in serum phosphorous levels (mmol/L), in open-label treatment periods in studies MCI-196-A05 and MCI-196-E07 (week 12, ITT)

	MCI-196-A05			MCI-196-E07					
	MCI-196			MCI-196			Sevelamer		
	n	Value	Change	n	Value	Change	n	Value	Change
Baseline	241	2.44		160	2.33		167	2.39	
Week 12 (LOCF)		1.94	-0.50		1.96	-0.36		1.69	-0.70

Table 17 Change from week 12 to week 16 in serum phosphorous levels (mmol/L) in double -blind placebo-controlled withdrawal periods in studies MCI-196- A05 and MCI-196-E07 (ITT)

	MCI-196-A05				MCI-196-E07			
	Placebo n=83		MCI-196 n=85		Placebo n=53		MCI-196 n=50	
	Value	LSM Change [a]	Value	LSM Change [a]	Value	LSM Change [a]	Value	LSM Change [a]
Week 12	2.00		1.85		1.79		1.87	
Week 16 (LOCF)	2.23	0.26	1.84	-0.06	2.20	0.35	1.80	-0.08
Difference in LSM change, p-value [a]	-0.33 p<0.001				-0.43 p<0.001			

a Results are from ANCOVA with treatment, pooled site as fixed effects and week 12 value as covariate

Table 18 Responder analysis: ≤1.78 mmol/L (5.5 mg/dL) or ≤1.95 mmol/L (6.0 mg/dL) during open-label treatment periods in studies MCI-196-A05 and MCI-196-E07 (ITT)

		MCI-196-A05		MCI-196-E07			
		MCI-196		MCI-196		Sevelamer	
		n/N	Response rate	n/N	Response rate	n/N	Response rate
Week 12 (LOCF)	≤1.78 mmol/L	105/241	43.6%	65/153	42.5%	111/164	67.7%
	≤1.95 mmol/L	135/241	56.0%	86/153	56.2%	129/164	78.7%

Add-on therapy: Combination treatment of MCI-196 with calcium-based phosphate binders was investigated in studies MCI-196-A01, MCI-196-A02, MCI-196-A03 and MCI-196-A04. Within treatment groups (MCI-196 alone, MCI-196 plus calcium acetate or calcium acetate alone) significant differences were seen in studies A02, A03 and A04. In study A01, although there was a tendency towards a reduction in serum phosphorus, no statistically significant difference between groups was demonstrated. The sizes of the studies with calcium acetate treatment arms were small and the results were inconsistent in determining whether or not MCI-196 added to the effect achieved by the calcium-based binders.

Clinical studies in special populations

Pivotal studies, as well as most other clinical studies, were undertaken in patients with chronic kidney disease and dialysis.

Supportive studies

Study MCI-196-A13 was a phase 1 US study to qualitatively measure the ability to swallow MCI-196 granules in healthy adult male and female subjects. In this open-label study, 20 subjects swallowed 3 grams of MCI-196 granules three times during 1 day. All 20 subjects swallowed to completion the morning, mid-day, and evening doses of the granules within 15 minutes. There was no residue in any of the subjects' mouths at any of the post-dose time points up to 180 minutes after any of the doses.

Study MCI-196-A01 was a phase 2, open label randomised parallel titration study to determine the safety and efficacy of MCI-196 in nondiabetic end stage renal disease (ESRD) patients with hyperphosphatemia on chronic hemodialysis. Twenty-three patients received MCI-196, 27 received MCI-196 and calcium acetate, and 25 received calcium acetate alone. The majority of patients in all 3 treatment groups had a decrease in serum phosphorous from baseline to endpoint during the 2- 8 weeks of active treatment. In the MCI-196 group 52.2% of patients had a decrease in serum phosphorous from baseline to endpoint, compared with 88.0% and 87.5% of patients in the MCI-196 + calcium acetate and the calcium acetate groups, respectively.

Study MCI-196-A02 was a phase 2, open-label, parallel, extension study to determine the long-term safety and efficacy of MCI-196 in non-diabetic ESRD patients with hyperphosphatemia on chronic hemodialysis and to evaluate the effect of MCI-196 on cholesterol, triglycerides and changes in aortic and coronary calcifications. The primary objective of this study was to evaluate the long-term safety and efficacy of MCI-196 in these patients. It was an extension to study MCI-196-A01 with up to 24 weeks of treatment. Patients who had completed the MCI-196-A01 study were eligible to participate if they had shown a satisfactory response to treatment.

Study MCI-196-A03 was a phase 2, open-label, randomised, parallel, titration study to determine safety and efficacy of MCI-196 in ESRD patients with hyperphosphataemia on chronic hemodialysis with type 2 diabetes. The primary objective and design of this study was the same as in study MCI-196-A01. Fifty-nine patients were randomised: 22 received MCI-196, 16 received MCI-196 and calcium acetate and 21 received calcium acetate alone. Most patients showed a decrease in serum phosphorous from baseline to endpoint (81-86% per group). A statistically significant difference was demonstrated in the MCI-196 group for the mean reduction in serum phosphorous concentration from baseline to endpoint by 0.45 mmol/L (1.4 mg/dL; $p<0.0001$); reductions were numerically greater in the MCI-196 plus calcium acetate and calcium acetate groups compared to the MCI-196 group. No statistically significant differences were observed between MCI-196 and the other treatments for the least squares mean change in serum phosphorous from baseline to endpoint.

Study MCI-196-A04 was a phase 2, open-label, parallel, extension study (to study MCI-196-A03) to determine the long-term safety and efficacy of MCI-196 in ESRD patients with hyperphosphaetemia on chronic hemodialysis that had type II diabetes, and to evaluate the effect of MCI-196 on glucose, cholesterol, triglycerides and changes in aortic and coronary calcifications. Patients who had completed MCI-196-A03 were eligible to participate if they had shown a satisfactory response to treatment. Of the 48 patients who had completed MCI-196-A03, 38 were enrolled in this study, of whom 14 received MCI-196, 10 received MCI-196 and calcium acetate and 14 received calcium acetate alone. The primary objective and design of this study were the same as in study MCI-196-A02. Only 20 patients completed the study. Overall, serum phosphorous levels were relatively unchanged during the study.

Study MCI-196-E06 was a phase 2, double-blind placebo-controlled fixed dose titration study that included 120 patients. The primary efficacy variable in the study showed a dose-related statistically significant change from baseline in serum phosphorous levels in the MCI-196 treatment groups ($p<0.05$). In this study, the 6 g/day and 9 g/day treatment groups showed a significant response after 3 weeks of treatment. Forty-one of the 57 patients who had completed MCI-196-A01 were enrolled in this study. All treatment groups showed nearly equivalent decreases from baseline to endpoint in serum phosphorous concentrations. The reductions in serum phosphorous were maintained over the course of the study.

Table 19 Change from baseline to endpoint in serum phosphorous levels (mmol/L) MCI-196-E06, ITT population

MCI-196-E06[a]				
			Week 3 (LOCF)	
Treatment	n	Baseline	LSM change	Difference in LSM change, p-value
Placebo	29	2.29	0.01	-
MCI-196 3 g/day	29	2.15	-0.06	-0.07 p=0.461
MCI-196 6 g/day	30	2.31	-0.21	-0.22 p=0.027
MCI-196 9 g/day	31	2.33	-0.19	-0.20 p=0.043

a MCI-196-E06 results are from ANCOVA with treatment + country as fixed effects and baseline as a covariate. All patients in the placebo groups are pooled together for the analysis; LOCF = last observation carried forward; LSM = least squares mean

Study MCI-196-A06 was a stand-alone long-term study. This phase 3 open-label, flexible dose, long-term safety study had a duration of 60 weeks and included 116 dialysis patients with hyperphosphataemia in the US and Canada. Patients started at MCI-196 6 g/day and then dose titration was similarly permitted every 2 weeks for the first 8 weeks, and every 4 weeks thereafter up to week 52. The primary objective of the study was to demonstrate long-term safety and tolerability of MCI-196.

Study MCI-196-E09 was a double-blind, randomised, placebo-controlled study of MCI-196 in combination with a low-dose calcium based phosphate binder. This study was prematurely terminated in January 2010 due to problems to include patients, after only 6 patients had been enrolled.

Study MCI-196-E10 was the extension study of MCI-196-E07, MCI-196-E08 and MCI-196 E09. In study MCI-196-E10, all patients who had been on MCI-196 were re-started at a dose of 6 g/day to maintain blind in the original studies, regardless of the dose they had previously been receiving. The

starting dose of sevelamer was the same dose these patients were receiving at their last visit in study MCI-196-E07 (i.e., individually optimised doses). Dose titration was permitted at certain intervals. The total exposure with original studies was 52 or 56 weeks. Results showed that serum phosphorous levels declined over the initial 12 weeks of treatment and then appeared to plateau and remain stable for the remainder of the study.

The proportion of responders also increased over time. There was no indication of development of tolerance or a reduction in efficacy over time. Patients who were randomised to MCI-196 or sevelamer in the original study MCI-196-E07 had comparable mean phosphorous levels below 1.78 mmol/L at week 52 (LOCF). Responder rates at week 52 (LOCF) were also comparable between MCI-196 and sevelamer in these patients.

Study MCI-196-E11 was a phase 3 multi-centre double-blind double-dummy randomised flexible-dose comparative study of MCI-196 versus simvastatin for the treatment of dyslipidaemia in subjects with chronic kidney disease on dialysis (incorporating a placebo-controlled withdrawal phase). In total, 260 patients were randomised, 218 (83.8%) completed the active comparison phase, and 218 patients were re-randomised of whom 215(98.6%) completed the placebo-controlled withdrawal phase. The primary objective of this study was to demonstrate the superiority of MCI-196 over placebo and non-inferiority with simvastatin in reducing serum LDL-C in patients with CKD Stage 5 on dialysis. A washout phase of 2 or 6 weeks duration was followed by an active comparison phase, where patients were randomised 1:1 to receive either MCI-196 or simvastatin, with a flexible dosing regimen allowing titration (up or down) every 4 weeks for a total of 16 weeks; and finally a placebo-controlled withdrawal phase where patients were re-randomised 1:1 to either continue on their current dose of active treatment or to receive placebo, for a total of 4 weeks. In the active treatment phase, based on 95% confidence intervals, MCI-196 was noninferior to simvastatin with regards to serum LDL-C (the percentage changes in LDL-C were 29.5% and 28.9% for MCI-196 and simvastatin respectively). In a responder analysis the odds ratio (MCI-196/simvastatin) for achieving serum LDL-C levels <2.59 mmol/L (100 mg/dL) with a >15% decrease from baseline was 0.88 (p=0.621), indicating that there was no greater likelihood of response with either MCI-196 or simvastatin at week 16 (LOCF). Serum phosphorous levels remained relatively stable with both MCI-196 and simvastatin. MCI-196 was associated with statistically significantly lower serum calcium and Ca x P levels than simvastatin.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The phosphate lowering effect of colestilan seems to be dose proportional up to a daily dose of 15 g in clinical studies. The posology proposed in the SmPC (a starting dose of 6-9 g daily and dose titration according to serum phosphorus concentration, up to a maximal daily dose of 15g) is supported by clinical study data from phase 2 studies E06, A01, and A03, and from phase 3 studies A05, E07, E10, and A06.

Study Subjects and Subject Disposition

Study A05 included dialysis patients with high serum phosphate levels requiring phosphate lowering therapy according to current medical practice and in accordance with KDOQI guidelines. Study objects were adequate and informative. Study protocol and statistical methods used in this study are considered to be appropriate. The withdrawal rate during the flexible dose titration period was 31%. Most discontinuations (AEs, withdrawal of consent and high phosphorus levels) occurred before week 6 which may, at least partly be a consequence of the recommended low starting dose and slow dose titration. It is however reassuring that withdrawal rates during the randomised phase was low and evenly distributed between colestilan and placebo study arms.

Inclusion and exclusion criteria in *study E07* resemble those for study MCI-196-A05. Size and design of the study are adequate. The primary objective for the study is identical to that of study MCI-196-A05. A comparison to sevelamer was one of the secondary objectives. In this study, the withdrawal rate was 36 % in the colestilan group compared to 19% in the sevelamer group during the open-label period. Adverse events (17%), withdrawal of consent (9.7%) and high phosphorous levels (4.8%) were the most common reasons for discontinuation in the colestilan group. The difference between colestilan and sevelamer groups, especially with respect to withdrawals due to adverse events, could partly be explained by the fact that 1/3 of patients in the sevelamer group had previously been treated with sevelamer and therefore could be expected to be tolerant to sevelamer. Further, the recommended low starting dose and slow dose titration for colestilan could explain the higher proportion of patients withdrawing due to high phosphorus levels. It is reassuring that withdrawal rate was low during the placebo-controlled withdrawal period (2.0 % in the colestilan group and 9.3 %in the placebo group).

In study *E08*, withdrawal rate was 36%, ranging from 28% in the colestilan 6g group to 42% in the placebo group. The most common reason for withdrawal was high phosphorous levels (placebo; 23%, colestilan 3g; 31%, colestilan 15g; 7%) adverse events (placebo; 3%, colestilan 3g; 1%, colestilan 15g; 13%) and withdrawal of consent (placebo; 5%, colestilan 3g; 5%, colestilan 15g; 15%). Thus, there were dose dependent withdrawals due to adverse events, but the incidence in the 15g group is not unexpectedly high. The withdrawal rate due to high phosphorus levels were considerably higher in the placebo group compared to the colestilan groups (doses 6g and higher).

Efficacy data and additional analyses

In the ITT population in *study A05*, baseline demographics were very similar in both treatment groups. In the randomised period weeks 12 – 16, colestilan was significantly more effective than placebo to control serum phosphate levels in subjects with chronic kidney disease grade 5 on dialysis (primary efficacy parameter). The serum P level mean change was -0.5 mmol/L (-1.54 mg/dL $p < 0.001$) which is a clinically relevant reduction. Colestilan was significantly more effective than placebo to lower serum Ca x P ion product, LDL-cholesterol, and HbA1c. Uric acid and PTH was also lower in the colestilan treated group. Responder analysis showed that about half of the colestilan treated patients were responders during study weeks 12 – 16. Subjects with higher baseline phosphorous levels had a greater decrease from week 12 than those with lower baseline phosphorous levels.

In study MCI-196-E07, no differences of importance concerning baseline demographics were found between study groups. Colestilan was superior to placebo with respect to lowering of serum phosphorous in the placebo-controlled withdrawal period: The difference between LS means for colestilan and placebo was 0.43 mmol/L (1.32 mg/dL, $p< 0.001$) at week 16.

A comparison to sevelamer was one of the secondary objectives. In the open-label period, non-inferiority of MCI-196 to sevelamer could not be concluded according to the pre-specified criteria (LS mean change from Baseline during the open-label period was -0,42 mmol/L [-1.30 mg/dL] for the colestilan group and -0.72 mmol/L [– 2.22 mg/dL] for the sevelamer group).

Colestilan and sevelamer lowered LDL-cholesterol to a comparable extent during this period while the serum C x P product was significantly lower with sevelamer ($p < 0.001$) and total cholesterol was significantly lower with colestilan ($p < 0.001$).

In studies A05 and E07, most patients required daily doses of 12 or 15 g of colestilan which resulted in clinically relevant results.

Study MCI-196-E08: Colestilan reduced serum phosphorous levels from baseline compared to placebo, in a dose-dependent manner with statistically significant differences compared to placebo at daily doses of 6g and higher. The difference compared to placebo in the 12+15g dose group was of clear

clinical relevance (i.e. reduction of 0.3 mmol/L). Colestilan also significantly lowered the Ca x P product, and serum triglycerides, compared to placebo. The effect seemed to be dose proportional, up to a daily dose of 15 g. Patients with baseline serum phosphorous level >2.42 mmol/L had a greater reduction in serum phosphate than those with lower baseline serum phosphorous level during colestilan treatment. There was no clear effect of dialysis type; however patients on peritoneal dialysis were few in the main clinical studies.

In the open long-term *studies E10 and A06*, serum phosphorus levels declined over the initial 12 weeks of dose titration and then appeared to plateau and remain stable for the remainder of the study up to 1 year. The rate of responders increased over time. Phosphorous levels and responder rates at week 52 (LOCF) were comparable between colestilan and sevelamer.

In *study MCI-196-E11*, a phase 3 study that included 260 patients, colestilan was superior to placebo and noninferior to simvastatin in reducing serum LDL-cholesterol in patients with CKD Stage 5 on dialysis.

Patients with baseline serum phosphorous level >2.42 mmol/L had a greater reduction in serum phosphate than those with lower baseline serum phosphorous level during colestilan treatment. There was no clear effect of dialysis type; however patients on peritoneal dialysis were few in the main clinical studies.

Considering that in studies A05 and E07, the superiority over placebo was demonstrated in a selected population (about one third of the patients were withdrawn due to lack of efficacy, adverse events etc, prior to randomisation), the applicant was requested to present responder analyses including all patients included in the open label periods in study A05 and E07, counting all patients withdrawing for any reason as non-responders.

The applicant undertook responder analyses for studies MCI-196-A05, MCI-196-E07 and MCI-196-E08 based on reductions of serum P level to ≤ 1.78 mmol/L and/or reductions of at least 0.3 mmol/L, where all patients withdrawing (both during the double-blind period and the open-label period) for any reason were counted as non responders,.

The results showed that for the requested analysis:

- In studies MCI-196-A05 and MCI-196-E07, at the end of the open-label phase (Week 12), the 'worse-case' responder rate was approximately 50%. At the end of the double-blind period (Week 16), colestilan consistently showed higher response rates compared with placebo, with the colestilan group in studies MCI-196 E07 and MCI-196-A05 achieving a responder rate of 43.8% and 50.4% respectively (placebo 26 and 30%, respectively).
- In the MCI-196-E08 trial, the response rates of colestilan from 6 g/day to 15 g/day increased with increasing dose and reached 47.5% for the highest dose, 15 g/day. In concurrence with all other analyses, 3 g/day was ineffective in lowering serum phosphorus. The response rates of most of the colestilan dose groups were significantly higher than placebo according to the 95% confidence intervals.
- Thus overall, this analysis showed a 41-52% responder rate for colestilan using these very strict criteria across all studies, confirming the claimed efficacy over placebo.

In conclusion, the results of the *ad-hoc* analysis show that within the SmPC recommended dose range, a dose-response exists, with 6 g/day showing a response of 43.2% and 15 g/day showing a response of 51.4%.

These analyses therefore demonstrate that even under the stringent conditions applied, substantial percentages of patients consistently show falls in serum phosphorus that have been proven to reduce long-term mortality.

2.5.4. Conclusions on the clinical efficacy

The effect of Colestilan was examined in two similar 12-week, open-label, flexible-dose studies followed by a 4-week double-blind withdrawal period in which the effect was compared to placebo). Treatment with colestilan for 12 weeks reduced serum phosphorus with 0.36 and 0.50 mmol/L, respectively (mean daily dose of 11.5 g and 13.1 g) which are clinically relevant reductions. During the 4-week double-blind withdrawal period, colestilan was superior to placebo. In an additional, fixed dose study (E08), the mean reduction of serum phosphorus from baseline to week 12 as compared to placebo was 0.16, 0.21 and 0.34 mmol/l at doses of 6, 9, 12 +15 g/day respectively. The effect of the highest doses is of clinical relevance.

In one of the flexible dose studies (E07), sevelamer was included as a comparator. The phosphate lowering effect of colestilan was inferior to sevelamer (difference 0.29 mmol/L) according to the pre-specified criteria for this study. The inferior results in study E 07 could partly be explained by the design of the study including a recommended low starting dose and slow dose titration. However, in the extension study E10, patients who were randomised to colestilan or sevelamer in the original study had comparable mean phosphorous levels below 1.78 mmol/L at week 52 (LOCF).

Responder rates during open-label treatment periods in the flexible dose studies showed that approximately 43% of patients treated with colestilan had a serum phosphate of ≤ 1.78 mmol/L and 56 % had serum phosphate ≤ 1.95 mmol/L.

Colestilan significantly lowered the serum calcium x phosphorous product and serum LDL-cholesterol and total cholesterol, as compared to placebo, but did not lower serum triglycerides.

The dropout rate in the open label periods of the flexible dose studies were 31-36%. The most common reasons for dropout were lack of effect, adverse events and withdrawal of consent. In study A05, this could to some extent be a consequence of the recommended low starting dose and slow dose titration. In addition, in study E07, the open label design and a substantial proportion of patients being previously treated with sevelamer (i.e being sevelamer tolerant) may have favoured sevelamer with respect to proportion of patients withdrawing due to adverse events. Further sensitivity analyses have been provided, counting all patients withdrawing for any reason as non-responders. Across studies, 41-52% of subjects treated with colestilan were responders in terms of achieving either 1.78 mmol/L and/or a fall of 0.3 mmol/L which is consistent with the original results in these studies.

The Dialysis outcome and practice pattern study (DOPPS) has suggested that a 0.3 mmol/L lower plasma phosphorous level is significantly associated with lower all-cause mortality and cardiovascular mortality. In the submitted studies, the differences compared to placebo were significant and of clinical relevance (at least 0.3 mmol/L reduction) in all studies. Thus, the phosphorus lowering effect of colestilan is considered to be of clinical relevance.

In summary, MCI-196 experienced about a 30% overall withdrawal rate in the clinical trial setting. The main reasons for the high rate of withdrawals could be a consequence of the study design - namely (1) low starting dose and cautious titration schedule (2) 4-week, double-blind withdrawal period unique to MCI-196 and (3) no restrictions on previous phosphorus-reduction therapy.

2.6. Clinical safety

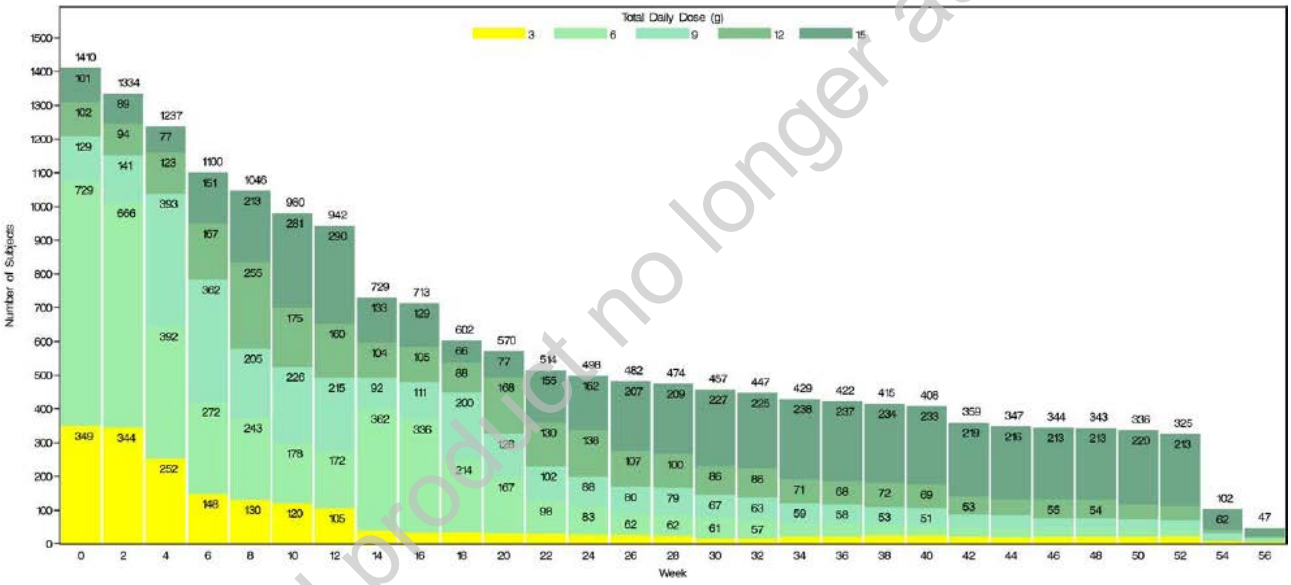
Patient exposure

Safety data from 9 phase 1, 5 phase 2, and 7 phase 3 studies are included in the safety analysis.

A total of 245 healthy volunteers were treated in the phase 1 studies. A total of 1920 patients with CKD Stage 5 on dialysis were enrolled in the phase 2 and 3 studies. Of the phase 2 and 3 study patients, 1410 in total received MCI-196: 1363 patients received MCI-196 alone and 47 patients received MCI-196 plus a calcium-based phosphate binder. A total of 49 patients received calcium-based phosphate binder alone, 169 patients received sevelamer, 131 patients received simvastatin, and 161 patients received placebo.

Based upon ex-factory shipment of the product, the estimated patient exposure in Japan between 1999 and December 2010 is approximately 1.45 million patients.

Figure 11 Summary of allocated total daily dose, all studies, safety population



Adverse events

Safety analyses were performed for each clinical study separately, and also pooled analyses for phase 2, phase 2 and phase 3 clinical studies, respectively. Safety analyses were also done on pooled safety data from all clinical studies with colestilan.

Table 20 Incidence of total Treatment-Emergent Adverse Events (TEAEs) in all clinical studies, safety population

	MCI-196[a] (N=1,410)	Placebo[b] (N=161)	Calcium[c] (N=49)	Sevelamer[d] (N=169)	Simvastatin[e] (N=131)
	Number (%) of Patients with ≥1 TEAE				
Overall	1058 (75.0%) (n=1,410)	73 (45.3%) (n=161)	46 (93.9%) (n=49)	153 (90.5%) (n=169)	93 (71.0%) (n=131)
(number of TEAEs)	5253	174	282	1033	265
	Rate				
Person-years	617.1	25.7	18.4	117.3	41.7
Incidence (person-year rate)	1058 (1.714)	73 (2.844)	46 (2.505)	153 (1.304)	93 (2.232)
Frequency	5253 (8.512)	174 (6.779)	282 (15.355)	1033 (8.804)	265 (6.359)

a) MCI-196 from pooled studies b) Placebo from studies MCI-196-E06 and MCI-196-E08 c) Calcium-based phosphate binder from studies MCI-196-A01/MCI-196-A02, and MCI-196-A03/MCI-196-A04 d) Sevelamer from studies MCI-196-E07/MCI-196-E10 e) Simvastatin from study MCI-196-E11
Person-year = sum of duration of treatment in days of all patients within treatment: Person-year rate = incidence of SOC/Preferred Term divided by person-year

There were no remarkable different incidences in TEAEs between all MCI-196 treated patients and patients with at least 52 weeks of exposure to MCI-196. The incidence of AEs for patients on colestilan was dose dependent.

Table 21 Summary of TEAEs reported by ≥5% of subjects in all groups, SAF, study MCI-196-E08

System Organ Class Preferred Term n(%)	MCI-196 3 g (N=104)	MCI-196 6 g (N=102)	MCI-196 9 g (N=98)	Placebo 9 tablets (N=79)	MCI-196 12 g (N=102)	MCI-196 15 g (N=101)	Pooled Placebo[a] (N=132)	Overall (N=639)
All TEAEs, n (%)	**49 (47.1)**	**44 (43.1)**	**49 (50.0)**	**37 (46.8)**	**55 (53.9)**	**59 (58.4)**	**68 (51.5)**	**324 (50.7)**
Gastrointestinal disorders	**22 (21.2)**	**27 (26.5)**	**27 (27.6)**	**12 (15.2)**	**35 (34.3)**	**41 (40.6)**	**25 (18.9)**	**177 (27.7)**
Nausea	4 (3.8)	9 (8.8)	12 (12.2)	0	20 (19.6)	20 (19.8)	0	65 (10.2)
Diarrhoea	5 (4.8)	5 (4.9)	6 (6.1)	5 (6.3)	4 (3.9)	5 (5.0)	7 (5.3)	32 (5.0)
Vomiting	2 (1.9)	4 (3.9)	8 (8.2)	2 (2.5)	12 (11.8)	6 (5.9)	2 (1.5)	34 (5.3)
Dyspepsia	4 (3.8)	8 (7.8)	7 (7.1)	1 (1.3)	5 (4.9)	9 (8.9)	1 (0.8)	34 (5.3)
Abdominal distension	0	3 (2.9)	2 (2.0)	1 (1.3)	7 (6.9)	6 (5.9)	4 (3.0)	22 (3.4)
Abdominal pain upper	1 (1.0)	3 (2.9)	0	1 (1.3)	3 (2.9)	6 (5.9)	2 (1.5)	15 (2.3)
Constipation	3 (2.9)	1 (1.0)	6 (6.1)	0	0	5 (5.0)	2 (1.5)	17 (2.7)
Metabolism and nutrition disorders	**8 (7.7)**	**5 (4.9)**	**4 (4.1)**	**5 (6.3)**	**12 (11.8)**	**7 (6.9)**	**9 (6.8)**	**45 (7.0)**
Hypocalcaemia	2 (1.9)	2 (2.0)	3 (3.1)	2 (2.5)	6 (5.9)	2 (2.0)	3 (2.3)	18 (2.8)
Decreased appetite	2 (1.9)	1 (1.0)	1 (1.0)	0	6 (5.9)	4 (4.0)	1 (0.8)	15 (2.3)
Vascular disorders	**5 (4.8)**	**8 (7.8)**	**7 (7.1)**	**1 (1.3)**	**5 (4.9)**	**7 (6.9)**	**4 (3.0)**	**36 (5.6)**
Hypertension	3 (2.9)	6 (5.9)	7 (7.1)	1 (1.3)	2 (2.0)	5 (5.0)	4 (3.0)	27 (4.2)

Note that the source table contains additional summary data that are not presented here. Subjects experiencing more than 1 AE within each preferred term and system organ class were only counted once.
Preferred terms reported by ≥5% of subjects in any treatment group (MCI-196 3 g, 6 g, 9 g, 12 g, 15 g; placebo 9 tablets, pooled placebo). SOCs with no preferred terms reported by ≥5% of subjects in any treatment group have not been included. a Includes placebo 9 tablets, 12 tablets and 15 tablets.

Gastrointestinal disorders: The most frequent TEAEs were GI disorders. Patients may experience constipation, or existing constipation may be aggravated, due to bulk of the drug substance taken, as is also the case with other substances with the same mechanism of action. The incidence of constipation as a TEAE was 6.4% (90/1410 patients) and that of treatment-related constipation was 4.5% (64/1410 patients). Constipation led to discontinuation of study medication in 9 patients on MCI-196 (0.6%). All but one of these TEAEs were considered possibly or probably related to study treatment. Constipation resolved without sequelae in 8 patients and with sequelae in 1 patient. One

case of constipation was reported as a serious TEAE. It was not considered to be related to MCI-196. The frequencies of intestinal obstruction and/or perforation among recipients of MCI-196 were: ileus (0.1%; 2 patients), intestinal obstruction (0.1%; 1 patient) and ileal perforation (0.1%; 1 patient). The intestinal obstruction (moderate; leading to interruption of study medication) occurred in the same patient who subsequently developed ileal perforation. This patient developed peritonitis which resulted in death. None of the events in this patient were considered to be related to MCI-196. The two cases of ileus did not lead to discontinuation of study medication.

Haemorrhage: There were 132 TEAEs of bleeding reported by 98 patients identified by analysing standardised MedDRA Queries (SMQs) haemorrhage terms. Among these 132 TEAEs, 47.0 % were mild, 40.9 % were moderate and 12.1 % were severe. Eight events (6.1 %) were considered possibly or probably related to MCI-196 treatment. There was no more bleeding or anaemia in colestilan treated patients than in patients treated with sevelamer or calcium-based phosphate binder. A non-clinical study with MCI-196 showed an increase in plasma prothrombin time and bleeding tendency in rats. In the clinical trials, vitamin K was slightly decreased and mean prothrombin time slightly increased with colestilan while INR was unchanged. In trial E06, the difference in APTT from baseline to week 12 was -2.1 s for the 15 g colestilan group, -6.1 s for the corresponding placebo group; difference in prothrombin time from baseline to week 12 was 0.54 s and 0.03 s, difference in vitamin K from baseline to week 12 was -0.49 nmol/l and -0.32 nmol/l, respectively.

Gastrointestinal haemorrhage: Five recipients of MCI-196 experienced 32 TEAEs involving GI bleeding. No action was required for 21 of these events (65.6%), treatment was interrupted for 2 (6.3%), and discontinued for 9 (28.1%). The majority of events (81.3%) resolved without sequelae, 9.4% resolved with sequelae, 6.3% were reported to be continuing, and the outcome was unknown for 3.1%. Among 6 events considered possibly or probably related to MCI-196, 4 led to treatment discontinuation and 2 required no action; 5 resolved without sequelae and 1 resolved with sequelae. Twelve of the events (37.5%) were serious, including 2 that were considered possibly or probably related to MCI-196 treatment: 1 case of ‘duodenal ulcer haemorrhage’ (for which treatment was discontinued, and which resolved with sequelae); and 1 case of ‘gastrointestinal haemorrhage’ (for which treatment was discontinued, and which resolved with no sequelae). Among the 32 TEAEs involving GI bleeding, which were experienced by recipients of MCI-196 in the phase 2 and phase 3 studies, 10 (31.3%) were mild, 19 (59.4%) were moderate and 3 (9.4%) were severe. Six events were considered to be possibly or probably related to MCI-196 treatment: 2 cases of ‘haemorrhoidal haemorrhage’, and 1 case each of ‘duodenal ulcer haemorrhage’, ‘gastrointestinal haemorrhage’, ‘rectal haemorrhage’ and ‘haematochezia’. The incidence of GI haemorrhage did not increase with length of treatment.

Table 22 Summary of subjects with TEAEs reported by ≥5% of subjects in either treatment group, SAF1 and SAF2, study MCI-196-E07

n (%)	Open-label Period (SAF1)[a]			Placebo-controlled Withdrawal Period (SAF2)[b]		
System Organ Class Preferred Term	MCI-196 (N=162)	Sevelamer (N=169)	Overall (N=331)	MCI-196 (N=50)	Placebo (N=53)	Overall (N=103)
At least 1 TEAE	136 (84.0)	131 (77.5)	267 (80.7)	21 (42.0)	24 (45.3)	45 (43.7)
Gastrointestinal disorders	**79 (48.8)**	**60 (35.5)**	**139 (42.0)**	**6 (12.0)**	**3 (5.7)**	**9 (8.7)**
Vomiting	27 (16.7)	9 (5.3)	36 (10.9)	1 (2.0)	0	1 (1.0)
Diarrhoea	21 (13.0)	16 (9.5)	37 (11.2)	2 (4.0)	1 (1.9)	3 (2.9)
Nausea	15 (9.3)	12 (7.1)	27 (8.2)	0	1 (1.9)	1 (1.0)
Dyspepsia	13 (8.0)	6 (3.6)	19 (5.7)	0	1 (1.9)	1 (1.0)
Constipation	13 (8.0)	11 (6.5)	24 (7.3)	2 (4.0)	0	2 (1.9)
Abdominal pain upper	10 (6.2)	8 (4.7)	18 (5.4)	1 (2.0)	0	1 (1.0)
Injury, poisoning and procedural complications	**24 (14.8)**	**25 (14.8)**	**49 (14.8)**	**3 (6.0)**	**3 (5.7)**	**6 (5.8)**
Haemodialysis-induced symptom	6 (3.7)	9 (5.3)	15 (4.5)	3 (6.0)	0	3 (2.9)
Vascular disorders	**16 (9.9)**	**21 (12.4)**	**37 (11.2)**	**1 (2.0)**	**2 (3.8)**	**3 (2.9)**
Hypertension	12 (7.4)	12 (7.1)	24 (7.3)	1 (2.0)	1 (1.9)	2 (1.9)
Blood and lymphatic system disorders	**9 (5.6)**	**8 (4.7)**	**17 (5.1)**	**1 (2.0)**	**4 (7.5)**	**5 (4.9)**
Anaemia	8 (4.9)	7 (4.1)	15 (4.5)	0	3 (5.7)	3 (2.9)

Note that the source tables contain additional summary data that are not presented here.
Subjects experiencing more than 1 adverse event within each preferred term and system organ class were only counted once.
SOCs with no preferred terms reported by ≥5% of subjects in either treatment group have not been included.
a Open-label Period Preferred terms reported by ≥5% of subjects in either treatment group, or included for the withdrawal period.
b Placebo-controlled Withdrawal Period Preferred terms reported by ≥5 subjects in either treatment group or included for the open-label period.

Serious adverse event / deaths / other significant events

Deaths: No deaths occurred in any subjects in the phase 1 studies. A total of 41/1920 patients (2.1%) in pooled phase 2 and 3 studies died: 31/1410 patients (2.2%) treated with MCI-196, 5/169 patients (3.0%) treated with sevelamer, 3/161 patients (1.9%) on placebo and 2/131 patients (1.5%) treated with simvastatin. The applicant provided listing of deaths for all treatments in the clinical studies. The majority of deaths were predominantly due to cardiovascular or respiratory events. The death of 1 patient (acute pulmonary oedema) was considered possibly related to study treatment; this patient was in the simvastatin treatment arm of study MCI-196-E11. The deaths of 3 patients were considered remotely related to study medication: 1 patient on placebo (cardiac arrest) and 2 patients on MCI-196 (metastatic prostate cancer; multi-organ failure). The deaths of all of the other patients were not considered by the investigator to be related to study treatment. One case of retroperitoneal haematoma and one case of haemorrhagic stroke occurred in patients on colestilan treatment; these cases were not by the investigator considered to be related to treatment.

Table 23 Incidence of TEAEs by severity, all studies, safety population

Exposure	Placebo[a] (N=161)	MCI-196[b] (N=1,410)	Sevelamer[c] (N=169)	Calcium[d] (N=49)	Simvastatin[e] (N=131)
	Number (%) of Patients with ≥1 TEAE				
Overall	73 (45.3%)	1058 (75.0%)	153 (90.5%)	46 (93.9%)	93 (71.0%)
Mild	39 (24.2%)	366 (26.0%)	54 (32.0%)	10 (20.4%)	42 (32.1%)
Moderate	25 (15.5%)	520 (36.9%)	72 (42.6%)	21 (42.9%)	48 (36.6%)
Severe	9 (5.6%)	172 (12.2%)	27 (16.0%)	15 (30.6%)	3 (2.3%)

a)Placebo from studies MCI-196-E06 and MCI-196-E08 b) MCI-196 from pooled studies c) Sevelamer from studies MCI-196-E07/MCI-196-E10 d) Calcium-based phosphate binder from studies MCI-196-A01/MCI-196-A02, and MCI-196-A03/MCI-196-A04 e) Simvastatin from study MCI-196-E11

Serious adverse events: Two SAEs occurred in the phase 1 studies, both in study MCI-196-J18. One of these subjects (on MCI-196 6 g/day) experienced severe, treatment-related constipation. Treatment was withdrawn and she was hospitalised 2 days later to treat an anal fissure, which was exacerbated by the constipation. The other subject, in the placebo group, underwent surgery to treat a shunt stenosis that was considered not related to treatment.

Laboratory findings

Haematology parameters were not significantly influenced by colestilan. Anaemia was common in this dialysis population, as expected.

Biochemistry parameters: Mean (SD) change from baseline to last assessment of *uric acid* was greater with MCI-196 (-27.5 [79.39] µmol/L) and sevelamer (-24.9 [75.73] µmol/L) compared with placebo (8.5 [71.70] µmol/L), although the data were highly variable.

ALP increased in clinical trials with MCI-196 (16.1 [53.0] U/L) and sevelamer (36.2 [55.6] U/L) compared with placebo (4.2 [19.4] U/L). There were no clinically important changes in *bilirubin, ALT, AST or GGT*. *PTH* was increased during calcium-based phosphate binder washout in the clinical trials and then decreased by MCI-196 or sevelamer treatment.

Mean (SD) change from baseline to last assessment of *chloride* was greater with MCI-196 (2.1 [4.31] mmol/L) and sevelamer (2.1 [3.83] mmol/L) than with placebo (0.1 [3.41] mmol/L). Mean (SD) *bicarbonate* decreased after baseline with MCI-196 (-0.85 [3.917] mmol/L) whereas there was an increase with placebo (0.41 [3.354] mmol/L) and no change with sevelamer (-0.08 [3.612] mmol/L). MCI-196 releases counter ions of chloride in the GI tract and it is therefore expected that chloride would increase and bicarbonate decrease. Dialysis corrects the ion balance.

While an increase in plasma prothrombin time was observed in non-clinical studies in rats, the impact of colestilan on *coagulation parameters* in clinical studies was minor.

Vitamins: Colestilan is an anion exchange resin, and as such has the potential to inhibit absorption of fat soluble vitamins in the GI tract. In the clinical studies, there were possible decreases in vitamin D, vitamin D3, vitamin K and folic acid. However, these values are borderline and within normal limits.

Safety in special populations

Age: Subgroup analysis was performed for age, gender and race. 170 patients ≥ 65 years and 49 patients ≥ 75 years received the drug for at least 12 weeks in clinical studies. The proportions of patients with TEAEs, serious TEAEs, treatment-related TEAEs and TEAEs that led to discontinuation were higher in patients aged ≥65 years compared with in patients aged <65 years overall. There were no important differences in the incidence and nature of the TEAEs in patients aged <65 and ≥65 years treated with MCI-196.

Gender: In the pooled safety population, there were 807 males and 603 females. The total incidence of TEAEs was 72.4 % of patients for males and 78.6 % of patients for females treated with MCI-196 in total. There were no important differences in the incidence and nature of the TEAEs for male and female patients.

Race: Most patients treated with colestilan were Caucasian or white (72.6 %), 15.3 % were black or African American and 9.3 % were Asian. The proportion of black and African American patients with TEAEs was higher than in Caucasian and White patients (31.0% vs. 16.3%), particularly in the subset of patients exposed to treatment for ≥52 weeks (62.1% vs. 19.8%). There were no individual serious TEAEs that accounted for this difference. Race is partially confounded with region; regions have different reporting rates.

Diabetes: There were no differences between patients with and without diabetes mellitus in the proportions of patients with TEAEs overall. A higher proportion of patients with diabetes mellitus who were treated with MCI-196 had serious TEAEs (28.5%) compared with patients without diabetes mellitus (14.7%). This was also true for patients treated with sevelamer (51.0% and 24.6% of patients with and without diabetes mellitus, respectively) or with calcium based phosphate binder. There were no important differences in the incidence and nature of the TEAEs for patients with and without diabetes mellitus treated with MCI-196. The most frequent serious TEAEs were infections and infestations followed by cardiac disorders in patients both with and without diabetes mellitus.

Geographic region: The proportion of patients treated with MCI-196 who had TEAEs varied across the geographic regions: 91.5% in Western Europe (n=106), 82.9% in North America (n=449), 75.6% in Russia (n=279), 68.6% in Asia/Other (n=121), 67.2% in Ukraine (n=58), and 64.5% in Eastern Europe (excluding Russia and Ukraine; n=397). However, the most frequent TEAEs in every geographic region were GI disorders and usually included nausea, vomiting, diarrhoea, constipation, dyspepsia and abdominal pain.

Immunological events

The applicant has not separately accounted for immunological events. In the SmPC, section 4.8, pruritus, rash and urticaria are mentioned among adverse reactions reported as uncommon (< 1% of patients).

Safety related to drug-drug interactions and other interactions

Five phase 1 drug interaction studies were conducted in healthy volunteers. In short, there were limited effects on bioavailability of co-administered drugs, however the evaluation of these studies is hampered by the low doses of colestilan administered in the studies and by dosing in relation to meals and in relation to interacting drug not being the same as recommended in the present SmPC proposal. Therefore, relevant information has been introduced into section 4.5 of the SmPC.

Discontinuation due to adverse events

Table 24 Incidence of discontinuations due to TEAEs by treatment (≥1% patients treated with MCI-196), all studies, safety population

System Organ Class/ Preferred Term	Placebo[a] (N=161)	MCI-196[b] Total (N=1,410)	Sevelamer[c] (N=169)	Calcium[d] (N=49)	Simvastatin[e] (N=131)
	Number (%) of Patients				
Patients discontinued due to ≥1 TEAE	6 (3.7%)	237 (16.8%)	26 (15.4%)	7 (14.3%)	10 (7.6%)
Gastrointestinal disorders	**3 (1.9%)**	**146 (10.4%)**	**12 (7.1%)**	**3 (6.1%)**	**6 (4.6%)**
Nausea	0	48 (3.4%)	4 (2.4%)	2 (4.1%)	3 (2.3%)
Vomiting	0	38 (2.7%)	4 (2.4%)	2 (4.1%)	0
Diarrhoea	2 (1.2%)	31 (2.2%)	3 (1.8%)	0	0
Abdominal pain upper	0	18 (1.3%)	2 (1.2%)	0	1 (0.8%)
Dyspepsia	1 (0.6%)	18 (1.3%)	1 (0.6%)	0	1 (0.8%)
Abdominal pain	1 (0.6%)	14 (1.0%)	3 (1.8%)	0	1 (0.8%)
Surgical and medical procedures	**0**	**17 (1.2%)**	**8 (4.7%)**	**0**	**0**
Renal transplant	0	16 (1.1%)	8 (4.7%)	0	0

a)Placebo from MCI-196-E06 and MCI-196-E08 b) MCI-196 from pooled studies c) Sevelamer from studies MCI-196-E07 and MCI-196-E10 d) Calcium-based phosphate binder from studies MCI-196-A01, MCI-196-A02, MCI-196-A03 and MCI-196-A04 e) Simvastatin from study MCI-196-E11

Post marketing experience

The product has been marketed in Japan since 1999, with the indication "Treatment of hypercholesterolaemia and familial hypercholesterolaemia". The recommended dose in Japan is 3 g (maximum dose 4 g) daily, given as a divided dose before breakfast and supper. The applicant has presented some post marketing safety data from Japan, and also provided the 6th PSUR report. Hypertriglyceridaemia was added as an uncommon adverse reaction to the applicant core safety information dated 13 May 2011.

In total, there have been 8 cases of rhabdomyolysis reported, 3 cases of cerebral infarction, and 2 cases of platelet count decreased. Four cases of heapatobiliary disorders were reported. The other unlisted serious adverse drug reaction reports are single episodes and include 9 GI disorders, including duodenal ulcer haemorrhage and enterocolitis. Patient exposure was estimated as the total quantity distributed from 1 April 2010 to 31 March 2011 (42799 kg)/average total dose per patient (372.7 g) and the estimated number of patients exposed during this period is calculated to be 114835. No cases reported by a non-healthcare professional were received during the reporting period.

2.6.1. Discussion on clinical safety

Clinical studies with colestilan have included a sufficient number of patients and a sufficient number of patients have been exposed to an adequate dose of the drug for at least 12 months, according to the rules applicable for a drug intended for long time medication in the ICH guideline CPMP/ICH/375/95. Patients in peritoneal dialysis constituted a minority of the study populations: 5.8 % (82 patients) of the colestilan treated patients and a comparable share of patients treated with placebo, sevelamer and calcium-containing phosphate binder, while they constituted 20 % of patients in the group treated with simvastatin. A majority of patients were caucasian, and were nondiabetics. The inhomogenity concerning populations was mostly related to the different geographic regions where the different studies were conducted. Since the subgroup analyses for safety did not indicate any differences of importance related to the different subgroups, the results can be considered valid for the entire included patient population.

As a whole, the pattern of adverse events for colestilan was as expected for a nonabsorbable anion exchange resin which is locally active in the gastrointestinal tract.

The rate of adverse events increases with the dose of colestilan. *Gastrointestinal disorders* was the most common type of TEAES and was about three times as common with colestilan as with placebo (45.1 % for colestilan, 17.4 % for placebo, and 53.8 % for sevelamer) in the pooled safety population in colestilan clinical studies. In the direct comparison with sevelamer, a higher incidence of gastrointestinal events was seen for colestilan (48.8 % versus 35.5 %). However, a substantial proportion of patients was previously treated with sevelamer and could be considered as sevelamer tolerant. One case of intestinal obstruction led to intestinal perforation with fatal outcome. Patients with severe GI disorders were not included in the studies and are recommended not to use colestilan. A warning has been included in section 4.4 of the SmPC on the risk of intestinal obstruction and ileus/subileus. The cases of intestinal obstruction are mentioned in section 4.8 of the SmPC.

In the fixed dose study MCI-196-E08, the total rate of TEAEs increased with increasing dose and was higher than placebo in the highest dose groups. In the 15 mg daily group, gastrointestinal disorders was twice as common as in the pooled placebo group. The increase over time of TEAEs was no greater for colestilan than for sevelamer during a one year study period in a limited number of patients. A higher incidence of TEAEs in patients aged 65 and over is not unexpected. Differences in rates of TEAEs between races can possibly be explained by regional reporting differences.

Infection and infestation TEAEs were significantly more common for all types of phosphate binders than for placebo or simvastatin. *Injury, poisoning and procedural complications* was more common with all active treatments than with placebo, and most common with sevelamer and with calcium-based phosphate binder. *Metabolism and nutrition disorders* was more common with all types of phosphate binders than with simvastatin or with placebo. The same was true for most other types of TEAES. Exceptions were *Skin and subcutaneous disorders*, that were more common with sevelamer and calcium-based phosphate binders than with the other treatments. *Vascular disorders* were more common with sevelamer than with the other phosphate binders. *Musculoskeletal and connective tissue disorders* were more common with sevelamer and with calcium-based phosphate binders than with other treatments. The applicant has not separately accounted for *immunological events*. In the SmPC, section 4.8, pruritus, rash and urticaria are mentioned among adverse reactions reported as uncommon (< 1% of patients).

The slightly disturbed pattern of some bleeding parameters in patients treated with colestilan in clinical studies did not translate into a generally increased bleeding incidence. However, the applicant should further analyse all cases of *haemorrhage* and of *gastrointestinal haemorrhage* in clinical studies with colestilan. With the background of preclinical positive findings and laboratory findings in clinical studies, haemorrhagic diathesis and gastrointestinal haemorrhage has been classed as *Identified risks* in the *Risk Management Plan* for this product. Further, serum vitamin levels of a number of vitamins decreased during colestilan treatment. Vitamin levels did not decrease further during 1 year of treatment. Whether these moderately lower vitamin levels are of importance is at present not known. Vitamin deficiency has been included as a *Potential Risk* in the *Risk Management Plan.*

Altogether, 0.9 % of patients treated with colestilan, 0.6 % of patients treated with sevelamer, 2.0 % of patients treated with calcium-based phosphate binder, 2.3 % of patients treated with simvastatin, and 0% of placebo treated patients had treatment-related emergent serious adverse events in pooled colestilan studies. Elevations of hepatocellular enzymes were demonstrated in a rat toxicology study and liver disorder is therefore considered to be a *Potential Risk* in the Risk Management Plan.

2.6.2. Conclusions on the clinical safety

As a whole, the type of adverse events for colestilan was as expected for a nonabsorbable anion exchange resin which is locally active in the gastrointestinal tract. The incidence of adverse effects was

dose dependent. The most common adverse events reported in clinical studies were gastrointestinal events, such as nausea, vomiting, dyspepsia, diarrhoea, constipation etc. Gastrointestinal adverse events were more common with colestilan than with sevelamer in the comparative study but not in the total safety population. Because potential interference with the absorption of a number of vitamins, a risk exists of decreased levels of these vitamins in serum, and impaired function of related functions, including coagulation and this may cause bleedings. Bleeding risk, especially the risk of gastrointestinal bleedings is a concern and it has been included in the RMP of the product.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 25 Summary of the risk management plan

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
Important Identified Risks		
Constipation	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.4 The safety and efficacy of BindRen has not been studied in patients with: • Severe gastrointestinal disorders such as **chronic or severe constipation**, intestinal stenosis, intestinal diverticulum, sigmoid colitis, gastrointestinal ulcers, or recent major gastrointestinal surgery Therefore, the use of BindRen is not recommended in patients with these disorders. Intestinal obstruction and ileus/subileus In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with BindRen. **Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with BindRen. In patients who develop severe constipation or other severe gastrointestinal symptoms alternative**

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
		treatment may need to be considered.
Intestinal obstruction / Ileus	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.4 Intestinal obstruction and ileus/subileus In very rare cases, **intestinal obstruction and ileus/subileus** have been observed in patients during treatment with BindRen. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with BindRen. In patients who develop severe constipation or other severe gastrointestinal symptoms alternative treatment may need to be considered.
Drug interaction	Both routine and additional pharmacovigilance activities will be conducted. The additional pharmacovigilance activity will consist of carrying out a post-authorisation drug-drug interaction study, with an objective to assess the effects of colestilan treatment on the pharmacokinetic (PK) profile of a suitable victim drug and active metabolite when administered in the absence of, or at one of three time points (1 hour prior to, at the same time as, or 3 hours after) in relation to a 5 g dose of colestilan in healthy subjects.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.5 **Interaction with other medicinal products and other forms of interaction** BindRen is not absorbed from the gastrointestinal tract but may affect the bioavailability or absorption rate of other medicinal products. In addition, reduced bioavailability of other medicinal products by changes in enterohepatic circulation, for example steroid hormones with potential impairment of the effectiveness of oral contraceptives, have been reported for medicinal products with a similar mechanism of action to BindRen. When administering any medicinal product where a reduction in the bioavailability could have a clinically relevant effect on safety or efficacy, the medicinal product should be administered at least 1 hour before, or 3 hours after BindRen. Concommitant treatment with medicinal products with a narrow therapeutic window requires close monitoring of drug concentrations or adverse events, on initiation or dose-adjustment of either BindRen or the concommitant medicinal product.

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
		Interaction studies have been conducted in healthy volunteers. Interactions have not been studied at doses >9 g daily, and greater interaction effects at higher doses of BindRen cannot be excluded. Single dose interaction studies demonstrated that the bioavailability of ciprofloxacin, warfarin and enalapril were not affected when co-administered with BindRen (6-9 g/day). BindRen lowered the bioavailability of digoxin by 16% and C_{max} by 17%, and the C_{max} of enalapril by 27%. Due to the high in vitro binding potential between BindRen and levothyroxine, closer monitoring of thyroid stimulating hormone (TSH) levels in patients receiving BindRen and levothyroxine is recommended. No in vivo data are available on the possible interaction of BindRen on the absorption of the immunosuppressant medicinal products mycophenolate mofetil, ciclosporin or tacrolimus. However, decreased blood concentrations have been reported for medicinal products with a similar mechanism of action to BindRen. Caution should be exercised when prescribing BindRen to patients receiving immunosuppressants. Patients with seizure disorders were excluded from clinical trials with BindRen. Caution should be exercised when prescribing BindRen to patients also taking anti-seizure medicinal products.
Gastrointestinal haemorrhage	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.4 The safety and efficacy of BindRen has not been studied in patients with: • Severe gastrointestinal disorders such as chronic or severe constipation, intestinal stenosis, intestinal diverticulum, sigmoid colitis, gastrointestinal ulcers, or recent major gastrointestinal surgery Therefore, the use of BindRen is not recommended in patients with these disorders.

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
		Gastrointestinal Haemorrhage Caution should be exercised when treating patients with conditions which predispose to GI haemorrhage, such as recent history of GI haemorrhage, GI ulcers, gastritis, diverticulosis, colitis and haemorrhoids.
Important potential risks		
Intestinal perforation	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	No additional risk minimisation activities are planned at present.
Haemorrhagic diathesis	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.4 Fat-soluble vitamins BindRen did not induce any clinically relevant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to 1 year. **However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption syndromes and patients treated with coumarin anticoagulants (e.g. warfarin)**. In these patients, monitoring vitamin A, D and E concentrations or assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.
Liver disorder	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, the SmPC specifies: Section 4.2 Special populations **Severe hepatic impairment** Patients with severe hepatic impairment were excluded from clinical studies. Therefore, the use of BindRen is not recommended in patients with severe hepatic impairment (see also section 4.4). No data are available

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
		Section 4.4 The safety and efficacy of BindRen has not been studied in patients with: • **Severe hepatic impairment** Therefore, the use of BindRen is not recommended in patients with these disorders.
Off-label use (use in pre-dialysis CKD patients)	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, the SmPC specifies: Section 4.2 <u>Special populations</u> <u>Renal impairment</u> BindRen is indicated for use in patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis. No data on the use of BindRen in **pre-dialysis patients** are available.
Difficulty in swallowing tablets	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness. Section 4.2 <u>Method of administration</u> BindRen is for oral use. Tablets should be taken whole. Granules should be taken whole as one dose from the sachet. The daily dose of BindRen tablets/granules should be taken in 3 equally divided doses with or immediately after meals with a sufficient amount of water **to aid swallowing.** Section 4.4: The safety and efficacy of BindRen has not been studied in patients with: • **Dysphagia or swallowing disorders** Therefore, the use of BindRen is not recommended in patients with these disorders.
Diverticulitis	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, the SmPC specifies: Section 4.4: The safety and efficacy of BindRen has not been studied in patients with: • Severe gastrointestinal disorders such as chronic

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
		or severe constipation, intestinal stenosis, **intestinal diverticulum**, sigmoid colitis, gastrointestinal ulcers, or recent major gastrointestinal surgery. Therefore, the use of BindRen is not recommended in patients with these disorders. <u>Gastrointestinal Haemorrhage</u> Caution should be exercised when treating patients with conditions which predispose to GI haemorrhage, such as recent history of GI haemorrhage, GI ulcers, gastritis, **diverticulosis**, colitis and haemorrhoids. <u>Intestinal obstruction and ileus/subileus</u> In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with BindRen. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with BindRen. In patients who develop severe constipation or other severe gastrointestinal symptoms alternative treatment may need to be considered.
Changes in serum chloride and bicarbonate levels	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, the SmPC specifies: Section 4.4: BindRen binds phosphate and bile acid, with the release of chloride which is available for systemic absorption. Changes in systemic ion balance with an increase in chloride and decrease in bicarbonate are therefore possible. However, BindRen did not induce any clinically relevant change in chloride and bicarbonate on treatment for up to one year.
Important missing information		

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
Use in pregnant and lactating women	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, these risks are addressed appropriately in the SmPC, in order to promote awareness: Section 4.6 BindRen is not absorbed and is not systemically available. No direct effects of Bindren are thus anticipated. However, other effects of BindRen may affect **pregnant and breast-feeding women** or influence fertility, see sections 4.4 and 4.5. **Pregnancy** No data are available to assess the safety and efficacy in pregnant women. Patients that become pregnant and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4. **Breast-feeding** No data are available to assess the safety and efficacy in breast-feeding women. Patients that breast-feed and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.
Effects on fertility	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, these risks are addressed appropriately in the SmPC, in order to promote awareness: Section 4.6 BindRen is not absorbed and is not systemically available. No direct effects of Bindren are thus anticipated. However, other effects of BindRen may affect pregnant and breast-feeding women or **influence fertility**, see sections 4.4 and 4.5. Fertility No data are available to assess the potential influence of BindRen on **fertility**
Use in children	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.2 Special populations **Paediatric population** The safety and efficacy of BindRen in children and adolescents aged under 18 years has not yet been

Safety concern	Proposed pharmaco-vigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
		established. No data are available.
Use in patients with severe hepatic impairment	Routine pharmacovigilance activities will be conducted. No additional pharmacovigilance activities are planned at present.	As a routine risk minimisation activity, this risk is addressed appropriately in the SmPC, in order to promote awareness: Section 4.2 Special populations **Severe hepatic impairment** Patients with severe hepatic impairment were excluded from clinical studies. Therefore, the use of BindRen is not recommended in patients with severe hepatic impairment (see also section 4.4). No data are available. Section 4.4 The safety and efficacy of BindRen has not been studied in patients with: • **Severe hepatic impairment** Therefore, the use of BindRen is not recommended in patients with these disorders.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The effect of colestilan was examined in two similar 12-week, open-label, flexible-dose studies followed by a 4-week double-blind withdrawal period (comparison to placebo) and in one double-blind, 12-week fixed-dose study with five colestilan groups (3, 6, 9, 12 and 15 g/day) and placebo.

In the flexible dose studies, mean serum phosphorus level at baseline was 2.33 and 2.44 mmol/L, respectively. Treatment with colestilan for 12 weeks reduced serum phosphorus with 0.36 and 0.50 mmol/L, respectively (mean daily dose of 11.5 g and 13.1 g). During the 4-week double-blind withdrawal period, colestilan was superior to placebo with respect to serum phosphorus control.

In the fixed dose study, the mean reduction from baseline to week 12 as compared to placebo was 0.16, 0.21, 0.19 and 0.37 mmol/l at 6, 9, 12 and 15 g/day respectively.

In one of the flexible dose studies, sevelamer was included as a comparator. The phosphate lowering effect of colestilan was inferior to sevelamer (difference 0.29 mmol/L). However, in the extension study E10, patients who were randomised to colestilan or sevelamer in the original study had comparable mean phosphorous levels below 1.78 mmol/L at week 52 (LOCF).

Responder rates during open label treatment periods in the flexible dose studies showed that approximately 43 % of patients treated with colestilan had a serum phosphate of ≤ 1.78 mmol/L and 56 % had serum phosphate ≤ 1.95 mmol/L. Responder rates for the comparator sevelamer was 67.7 and 78.7 % using the same responder criteria (placebo 26 and 30%, respectively).

Colestilan significantly lowered the serum phosphorus level, serum calcium x phosphorous product and serum LDL-cholesterol and total cholesterol, as compared to placebo, but did not lower serum triglycerides.

Uncertainty in the knowledge about the beneficial effects

The dropout rate in the flexible dose studies was 31-36%, and higher for colestilan than for sevelamer in study E07. The most common reasons for dropout were lack of effect, adverse events and withdrawal of consent. In study A05, this could to some extent be a consequence of the recommended low starting dose and slow dose titration. In addition, in study E07, the open label design and a substantial proportion of patients being previously treated with sevelamer (i.e being sevelamer tolerant) may have favoured sevelamer with respect to withdrawals due to adverse events. Further sensitivity analyses have been provided, counting all patients withdrawing for any reason as non-responders. Across studies, 41-52% subjects were responders in terms of achieving either 1.78 mmol/L and/or a fall of 0.3 mmol/L.

The results of study E08 indicate some uncertainties concerning the effect of the 6 and 12 g dose. The Applicant has performed an ad hoc sensitivity analysis in patients whose Visit 6 phosphorus level was ≥1.95 mmol/L and showed ≥15% increase from pre-washout level. These results indicate an appropriate dose response for all groups. Theoretically, a combination with a calcium based phosphorous binder could be advantageous, as such a combination could possibly be efficacious and improve the safety profile. However, studies with the combination of calcium acetate and colestilan were small and the results were inconsistent in determining whether or not MCI-196 added to the effect achieved by the calcium-based binders.

Risks

Unfavourable effects

Colestilan is a non-absorbable, non calcium containing, anion exchange resin which is locally active in the gastrointestinal tract. Thus, the expected safety profile includes GI AEs and potentially also bleedings due to mechanical reasons or impaired absorption of vitamin K.

The rate of adverse events increases with the dose of colestilan. *Gastrointestinal disorders* was the most common type of TEAES and was about three times as common with colestilan as with placebo (45.1 % for colestilan, 17.4 % for placebo, and 53.8 % for sevelamer) in the pooled safety population in colestilan clinical studies. In the direct comparison with sevelamer, a higher incidence of gastrointestinal events was seen for colestilan (48.8 % versus 35.5 %). However, a substantial proportion of patients was previously treated with sevelamer and could be considered as sevelamer tolerant. One case of intestinal obstruction led to intestinal perforation with fatal outcome. Patients with severe GI disorders were not included in the studies and are recommended not to use colestilan.

Bowel obstruction is a contraindication, as reflected in the SmPC, in line with the recommendations for similar products.

In all patients receiving colestilan, 98 patients (6.95%) experienced haemorrhage, (including all GI haemorrhages) versus 26 patients (15.38%) treated with sevelamer. In all studies, there were 25 (1.77%) patients treated with MCI-196 who experienced GI bleeding, and for sevelamer 3 patients, (1.78%).

As a whole, the pattern of adverse events for colestilan was as expected for a non-absorbable anion exchange resin which is locally active in the gastrointestinal tract.

Uncertainty in the knowledge about the unfavourable effects

Adverse events considered by the investigator to be dialysis related were not reported in clinical studies, which may make the AE incidences reported more uncertain. However, since all serious adverse events were captured this is acceptable.

In general, withdrawal rates were high in phase 3 studies (in study MCI-196-E07 withdrawal rate was 36.4% in the colestilan group and 18.7% in the sevelamer group). The most common reason for study withdrawal was adverse events (17.0 % of patients on colestilan versus 5.8 % of patients on sevelamer in study E07). Factors such as the open-label nature of the study, the non-symmetrical design (no double-blind phase for sevelamer), the cautious dose titration for colestilan versus the variable starting dose for sevelamer, and the randomisation of patients previously on sevelamer could be potential sources of bias that may favour sevelamer.

Colestilan is an anion exchange resin, and as such has the potential to inhibit absorption of fat soluble vitamins in the GI tract. In the clinical studies, there were small decreases in vitamin D, vitamin D3, vitamin K and folic acid, however, within normal values.

It is not known whether a potential impairment of absorption of vitamin K could impair coagulation to a clinically relevant extent in sensible patients or after very long time treatment with colestilan. However, current analyses of bleeding do not indicate an increased risk compared to sevelamer. Further, the background incidence of bleedings in the target population is rather high (at least 3% according to literature). Hemorrhagic diathesis is included in the RMP as an important potential risk.

Gastrointestinal bleeding in subjects with underlying GI pathology secondary to the irritative nature of the granules is included in the RMP as an identified risk.

Colestilan binds phosphate and bile acid, with the release of chloride which is available for systemic absorption. Changes in systemic ion balance with an increase in chloride and decrease in bicarbonate are therefore possible. Even though the changes in serum bicarbonate and chloride were limited in the clinical studies, this is still a potential risk. The information in the SmPC has been moved from 5.1 to 4.4 and the risk has been included in the RMP as a potential risk.

From a pharmacokinetic point of view, uncertainties remain related to the potential for colestilan to interact with other medicinal products. A post-approval drug-drug interaction study designed to mirror a worst-case scenario has been agreed by the applicant.

Benefit-risk balance

Importance of favourable and unfavourable effects

The Dialysis outcome and practice pattern study (DOPPS) has suggested that a 0.3 mmol/L lower plasma phosphorous level is significantly associated with lower all-cause mortality and cardiovascular mortality. In the submitted studies, the differences compared to placebo were statistically significant and of clinical relevance (at least 0.3 mmol/L reduction). In studies A05 and E07, the superiority over placebo was demonstrated in a selected population (about one third of the patients were withdrawn due to lack of efficacy, adverse events etc, prior to randomisation). However, conservative sensitivity analyses have shown that a relevant phosphorus lowering effect of colestilan can be expected in approximately 41-52% of patients. Further, the effect of the treatment is monitored and the dose will be uptitrated until a relevant result has been achieved. The effect is thus of clear clinical relevance.

Based on the results of study E07 , it is uncertain if colestilan is as effective as sevelamer. However, it is acknowledged that the design of study E07 may have favoured sevelamer (e.g. longer time on optimal dose, some patients sevelamer tolerant) and that the lowering phosphorus effects were comparable for colestilan and sevelamer in the extension study E10. Non-inferiority to sevelamer can therefore neither be shown nor refuted, but may not be of crucial importance considering that the treatment effect is monitored.

Colestilan lowers LDL-cholesterol, total cholesterol and HbA1c to an extent comparable to sevelamer, which is a benefit for the patients.

Colestilan is a non-absorbable anion exchange resin which is locally active in the gastrointestinal tract. Thus, the expected safety profile includes GI AEs and potentially also bleedings due to mechanical reasons or impaired absorption of vitamin K.

The absolute risk of gastrointestinal adverse effects is high while the relative incidence compared to sevelamer is difficult to apprehend due to the design of the comparative study including patients previously treated with sevelamer. GI adverse events are expected, and the need for caution in high risk patients is reflected in the SmPC. The incidence of haemorrhages does not seem to be higher compared to sevelamer. Hemorrhagic diathesis is included in the RMP as an important potential risk. Gastrointestinal bleeding in subjects with underlying GI pathology secondary to the irritative nature of the granules is included in the RMP as an identified risk.

Benefit-risk balance

Discussion on the benefit-risk balance

The absolute effect of colestilan is of clinical relevance according to literature data. The reported safety profile is what could be expected from a non-absorbable anion exchange resin which is locally active in the gastrointestinal tract with mainly GI adverse events which are detectable and reversible.
The long-term efficacy of colestilan in treating hyperphosphataemia, is comparable with other EU-licensed non-absorbed, oral resins. The control of serum phosphorus is maintained for at least one year, is effective at lowering high levels of serum phosphorus that are associated with a significant lowering of patient mortality and morbidity (KDOQI 2003), and no dose adjustment is required in respect of gender or age, up to 75 years. The absolute benefit/risk balance is therefore considered as positive.

Colestilan was demonstrated to be superior to placebo to control serum phosphorus in subjects with chronic kidney disease on dialysis. Based on the results of the comparative study E07, it is indicated that the phosphorus lowering effect of colestilan may be somewhat lower compared to sevelamer and that GI adverse events may be more common. However, several limitations in the study design may question the robustness of these results and the results were not confirmed in the long term study in which the phosphorus lowering effect of colestilan and sevelamer was similar.

The absolute effect of colestilan is of clinical relevance and treatment results are monitored. Further, the reported safety profile is what could be expected from a non-absorbable anion exchange resin which is locally active in the gastrointestinal tract with mainly GI adverse events which are detectable and reversible. The absolute benefit/risk balance is therefore considered as 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 colestilan in the treatment of BindRen is indicated for the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The applicant must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The applicant shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

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

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that colestilan is to be qualified as a new active substance.