



European Medicines Agency

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**CHMP ASSESSMENT REPORT**

**FOR**

**Renvela**

International Nonproprietary Name: **sevelamer carbonate**

**Procedure No. EMEA/H/C/000993**

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

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# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant Genzyme Europe B.V. submitted on 06 March 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Renvela, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC, as amended for a complete and independent application known active substance.

The applicant applied for the following indication:

Control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis, and in adult patients with chronic kidney disease not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l.

### Scientific Advice:

The applicant received Scientific Advice from the CHMP on 26 May 2005. The Scientific Advice pertained to clinical aspects of the dossier.

### Licensing status:

Renvela has been given a Marketing Authorisation in the following countries:

Country	Date approved
United States of America	19/10/2007
India	03/02/2009
Argentina	05/11/2008
Chile	21/01/2009
Kuwait	25/09/2008

A new application was filed in the following countries: Brazil, Canada, China, Philippines, Singapore, Thailand.

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

Rapporteur: **Pieter Neels**

Co-Rapporteur: **Barbara van Zwieten-Boot**

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 6 March 2008.
- The procedure started on 26 March 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 24 June 2008. (Annex 4.1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2008 (Annex 4.2).
- During the meeting on 24 July 2008, 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 25 July 2008 (Annex 4.3).

- A clarification meeting on the CHMP Day120 List of Questions with the Rapporteurs was held on 28 August 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 December 2008. (Annex 4.5).
- During the CHMP meeting on 15-18 December 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant (Annex 4.6).
- Written explanations were provided by the applicant on 16 January 2009.
- A clarification meeting on the CHMP Day180 List of Outstanding Issues with the Rapporteurs was held on 19 January 2009.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 February 2009. (Annex 4.7)
- During the CHMP meeting on 16-19 February 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 16-19 March 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion by majority for granting a Marketing Authorisation to Renvela on 19 March 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 March 2009 (Annex 4.8).

## 2 SCIENTIFIC DISCUSSION

### 2.1 Introduction

Hyperphosphataemia is common in patients with end-stage renal failure (ESRF) and may be associated with debilitating sequelae. Treatment of hyperphosphataemia consists of dietary phosphorus restriction and/or dialysis and phosphate binders. Almost all dialysis patients require phosphate binders. The use of calcium-based phosphate binders (calcium acetate, calcium carbonate) can result in chronic calcium overload, hypercalcemia and soft tissue calcification. Hypercalcemia is particularly common in patients treated with calcitriol and other vitamin D analogues. Aluminium-based phosphate binders (aluminium hydroxide) are associated with significant toxicity due to small amounts of absorbed aluminium (encephalopathy, osteomalacia, myopathy).

Sevelamer is a non-absorbed phosphate binding poly (allylamine hydrochloride) polymer, free of aluminium and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines become partially protonated in the intestine and interact with phosphate ions through ionic and hydrogen bonding. By binding phosphate in the gastrointestinal tract, sevelamer lowers the phosphate concentration in the serum. Sevelamer decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone, probably because the product itself does not contain calcium.

Genzyme initially developed sevelamer hydrochloride (Renagel®), which is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis (Marketing Authorisation Application [MAA] EU/1/99/123/004-012). Sevelamer hydrochloride capsules were approved in the United States on 30 October 1998, and in the European Union, via the Centralised Procedure, on 28 January 2000 for use in adult haemodialysis patients. Approval for the tablet form followed on 23 April 2001. The indication was extended in 2007 for use in peritoneal dialysis patients. Sevelamer hydrochloride is restricted for use in adult patients receiving dialysis.

Genzyme continued the development of sevelamer, seeking another salt which would have equivalent phosphate binding properties for use in the hyperphosphataemic CKD (chronic kidney disease) population regardless of dialysis status, and this led to the development of sevelamer carbonate. Sevelamer carbonate is classified pharmacologically as a phosphate binder (ATC Code: V03AE02).

Sevelamer carbonate has been formulated as a tablet and as a powder for oral suspension. The powder formulation provides an alternative dosage form for those patients who dislike tablets or have difficulties in swallowing tablets, or who have a high pill burden. In addition, a powder formulation provides an appropriate dosage form for use in paediatric patients. However, no data in the paediatric population has been submitted.

The indication as proposed by the applicant was:

“Renvela is indicated for the control of serum phosphorus in hyperphosphataemic adult patients with chronic kidney disease.”

Approved indication:

“Renvela is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

Renvela is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l.

Renvela should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D<sub>3</sub> or one of its analogues to control the development of renal bone disease.”

The recommended starting dose of sevelamer carbonate is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Renvela tablets or powder must be taken three times per day with meals. For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Renvela should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

Serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated every 2 to 4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter. Patients taking Renvela should adhere to their prescribed diets. The daily dose is expected to be an average of approximately 6 g per day.

## 2.2 Quality aspects

### Introduction

Renvela is presented as film-coated tablets containing 800 mg of anhydrous sevelamer carbonate or as powder for oral suspension containing 1.6 g and 2.4 g of sevelamer carbonate. Sevelamer carbonate is a new sevelamer salt, a cross-linked polymer with the same structure as sevelamer hydrochloride, where carbonate replaces chloride as the anion. While the anions differ for the two salts, the polymer, which is the active moiety responsible for binding of phosphate, is the same.

### Drug Substance (to be changed in the EPAR to “Active Substance”)

Sevelamer carbonate is a cross-linked poly (allylamine carbonate) polymer. The cross-linking agent is epi-chlorohydrin (1-chloro-2,3-epoxypropane). The cross-linking groups consist of two secondary amine groups derived from the starting material, poly (allylamine hydrochloride) and one molecule of epichlorohydrin giving 2-hydroxypropyl linkers. A portion of the amine is present as the carbonate salt, at 14 – 21% by weight; this is similar to sevelamer hydrochloride where the chloride salt is present at 15 – 20%, by weight.

There is no evidence for stereoregularity of the cross-linked polymer according to <sup>1</sup>H and <sup>13</sup>C NMR data. Similarly, there is no stereochemical preference for the cross-linking reaction, i.e., randomly distributed crosslinks are expected.

Sevelamer carbonate is a highly cross-linked polymer of varying size, and each particle can be considered as one molecule. Since the molecular weight is equal to the weight of the particle itself, the molecular weight distribution of a cross-linked polymer is a function of the distribution of particle

sizes.

Sevelamer carbonate is a white to off-white, free-flowing, non-crystalline powder that is insoluble in all tested solvents.

- **Manufacture**

Sevelamer carbonate is manufactured by two manufacturers using comparable manufacturing processes. Briefly, sevelamer carbonate is manufactured by cross-linking (using epichlorohydrin) a partially neutralized solution of poly (allylamine hydrochloride) to give an insoluble gel (sevelamer hydrochloride). The gel is treated with strong base to generate sevelamer free base, which is washed with water to a conductivity limit that ensures adequate removal of the water soluble impurities. The free base suspension in water is reacted with carbon dioxide to give sevelamer carbonate, the product is then dried to give sevelamer carbonate powder which is screened and packaged.

The comparability of the drug substance manufactured by all processes and facilities has been demonstrated and compared with the clinical trial material. Considering that the cross-linking and carbonation chemistry to produce sevelamer carbonate are the same for both manufacturing processes, there were no adverse or unexpected outcomes as a result of the comparability analyses.

Sevelamer carbonate has been characterised by density, elemental analysis, extractables and leachables, TGA, TGA-MS, DSC, FTIR, Raman spectroscopy, particle size distribution by laser scattering, solid state <sup>13</sup>C NMR, pH and X-ray powder diffraction.

- **Specification**

The active substance tests and corresponding specifications have been chosen to conform to ICH Q6A and include such tests as include tests for appearance, (visual examination), identification (ATR-FTIR), loss on drying (NIR and TGA), titratable amines (Acid-base titration), carbonate (NIR and TGA), swell index, soluble oligomers (UV-VIS), residual substances (GC), allylamine (HPLC), heavy metals, (Ph. Eur.) residue on ignition (Ph. Eur.), total halides as chloride (titrimetry) and microbial limits (Ph. Eur.). Specification limits were developed from historical batch release and stability data as well as statistical analysis where applicable.

Batch analysis results were provided for sevelamer carbonate manufactured during various campaigns. All the batches complied with the requirements in the active substance specification.

- **Stability**

The stability of sevelamer carbonate was investigated in six production-scale batches at 25°C/60%RH for 18 months and in additional 3-production scale batches for 12 months. At accelerated conditions (40°C/75%RH), results were provided for up to one year. Stability studies were performed under stressed conditions (exposure to light, high temperature, hydrolysis and freeze-thaw conditions).

Fourteen batches from the alternative manufacturer of sevelamer carbonate were placed on stability at real time storage conditions of 25 ± 2°C/60 ± 5% RH and accelerated storage conditions of 40 ± 2°C/75 ± 5% RH.

The active substance was tested for appearance, loss on drying, carbonate, titratable amines, swell index, soluble oligomers and residual allylamine. The microbiological limits were controlled annually.

The data provided is sufficient to confirm the proposed re-test period.

## **Drug Product 1 (film-coated tablets) (To be changed in the EPAR to “Medicinal Product”)**

- **Pharmaceutical Development**

Sevelamer carbonate was developed as an alternative to the existing sevelamer hydrochloride.

Sevelamer carbonate film-coated tablets contain 800 mg of sevelamer carbonate. They are packed in HDPE bottles containing either 30 or 180 tablets. Film-coated tablets were chosen as it is the most convenient and suitable dosage form.

The excipients used in the formulation of sevelamer carbonate are those typically used in the preparation of film-coated tablets such as microcrystalline cellulose, zinc stearate, sodium chloride, water and opadry (film-coating). All excipients comply with PhEur specifications, except the coating materials that are commercially available mixtures of standard components used for film coating. The compatibility of sevelamer carbonate with the proposed excipients was demonstrated through stability studies.

- **Adventitious Agents**

None of the excipients used in the formulation of sevelamer carbonate film-coated tablets are of animal or human origin.

- **Manufacture of the Product**

The manufacturing process for sevelamer carbonate film-coated tablets consists of the following major steps:

1. Dispensing and wetting
2. Milling and blending
3. Compression
4. Coating
5. Printing

The manufacturing process development of the drug product has been appropriately described and validated. Validation of the manufacturing process showed that the manufacturing process is robust and consistently produces a finished product, which meets the proposed requirements. Adequate in-process controls have been selected to monitor the manufacturing process.

- **Product Specification**

The finished product tests and corresponding specifications have been chosen to conform to ICH Q6A and include such tests as appearance, identification, loss on drying, uniformity of mass, disintegration, potency, residual substances and microbial purity. Specification limits were developed from historical batch release and stability data as well as statistical analysis where applicable. These lots were used clinically, for registration purposes or related to process validation.

The analytical methods have been satisfactorily described and validated in accordance with ICH guidelines. Batch analysis data was provided for 6 commercial-scale batches. The results comply with the specification and confirm the consistency of the product.

- **Stability of the Product**

The stability studies included 13 batches manufactured with active substance from both suppliers. The studies were performed at long term (25°C/60%RH) for up to 18 to 24 months and accelerated conditions (40°C/75%RH) for up to 6 to 12 months. In addition, two batches were also evaluated when exposed to stress conditions, i.e. open container (in-use), light, humidity and thermal cycling.

The finished product was tested for appearance, titratable amines, other residual substances, soluble oligomers, loss on drying, disintegration and microbiological limits.

No changes were observed for appearance of the tablets. In addition, the microbiological properties are satisfactory for the period tested. For all other parameters, the results are within the specifications and statistical evaluation of the results was also performed to detect any trend and to predict the shelf life.

In summary, the stability results support the shelf-life and storage conditions as defined in the SPC.

### **Drug Product 2 (powder for oral suspension) (To be changed in the EPAR to “Medicinal Product”)**

- **Pharmaceutical Development**

Sevelamer carbonate powder for oral suspension was developed as an alternative to sevelamer carbonate tablets for patients with swallowing difficulties. It is packed in sachet containing 1.6 g and 2.4 g sevelamer carbonate. A child resistant sachet was selected made of foil consisting of ethylene methacrylic acid copolymer, polyester, low density polyethylene and aluminum foil laminate. Stability data indicates it provides an appropriate moisture barrier protection.

The excipients used in the preparation of sevelamer carbonate powder for oral suspension are propylene glycol alginate (PGA), sucralose, sodium chloride, ferric oxide yellow and citrus cream flavouring.

The compatibility of the powder with the diluent for reconstitution (water) was studied for up to 24 hours. The reconstituted suspension was tested and all results were satisfactory up to 6 hours.

- **Adventitious Agents**

All excipients are of vegetable or mineral origin therefore no TSE risk assessment is needed.

- **Manufacturing process**

The manufacturing process consists of (1) blending the powder and (2) filling the blend into the sachets. Different trials were performed to improve blend homogeneity and to prevent the presence of aggregates. Screening of the ingredients and the use of a suitable mixer were demonstrated to be suitable to obtain a homogeneous blend without aggregates.

- **Product Specification**

The specification for sevelamer carbonate includes validated tests for appearance (visual examination), appearance of the reconstituted product (visual examination), identification (FTIR), Uniformity of Mass (PhEur), total titratable amines (titration), residual substances (HPLC), loss on drying (TGA), residual soluble oligomers, microbial purity (PhEur).

Batch data was provided on 14 batches of sevelamer carbonate. The results comply with the specification and confirm the consistency of the product.

- **Stability of the Product**

Stability studies were performed on nine clinical batches and four commercial size batches manufactured with active substance from both suppliers and packed in sachets of 0.8g, 1.6g, 2.4g, 3.2g and 7.2g. Although only the 1.6g and 2.4g pack sizes are proposed for marketing, the 0.8g and 1.6g pack sizes represent the worst cases when the headspace and contact area of the powder with the laminate are taken into consideration. A total of 3 batches of each the 1.6g and 2.4g sachets were placed on stability.

The stability studies included 13 batches manufactured with active substance from both suppliers. The studies were performed at long term (25°C/60%RH) for up to 18 to 24 months and accelerated conditions (40°C/75%RH) for up to 6 to 12 months. In addition, three batches were also evaluated when exposed to stress conditions, i.e., light, humidity and thermal cycling.

The finished product was tested for appearance, appearance of the reconstituted product, titratable amines, allylamine, soluble oligomers, loss on drying and microbiological limits, according to the specifications.

In summary, the stability results support the shelflife and storage conditions as defined in the SPC.

### **Discussion on chemical, pharmaceutical and biological aspects**

The active substance and both finished products have been adequately described. The excipients used in the preparation of the film-coated tablets and the powder for oral suspension, and the manufacturing process selected are typical of such preparations.

The film-coated tablets are manufactured by blending the ingredients with water before compression and film-coating. Sevelamer carbonate powder for oral suspension was developed to provide a convenient alternative dosing form to the sevelamer carbonate tablets that may benefit those patients who dislike or have difficulties in swallowing multiple tablets. The powder for oral suspension is packed in sachets and dispersed in water before administration. The pharmaceutical development mainly focused on the taste and dispersion improvement.

At the time of the CHMP opinion, there were minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

## **2.3 Non-clinical aspects**

### **Introduction**

Since the active moiety in both Renagel and Renvela, responsible for phosphate binding, is the same (i.e., sevelamer), non-clinical and clinical data generated using sevelamer hydrochloride are submitted to support the sevelamer carbonate application.

In addition, three studies were conducted with sevelamer carbonate in order to bridge from the toxicology and pharmacokinetic data already available for the hydrochloride salt of sevelamer::

- 28-day multi-dose radiolabelled ADME study in dogs (GT-153-PK-1)
- 4-week oral toxicity study in rats (GT-153-TX-1)
- 4-week oral toxicity study in dogs (GT-153-TX-2)

The three bridging sevelamer hydrochloride/carbonate studies were stated to be conducted in compliance with GLP.

The majority of the studies conducted with sevelamer hydrochloride were done in compliance with GLP regulations. One toxicology study (TX95-217) was not fully GLP compliant, in that it did not have proper authentication by the study director. In addition, some of the non-pivotal sevelamer hydrochloride studies providing additional information on coagulation, vitamin supplementation and electrolytes were not GLP compliant.

### **Pharmacology**

- Primary pharmacodynamics

The pharmacodynamic action of sevelamer has been studied *in vitro* and *in vivo*. Sevelamer contains partially protonated polymer amines, which bind to negatively charged phosphates. As phosphate is liberated during digestion, the free phosphate can diffuse into the polymer and interact with the protonated (cationic) polymer amines. Phosphate is preferentially bound because it is polyvalent. Since the polymer is not absorbed, neither are the phosphate ions and both are excreted in the faeces. The equivalence of the binding capacity for both sevelamer carbonate and sevelamer hydrochloride has been established.

Several short term (4-5 day) animal studies were conducted to investigate the phosphate binding capacity of sevelamer hydrochloride *in vivo*. Oral administration of sevelamer to rats significantly increased faecal excretion of phosphate and decreased urinary phosphorus levels.

Sevelamer did not affect phosphataemia in dogs and there is a paradoxically increased phosphataemia in rats. Increased serum phosphorus accompanied with a decreased urine phosphorus concentration was also observed in the rat toxicology studies and is in contrast with the intended pharmacological action of Renvela. However, the primary endpoint (reduction of gut phosphate absorption) has been demonstrated in animals. Moreover compensatory mechanisms might complicate the relationship between phosphate absorption and phosphataemia, and these mechanisms might operate differently in animals and patients.

Studies on urinary and serum electrolytes in rats provide evidence that sevelamer releases chloride ions, in exchange for hydrogen phosphate ( $\text{HPO}_4$ ). Release of chloride ions was confirmed in the repeat dose toxicity studies in rats and dogs.

In addition to binding dietary phosphates, sevelamer significantly increased faecal excretion of bile acids which indicates that it also binds bile acids due to its ion exchange properties. This may lead to changes in absorption of fat-soluble vitamins and cholesterol. It may also affect the pharmacokinetics of drugs having enterohepatic circulation.

- Secondary pharmacodynamics

The only effect of sevelamer found in secondary pharmacology studies was an increased resting tension of guinea pig ileum and rat gastric fundus. Sevelamer had no effect on general behaviour, locomotor activity or other CNS activity, body temperature, cardiovascular or respiratory control in experimental animals. These findings are in line with the known mode of action of sevelamer and the lack of absorption from the intestine.

- Safety pharmacology programme

Safety pharmacology studies have not been performed according to the current standards. It is recognised that safety pharmacology studies may not be needed when systemic exposure is demonstrated to be low.

An *in vivo* safety pharmacology study in anesthetized dogs with up to 2000 mg/kg did not show any adverse effects of the drug product.

- Pharmacodynamic drug interactions

Sevelamer increases faecal excretion of bile acids and thus may also change elimination of drugs having enterohepatic circulation.

## **Pharmacokinetics**

The pharmacokinetic studies carried out with sevelamer in rats and dogs collectively demonstrate that sevelamer is not absorbed from the gastro-intestinal tract. No *in vivo* metabolism studies with sevelamer carbonate were therefore conducted since sevelamer is not absorbed. This is considered acceptable.

Sevelamer is excreted in faeces in both rats and dogs, with a slower excretion in dogs.

The excretion rate in dogs seems to be different for the hydrochloride and the carbonate salt. In dogs, sevelamer carbonate is excreted faster than sevelamer hydrochloride (94 % and 50-75% of the total recovered radioactivity was eliminated in faeces within 24 hours respectively). Only trace amounts of radioactivity were found in the urine.

The applicant conducted some preclinical drug interaction studies. Studies in beagle dogs showed that absorption of oestrone, propranolol and thyroxin may be delayed by concomitant absorption with sevelamer. A possible interaction with thyroxin has been confirmed in humans (SPC section 4.4 and 4.5). A possible interaction with oestrone and propranolol is not reflected in the SPC. However, a general statement is included in the SPC section 4.5 :

“Renvela is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Renvela, or the physician should consider monitoring blood levels.”

## **Toxicology**

- Single dose toxicity

Single dose toxicity studies in rodents and dogs showed that sevelamer has a low acute toxicity profile, with the highest doses tested being well tolerated.

- Repeat dose toxicity

Repeated dose toxicity of sevelamer after oral administration was studied in rats (up to 26 weeks) and dogs (up to 52 weeks). Chronic sevelamer treatment was generally well tolerated. In the rat studies increased numbers of haemorrhages were found, with mortalities particularly in males at high dose groups (10 g/kg/day). When high dose sevelamer was given with fat soluble vitamins D, E and K no haemorrhages were seen. Moreover, APTT and PT were increased (APTT being the most sensitive parameter). Both effects are likely to be due to reduced absorption of fat soluble vitamins and particularly that of vitamin K.

Other observations in rats and dogs were decreased levels of vitamins D and E (but not vitamin A). Also, vitamin D was inconsistently increased or decreased in females.

In a number of studies alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) were increased in both male and female animals. Since the rises were only moderate and since no histopathological changes in organs contributing to enzyme levels in blood were observed, these observations are considered of no clinical relevance.

Treatment with sevelamer hydrochloride may be associated with an increase in serum chloride and/or reduction in serum bicarbonate and the potential for worsening of pre-existing metabolic acidosis. The chloride anion liberated from the sevelamer backbone may contribute to these effects. The applicant developed sevelamer carbonate, expecting that acid base disturbances observed in clinical studies with sevelamer hydrochloride would not occur with another salt. However, in the repeated dose toxicity in rats and dogs, the impact on acid-base balance of sevelamer carbonate as compared to sevelamer hydrochloride was not studied.

No target organ toxicity was observed in rats or dogs as evidenced by gross anatomical observations and histopathological studies. Some evidence of gastrointestinal toxicity was found in rats, as gastric mucosa thickening was occasionally seen (a dose-dependent phenomenon in female rats). In addition, eosinophilic crystalloid material, which is likely to be sevelamer based, was found in intestinal lumen in high dose rats. A possible explanation for this is that high dose sevelamer could induce submucosal oedema due to increased osmotic pressure. These findings were not considered to be of clinical relevance.

- Genotoxicity

Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay. After metabolic activation sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations in a mammalian cytogenetic assay with Chinese Hamster Ovary (CHO) cells. The *in vivo* study was considered invalid since sevelamer is not absorbed. However, additional mutagenicity assays are not requested, since no concerns related to genotoxic properties from sevelamer were raised from repeated dose toxicity, carcinogenicity or reproductive toxicity studies.

- Carcinogenicity

Carcinogenicity studies were performed in mice and rats over a period of 104 weeks.

In the mice study, lymphomas were observed in the high dose female group (50,000 ppm), which represents a two to four-fold safety factor. The percentage of lymphomas in female mice, was above the limit of control groups. However, when compared to the historical control data (same strain, same site) of the incidence of lymphoma in studies carried out within a time span of +/- 5 years of the study termination, a wide range of up to 46 % lymphoma incidences was detected in female control animals. CHMP accepted that the occurrence of lymphoma is not related to treatment with sevelamer.

Treatment at the high dose of 3 g/kg/day in male rats is associated with proliferative findings in the transitional epithelium of the urinary tract. In contrast to what is claimed by the applicant (20 times the maximum projected human dose), this dose represents only a two-fold safety factor when the doses are compared on a mg/m<sup>2</sup> basis (for a human max dose of 14.4 g/d). In these high dose male rats, both the incidence and severity of transitional cell hyperplasia were increased in the kidney and in the urinary bladder when compared with the control groups. Urinary bladder transitional papillomas and carcinoma were also observed in the high dose males. The applicant considers these changes to be a response to the abnormal crystalline deposits evident in the urine as well as to the systemic mineral imbalance and as such do not represent a carcinogenic effect. CHMP agreed that tumor formation most likely occurs as a secondary effect and a direct carcinogenic effect of the substance is very unlikely, since sevelamer is not absorbed. However, as this is clearly a treatment related effect, the results of this study are included in the SPC section 5.3. Furthermore as requested by CHMP the Applicant committed to conduct further studies to investigate the mechanism of action of proliferative findings in the transitional epithelium addressing questions such as the nature of the crystalline deposits seen in the urine, under what conditions they are formed, whether there any critical conditions to look for to prevent their occurrence, and if similar crystals can occur in humans. The results of such studies will apply equally to both Renvela and Renagel.

- Reproduction Toxicity

Reproduction toxicity was investigated in rats and rabbits.

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study.

In pregnant rats given sevelamer hydrochloride during organogenesis, reduced or irregular ossification of foetal bones occurred in mid- and high dose groups, probably due to a reduced absorption of fat-soluble vitamin D. This was at a human equivalent dose of twice the maximum clinical trial dose.

In pregnant rabbits given sevelamer hydrochloride by gavage during organogenesis, an increase of early resorption occurred in the high dose group. This was at a human equivalent dose of three times the maximum clinical trial dose.

The fact that sevelamer reduces the absorption of different vitamins including folic acid is included in the SPC Pregnancy section 4.6 with a cross-reference to paragraph 4.4 Special warnings and precautions for use.

A pre-and post-natal development study was performed. The highest dose tested was 1000mg/kg/day, since a higher dose of 1.5 or 2 g/kg was not feasible via oral gavage without stimulating a reflux response. Since the Applicant accepted to include the warnings in the SPC 4.4 on reduced absorption

of several vitamins and the warning in the SPC 4.6 on use in pregnancy and lactation, the study design of the pre-and post-natal development study has been accepted.

- Toxicokinetics

Since sevelamer carbonate and sevelamer hydrochloride are non-absorbed products, no toxicokinetic analyses were performed; this is acceptable.

- Local tolerance

No local tolerance studies were performed, and this is acceptable for an orally administered product.

- Other toxicity studies

Coagulation studies were conducted with sevelamer hydrochloride; these were discussed under the section Repeat Dose Toxicity.

### **Ecotoxicity/environmental risk assessment**

The applicant has provided an environmental risk assessment (Phase I, Phase II Tier A & B). The use of sevelamer carbonate does not seem to represent a risk to the environment.

## **2.4 Clinical aspects**

### **Introduction**

The sought indication for sevelamer carbonate (tablet and powder) is for control of serum phosphorus in hyperphosphataemic adult patients with chronic kidney disease (CKD). This includes both CKD patients on dialysis (haemodialysis or peritoneal dialysis) and CKD patients not on dialysis. In addition, the applicant investigated a different dosing regimen (once daily (OD) of sevelamer carbonate versus three times per day (TID)). The latter corresponds to the current dosing regimen of sevelamer hydrochloride.

To support the current application, clinical efficacy was studied in four phase 3 studies with sevelamer carbonate (Table xx). No sevelamer carbonate studies were performed in patients on peritoneal dialysis.

Supportive data is provided from existing studies conducted with sevelamer hydrochloride, which have been previously submitted and assessed as part of the sevelamer hydrochloride MAA and subsequent post-approval activities

Scientific advice was sought by Genzyme regarding the design of a clinical dose titration study using sevelamer carbonate in hyperphosphataemic CKD patients not on dialysis (study SVCARB00105). Advice was provided by the CHMP on 26 May 2005. The Company did not completely follow the Scientific Advice; the points of dissent (number of patients studied and comparator-arm) are discussed in the section “Clinical Efficacy”.

### **GCP**

The pivotal Clinical trials (GD3-163-201, SVCARB00205, GD3-199-301 and SVCARB00105) 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.

A routine EMEA GCP Inspection was done at the sponsor site Genzyme Europe BV, The Netherlands and at one investigator site (UK) for the clinical study SVCARB00205, in accordance with Article 57 of Council Regulation (EC) No. 726/2004.

These inspections revealed critical and major issues, with regard to eligibility criteria, drug compliance, and adverse event reporting:

Inspection at the investigator site revealed critical, major and minor findings.

Inspection at the sponsor site revealed critical and major findings.

Based on these deviations the inspection team concluded that the conduct of the study SVCARB00205 at the investigator site was not fully compliant with GCP and the sponsor did not adequately manage this non-compliance. The nature of the shortcomings and critical finding are of relevance for the potential use of this study in a Marketing Authorization Application. The inspectors recommended the assessors to carefully look into the non-compliances with the protocol (especially eligibility criteria, drug compliance, adverse event reporting) in order to assess their importance for the integrity of the statistical analysis of the PPS and the extrapolation of the conclusion to the population as a whole.

The inspected investigator site participated in two of the carbonate pivotal clinical trials: *SVCARB00205 & SVCARB00105*. As critical and major observations were made during the inspection of this site, compliance with GCP for both trials was questioned. As these trials are proposed to be supportive for the powder formulation on one side and the Applicant's broad indication claim – to include non dialysis CKD patients- a major objection was endorsed by CHMP.

In response to the CHMP List of Outstanding Issues the Applicant presented a sensitivity analysis and addressed this issue at the oral explanation.

Based on the data presented the majority of the CHMP members accepted that the proposed data could be accepted to support the claimed indications, provided that additional data are gathered in a post-marketing study to reinforce the safety data set (see discussion under Risk Management Plan below).

## **Pharmacokinetics**

To support the pharmacokinetics of sevelamer carbonate, the pharmacokinetic studies submitted for sevelamer hydrochloride are also submitted in this application:

- GTC-10-801 - absorption study of C14- sevelamer hydrochloride
- ICR013769 - interaction study with digoxin
- ICR013821 - interaction study with warfarin
- GTC-45-803 - interaction study with metoprolol
- GTC-45-804 - interaction study with enalapril
- GTC-45-807 - interaction study with ciprofloxacin
- GTC-45-808 - interaction study with iron

In addition, an in vitro equilibrium and kinetic binding study (study TR-2527-07-SC) is submitted to bridge data between different formulations and salts. As the 2 products only differ regarding the salt form, it is considered acceptable to use the studies submitted for sevelamer hydrochloride. A difference in pharmacokinetics is not expected, as the sevelamer molecule will not be absorbed.

- Absorption

Based upon a study in 20 healthy subjects (young and elderly) and use of 14C-labelled medicinal product, sevelamer (at the clinically relevant daily dose of approximately 7g) is not absorbed from the gastro-intestinal tract. Less than 0.2% of the administered radioactivity dose could be recovered in urine, but this may represent unlabelled radioactivity, and absorption in healthy subjects is considered negligible. However, it cannot be ruled out that absorption may increase in the presence of bowel obstruction or inflammatory bowel disease.

Comparison of trial formulations with finished product:

Sevelamer is not absorbed and therefore conventional pharmacokinetic studies cannot be applied to bridge data between different formulations and salts. Instead an in vitro equilibrium and kinetic binding study (study TR-2527-07-SC) is submitted, to compare sevelamer HCl, sevelamer carbonate tablets and sevelamer carbonate powder for oral suspension. The applied in vitro method to study phosphate binding is adapted from the FDA guidance for the in vitro method for cholestyramine. Phosphate binding was evaluated using different phosphate concentrations (2.5 and 38.7 mM), and with or without pre-treatment with acid, as well as constant concentrations of phosphate for varying lengths of time. The in vitro studies showed comparable phosphate binding of sevelamer hydrochloride, and sevelamer carbonate (tablets and powder).

- Distribution
- Elimination
- Dose proportionality and time dependencies
- Special populations

As sevelamer carbonate is not absorbed; these pharmacokinetic studies were not possible. This is also considered to be the case in special patient groups such as patients with impaired renal function or impaired hepatic function.

- Pharmacokinetic interaction studies

Sevelamer may bind active medicinal product substances, and thereby interfere in the absorption. According to preclinical studies, sevelamer is a bile-acid binding compound. In contrast, in vivo clinical pharmacokinetic interaction studies in healthy volunteers did not reveal any clinically significant interactions between sevelamer and digoxin (known to interact with cholestyramine, enterohepatic circulation), warfarin (known to interact with cholestyramine, positive in vitro binding to sevelamer), enalapril (positive in vitro binding), metoprolol, and iron.

For ciprofloxacin, a statistically significant decrease by about 50% in AUC and C<sub>max</sub> is observed.

As was the case for sevelamer hydrochloride, interactions are difficult to predict. In line with the SPC of sevelamer hydrochloride a general statement is included in the SPC with regard to a possible interaction where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, and administration of the medicinal product should be at least one hour before or three hours after sevelamer carbonate administration.

The amount of data available on interactions is limited; as these interactions are difficult to predict CHMP was of the opinion that the Applicant should put much more effort in elucidating its full interaction profile. Two clinical studies in healthy subjects were performed to assess the interaction profile of larger (9.6g), single doses of sevelamer carbonate powder with digoxin and warfarin, respectively. The Clinical Study Report for the healthy volunteer study (SVCARB01107) with warfarin was submitted with the responses to the Day 120 List of Questions. Sevelamer carbonate powder was found to have no effect on the bioavailability of warfarin. The second interaction study with digoxin (SVCARB01307) has been completed. The applicant has committed to submit the study report as part of the Follow-up measures.

- Pharmacokinetics using human biomaterials  
Not applicable

## **Pharmacodynamics**

- Mechanism of action

Sevelamer carbonate is a non-absorbed, insoluble, cross-linked polymer formulated as a coated tablet or powder for oral suspension. The amines in the polymer exist in a partly protonated form and can bind to negatively charged ions. It exerts its primary pharmacodynamic action in the small intestine through binding of negatively charged phosphates liberated during the digestive process. Phosphate sequestered in the polymer is not absorbed into the body, but passes through the intestine and is

excreted in the faeces resulting in reduced phosphorus absorption from the gastrointestinal tract.. While the anions differ for the sevelamer carbonate and sevelamer hydrochloride, the polymer itself, the active moiety responsible for binding of phosphate, is the same.

- Primary and Secondary pharmacology

The primary pharmacodynamic action of sevelamer hydrochloride (binding of dietary phosphate) was adequately demonstrated before in the development of sevelamer hydrochloride. As the active moiety responsible for binding of phosphate is the same in sevelamer carbonate, it is acceptable that no new pharmacodynamic studies were performed.

Study GTC-02-101 was a single centre, randomised, double-blind, placebo-controlled, parallel-group study in healthy volunteers on a phosphate-controlled diet. The study demonstrated the phosphate-binding capacity of sevelamer following repeated dose administration (placebo or 1, 2.5 and 5 g t.i.d. for 8 days). A dose-dependent decrease in total urine phosphorus (indicating decreased absorption of phosphorus) and increases in the ratio of stool to urine phosphorus (to assess the effect of sevelamer hydrochloride on dietary phosphorus absorption) were observed

Secondary pharmacodynamic actions of sevelamer relate to the ability to bind bile acids, which was shown for sevelamer hydrochloride *in vitro* and *in vivo* in experimental animal models. In clinical studies, sevelamer hydrochloride lowered low-density lipoprotein cholesterol (LDL) and total cholesterol. The lowering of LDL may be beneficial to the patient as most CKD patients on dialysis have cardiovascular morbidity and approximately 30% to 40% have elevated LDL cholesterol levels. Therefore, the effect on LDL cholesterol was considered a secondary efficacy endpoint in the studies and is discussed in the assessment of clinical efficacy.

### **Clinical efficacy**

Efficacy data for sevelamer carbonate are based on four clinical studies:

In CKD patients on dialysis two trials were designed to demonstrate therapeutic equivalence of sevelamer carbonate with sevelamer hydrochloride (study GD3-163-201 and study SVCARB00205) in CKD patients on haemodialysis. One study (study GD3-199-301) was designed to demonstrate non-inferiority of sevelamer carbonate powder once daily to sevelamer hydrochloride tables three times daily in CKD patients on haemodialysis.

In CKD patients not on dialysis one study (study SVCARB00105) was designed to demonstrate efficacy and safety of sevelamer carbonate in CKD patients not on dialysis.

No studies with sevelamer carbonate were performed in peritoneal dialysis patients. The applicant had performed one study with sevelamer hydrochloride in patients receiving peritoneal dialysis (REN-003-04).

An overview of the clinical development program (efficacy and safety studies) with sevelamer carbonate is given on the next page in tabular format (table 1).

**Table 1: Description of sevelamer carbonate clinical efficacy and safety studies, by patient population.**

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjects by arm entered/ completed	Duration	Gender M/F Mean /Median Age (range)	Diagnosis Incl. criteria	Primary Endpoint
<b>Studies in CKD patients on haemodialysis</b>									
GD3-163-201	13 sites in the USA	Double blind, randomised, crossover study	Sevelamer carbonate 800 mg tablets  Sevelamer hydrochloride 800 mg tablets  Orally TID  Mean actual dose for both (per protocol set): 6.0 ± 2.8 g/day  Mean actual dose (safety set):  Sevelamer carbonate: 5.8 ± 2.8 g/day Sevelamer hydrochloride: 5.6 ± 2.9 g/day	Therapeutic equivalence efficacy and safety	Treated: 79 Completed: 69 Completed washout: 40	23 weeks: 5-week sevelamer hydrochloride run-in period; two 8-week randomised treatment periods; 2-week washout period	51% M, 49% F  58 yrs/58 yrs (29-88 yrs)	CKD patients on haemodialysis who use sevelamer hydrochloride alone or in combination with calcium phosphate binder.  Before randomization: Serum phosphorus ≥ 3.0 and ≤ 6.5 mg/dl	Time weighted average of serum phosphorus
SVCARB0205	7 sites in UK	Open label, randomised, cross-over study	Sevelamer carbonate powder 0.8 g/ sachet  Sevelamer hydrochloride 800 mg tablets  Orally TID  Mean actual dose (safety set) Sevelamer carbonate:	Therapeutic equivalence efficacy and safety	Safety set: 31 Completed treatment: 24	15 weeks: 2-week washout period; 4-week sevelamer hydrochloride run-in period; two 4-week randomised treatment periods; 1-week follow-up period	68% M, 32% F  53 yrs/51 yrs (27-80 yrs)	CKD patients on haemodialysis who use sevelamer hydrochloride alone or in combination with calcium/metal phosphate binder.  Before randomization: Serum phosphorus ≥ 3.0 and ≤ 6.5 mg/dl	Time weighted average of serum phosphorus

5.9 ± 2.7 g/day

Sevelamer  
hydrochloride: 6.5 ±  
3.3 g/day

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**Table 1-continued. Description of Sevelamer clinical efficacy and safety studies, by patient population**

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjects by arm entered/ completed	Duration	Gender M/F Mean/ Median Age (range)	Diagnosis Incl. criteria	Primary Endpoint
GD3-199-301	29 sites in the United States	Open label, randomised, parallel study	Sevelamer carbonate powder for oral suspension 2.4 g sachets, OD with meal  Sevelamer hydrochloride tablets 800 mg, TID with meal  Mean actual dose (Safety Set) Sevelamer carbonate: 6.2 ± 2.6 g/day  Sevelamer Hydrochloride: 6.7 ± 3.0 g/day	Non-inferiority efficacy and safety	Sevelamer carbonate powder OD: 141/93 Sevelamer hydrochloride TID: 72/62	26 weeks: 2-week washout period, 24-week randomised treatment period.	61% M, 39% F  58 yrs/ 59 yrs (20-85 yrs)	CKD patients on haemodialysis using phosphate binders  Before randomization: Serum phosphorus ≥ 5.5 mg/dl	Change in serum phosphorus level from baseline
<b>Studies in CKD patients not on dialysis</b>									
SVCARBO 0105	25 sites: 20 sites in Europe and 5 sites in Australia	Open label, single arm, dose titration study	Sevelamer carbonate tablets: 1.6 g orally TID with meals  Mean actual dose (Safety Set) Sevelamer carbonate: 5.38 ± 1.69 g/day	Efficacy and safety	Sevelamer carbonate: 49/41	12 weeks: 2-week washout period† 8-week treatment period 2-week washout period	65% 35%  62 yrs / 64 yrs (23-81 years)	CKD patients not on dialysis Serum phosphorus ≥ 5.5 mg/dl before treatment	Change in serum phosphorus

† The two-week washout period was required only for patients on binder therapy at screening.

- Dose response study(ies)

No separate dose-response studies were performed with sevelamer carbonate to be used in CKD patients on haemodialysis. The dose was based on the titrated dose of sevelamer hydrochloride obtained during the run-in period (studies GD3-163-201 and SVCARB00205) or the highest starting dose of sevelamer hydrochloride as proposed in the SPC (study GD3-199-301). The starting dose of sevelamer hydrochloride ranges from 2.4 g/day to 4.8 g/day, and is titrated at regular intervals based on serum phosphorus levels until an acceptable serum phosphorus level is reached. If prescribed as an alternative phosphate binder, sevelamer hydrochloride is given in equivalent doses on a gram for gram basis compared to the patient's previous phosphate binder.

The starting dose of sevelamer carbonate in CKD patients not on dialysis (study SVCARB00105) was based on the phase 2 dose titration study with sevelamer hydrochloride in CKD patients not on dialysis (study GTC-45-204,). Study SVCARB00105 is both a dose titration study and a pivotal study for clinical efficacy and safety in CKD patients not on dialysis. Therefore this study is discussed in the section main studies.

- Main study(ies)

### CKD patients on dialysis

The Applicant has submitted the following data set of patients on haemodialysis (table 2). In this table GD3-199-301 is not presented as it is a comparison of OD versus a three times daily intake.

<i><u>Table 2: Overview Number of Patients Treated with Sevelamer in Dialysis Studies</u></i>		
<b>Protocol Number</b>	<b>Patients Treated with Sevelamer Hydrochloride</b>	<b>Patients Treated with Sevelamer Carbonate</b>
<a href="#">GTC-10-201</a>	24	
<a href="#">GTC-10-202</a>	48	
<a href="#">GTC-36-203</a>	75	
<a href="#">GTC-36-301</a>	84	
<a href="#">GTC-36-302</a>	172	
<a href="#">GTC-45-901</a>	192 <sup>†</sup>	
<a href="#">GTC-49-301</a>	100	
<a href="#">REN-003-04</a>	97	
<a href="#">GD3-163-201</a>	78	73 <sup>‡</sup>
<a href="#">SVCARB00205</a>	28	31 <sup>‡</sup>

<sup>†</sup> 7 patients were naïve to sevelamer; all other study participants took part in a previous sevelamer hydrochloride study.

<sup>‡</sup> Studies GD3-163-201 and SVCARB00205 were both cross over studies. In both studies, not all patients proceeded to the cross-over treatment phase and thus did not receive therapy with both agents.

Only two small trials are submitted comparing sevelamer hydrochloride with sevelamer carbonate. The studies GD3-163-201 (sevelamer carbonate tablets) and SVCARB00205 (sevelamer carbonate powder) were designed to demonstrate therapeutic equivalence of sevelamer carbonate and sevelamer hydrochloride in CKD patients on haemodialysis. Study GD3-163-201 was a double-blind, randomized, crossover study whereas study SVCARB00205 was an open-label, randomized, crossover

study. Because of the similarity in study design and methodology, the methods of these studies are described in a combined section. The results of the individual studies are described separately.

## METHODS

### *Study Participants*

Adult (>18 years) patients with CKD on haemodialysis treatment for three months or longer, who were on oral phosphate binder treatment.

Other major inclusion criteria included stable vitamin D dose, stable diet, stable dose of cinacalcet, negative pregnancy test and an acceptable contraceptive method. Patients should be willing and able to avoid antacids and phosphorus binders containing aluminium, magnesium, calcium or lanthanum for the duration of the study unless prescribed as an evening calcium supplement.

In study GD3-163-201, serum phosphorus was  $\geq 1.0$  and  $\leq 2.1$  mmol/l and iPTH  $\leq 66$  pmol/l before screening and at randomisation. In study SVCARB00205, serum phosphorus was  $\geq 1.0$  and  $\leq 2.3$  mmol/l and iPTH  $\leq 99$  pmol/l before screening. Patients had a serum phosphorus level  $\geq 1.8$  mmol/l after the two weeks washout period and serum phosphorus was  $\geq 1.0$  and  $\leq 2.1$  mmol/l and iPTH  $\leq 88$  pmol/l prior to randomisation.

Major exclusion criteria included poorly controlled diabetes mellitus, poorly controlled hypertension, active dysphagia, swallowing disorder, bowel obstruction, or severe gastrointestinal motility disorder.

### *Treatments*

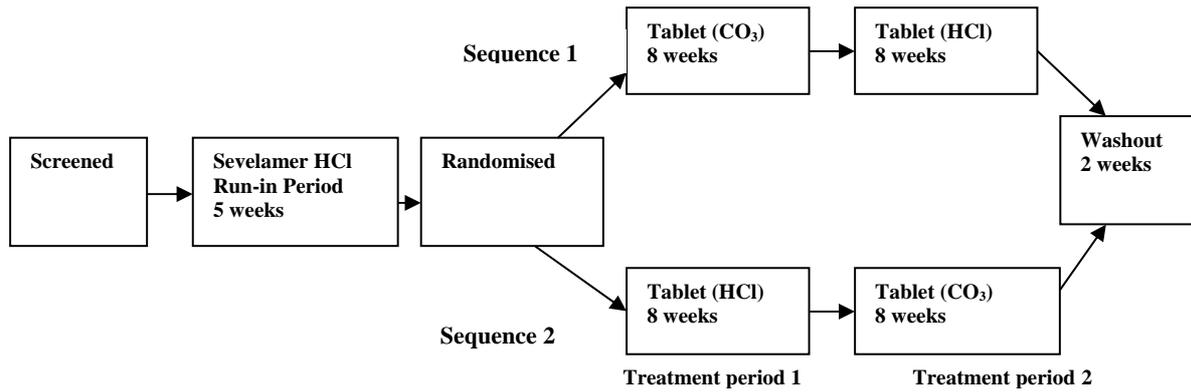
Both studies were cross-over studies in which patients were randomly assigned to two treatment sequences; sevelamer carbonate followed by sevelamer hydrochloride or vice versa (eight weeks each in study GD3-163-201 and four weeks each in study SVCARB00205). The major difference in study design was the place of the washout period. In study GD3-163-201 the patients entered a two-week washout period after the randomisation period whereas in study SVCARB00205 patients entered a two-week washout period prior to the sevelamer hydrochloride run-in period (see Figure 1).

The randomisation period was preceded by a sevelamer hydrochloride run-in period. The starting dose of the sevelamer hydrochloride was based on the most recently prescribed phosphate binder dose prior to screening on a gram per gram basis and with an opportunity to titrate the sevelamer hydrochloride dose (once in study GD3-163-201 and twice in study SVCARB00205 at week -3 and -2 before randomisation). The starting dose during the randomised treatment periods was individualised for each patient based on the prescribed daily dose during the run-in period and patients were instructed to maintain a fixed daily dose throughout both treatment periods. In study SVCARB00205, patients were instructed to return to their pre-study phosphate binder medication at the end of the treatment period and patients returned for a follow-up visit 7 days later.

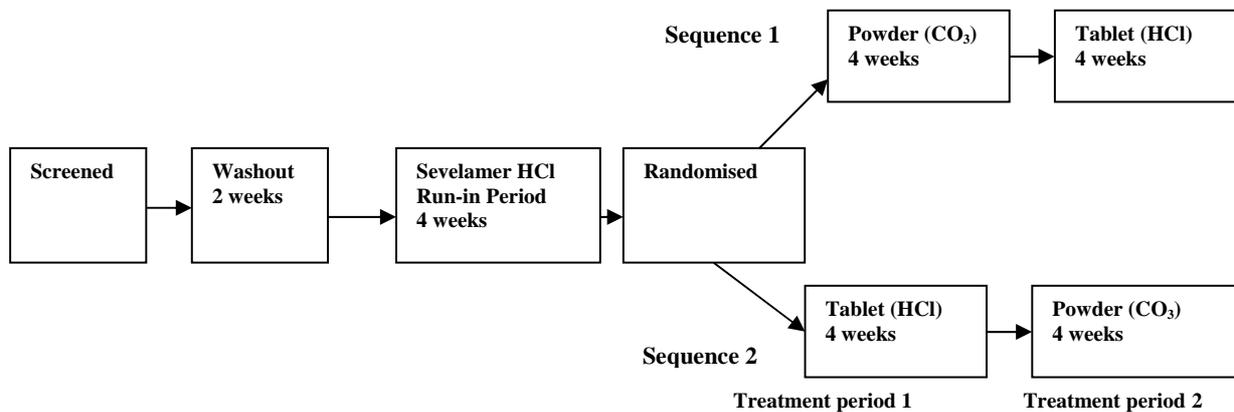
During the randomisation period, patients had weekly visits in study GD3-163-201 during each treatment period. In study SVCARB00205, patients had weekly study visits for the first 2 weeks and 2 study visits during each of the last 2 weeks of each treatment period.

## [Figure 1: Design of Study GD3-163-201 and Study SVCARB00205](#)

### Study GD3-163-201



**Study SVCARB00205**



CO<sub>3</sub>: Carbonate; HCl: Hydrochloride

*Dosing*

Study GD3-163-201: The mean actual dose during the randomized treatment periods was 5.8 ± 2.8 g/day of sevelamer carbonate tablets and 5.6 ± 2.9 g/day of sevelamer hydrochloride tablets in the full analysis population (FAS, for definition, see section on statistical methods). In the Per Protocol Set (PPS), the mean actual dose during the randomized treatment periods was 6.0 ± 2.8 g/day of sevelamer carbonate tablets and 6.0 ± 2.8 g/day of sevelamer hydrochloride tablets.

In study SVCARB00205, the mean actual dose during the randomised treatment periods was 5.9 ± 2.8 g/day of sevelamer carbonate powder and 6.5 ± 3.3 g/day of sevelamer hydrochloride tablets in the FAS.

In the PPS, the mean actual dose during the randomised treatment periods was 6.0 ± 3.1 g/day of sevelamer carbonate powder and 6.4 ± 3.3 g/day of sevelamer hydrochloride tablets.

In both studies, none of the patients changed their prescribed dose during the randomized treatment periods.

*Objectives*

**Primary objectives:**

- Therapeutic equivalence of sevelamer carbonate tablets (GD3-163-201) or powder (SVCARB00205) and sevelamer hydrochloride tablets (dosed TID with meals) on the control of serum phosphorus
- To compare the safety and tolerability of sevelamer carbonate tablets (GD3-163-201) or powder (SVCARB00205) and sevelamer hydrochloride tablets (dosed TID with meals)

#### **Secondary objectives:**

- To compare the effects of sevelamer carbonate tablets (GD3-163-201) or powder (SVCARB00205) and sevelamer hydrochloride tablets (dosed TID with meals) on serum lipid profiles

SVCARB00205 only:

- To compare the effects of sevelamer carbonate powder and sevelamer hydrochloride tablets (dosed TID with meals) on serum calcium-phosphorus product

#### *Outcomes/endpoints*

##### **Primary efficacy endpoint:**

The time-weighted mean of the serum phosphorus values was used as the primary efficacy endpoint. In study GD3-163-201, this endpoint was calculated from the last two weeks of each treatment period (mean of non-missing measurements from week 6 and 8 and from week 14 and 16). In study SVCARB00205, this endpoint was calculated from the last two weeks of each treatment period (mean of non-missing assessments from week 3, 3a, 4 and 4a and from week 7, 7a, 8, 8a).

**Safety endpoints:** These included incidence of adverse events (AEs) and serious adverse events (SAEs), clinically relevant changes in vital signs and clinically relevant changes in laboratory evaluations. Changes were assessed from baseline until end of treatment (ET, week 8 or week 16 in study GD3-163-201 and week 4a or 8a in study SVCARB00205). Clinical relevance was assessed by the investigator and included a medical intervention.

##### **Secondary efficacy endpoint:**

Study GD3-163-201: The mean serum lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) calculated by the mean of the measurements at weeks 4 and 8 or the mean of the measurements of weeks 12 and 16.

Study SVCARB00205: Serum lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) at the end of the treatment period (week 4a and week 8a).

For calcium-phosphorus product, the time-weighted mean of the serum calcium-phosphorus values calculated from the last two weeks of each treatment period (mean of non-missing assessments from week 3, 3a, 4 and 4a and from week 7, 7a, 8, 8a) were used.

#### *Sample size*

Study GD3-163-201: One hundred twenty enrolled and 80 randomised patients were planned for this study. Sample size calculations showed that 7 evaluable patients per sequence for a total of 14 evaluable patients were required to achieve 90% power to detect equivalence based on a 5% equivalence test. This was based on the assumption that the expected ratio of means is 1 and the within subject mean square error from a crossover analysis of variance (ANOVA) is 0.0265. The latter was derived from a simulation based on serum phosphorus levels during a steady-state phase of a prior parallel arm study since no direct data was available. Additional patients were planned to account for dropouts and to expose additional patients to study treatment for the evaluation of safety.

Study SVCARB00205: Allowing for withdrawals, a sample size of 12 patients per sequence (powder/tablet vs. tablet/powder; 24 in total) are required to be randomized to achieve 90% power to detect equivalence based on a 5% Two One-Sided Test (TOST) equivalence test (i.e., reject both the null hypotheses that the ratio of the powder to tablet mean is less than 0.8 and that the ratio of the powder to tablet mean is above 1.25 at the 5% level) assuming that the expected ratio of means is 1 and the standard deviation of the difference between treatments on the log scale is 0.22 (derived from pilot data comparing once-a-day versus TID dosing with sevelamer hydrochloride tablets).

For both studies, no interim analyses were planned.

#### *Randomisation*

Study GD3-163-201: The patients were randomized in a 1:1 fashion to one of the two treatment sequences: sevelamer carbonate for 8 weeks followed by sevelamer hydrochloride for 8 weeks or sevelamer hydrochloride for 8 weeks followed by sevelamer carbonate for 8 weeks. No stratification was performed.

Study SVCARB00205: Patients were randomised within each site on a 1:1 basis in blocks of 4 to one of the two treatment sequences: sevelamer carbonate powder TID for four weeks followed by sevelamer hydrochloride tablets TID for four weeks, or sevelamer hydrochloride tablets TID for four weeks followed by sevelamer carbonate powder TID for four weeks.

#### *Blinding (masking)*

In study GD3-163-201 the patients were blinded to the study medication during the run-in period and both the investigator and the patients were blinded to the treatment sequence assignment and study treatment during the randomisation period. There was no blinding in study SVCARB00205.

#### *Statistical methods*

##### Populations analysed:

The safety set included all randomised patients who received at least one dose of randomised study medication. The full analysis set (FAS) included all randomized patients with at least one post-baseline assessment of serum phosphorus. In study GD3-163-201, the Per Protocol Set (PPS) included all FAS-evaluable patients who completed both Treatment Period 1 and Treatment Period 2 with no significant protocol deviations. In study SVCARB00205, the PPS included all FAS-evaluable patients who completed at least 3 weeks of each treatment period and with no significant protocol deviations.

##### Primary analysis:

The primary analysis set used in both studies to demonstrate **therapeutic equivalence** was the Per-Protocol Population. Therapeutic equivalence was assessed using natural-log transformed time-weighted mean serum phosphorus data. Least squares means for each treatment and the mean squared error from a 2x2 ANOVA with a random subject effect and fixed sequence, period, and treatment effects was used to derive the 90% confidence interval for the difference between sevelamer carbonate (test) and sevelamer hydrochloride (reference) data on the log scale. Back transformation to the original scale yielded an estimate of the ratio (test/reference) and corresponding 90% confidence interval which was the basis of a 5% Two One-Sided Test (TOST) equivalence test. This test required that the 90% confidence interval for the ratio be within the interval (0.80, 1.25) to conclude equivalence.

If the sequence effect is significant ( $p\text{-value} \leq 0.05$ ), then equivalence inferences will be drawn from the treatment period 1 results.

The primary analysis set for **safety** included all randomised patients who were treated with at least one dose of randomised study medication. Adverse events were collected at each visit and treatment groups were compared using McNemar's test (statistical analysis only in study GD3-163-201). Vital signs and laboratory measurements were compared among treatment groups using the Wilcoxon rank sum test, while within treatment group changes were analysed using the Wilcoxon signed rank test.

##### Secondary analyses:

For the secondary efficacy analysis to assess the differences between sevelamer carbonate and sevelamer hydrochloride dosing on lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels) or calcium-phosphorus product (SVCARB00205 only), a 2x2 ANOVA model based on natural-log transformed data with a random subject effect and fixed sequence, period, and treatment effects was used. Comparisons between the treatment groups were tested at the 5% level.

In study GD3-163-201 the mean of the lipid measurements from the two visits in each treatment period (mean of Weeks 4 and 8 and mean of Weeks 12 and 16) was used, while in study SVCARB00205 lipids were assessed only at the end of the study treatment (week 4 and 8). For calcium-phosphorus product (study SVCARB00205) the time-weighted average was used.

In study SVCARB00205 also the geometric least squares means ratio and corresponding 90% confidence intervals was derived for lipids and calcium-phosphorus product as described for the primary efficacy parameter to provide a relative sense of magnitude of any difference that is observed.

**Changes in the planned analysis:**

The original protocol of study GD3-163-201 specified that lipids would be assessed for equivalence. At the analysis planning phase and prior to unblinding, it was decided that such a hypothesis was not necessary and a simple assessment of differences in lipid profiles between the two regimens was appropriate.

The Wilcoxon signed rank test was used rather than the Wilcoxon rank sum test to compare the treatment regimens for the bicarbonate concentration of the dialysate bath, dietary parameters, laboratory measures and vital signs due to the paired nature of the data.

No changes were made in study SVCARB00205.

**RESULTS****RESULTS OF STUDY GD3-163-201***Participant flow*

Overall, 101 patients were enrolled for screening, 97 entered the sevelamer hydrochloride run-in period and 79 were randomised to treatment sequence 1 (carbonate/hydrochloride) or sequence 2 (hydrochloride/carbonate) (see Figure 2). Seven patients did not enter the randomisation phase due to withdrawal of consent, 4 patients did not meet exclusion/inclusion criteria, two patients experienced adverse events and 5 were excluded because of other reasons.

Of the 40 patients assigned to the carbonate/hydrochloride sequence, 39 (97.5%) completed treatment period 1 and 37 (92.5%) patients completed treatment period 2. One patient discontinued during treatment period 1 because of non-compliance with study procedures, one patient discontinued treatment period 2 because of an adverse event and one due to another reason. Twenty-five patients (62.5%) entered the washout period, 12 withdrew consent. The original study design did not include the two-week phosphate binder washout period, but was added to the study to confirm the patients included in the study were hyperphosphataemic. As this change was implemented while the study was in progress, not all patients opted to participate in the washout period.

Of the 39 patients assigned to the hydrochloride/carbonate sequence, 35 (89.7%) completed treatment period 1. All patients discontinued because of an adverse event. One patient discontinued between treatment period 1 and 2 because of an adverse event. Of the 34 patients entering treatment period 2, 32 (82.1%) completed this period. One patient died and the other patient was lost to follow-up. Twenty-two patients entered the washout period and 21 completed this period.

*Recruitment*

The first patient signed informed consent on March 30, 2005 and the last patient completed on March 15, 2006. The study was conducted in the United States.

*Conduct of the study*

There was one protocol amendment before the end of the study, dated July 11, 2005. The most important change was the inclusion of the two-week phosphate binder washout period, to confirm that patients included in the study were hyperphosphataemic.

*Baseline data*

The most important baseline characteristics of the safety set are shown in Table 3. Overall, the baseline characteristics were comparable for both sequences. About 50% of the patients was male and the mean age was 58 years. The primary cause of CKD was diabetes, followed by hypertension. The median time on dialysis was 3.2 years for patients receiving treatment sequence 1 and 2 years for patients receiving treatment sequence 2. The percentage of patients with partial parathyroidectomy varied from 3%-8% and over 80% of the patients were on vitamin D.

**Table 3: Summary of demographics in sevelamer carbonate studies in CKD patients on haemodialysis.**

Variable		Sequence A Carbonate/hydrochloride (N=38)	Sequence B Hydrochloride/carbonate (N=40)
<b>Demographics</b>			
<b>Gender, n (%)</b>			
	Male	20 (53%)	20 (50%)
	Female	18 (47%)	20 (50%)
<b>Ethnicity, n (%)</b>			
	Caucasian	10 (26%)	11 (28%)
	Black	26 (68%)	26 (65%)
	Other	2 (5%)	3 (8%)
<b>Age (years) at screening</b>			
	Mean ± sd	57.01 ± 12.50	59.08 ± 12.16
	Median	56.9	60.0
	Range	29.3 - 79.3	37.4 - 88.0
<b>Renal history</b>			
<b>Primary cause of ESRD, n (%)</b>			
	Hypertension	10 (26.3%)	8 (20.0%)
	Diabetes	15 (39.5%)	18 (45.0%)
	Glomerulonephritis	4 (10.5%)	3 (7.5%)
	Other	9 (23.7%)	11 (27.5%)
<b>Time on dialysis (years)</b>			
	Mean ± sd	5.00 ± 4.73	3.88 ± 5.10
	Median	3.2	2.0
	Range	0.5 – 18.8	0.3 – 23.4
<b>Pre-study phosphate binder, n (%)</b>			
	Sevelamer hydrochloride	34 (89%)	38 (95%)
	Sevelamer hydrochloride and calcium	4 (11%)	2 (5%)
	Other	0	0
<b>Parathyroidectomy, yes n (%)</b>			
		3 (8%)	1 (3%)
<b>Currently on vitamin D, yes, n (%)</b>			
		34 (89%)	33 (83%)

#### *Concomitant medication / dietary intake*

All patients used concomitant medication, which reflects the disease status of the patients. For patients receiving sequence 1, 14 started or changed vitamin D analogues while on sevelamer carbonate and 7 while on sevelamer hydrochloride. For patients receiving sequence 2, 9 started or changed vitamin D analogues while on sevelamer carbonate and 7 while on sevelamer hydrochloride. The dietary intake of calcium, phosphorus and vitamin D seemed comparable during both treatment periods within one sequence.

#### *Numbers analysed*

Seventy-nine patients were randomized, but one patient never received study medication, therefore there are 78 patients in the safety set. All patients in safety set had post-baseline efficacy data, therefore the FAS (Full Analysis Set) also included 78 patients. The total number of patients included in the PPS (Per Protocol Set) was 56. Twenty-two (22) patients had had one or more protocol deviations for which they were excluded from the PPS: 9 patients had a greater than 15% difference in compliance between treatment periods, 9 patients had less than 6 weeks of treatment in either of the treatment periods, 7 patients changed their Vitamin D or Vitamin D analogue significantly, one patient had a significant study medication interruption, and 1 patient used a proscribed medication.

Three patients were treated in an opposite sequence than was delineated by the randomization schedule. These patients were analyzed according to their randomized sequence for the FAS, but were analyzed according to their actual sequence for the safety set and PPS analyses.

#### *Outcomes and estimation*

### Primary efficacy endpoint

For patients in sequence 1, the mean serum phosphorus was  $1.5 \pm 0.3$  mmol/l during sevelamer carbonate and sevelamer hydrochloride treatment. For patients in sequence 2, the mean serum phosphorus was  $1.5 \pm 0.2$  mmol/l during sevelamer hydrochloride treatment and  $1.5 \pm 0.3$  mmol/l during sevelamer carbonate treatment. There was no sequence effect and the results of the mean serum phosphorus level for both treatments and of the equivalence tests for both the PPS and FAS are shown in Table . There was no statistical difference between the mean serum phosphorus levels and the 90% CI of the geometric least square mean ratio (sevelamer carbonate /sevelamer hydrochloride) was within the range of 80%-125%. The 95% CI of the ratio for the PPS was 0.94-1.03.

**Table 4: Serum Phosphorus Time-Weighted Averages (mmol/l)**

Analysis set	Sevelamer carbonate, TID	Sevelamer hydrochloride, TID	Geometric Least Square Mean Ratio	90% CI	95% CI
<b>Study GD3-163-201, tablets</b>					
<b>PPS</b> Mean $\pm$ sd	$1.5 \pm 0.3$ (N=56)	$1.5 \pm 0.3$ (N=56)	0.99	0.95, 1.03	0.94, 1.03
<b>FAS</b> Mean $\pm$ sd	$1.6 \pm 0.3$ (N=73)	$1.6 \pm 0.3$ (N=78)	0.99	0.96, 1.02	

A total of 40 patients entered the washout period. At the end of the treatment period the serum phosphorus was  $1.6 \pm 0.4$  mmol/l in all FAS patients participating in the washout period ( $1.5 \pm 0.4$  mmol/l in patients treated according to sequence 1 and  $1.7 \pm 0.5$  mmol/l in patients treated according to sequence 2). Following the two-week washout period, the serum phosphorus level increased significantly to  $2.1 \pm 0.6$  mmol/l with an overall increase of serum phosphorus level of  $0.5 \pm 0.6$  mmol/l (Sequence 1: increase of  $0.5 \pm 0.5$  mmol/l; Sequence 2: increase of  $0.4 \pm 0.7$  mmol/l).

### Secondary efficacy endpoint

At baseline, the mean LDL cholesterol was  $1.5 \pm 0.6$  mmol/l in the sevelamer carbonate treated group and  $1.5 \pm 0.7$  mmol/l in the sevelamer hydrochloride treated group. After treatment, the mean LDL cholesterol was  $1.5 \pm 0.6$  mmol/l during sevelamer carbonate treatment and  $1.4 \pm 0.6$  mmol/l during sevelamer hydrochloride treatment, which was statistically different. The geometric least square mean ratio (sevelamer carbonate /sevelamer hydrochloride) was 1.07 (90% CI: 1.01-1.12) (see Table 5). No differences were observed with regard to HDL cholesterol and triglycerides. The differences in total cholesterol ( $3.7 \pm 0.9$  mmol/l with sevelamer carbonate and  $3.6 \pm 0.9$  mmol/l with sevelamer hydrochloride) reflected the differences in LDL cholesterol. Safety analyses assessing the change from baseline to end of treatment only showed statistically significant changes for total cholesterol.

**Table 5: Analysis of serum lipids (mmol/l) - Full Analysis Set**

Serum lipids	Sevelamer carbonate, TID	Sevelamer hydrochloride, TID	Geometric Least Square Mean Ratio	90% CI
Total cholesterol	$3.7 \pm 0.9$	$3.6 \pm 0.9$	1.04	1.01 – 1.06
LDL cholesterol	$1.5 \pm 0.6$	$1.4 \pm 0.6$	1.07	1.01 – 1.12
HDL cholesterol	$1.3 \pm 0.5$	$1.3 \pm 0.4$	1.01	0.98 – 1.03
Triglycerides*	$2.0 \pm 1.3$	$1.9 \pm 1.2$	1.03	0.99 – 1.07

\*median

*Ancillary analyses*

Post-hoc analyses were performed for the primary efficacy parameter to understand the results across dose level as a marker for degree of underlying hyperphosphataemia. The geometric mean ratio of serum phosphorus level (carbonate/hydrochloride) was 0.97 (90% CI: 0.91-1.04) for a dose  $\leq$ 4.8 gram, 0.95 (90% CI: 0.85-1.05) for a dose  $>$  4.8 -  $<$ 9.6 gram, and 1.04 (90% CI: 0.98-1.10) for a dose  $\geq$  9.6 gram. A regression analysis of the equivalence ratio (sevelamer carbonate/sevelamer hydrochloride) on prescribed dose showed a flat regression line and a non-significant p-value ( $y=0.95 +0.01*x$ ;  $p=0.2745$ ) indicating that the equivalence ratio is invariant to prescribed dose.

### **Change in serum phosphorus, calcium-phosphorus product, iPTH, calcium and vitamin D**

For safety analysis, changes from baseline to end of treatment (week 8/16/final) were calculated for amongst others calcium (adjusted for albumin), calcium-phosphorus product, iPTH, 25 hydroxy vitamin D and 1-25 dihydroxyvitamin D. (The values in mmol/l, etc were calculated as these were not provided by the applicant).

There was a small, but statistically significant increase in **calcium-phosphorus product** during sevelamer hydrochloride treatment (mean change of  $0.25 \pm 0.91 \text{ mmol}^2/\text{l}^2$ ; from  $3.4 \pm 0.86 \text{ mmol}^2/\text{l}^2$  to  $3.6 \pm 0.94 \text{ mmol}^2/\text{l}^2$ ), but not during sevelamer carbonate treatment (mean change of  $0.17 \pm 0.89 \text{ mmol}^2/\text{l}^2$ ; from  $3.4 \pm 0.82 \text{ mmol}^2/\text{l}^2$  to  $3.6 \pm 0.89 \text{ mmol}^2/\text{l}^2$ ). Again, there was no statistically significant difference in the change in calcium-phosphorus product between the treatment regimens.

**Median iPTH** increased significantly during both sevelamer carbonate treatment (from 27.0 pmol/l to 32.7 pmol/l) and sevelamer hydrochloride treatment (from 27.4 pmol/l to 28.4 pmol/l). The difference between treatment regimens was statistically significant.

There was no statistically significant change in serum **calcium** during either treatment (from  $2.3 \pm 0.2 \text{ mmol/l}$  at baseline to  $2.3 \pm 0.1 \text{ mmol/l}$  after treatment for sevelamer carbonate and from  $2.3 \pm 0.2 \text{ mmol/l}$  at baseline to  $2.3 \pm 0.2 \text{ mmol/l}$  after treatment for sevelamer hydrochloride) and no statistically significant difference in the change in serum calcium between the treatment regimens.

There were no statistically significant changes in the **vitamin D measures** for either treatment and no statistically significant difference in change in these parameters between the treatments. 25 Hydroxyvitamin changed from  $75.2 \pm 48.1 \text{ nmol/l}$  at baseline to  $79.7 \pm 52.1 \text{ nmol/l}$  after treatment with sevelamer carbonate and from  $75.4 \pm 46.7 \text{ nmol/l}$  at baseline to  $75.7 \pm 43.3 \text{ nmol/l}$  after treatment with sevelamer hydrochloride. 1-25 Dihydroxyvitamin changed from  $70.5 \pm 26.4 \text{ pmol/l}$  at baseline to  $68.1 \pm 28.8 \text{ pmol/l}$  after treatment with sevelamer carbonate and from  $71.7 \pm 26.4 \text{ pmol/l}$  at baseline to  $65.2 \pm 24.9 \text{ pmol/l}$  after treatment with sevelamer hydrochloride.

## **Results of study SVCARB00205**

### *Participant flow*

Overall, 75 patients individuals enrolled for screening of which one was re-screened and counted twice in pre-randomisation disposition data, giving an overall of 76 patients. Of the screened patients enrolling the two-week washout period, 42 (55.3%) entered the run-in period. The most common reason for not entering the run-in period was screen failure (26/34, 76%) (predominantly (17/26) because of serum phosphorus levels below 1.78 mmol/l). Of the 42 patients entering the run-in period, 31 (40.8%) were randomised to study treatment, 7 patients were excluded because of screen failure (mostly because of high iPTH levels or high phosphorus levels), 1 because of non-compliance and 3 patients were excluded for other reasons.

Of the 17 patients assigned to the carbonate/hydrochloride sequence (sequence 1), 14 completed both treatment period 1 and 2. One patient discontinued during treatment period 1 because of an adverse event and two patients withdrew consent.

Of the 14 patients assigned to the hydrochloride/carbonate sequence (sequence 2), 14 completed treatment period 1 and 10 completed treatment period 2. One patient discontinued because of an adverse event and three patients withdrew consent.

### *Recruitment*

The first patient signed informed consent on 31 January 2006 and the last patient completed the last visit on 21 March 2007. The study was conducted in the United Kingdom.

### *Conduct of the study*

There was one amendment to the clinical study report, dated January 11, 2008. Additional information not reported during the study was identified by the sponsor at site 02 during preparatory activities for a site inspection by the Medicines and Healthcare products Regulatory Agency (MHRA). The amendment describes changes in the text and tables from the original clinical study report, the original study report was not modified to reflect these changes.

The main changes in the conduct of the study included:

- a. Increase in number of patients to be screened was changed from approximately 35 to approximately 75 due to a higher than anticipated screening failure rate.
- b. Sevelamer hydrochloride did not need to be the primary phosphate binder in those patients taking combination therapy before entry into the study.
- c. Study entry limits of iPTH and serum phosphorus levels measured at the local laboratory were increased due to the variation between local and central laboratory analyses, which meant that some patients may not be considered eligible by the local analysis and would therefore not be screened.

### *Baseline data*

The most important baseline characteristics of the safety set are shown in Table 6. Overall, the baseline characteristics were comparable for both sequences. The majority of patients was male (65% in treatment sequence 1 and 71% in treatment sequence 2) and the mean age was 52-55 years. The primary cause of CKD was glomerulonephritis. The median time on dialysis was 4.4 years for patients receiving treatment sequence 1 and over 4.6 years for patients receiving treatment sequence 2. The percentage of patients with partial parathyroidectomy varied from 12%-14%. The majority of patients received vitamin D (88% of patients in treatment sequence 1 and 71% in treatment sequence 2).

### *Concomitant medication / dietary intake*

Thirteen percent of the patients had partial parathyroidectomy and 81% were on vitamin D.

For patients receiving sequence 1, 1 patient started, stopped or changed vitamin D analogues while on sevelamer carbonate and for patients receiving sequence 2, 2 patients started, stopped or changed vitamin D analogues while on sevelamer carbonate.

**Table 6: Summary of baseline demographics in study SVCARB00205**

Variable	Sequence 1 Carbonate/hydrochloride (N=17)	Sequence 2 Hydrochloride/carbonate (N=14)
<b>Demographics</b>		
<b>Gender, n (%)</b>		
Male	11 (64.7%)	10 (71.4%)
Female	6 (35.3%)	4 (28.6%)
<b>Ethnicity, n (%)</b>		
Caucasian	14 (82.4%)	8 (57.1%)
Black	1 (5.9%)	2 (14.3%)
Other	2 (11.8%)	4 (28.6%)
<b>Age (years) at screening</b>		
Mean ± sd	51.6 ± 14.8	54.5 ± 11.4
Median	47	55
Range	27-80	39-73
<b>Renal history</b>		
<b>Primary cause of ESRD, n (%)</b>		
Hypertension	0	1 (7.1%)
Diabetes	0	4 (28.6%)
Glomerulonephritis	4 (23.5%)	4 (28.6%)
Other	13 (76.5%)	5 (35.7%)
<b>Time on dialysis (years)</b>		
Mean ± sd	8.00 ± 9.05	6.27 ± 6.70
Median	4.4	4.6

	Range	0.2-30.3	0.5-24.2
<b>Pre-study phosphate binder, n (%)</b>			
	Sevelamer hydrochloride	9 (52.9%)	9 (64.3%)
	Sevelamer hydrochloride and calcium	7 (41.2%)	4 (28.6%)
	Other	1 (5.9%)	1 (7.1%)
<b>Parathyroidectomy, yes n (%)</b>			
		2 (11.8%)	2 (14.3%)
<b>Currently on vitamin D, yes, n (%)</b>			
		15 (88.2%)	10 (71.4%)

### Numbers analysed

Thirty-one patients were randomised and treated and all included in the safety set. All but 1 patient in the safety set had post-baseline serum phosphorus data, and therefore there are 30 patients in the FAS. Nine patients were excluded from the FAS, and therefore the PPS includes 21 patients. Of the nine patients excluded, 6 were on study medication for less than 3 weeks in both treatment periods and 3 had at least 30% difference in compliance between treatment periods.

### Outcomes and estimation

#### Primary efficacy endpoint

For patients in sequence 1, the mean serum phosphorus was  $1.59 \pm 0.54$  mmol/l during sevelamer carbonate treatment and  $1.67 \pm 0.34$  mmol/l during sevelamer hydrochloride treatment. For patients in sequence 2, the mean serum phosphorus was  $1.62 \pm 0.42$  mmol/l during sevelamer hydrochloride treatment and  $1.66 \pm 0.38$  mmol/l during sevelamer carbonate treatment. There was no sequence effect and the results of the mean serum phosphorus level for both treatments and of the equivalence tests for both the Per Protocol Set and Full Analysis Set are shown in Table 7.

There was no statistically difference between the mean serum phosphorus levels and the 90% CI of the geometric least square mean ratio (sevelamer carbonate /sevelamer hydrochloride) was within the range of 80%-125%. The 95% CI of the ratio for the PPS was 0.85-1.05.

**Table 7: Serum Phosphorus Time-Weighted Averages (mmol/l)**

Analysis set	Sevelamer carbonate, TID	Sevelamer hydrochloride, TID	Geometric Least Square Mean Ratio	90% CI	95% CI
<b>PPS</b> Mean $\pm$ sd	$1.6 \pm 0.5$ (N=21)	$1.7 \pm 0.4$ (N=21)	0.95	0.87, 1.03	0.85, 1.05
<b>FAS</b> Mean $\pm$ sd	$1.6 \pm 0.5$ (N=25)	$1.7 \pm 0.4$ (N=28)	0.96	0.88, 1.05	

### Phosphorus during screening/washout and run-in period

The mean serum phosphorus at screening, at the end of the washout period, and before randomisation are shown in Table 8 for the PPS. Overall, the mean serum phosphorus level was  $1.6 \pm 0.3$  mmol/l at screening and increased to  $2.5 \pm 0.6$  mmol/l (mean change  $0.9 \pm 0.7$  mmol/l). Serum phosphorus levels subsequently decreased to  $1.6 \pm 0.4$  mmol/l after the sevelamer hydrochloride run-in period. Comparable changes were observed in the FAS and Safety Set.

**Table 8: Serum phosphorus (mmol/l) at screening, after washout and before randomisation – Per Protocol Set.**

	Overall (n=21) [mean $\pm$ sd]	Sequence 1 (Carbonate/hydrochloride) (n=13) [mean $\pm$ sd]	Sequence 2 (Hydrochloride/carbonate) (n=8) [mean $\pm$ sd]
Screening	$1.6 \pm 0.3$	$1.5 \pm 0.4$	$1.8 \pm 0.1$
After washout	$2.5 \pm 0.6$	$2.5 \pm 0.5$	$2.4 \pm 0.7$
Change	$0.9 \pm 0.7$	$1.0 \pm 0.6$	$0.6 \pm 0.7$
P-value	<0.001	<0.001	0.055
After Run-in/before randomisation (range)	$1.6 \pm 0.4$ (0.8 – 2.6)	$1.6 \pm 0.4$ (0.8 – 2.6)	$1.6 \pm 0.4$ (1.0 – 2.2)

### Secondary efficacy endpoint

#### Serum calcium (albumin-adjusted)-phosphorus product (Ca x Pi)

The overall average serum calcium (albumin-adjusted)-phosphorus product at randomisation was  $3.8 \pm 0.8 \text{ mmol}^2/\text{l}^2$  and comparable for both treatment sequences. There was no sequence effect and the average Ca x Pi product was  $3.7 \pm 1.1 \text{ mmol}^2/\text{l}^2$  upon sevelamer carbonate treatment and  $3.7 \pm 0.8 \text{ mmol}^2/\text{l}^2$  upon sevelamer hydrochloride treatment (FAS). The geometric least squares mean ratio (sevelamer carbonate powder/sevelamer hydrochloride tablets) was 0.98 with a corresponding 90% confidence interval of 0.88-1.09.

The mean serum calcium (albumin-adjusted)-phosphorus product at screening was  $3.8 \pm 0.9 \text{ mmol}^2/\text{l}^2$  and increased to  $5.4 \pm 1.5 \text{ mmol}^2/\text{l}^2$  (mean change  $1.6 \pm 1.8 \text{ mmol}^2/\text{l}^2$ ;  $p < 0.001$ ) after the washout period.

### Serum lipids

There were no differences between treatments with regard to LDL cholesterol, HDL cholesterol, triglycerides, or total cholesterol as shown in Table 9.

**Table 9: Analysis of serum lipids (mmol/l) – Full analysis set.**

Serum lipids	Sevelamer carbonate, TID	Sevelamer hydrochloride, TID	Geometric Least Square Mean Ratio	90% CI
Total cholesterol	$3.5 \pm 0.7$	$3.3 \pm 0.8$	1.02	0.99 – 1.06
LDL cholesterol	$1.8 \pm 0.5$	$1.8 \pm 0.7$	1.05	1.00 – 1.10
HDL cholesterol	$1.2 \pm 0.5$	$1.1 \pm 0.4$	0.98	0.93 – 1.04
Triglycerides*	$2.2 \pm 1.6$	$2.1 \pm 1.5$	1.0	0.89 – 1.12

\*median

Analysis of the PPS showed a statistically significant treatment sequence effect for LDL cholesterol and therefore the results were analysed using treatment period 1. No differences were observed between treatment regimens when only the results of treatment period 1 were analysed.

### Ancillary analyses

**Median serum iPTH** increased significantly during sevelamer hydrochloride tablet treatment (median change 4.4 pmol/l; from 23.1 pmol/l to 28.3 pmol/l). Median serum iPTH levels also increased during sevelamer carbonate powder treatment (3.1 pmol/l; from 30.6 pmol/l to 41.0 pmol/l) but the change from baseline was not statistically significant. There was no statistically significant difference between treatment regimens with regards to change in serum iPTH levels.

There was no statistically significant change in serum **calcium** (albumin-adjusted) during either treatment (serum calcium level of  $2.3 \pm 0.2 \text{ mmol/l}$  at baseline and after treatment for both treatment regimens).

There were no statistically significant changes from baseline to end of treatment in 25-hydroxyvitamin levels (sevelamer carbonate: from  $53.6 \pm 32.7 \text{ nmol/l}$  to  $47.6 \pm 29.0 \text{ nmol/l}$ ; sevelamer hydrochloride: from  $54.7 \pm 32.7 \text{ nmol/l}$  to  $52.1 \pm 34.4 \text{ nmol/l}$ ) and 1,25 dihydroxyvitamin D levels (sevelamer carbonate: from  $58.5 \pm 27.7 \text{ pmol/l}$  to  $69.3 \pm 45.7 \text{ pmol/l}$ ; sevelamer hydrochloride: from  $56.5 \pm 28.3 \text{ pmol/l}$  to  $64.2 \pm 23.4 \text{ pmol/l}$ ).

## CKD PATIENTS NOT ON DIALYSIS

**Study SVCARB00105:** A phase 3, multi-centre, open-label, single arm, dose titration study in hyperphosphataemic CKD patients not on dialysis, designed to evaluate the safety and efficacy of sevelamer carbonate tablets dosed TID with meals.

### Scientific advice

Scientific advice was sought by Genzyme regarding the design of a dose titration study using sevelamer carbonate in hyperphosphataemic CKD patients not on dialysis (study SVCARB00105). Advice was provided by the CHMP on 26 May 2005. This advice concerned; the proposed sample size, study design with respect to the use of an active comparator or placebo, proposed starting and maintenance dose.

In summary, the Company did not completely follow the Scientific Advice. The points of dissention are:

- It can be argued whether 49 pre-dialysis CKD patients recruited across 18 sites (41 patients completed the study) is a “reasonable number of patients in clear need for phosphate binders” for such a prevalent disease. The safety database in pre-dialysis CKD patients is very small.
- The Company did not follow the suggestion that “Descriptive data from a reasonably large randomised, active comparator-controlled study with patients in real need for treatment with a phosphate binder without predefined non-inferiority criteria would nevertheless be regarded as informative by the CHMP.” In particular, the non-comparative nature of study SVCARB00105 makes it impossible to examine safety issues related to calcium and PTH levels. Calcium carbonate is registered in a number of EU countries for the indication hyperphosphataemia, regardless of dialysis status, and it could have been considered as an adequate active control.

## METHODS

### *Study Participants*

Inclusion criteria:

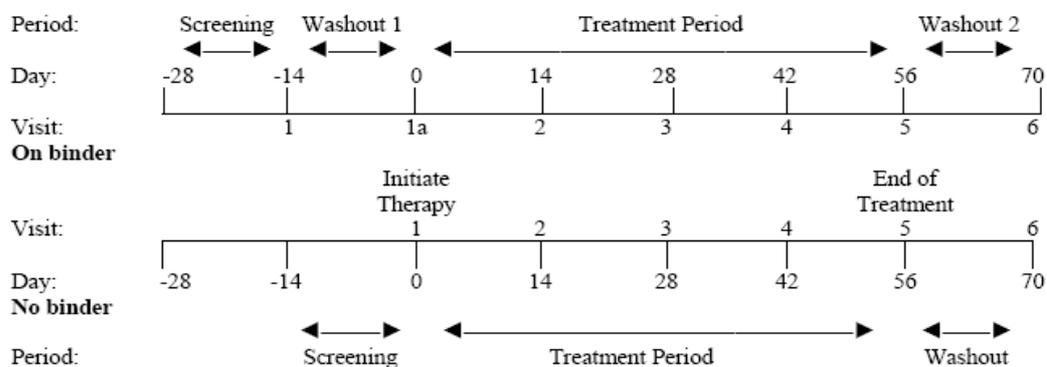
Adult (>17 years) patients with CKD not on dialysis. Patients did or did not use phosphate binders at screening and had iPTH  $\leq 88$  pmol/l and 25 hydroxyvitamin D  $\geq 25$  nmol/l. Other major inclusion criteria included stable diet, negative pregnancy test and an acceptable contraceptive method. Patients should be willing and able to avoid antacids and phosphorus binders containing aluminium, magnesium, calcium or lanthanum for the duration of the study unless prescribed as an evening calcium supplement. Patients with a serum phosphorus level  $> 1.78$  mmol/l either at screening or after the two week washout period (in case patients were on phosphate binder therapy at screening) were eligible for study treatment.

Major exclusion criteria included poorly controlled diabetes mellitus, poorly controlled hypertension, active dysphagia, swallowing disorder, bowel obstruction, or severe gastrointestinal motility disorder.

### *Treatments*

The study consisted of four periods: a 2-week screening period, a 2-week washout period, an 8-week treatment period followed by a second 2-week washout period (see Figure 2). The initial 2-week washout period was only applicable for those eligible patients taking phosphate binder(s) at screening.

**Figure 2: Schematic presentation of study SVCARB00105**



Eligible patients who were not taking phosphate binder(s) at screening proceeded directly to the start of the 8-week treatment period. Patients started treatment with sevelamer carbonate at a dose of 4.8 g daily (2 x 800 mg tablets TID). The starting dose of sevelamer carbonate of 4.8 g/day was based on data from a Phase 2 study, GTC-45-204, with sevelamer hydrochloride in hyperphosphataemic CKD patients not on dialysis, where a statistically significant reduction in serum phosphorus was

demonstrated with an average dose of sevelamer hydrochloride of 3.53 g/day. However this study showed the number of patients attaining serum phosphorus within the target range was not as high, and the magnitude of reduction in serum phosphorus was lower than previously seen in clinical trials involving haemodialysis patients where average doses of approximately 6 g/day were used. Therefore, the starting dose for the current study was set at 4.8 g daily. The sevelamer carbonate dose was titrated to a maximum dose of 12 g/day (15 x 800 mg tablets) during the treatment period in increments of 2.4 g daily (1 x 800 mg tablet TID) at visits on Days 14, 28, and 42 to attain a target serum phosphorus level  $\geq 0.86$  and  $\leq 1.47$  mmol/l. At day 56/ET blood samples were taken, sevelamer carbonate was stopped and patients entered a second washout phase of two weeks. During the treatment period, patients were supplemented with a daily dose of 400 IU of the native form of vitamin D to minimize the effects of any dietary absorption of vitamin D that may occur during treatment with sevelamer carbonate, this was to be taken at bedtime away from the dose of sevelamer carbonate. This supplement was to be given in addition to any active vitamin D therapy routinely prescribed at the start of the study. After the second washout period, patients were returned to their pre-treatment phosphate binders(s), if applicable.

Blood draws were obtained every 2 weeks for the 8-week treatment period beginning at baseline (i.e. Days 0, 14, 28, 42, and 56) and at day 70 after the second washout period.

At the end of treatment, the mean prescribed daily dose for the Safety Set was 7.59 g/day, similar to that in the FAS and PPS. The mean actual daily dose for all three analysis populations was similar; for the Safety Set it was 5.38 g/day; for the FAS it was 5.52 g/day; and for the PPS it was 5.93 g/day.

#### *Objectives*

##### **Primary objectives:**

1. To evaluate the efficacy of sevelamer carbonate tablets dosed three times a day (TID) with meals in controlling serum phosphorus levels in CKD patients not on dialysis.
2. To evaluate the safety and tolerability of sevelamer carbonate tablets dosed TID with meals in CKD patients not on dialysis.

##### **Secondary objectives:**

1. To evaluate serum calcium-phosphorus product
2. To evaluate serum lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol and low density lipoprotein [LDL] cholesterol)
3. To evaluate percent responders (serum phosphorus between 0.86 mmol/l and 1.47 mmol/l at day 56/early termination (ET)).

#### *Outcomes/endpoints*

##### **Primary efficacy endpoint:**

The primary efficacy variable was the change in serum phosphorus from baseline to day 56/ET.

##### **Secondary efficacy endpoint:**

1. Change in serum calcium-phosphorus product (Ca x Pi) from baseline to day 56/ET
2. Change in total cholesterol, LDL cholesterol, HDL cholesterol from baseline to day 56/ET
3. Percent responders (serum phosphorus between 0.86 and 1.47 mmol/l) at day 56/ET

##### **Safety endpoints:**

These included incidence of adverse events and serious adverse event, changes in vital signs, physical examination abnormal changes, and changes in clinical laboratory evaluations.

#### *Sample size*

To detect a 0.32 mmol/l average change from baseline based on a two-sided paired t-test with 5% type I error rate and an assumed standard deviation for the change from baseline of 0.45 mmol/L it was calculated that 23 evaluable (Full Analysis Set) patients were required. To account for a possible 20% dropout rate, a minimum of 28 patients needed to be treated. However recruitment continued until 30th September 2006 to maximize generation of safety data for this population.

No interim analysis was planned.

*Randomisation*  
Not applicable

*Blinding (masking)*  
Not applicable

*Statistical methods*

For the **primary efficacy analysis** (i.e., change in serum phosphorus at day 56/ET), a wilcoxon signed rank test was used to assess the changes. The last non-missing post-baseline observation (scheduled or unscheduled) was carried forward to represent the day 56/ET value for patients who terminated from the study prior to day 56 and did not complete day 56/ET visit.

The primary analysis set for **safety** included all randomised patients who were treated with at least one dose of randomised study medication. Descriptive statistics of adverse events were shown, no statistical testing was performed. Changes in vital signs and laboratory measurements were analysed using the Wilcoxon signed rank test.

For the **secondary efficacy analyses**, the changes between baseline and day 56/ET for total cholesterol, LDL cholesterol, HDL cholesterol, and calcium-phosphorus product were assessed using a Wilcoxon signed rank test.

**Changes in the planned analysis:**

No changes were made to the protocol-defined analysis.

Additional post hoc analyses that were performed among the FAS included serum phosphorus over time by CKD Stage (4 versus 5), serum phosphorus over time among the subset of patients who were on phosphate binder(s) at study entry, serum phosphorus over time by investigative site and compliance, dosing, and baseline serum phosphorus by serum phosphorus responder status at day 56/ET

RESULTS

*Participant flow*

A total of 129 individual patients were screened for this study, of which 12 were re-screened. Forty-nine patients entered the treatment phase of which 41 completed the study. Four patients discontinued due to an adverse event, 2 patients withdrew consent and 2 patients discontinued due to “other” reasons.

*Recruitment*

Patients were screened for study entry at 19 study centres and patients were treated in 18 centres (14 in Europe and 4 in Australia). The first patient signed informed consent on 14 February, 2006 and the last patient completed the last visit on 23 January, 2007.

*Conduct of the study*

There was one protocol amendment made, to allow additional enrolment of patients for the purpose of increasing the understanding of the safety profile in the CKD population, dated 21 August, 2006.

This amendment specifically made provision for including study sites in Australia and raising the number of sites in Europe, extension of study enrolment period and increasing the number screened and treated patients and extension of the time of AE and concomitant medication recording from start of screening to time of signing informed consent.

*Baseline data*

Baseline demographics and characteristics are shown in Table 10. Sixty-five percent (n=32) of patients were male and 35% (n=17) of patients were female, with a mean age of 62.0 years (sd=12.2; range: 23-81). Most patients were Caucasian (n=45, 92%). The most common primary causes of chronic kidney disease were diabetes (n=9, 18%), glomerulonephritis (n=8, 16%) and polycystic kidney disease (n=8, 16%). Sixty-one percent (n=30) of patients were taking a phosphate binder prior to entry and 49% (n=24) used vitamin D pre-study. A total of 35% (n=17) of the patients were classified as

[Table 10: Summary of demographics and characteristics in sevelamer carbonate studies in CKD patients not on haemodialysis.](#)

CKD stage 4 (GFR 15-29 mL/minute/1.73m<sup>2</sup>), with the remaining 65% (n=32) of the patients being classified CKD stage 5 (GFR <15 mL/minute/1.73m<sup>2</sup>) according to KDOQI definitions.

Variable	Sevelamer carbonate tablets TID (N=49)
<b>Demographics</b>	
<b>Gender, n (%)</b>	
Male	32 (65.3%)
Female	17 (34.7%)
<b>Ethnicity, n (%)</b>	
Caucasian	45 (91.85)
Black	1 (2.0)
Other	3 (6.15)
<b>Age (years) at screening</b>	
Mean ± sd	62.0 ± 12.1
Median	64
Range	23-81
<b>Renal history</b>	
<b>Primary cause of ESRD, n (%)</b>	
Hypertension	7 (14.3%)
Glomerulonephritis	8 (16.3%)
Diabetes	9 (18.4%)
Polycystic kidneys	8 (16.3%)
Pyeolonephritis	4 (8.2%)
Other	13 (26.5%)
<b>Pre-study phosphate binder, n (%)</b>	
Calcium acetate	5 (10.2%)
Calcium acetate + Renagel	1 (2.0%)
Calcium carbonate	23 (46.9%)
Calcium carbonate + Renagel	1 (2.0%)
N/A	19 (38.8%)
<b>Parathyroidectomy, n (%)</b>	
Yes	0
<b>Currently on vitamin D, n (%)</b>	
Yes	24 (49.0%)
<b>Chronic Kidney Disease state, n (%)</b>	
Stage 1-3	0
Stage 4 (15-29 GFR ml/minute/1.73 m <sup>2</sup> )	17 (34.7%)
Stage 5 (<15 GFR ml/minute/1.73 m <sup>2</sup> )	32 (65.3%)

### *Numbers analysed*

The Safety Set included all patients who received at least one dose of sevelamer carbonate. One hundred and twenty nine individual patients were screened, of these, 49 patients were dispensed and administered sevelamer carbonate and are included in the Safety Set.

The FAS included the subset of patients in the Safety Set with a baseline and at least one post-baseline serum phosphorus measure during the study treatment period (± 5 days). All but three patients in the Safety Set had post-baseline efficacy data, therefore the FAS includes 46 patients.

The PPS includes all FAS-evaluable patients with no significant protocol deviations who had more than 75% treatment compliance, and were on treatment for at least 42 days. A total of 11 patients (11/46=24%) were excluded for the PPS-analysis, mostly (n=6) because treatment compliance was below 75%. Other reasons for exclusion were entry criteria violation (n=1), treatment for less than 42 days (n=1), proscribed medication usage (n=2) and other (n=1). Thus, the PPS includes 35 patients.

### *Outcomes and estimation*

#### Primary efficacy endpoint

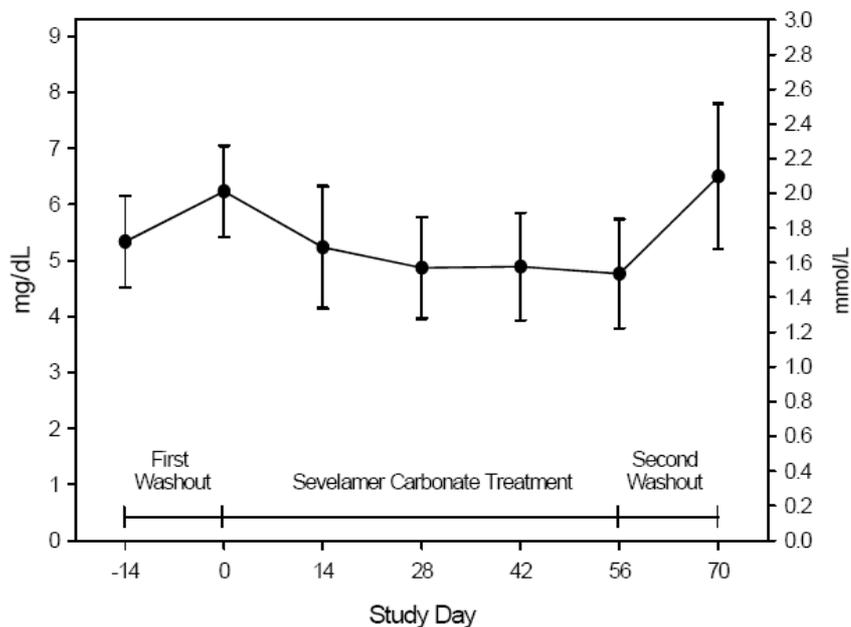
The primary efficacy analysis was the change from baseline in serum phosphorus levels. Mean baseline serum phosphorus levels were 2.01 mmol/l for the FAS. The corresponding mean levels at Day 56/ET were 1.56 mmol/l and the mean change from baseline was -0.45 mmol/l (95%CI: -0.55, -0.35). The decrease in serum phosphorus values from baseline to Day 56/ET was statistically significant. The results of the PPS-analysis were comparable (mean change from baseline to day 56/ET of -0.45 mmol/l, 95% CI: -0.57, -0.34).

**Table 11: Serum phosphorus levels and change in serum phosphorus with sevelamer carbonate in CKD patients not on dialysis (Full Analysis Set).**

Time point statistics	Serum phosphorus (mmol/l)
Baseline (n=46)	
Mean ± sd	2.01 ± 0.26
Median (range)	1.95 (1.51 - 2.72)
Day 56/ET (n=46)	
Mean ± sd	1.56 ± 0.32
Median (range)	1.46 (0.85 - 2.36)
Change from baseline to day 56/ET (n=46)	
Mean (95% CI)	-0.45 (-0.55 - -0.35)
Day 70, washout (n=40)	
Mean ± sd	2.10 ± 0.42
Median (range)	2.14 (1.05 - 2.96)
Change from day 56 to day 70 (n=40)	
Mean (95% CI)	0.55 (0.44 - 0.66)

Analysis of serum phosphorus levels over time clearly showed a decrease in serum phosphorus level during treatment and an increase of serum phosphorus level during the phosphate binder washout period (Figure 3).

**Figure 3: Serum phosphorus levels over time (Full Analysis Set)**



First washout is only applicable for patients taking phosphate binders at study entry

A comprehensive literature search by the applicant yielded only a small number of randomised clinical trials in hyperphosphataemic CKD patients not on dialysis using calcium as a phosphate binder.

Secondary efficacy endpoints

**Serum phosphorus responders**

By the end of study treatment (Day 56/ET), 50% (95% CI: 35.6%, 64.5%) of patients in the FAS reached the titration target level of serum phosphorus  $\geq 0.86$  and  $\leq 1.47$  mmol/l following treatment

with sevelamer carbonate. Comparable results were obtained when only patients with a day 56 response were analysed (54% responders; 95% CI: 38.4%, 68.9%). Using descriptive statistics of baseline serum phosphorus, compliance and mean dose, these seemed comparable for responders and non-responders.

#### **Calcium (albumin-adjusted)-phosphorus product**

The mean level of calcium (albumin-adjusted)-phosphorus product at baseline was  $4.3 \pm 0.57$  mmol<sup>2</sup>/l<sup>2</sup> and significantly decreased to  $3.4 \pm 0.65$  mmol<sup>2</sup>/l<sup>2</sup> at day 56/ET in the FAS population (mean change:  $-0.8 \pm 0.73$  mmol<sup>2</sup>/l<sup>2</sup>, n=43). During washout, Ca x Pi increased again (mean change:  $1.1 \pm 0.77$  mmol<sup>2</sup>/l<sup>2</sup>, n=40). Comparable results were obtained for the PPS population.

#### **Serum lipids**

In the FAS population, serum levels of total cholesterol significantly decreased during treatment with a mean change from baseline to day 56/ET of  $-0.9 \pm 0.79$  mmol/l (mean percent change:  $-19.5 \pm 17.1\%$ ; from  $4.5 \pm 1.08$  mmol/l to  $3.5 \pm 0.94$  mmol/l). The mean change in serum LDL cholesterol from baseline to day 56/ET was  $-0.9 \pm 0.58$  mmol/l (mean percent change:  $-31.9 \pm 18.1\%$ ; from  $2.7 \pm 0.87$  mmol/l to  $1.8 \pm 0.65$  mmol/l), which was statistically significant. Serum HDL and triglycerides did not change significantly during treatment. Comparable results were observed with the PPS-population.

#### *Ancillary analyses*

Subgroup analyses stratified for CKD stage 4 and 5, show that statistically significant decreases from baseline to day 56/ET in serum phosphorus levels were found for both CKD Stage 4 and Stage 5 patients.

A subgroup analysis in patients on phosphate binders at screening showed a statistically significant decrease in baseline to day 56/ET in serum phosphorus level.

#### **Change in iPTH, calcium and vitamin D**

Median iPTH was 36 pmol/l at baseline, 34 pmol/l at day 56/ET, and 38 pmol/l at day 70 in the safety set. Median iPTH levels decreased significantly from baseline to Day 56/ET, (mean change  $-4$  pmol/l;  $p = 0.013$ ).

Mean **calcium** (albumin-adjusted) was  $2.13 \pm 0.22$  mmol/l at baseline,  $2.20 \pm 0.19$  mmol/l at day 56/ET, and  $2.14 \pm 0.14$  mmol/l at day 70. Mean serum calcium (albumin-adjusted) increased significantly from baseline to day 56/ET (mean change  $0.08$  mmol/l;  $p < 0.001$ ).

The mean **25-hydroxyvitamin D** was  $72.2 \pm 40.6$  nmol/l at baseline and  $77.5 \pm 32.1$  nmol/l at day 56/ET. There was a slight but not statistically significant increase ( $5.1 \pm 25.7$  nmol/l;  $p = 0.080$ ) in mean levels of 25-hydroxyvitamin D from baseline to day 56/ET.

Mean levels of **1, 25 dihydroxyvitamin D** increased over the course of the study. At baseline, the mean 1, 25 dihydroxyvitamin D level was  $60.9 \pm 24.2$  pmol/l which increased to  $76.4 \pm 29.0$  pmol/l at day 56/ET. This represents a statistically significant mean increase of  $12.8 \pm 35.6$  pmol/l ( $p = 0.025$ ) from baseline to day 56/ET.

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

Not applicable

- Clinical studies in special populations

No clinical studies in other special populations than patients with CKD were performed.

- Supportive study(ies)

#### **CKD patients on haemodialysis**

In clinical study GD3-199-301, sevelamer carbonate powder administered once per day resulted in clinically and statistically significant reductions in serum phosphorus from baseline, but it did not demonstrate non-inferiority to sevelamer hydrochloride tablets dosed three times per day (Table 12).

[Table 12: Change in Serum Phosphorus in the Per Protocol Set in Study GD3-199-301](#)

**Table 2.5-2: Change in Serum Phosphorus in the Per Protocol Set in Study GD3-199-301**

Parameter	Sevelamer Carbonate Powder once per day (N=97)	Sevelamer Hydrochloride Tablets three times per day (N=51)
Mean serum phosphorus at Baseline	2.36 ± 0.43 mmol/L (7.3 ± 1.3 mg/dL)	2.45 ± 0.41 mmol/L (7.6 ± 1.3 mg/dL)
Mean serum phosphorus at Week 24/ early termination	1.71 ± 0.45 mmol/L (5.3 ± 1.4 mg/dL)	1.50 ± 0.32 mmol/L (4.6 ± 1.0 mg/dL)
Change from Baseline	-0.66 ± 0.57 mmol/L (-2.0 ± 1.8 mg/dL) p<0.001	-0.96 ± 0.42 mmol/L (-2.9 ± 1.3 mg/dL) p<0.001

Reference: GD3-199-301 Table 14.2.1.1; Table 14.2.1.2; Table 14.2.1.2; Table 14.2.1.4

The upper confidence bound was 0.48 mmol/l (1.50 mg/dl). Therefore, based on a pre-specified non-inferiority margin of 1 mg/dl, non-inferiority of sevelamer carbonate powder once per day compared to sevelamer hydrochloride tablets three times per day was not demonstrated. The percentage of serum phosphorus responders (serum phosphorus between 1.13 and 1.76 mmol/l [3.5 and 5.5 mg/dl]) was higher in the sevelamer hydrochloride tablets TID group (73%) than in the sevelamer carbonate powder OD group (56%). Thus the Applicant's claim for once daily administration was not granted by CHMP.

#### **CKD patients not on haemodialysis**

The applicant performed a phase 2 open-label, dose titration study of sevelamer hydrochloride in chronic renal failure patients not requiring dialysis to determine the efficacy and safety of sevelamer hydrochloride. After discontinuing any phosphate binders, patients entered a 4-week phosphate binder washout period. Patients who developed hyperphosphataemia (serum phosphorus > 1.61 mmol/l) received sevelamer hydrochloride treatment for 12 weeks. The dose was titrated during the treatment period to achieve a serum phosphorus level between 0.81 and 1.45 mmol/l. The average dose of sevelamer hydrochloride was 3.5 g/day. A statistically significant mean decrease in serum phosphorus level was noted during the treatment period (-0.26 mmol/l; p < 0.001). These changes reversed within 4 weeks after sevelamer hydrochloride treatment ended.

#### **CKD patients on peritoneal dialysis**

No studies with sevelamer carbonate were performed in peritoneal dialysis patients.

The applicant submitted study REN-003-04 (An Open Label, Randomized, Parallel Design Study to Investigate the Efficacy and Safety of Sevelamer Hydrochloride (dosed three times per day) Compared with Calcium Acetate in Peritoneal Dialysis Patients) to support both safety and efficacy. A total of 143 patients on peritoneal dialysis were randomised to study treatment in a 2:1 fashion: 97 patients received sevelamer hydrochloride tablets three times per day and 46 patients received calcium acetate tablets three times per day. Based on the data from study REN-003-04, the indication for sevelamer hydrochloride was extended in 2007 to include hyperphosphataemic patients on peritoneal dialysis following approval of a Type II variation by CHMP.

In study REN-003-04, treatment with sevelamer hydrochloride for 12 weeks was non-inferior to 12-week treatment with calcium acetate in reducing serum phosphorus levels. In the Per Protocol Set, there were statistically significant changes from baseline in serum phosphorus (p<0.001) of -0.52 mmol/L (-1.61 mg/dL) and -0.58 mmol/L (-1.81 mg/dL) for the sevelamer hydrochloride group and the calcium group, respectively. The difference in mean change (difference = sevelamer hydrochloride – calcium) was 0.061 mmol/L (0.197 mg/dL) with an upper 97.5% confidence bound of 0.237 mmol/L (0.741 mg/dL) thus establishing non-inferiority of sevelamer hydrochloride compared to calcium acetate based on a pre-specified non-inferiority margin of 0.3 mmol/L (0.929 mg/dL). Similar results were found with the Full Analysis Set.

- Discussion on clinical efficacy

### **CKD patients on haemodialysis**

Only two small trials are submitted comparing HCl formulation with the carbonate formulation (TID dosing). The studies GD3-163-201 (sevelamer carbonate tablets) and SVCARB00205 (sevelamer carbonate powder) were designed to demonstrate therapeutic equivalence of sevelamer carbonate and sevelamer hydrochloride in CKD patients on haemodialysis. Study GD3-163-201 was a double-blind, randomized, crossover study whereas study SVCARB00205 was an open-label, randomized, crossover study.

A large amount of patients were excluded, in particular patients with active dysphagia, swallowing disorders, bowel obstruction, severe gastrointestinal motility disorders or any unstable medical condition which in the opinion of the investigator would prohibit the patient's participation. This hampers the extrapolation of the clinical data set to the real life use of the medicinal product.

In study GD3-163-201, the mean serum phosphorus was  $1.49 \pm 0.3$  mmol/l ( $4.6 \pm 0.9$  mg/dl) during sevelamer carbonate treatment and  $1.52 \pm 0.3$  mmol/l ( $4.7 \pm 0.9$  mg/dl) during sevelamer hydrochloride treatment. The geometric least square mean ratio (sevelamer carbonate/sevelamer hydrochloride) was 0.99 with a corresponding 90% confidence interval of 0.95-1.03. The confidence interval is within the interval of 0.80-1.25, indicating that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus. The results of a confirmatory analysis conducted with the Full Analysis Set (FAS) are similar. Post-hoc analyses were performed to understand the results across dose levels as a marker for the degree of underlying hyperphosphataemia. An analysis of the geometric least squares mean ratio (sevelamer carbonate/sevelamer hydrochloride) was conducted by dose group and is presented in Table 13. The confidence intervals for each of the dose groups are within the interval of 0.80-1.25 indicating that sevelamer carbonate and sevelamer hydrochloride are equivalent in controlling serum phosphorus regardless of dose group.

**Table 13: Serum Phosphorus by Dose Group in GD3-163-201**

<b>Prescribed Daily Dose (grams)</b>	<b>N</b>	<b>Geometric LS Mean Ratio</b>	<b>90% Confidence Interval of Ratio</b>
$\leq 4.8$	22	0.97	0.91-1.04 <sup>†</sup>
$> 4.8$ to $< 9.6$	14	0.95	0.85-1.05 <sup>†</sup>
$\geq 9.6$	20	1.04	0.98-1.10 <sup>†</sup>
Reference: <a href="#">GD3-163-201</a>			

<sup>†</sup> 90% CI for the ratio is within the interval (0.8, 1.25).  
Data Source: study GD3-163-201 Post-hoc Table 3

In study SVCARB00205, the mean serum phosphorus level was  $1.6 \pm 0.5$  mmol/l ( $5.0 \pm 1.5$  mg/dl) during sevelamer carbonate powder treatment and  $1.7 \pm 0.4$  mmol/L ( $5.2 \pm 1.1$  mg/dl) during sevelamer hydrochloride tablet treatment. The geometric least square mean ratio (sevelamer carbonate powder/sevelamer hydrochloride tablets) was 0.95 with a corresponding 90% CI of 0.87-1.03. The CI is within the interval of 0.80-1.25, indicating that sevelamer carbonate powder and sevelamer hydrochloride tablets, each dosed TID with meals, are equivalent in controlling serum phosphorus. The results of a confirmatory analysis conducted with the FAS were similar. In the FAS, the mean serum calcium (albumin-adjusted)-phosphorus product was  $3.7 \pm 1.1$  mmol<sup>2</sup>/l<sup>2</sup> ( $45.9 \pm 13.8$  mg<sup>2</sup>/dl<sup>2</sup>) during sevelamer carbonate powder treatment and  $3.7 \pm 0.8$  mmol<sup>2</sup>/l<sup>2</sup> ( $45.8 \pm 10.0$  mg<sup>2</sup>/dl<sup>2</sup>) during sevelamer hydrochloride tablet treatment. No statistically significant differences were observed between sevelamer carbonate powder and sevelamer hydrochloride tablets with regards to serum calcium (albumin-adjusted)-phosphorus product. The geometric least square mean ratio (sevelamer carbonate powder/sevelamer hydrochloride tablets) was 0.98 with a corresponding 90% CI of 0.88-1.09, which is within the 0.80-1.25 interval.

**Table 14: Serum Phosphorus Time-Weighted Averages for the Per Protocol Set in Studies GD3-163-201 and SVCARB00205**

	Equivalence Test Arm (sevelamer carbonate TID)	Reference Data (sevelamer hydrochloride tablets TID)	Geometric Least Square Mean Ratio	90% CI Ratio
Serum Phosphorus (mmol/L)				
GD3-163-201 N=56 mean ± SD	1.5 ± 0.3 (tablets TID)	1.5 ± 0.3	0.99	0.95, 1.03
SVCARB00205 N=21 mean ± SD	1.6 ± 0.5 (powder TID)	1.7 ± 0.4	0.95	0.87, 1.03
Serum Phosphorus (mg/dL)				
GD3-163-201 N=56 mean ± SD	4.6 ± 0.9 (tablets TID)	4.7 ± 0.9	0.99	0.95, 1.03
SVCARB00205 N=21 mean ± SD	5.0 ± 1.5 (powder TID)	5.2 ± 1.1	0.95	0.87, 1.03

Reference: GD3-163-201 Table 14.2.1.1; SVCARB00205 Table 14.2.1.1.1, Table 14.2.1.1.2

TID = three times per day

The first two weeks of study treatment were not included in time-weighted average to allow time for a patient's phosphorus levels to adjust to a long-term plateau level.

With regard to the Secondary Efficacy Parameter-LDL Cholesterol- in Dialysis Patients the most direct comparisons of sevelamer carbonate and sevelamer hydrochloride on LDL cholesterol are provided by studies GD3-163-201 and SVCARB00205. In these studies, there were no clinically significant differences in LDL cholesterol between treatments. The geometric least squares ratios (sevelamer carbonate/sevelamer hydrochloride) and corresponding 90% confidence intervals were calculated (GD3-163- 201: ratio=1.07; CI 1.01-1.12; SVCARB00205: ratio=1.05; CI 1.00-1.10) and observed to be well within the traditional equivalence boundary criteria, 0.80-1.25.

In addition, study GD3-199-301 (open label, randomised, parallel study) was designed to demonstrate non-inferiority of sevelamer carbonate powder once daily (QD) to sevelamer hydrochloride tablets three times daily (TID) in CKD patients on haemodialysis. Sevelamer carbonate powder administered once per day resulted in clinically and statistically significant reductions in serum phosphorus from baseline, but it did not demonstrate non-inferiority to sevelamer hydrochloride tablets dosed three times per day.

#### ***CKD Patients Not on Dialysis***

Study SVCARB00105 was an open label, single arm, dose titration study conducted in hyperphosphatemic CKD patients not on dialysis with sevelamer carbonate tablets dosed three times per day. This is a very small clinical trial including less than 50 patients (49 included, 41 finishing the trial).

**Table 15: Demographics for CKD Patients not on Dialysis**

**Table 2.7.3—9: Demographics for CKD Patients not on Dialysis**

Demographic Variable	SVCARB00105
Sex (%): M/F	65/35
Race B/C/O (%):	2/92/6
Mean age (yrs)	62
<b>Primary Cause of ESRD (%)</b>	
hypertension	14
diabetes	18
polycystic kidney disease	16
glomerulonephritis	16
other	22
<b>Previous Phosphate Binder (%):</b>	
calcium carbonate	47
calcium acetate	10
aluminium	NA
sevelamer	NA
combination	4
other	NA
none	39
<b>Vitamin D (if not in con meds) (%)</b>	49

ND = Not Done NA = Not Applicable. B/C/O= Black, Caucasian, Other  
Data source: SVCARB00105 CSR Tables 14.1.3.1, 14.1.4.1 and 14.1.8

The mean serum phosphorus level decreased from 2.0 mmol/L (6.2 mg/dl) at baseline to 1.6 mmol/l (4.8 mg/dl) at the end of treatment (Day 56/ET). The decrease in serum phosphorus level was statistically significant (mean -0.5 mmol/L [-1.4 mg/dl], p value <0.001). During the post-treatment washout period, there was a statistically significant (p<0.001) increase in serum phosphorus level of 0.6 mmol/l (1.7 mg/dl) confirming the efficacy of sevelamer carbonate in hyperphosphataemic CKD patients not on dialysis.

The mean actual daily dose of sevelamer carbonate in SVCARB00105 was 5.5 g/day, a dose not dissimilar to that documented for dialysis patients despite the differences in trial design.

There are several concerns with the efficacy data in study SVCARB00105:

- The dataset is very small (n=41 patients completing this 8-week active treatment study).
- Patients with active dysphagia, swallowing disorders, bowel obstruction, severe gastrointestinal motility disorders or any unstable medical condition which in the opinion of the investigator would prohibit the patient's participation were among those excluded. This limits the external validity of the trial.
- By the end of study treatment (Day 56/ET), only 50% of patients in the Full Analysis Set reached the titration target level of serum phosphorus  $\geq 0.86$  mmol/l and  $\leq 1.47$  mmol/l ( $\geq 2.7$  and  $\leq 4.6$  mg/dl). Mean doses of sevelamer carbonate  $>5.5$  g/day may be needed for this population, but the safety of such high doses in this population is unknown.
- Four patients (8-10%) discontinued due to adverse events during this short trial. Four discontinued for other reasons.
- Median iPTH was 36 pmol/l at baseline, 34 pmol/l at day 56/ET, and 39 pmol/l at day 70 in the safety set. Median iPTH levels decreased significantly from baseline to Day 56/ET, (mean change 4 pmol/l; p = 0.013). Mean calcium (albumin-adjusted) was  $2.13 \pm 0.22$  mmol/l at baseline,  $2.20 \pm 0.19$  mmol/l at day 56/ET, and  $2.14 \pm 0.14$  mmol/l at day 70. Mean serum calcium (albumin-adjusted) increased significantly from baseline to day 56/ET (mean change 0.08 mmol/l; p < 0.001). Although small, these changes may indicate a trend following treatment with sevelamer carbonate.

CHMP was of the opinion that this trial is at most supportive but is not sufficiently large to support an indication for such a large group of patients. The applicant was asked to address this issue during an oral explanation and the majority of CHMP members concluded that although the database is very

small, sevelamer carbonate is approvable for pre-dialysis CKD patients with serum phosphorus level  $\geq 1.78$  mmol/l (the population included in the study), as these patients are CKD patients (stage 4 and 5 CKD) with the same underlying disease as those patients on dialysis. The absolute decrease in serum phosphorus and the percentage of responders was similar to that observed in haemodialysis patients. Moreover, the type of AEs and the frequencies observed were in line with those observed in sevelamer-naïve patients in the sevelamer hydrochloride studies. Information on AEs in a larger population including drug interactions can be followed as part of the Risk Management Plan. CHMP found there is a need for regular monitoring of these patients (this was added in the SPC). In addition, the applicant committed to perform a post-marketing surveillance trial in patients not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l to obtain additional safety data. CHMP considered the data are insufficient to extrapolate safety and efficacy to the entire population of CKD patients not on dialysis.

***Table 16: Change in Serum Phosphorus over Time in Study SVCARB00105***

Timepoint statistics	Serum Phosphorus mmol/L	Serum Phosphorus mg/dL
<b>Pre-Washout (n=27)</b>		
Mean $\pm$ SD	1.7 $\pm$ 0.3	5.3 $\pm$ 0.8
Median (Range)	1.7 (1.3-2.3)	5.2 (3.9-7.0)
<b>Baseline (n=46)</b>		
Mean $\pm$ SD	2.0 $\pm$ 0.3	6.2 $\pm$ 0.8
Median (Range)	2.0 (1.5-2.7)	6.0 (4.7-8.4)
<b>Day 56/ET (n=46)</b>		
Mean $\pm$ SD	1.6 $\pm$ 0.3	4.8 $\pm$ 1.0
Median (Range)	1.5 (0.9-2.4)	4.5 (2.6-7.3)
<b>Day 70 (n=40)</b>		
Mean $\pm$ SD	2.1 $\pm$ 0.4	6.5 $\pm$ 1.3
Median (Range)	2.1 (1.1-3.0)	6.7 (3.3-9.2)
<b>Change from Pre-Washout to Baseline (n=27)</b>		
Mean $\pm$ SD	0.4 $\pm$ 0.3	1.1 $\pm$ 0.9
Median (Range)	0.4 (-0.2-1.0)	1.1 (-0.7-3.1)
<b>Change from Baseline to Day 56/ET (n=46)</b>		
Mean $\pm$ SD	-0.5 $\pm$ 0.3	-1.4 $\pm$ 1.0
Median (Range)	-0.5 (-1.2-0.2)	-1.5 (-3.7-0.7)
P value	< 0.001	< 0.001
<b>Change from Day 56 to Post-Washout (Day 70) (n=40)</b>		
Mean $\pm$ SD	0.6 $\pm$ 0.3	1.7 $\pm$ 1.1
Median (Range)	0.6 (-0.2-1.4)	2.0 (-0.6-4.4)
P value	< 0.001	< 0.001

P values determined using Wilcoxon signed rank tests  
SD= Standard deviation; ET = end of treatment  
Data Source SVCARB00105 Table 14.2.1.1

As observed in dialysis patients, sevelamer carbonate treatment also reduced LDL cholesterol levels in hyperphosphataemic CKD patients not on dialysis. In study SVCARB00105, LDL cholesterol levels decreased from  $2.7 \pm 0.87$  mmol/l ( $104.7 \pm 33.64$  mg/dl) at baseline to  $1.8 \pm 0.65$  mmol/l ( $69.7 \pm 25.17$  mg/dl) at the end of treatment. The decrease from baseline in LDL cholesterol ( $-0.9$  mmol/l [ $-35.1$  mg/dl]) was statistically significant ( $p < 0.001$ ). The reduction is of similar magnitude to that seen in dialysis patients in studies of differing design.

### ***CKD patients on peritoneal dialysis***

No studies with sevelamer carbonate were performed in peritoneal dialysis patients. Further to the oral explanation CHMP nevertheless agreed to peritoneal dialysis as part of the indication for sevelamer carbonate, based on the data available for sevelamer hydrochloride in this population, the demonstration of therapeutic equivalence in haemodialysis and the scientific rationale that use of the carbonate salt (instead of the hydrochloride salt) is not expected to impact negatively on patients' safety.

### **Clinical safety**

- Patient exposure

The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with sevelamer carbonate), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and

Very few non-dialysis patients received sevelamer (128 patients in total: 79 for sevelamer hydrochloride; 49 for sevelamer carbonate).

Treatment duration ranged from approximately 4 to 50 weeks. The mean actual dose of sevelamer varied across studies from 3.6 to 6.7 g/day. In dialysis studies, the maximum average actual daily dose was 15 g for sevelamer hydrochloride and 14 g for sevelamer carbonate (both recorded in study GD3-199-301 and including some patients who took 14 g as a single daily dose). In hyperphosphataemic CKD patients not on dialysis, the maximum average actual daily dose was 6.7 g for sevelamer hydrochloride in study GTC-45-204 and 10 g for sevelamer carbonate in study SVCARB00105.

The mean age of patients was similar in each study and ranged from 53 to 64 years. Within each study, more male than female patients were treated.

- Adverse events

The safety profile of sevelamer carbonate dosed three times per day in hyperphosphataemic CKD patients is similar to the established safety profile of the sevelamer hydrochloride. An assessment of the safety data submitted for sevelamer showed the following:

- ❖ The AE profiles of sevelamer hydrochloride tablet, sevelamer carbonate tablet and sevelamer carbonate powder formulations are comparable when administered three times per day with meals to hyperphosphataemic CKD patients.
- ❖ The safety profiles of sevelamer hydrochloride and sevelamer carbonate were similar in hyperphosphataemic CKD patients on dialysis and not on dialysis.
- ❖ The safety profile seen with sevelamer carbonate is similar to the established safety profile of sevelamer hydrochloride, as represented in the sevelamer hydrochloride clinical studies, the sevelamer hydrochloride post-marketing safety profile, and the sevelamer hydrochloride SmPC.
- ❖ AEs for both sevelamer hydrochloride and sevelamer carbonate were distributed across similar system organ classes, and the majority of AEs were of mild or moderate intensity.
- ❖ The most common treatment emergent AEs observed for sevelamer hydrochloride and sevelamer carbonate across studies were gastrointestinal events, including nausea and vomiting. The sevelamer safety profile was consistent with the non-absorbed nature of the product.
- ❖ Overall, AEs seen during treatment with sevelamer carbonate powder and tablets in clinical studies were similar in nature to adverse drug reactions spontaneously received by Genzyme during sevelamer hydrochloride post-marketing surveillance.

The most common all causality AEs during sevelamer carbonate treatment were nausea, vomiting, urinary tract infection, arteriovenous fistula operation, diarrhoea, muscle spasms and arteriovenous fistula complication.

In study REN-003-04, apart from peritonitis the reported AEs are consistent with the safety profile of sevelamer hydrochloride in haemodialysis patients. The AE of peritonitis is a known risk of peritoneal dialysis and the SPC recommends that patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

As requested by CHMP Genzyme has undertaken, as part of extended safety surveillance to collect additional safety information in patients receiving peritoneal dialysis who are taking sevelamer hydrochloride or carbonate (Observations study by the French Language Peritoneal Dialysis Registry (RDPLF database).

- Serious adverse event/deaths/other significant events

In study SVCARB00205 (an open-label, randomised, cross-over study, of sevelamer carbonate powder dosed TID with meals versus sevelamer hydrochloride tablets dosed TID with meals in hyperphosphataemic CKD patients on haemodialysis) the frequency of SAEs was low in each treatment regimen .

Overall, the majority of SAEs observed during sevelamer hydrochloride and sevelamer carbonate treatment was consistent with the patients' underlying co-morbidities of CKD and was considered by the investigators as not related to sevelamer.

For both sevelamer carbonate and sevelamer hydrochloride, deaths were rare and were generally consistent with the patients' underlying CKD.

- Laboratory findings

Across clinical studies, fluctuations in laboratory parameters were most often representative of co-morbidities in hyperphosphataemic CKD patients.

- Safety in special populations

No paediatric studies have yet been conducted with sevelamer carbonate.

- Safety related to drug-drug interactions and other interactions

Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that Renvela can bind fat-soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on sevelamer, serum vitamin A, D, E and K status should be assessed regularly. It is recommended that vitamin supplements be given if necessary. It is recommended that CKD patients not on dialysis are given vitamin D supplements (approximately 400 IU of native vitamin D daily) which can be part of a multivitamin preparation to be taken apart from their dose of Renvela. In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

There is at present insufficient data to exclude the possibility of folate deficiency during long term Renvela treatment.

In interaction studies in healthy volunteers, sevelamer hydrochloride decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer should not be taken simultaneously with ciprofloxacin.

In healthy volunteers, sevelamer hydrochloride, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (i.e graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of ciclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.

Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving sevelamer carbonate and levothyroxine.

Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Caution should be exercised when prescribing sevelamer carbonate to patients also taking these medicinal products.

Sevelamer carbonate is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after sevelamer carbonate, or the physician should consider monitoring blood levels.

- Discontinuation due to adverse events

Across studies with both sevelamer hydrochloride and sevelamer carbonate, AEs leading to study discontinuation were most commonly gastrointestinal disorders or renal transplant. Renal transplant is common in CKD dialysis patients, as many patients on dialysis are awaiting kidney transplantation. Gastrointestinal events which led to study discontinuation are consistent with the sevelamer hydrochloride safety profile.

- Post marketing experience

Sevelamer carbonate has been given a Marketing Authorisation in the following countries: USA (2007), Argentina, Kuwait (both 2008), Chile and India (2009).

Furthermore sevelamer hydrochloride has been on the EU market since 2000 (haemodialysis) and 2007 (peritoneal dialysis).

## **2.5 Pharmacovigilance**

### **Detailed description of the Pharmacovigilance system**

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

### **Risk Management Plan**

The MAA submitted a risk management plan, which included a risk minimisation plan.

The safety of sevelamer hydrochloride has been well characterised from the clinical development programme and from nearly ten years of post-marketing experience with sevelamer hydrochloride in hyperphosphataemic CKD patients on dialysis. Overall, the safety profile of sevelamer is consistent with the non-absorbed nature of the product (sevelamer) with gastrointestinal adverse effects the most common adverse effects experienced.

The two sevelamer salts have been shown to be pharmacodynamically equivalent in terms of control of serum phosphorus and adverse event profile.

Renvela is proposed under 2 pharmaceutical forms, as tablets or powder for oral suspension. The formulation administered may be based on patient preference.

The EU RMP is well written and globally acceptable. The identified and potential risks associated with the use of sevelamer carbonate are Intestinal Obstruction/Ileus, Vitamin Deficiency, Potential Peritonitis, Drug Interactions, and Pregnancy and Lactation. These safety concerns have not been identified or studied with sevelamer carbonate in clinical trials but are mainly the results of the clinical or post-marketing experience with sevelamer hydrochloride (Renagel) use in the haemodialysis patients. Consequently, similar pharmacovigilance actions are proposed for sevelamer carbonate.

It is acknowledged that the major potential mechanism by which sevelamer carbonate can interact with other drugs is by affecting their absorption, or in the case of drugs undergoing enterohepatic circulation, by affecting excretion. Interaction studies were performed with sevelamer hydrochloride in healthy volunteers but not with sevelamer carbonate. Consequently, the applicant has proposed to include the same warnings of sevelamer hydrochloride in sections 4.4. and 4.5. of the SPC of sevelamer carbonate, and this was accepted by the CHMP.

The risk of intestinal obstruction/ileus is included in the Renvela RMP. A total of 20 reports of intestinal obstruction/ileus have been received for patients on sevelamer hydrochloride 403 mg capsules, 400 mg and 800 mg tablets. Of these reports, 7 were assessed as severe by the reporter, and 1 was assessed as moderate. Because sevelamer carbonate contains the same active moiety as sevelamer hydrochloride similar risks are expected for both sevelamer salts. Consequently, the conclusion that intestinal obstruction/ileus is a potential serious identified risk is endorsed. The warnings in proposed sevelamer carbonate SPC for intestinal obstruction, ileus and constipation are acceptable.

Peritonitis is a major risk in the PD population. In a single Peritoneal Dialysis Study with sevelamer hydrochloride (REN00304), a total of 11 patients (11.3%) on sevelamer hydrochloride experienced peritonitis. Eight of the 11 (8.2%) reports of peritonitis were serious. In this study, there was no statistical difference in the frequency of peritonitis in patients treated with sevelamer hydrochloride versus those treated with calcium acetate, although this may be explained by the large confidence intervals. However, the rates of peritonitis in the calcium acetate treated arm were lower than the background rates of peritonitis anticipated in this population (0.31 episodes/patient year). This unbalanced distribution was not observed in the French RDPLF registry data, where a decreased peritonitis risk was observed in the sevelamer hydrochloride (Renagel) group. The potential mechanisms are infection from skin organisms such as coagulase negative Staphylococcus, Streptococcal species, Corynebacterium, Bacillus species; unwashed hands/fingers contaminating dialysate/catheter.

The proposed risk minimisation activities are acceptable:

- Provision of educational material to patients and health professionals containing information on the risk factors for and prevention of peritonitis.
- Warning in the proposed sevelamer carbonate SPC.
- Comprehensive post-marketing surveillance as part of routine PV practice; 6-month PSURs to include an analysis of cases of peritonitis.

The risk minimisation measures proposed for sevelamer carbonate in peritoneal dialysis patients are a continuation of those already in place for sevelamer hydrochloride. An observational study will be conducted with the French registry (RDPLF) to determine whether the risk of peritonitis differs in PD patients taking sevelamer hydrochloride or sevelamer carbonate, compared to patients receiving treatment with other phosphate binders.

The objectives of this study are:

- 1) To determine, whether the risk of peritonitis differs in peritoneal dialysis (PD) patients with sevelamer use compared to patients receiving treatment with other phosphate binders.
- 2) To estimate, the rates of peritonitis in peritoneal dialysis (PD) patients on treatment with sevelamer, and those who are receiving treatment with other phosphate binders.
- 3) To evaluate the identity of causative organisms in peritonitis infections in peritoneal dialysis (PD) patients on treatment with sevelamer compared to patients receiving treatment with other phosphate binders.

As sevelamer carbonate may be used off-label (e.g. in less than 18 year old patients), the applicant is requested to provide risk minimisation measures to monitor and avoid risk of such off-label use. In addition, all cases of off-label use in children should be clearly reviewed and discussed in the PSURs.

Finally the Applicant agreed to perform a post-marketing study in CKD patients not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l in order to better document the safety of the product in these patients.

Table 17. Summary of the RMP

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Vitamin deficiency	<p><b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice</p>	<p><b>Routine:</b> proposed SmPC Section 4.4 contains the following warning:            “Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that Renvela can bind fat soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on sevelamer, serum vitamin A, D, E and K status should be assessed regularly. It is recommended that vitamin supplements be given if necessary. It is recommended that CKD patients not on dialysis are given vitamin D supplements (approximately 400 IU of native vitamin D daily) which can be part of a multivitamin preparation to be taken apart from their dose of Renvela. In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.            There is at present insufficient data to exclude the possibility of folate deficiency during long term Renvela treatment.”  <b>Additional:</b> Educational materials will be prepared for patients and health professionals on the need for vitamin supplementation</p>
Peritonitis	<p><b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice</p>	<p><b>Routine:</b> proposed SmPC Section 4.4 contains the following warning:            “Patients receiving dialysis are subject to certain risks for infection specific to dialysis modality. Peritonitis is a known complication in patients receiving peritoneal dialysis and in a clinical study with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis”.  <b>Additional:</b> Educational materials will be prepared for patients and health professionals on the risk</p>

		factors for peritonitis <b>Additional:</b> Epidemiological study report from the RDPLF to evaluate the risk of peritonitis in PD patients receiving Renagel and Renvela
Intestinal obstruction/ ileus	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<b>Routine:</b> Proposed SmPC Sections 4.3 contains the following contraindication “Bowel obstruction” and Section 4.4 contains the following warnings: “In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Renvela. Renvela treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms”. Section 4.8 contains the following undesirable effects: in very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate.
Increased thyroid stimulating hormone levels/Hypothyroidism	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<b>Routine:</b> Proposed SmPC Section 4.5. contains the following warning: “Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving sevelamer carbonate and levothyroxine”.
Drug interactions	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<b>Routine:</b> Proposed SmPC Section 4.4 contains the following warning regarding concomitant use of anti-arrhythmics and anti-epileptics: “Caution should be exercised when prescribing Renvela to patients also taking arrhythmias and anti-seizure medicinal products (see section 4.5).” And Section 4.5 includes the following statement regarding bioavailability of other medicines: “Interaction studies have not been conducted in patients on dialysis.

		<p>In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Renvela, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, Renvela should not be taken simultaneously with ciprofloxacin.</p> <p>Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (i.e graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of ciclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.</p> <p>Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving sevelamer carbonate and levothyroxine.</p> <p>Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Caution should be exercised when prescribing Renvela to patients also taking these medicinal products.</p> <p>In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Renvela, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.</p> <p>Renvela is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Renvela, or the physician should consider</p>
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		monitoring blood levels.
Pregnancy and lactation	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<p><b>Routine:</b> Proposed SmPC Section 4.6. contains the following statements regarding use during pregnancy and lactation:</p> <p>“ Pregnancy: There are no data from the use of sevelamer in pregnant women. Studies in animals have shown some reproductive toxicity when sevelamer was administered to rats at high doses (see section 5.3). Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid (see sections 4.4 and 5.3). The potential risk to humans is unknown. Renvela should only be given to pregnant women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the foetus.</p> <p>Lactation: It is unknown whether sevelamer is excreted in human breast milk. The non-absorbed nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Renvela should be made taking into account the benefit of breast-feeding to the child and the benefit of Renvela therapy to the woman.”</p>
Hepatic impairment, immunocompromised patients	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	All SmPC statements apply to this population
Hyperphosphataemic CKD patients not on dialysis with serum phosphorus $\geq 1.78$ mmol/l	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<p>All SmPC statements apply to this population</p> <p><b>Additional:</b> Risk minimization activities for sevelamer carbonate use in hyperphosphataemic CKD patients not on dialysis will include query of Drug Utilization Databases and other appropriate databases, to evaluate sevelamer carbonate use in hyperphosphataemic CKD patients not on dialysis.</p> <p>A summary of the information obtained from these strategies will be presented to the EMEA in Renvela PSUR.</p> <p>Post-marketing observational study to monitor the clinical use in adult hyperphosphataemic CKD patients</p>

		not on dialysis with serum phosphorus $\geq 1.78$ mmol/l. This is an observational, open-label, post-marketing study of Renvela (800 mg tablets and 2.4 g powder for oral suspension) in adult hyperphosphataemic CKD patients not on dialysis with serum phosphorus $\geq 1.78$ mmol/L treated in accordance with the Renvela Summary of Product Characteristics (SmPC) and followed-up according to the investigator's routine clinical practice management
Hyperphosphataemic CKD patients on peritoneal dialysis	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	All SmPC statements apply to this population  <b>Additional:</b> Risk minimization activities for sevelamer carbonate in peritoneal dialysis patients will include query of Drug Utilization Databases and other appropriate databases, to evaluate sevelamer carbonate use in hyperphosphataemic CKD patients on peritoneal dialysis.  A summary of the information obtained from these strategies will be presented to the EMEA in Renvela PSUR.
AV fistula site adverse reactions	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<b>Additional:</b> Provision of educational material to patients and health professionals containing information on the risk factors for and prevention of AV fistula complications
Off- label use in patients less than 18 years	<b>Routine:</b> Comprehensive post-marketing surveillance as part of routine Pharmacovigilance practice	<b>Routine:</b> As mentioned in the proposed SmPC (Section 4.2), the safety and efficacy of Renvela has not been established in children below the age of 18 years. Renvela is not recommended in children below the age of 18 years.  Drug Utilization Databases and other appropriate databases, will be queried to determine the extent of use Renvela in patients less than 18 years. Periodic querying of these databases can be employed to monitor use over time. If the rate of use of Renvela in the paediatric population exceeds 1 per marp (million of the age-related population) Genzyme will institute a program to communicate with appropriate groups. A summary of the information obtained from these strategies will be presented in the

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report

## 2.6 Overall conclusions, risk/benefit assessment and recommendation

### Quality

The active substance and both finished products have been adequately described. The excipients used in the preparation of the film-coated tablets and the powder for oral suspension, and the manufacturing process selected are typical of such preparations.

The results of the tests indicate that the active substance and the film-coated tablets as well as the powder for oral suspension can be reproducibly manufactured and therefore the products should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow-up measures after the opinion, within an agreed timeframe.

### Non-clinical pharmacology and toxicology

The main pharmacodynamic effect of sevelamer and its mechanism of action have been adequately demonstrated in the primary pharmacodynamic studies. The secondary pharmacology studies showed that sevelamer is devoid of any measurable effects on general behaviour, locomotor activity or other CNS activity, body temperature, cardiovascular or respiratory control in experimental animals. Preclinical pharmacokinetic studies demonstrated that sevelamer is excreted entirely in the faeces without significant systemic absorption.

Overall, the toxicology program revealed that sevelamer is generally well tolerated without any major signs of systemic toxicity. The decreased serum levels of vitamin D, vitamin E and folic acid as well as the coagulation defect detected at high doses in rats, likely to result from vitamin K deficiency, can be ascribed to adsorption of the vitamin itself (in the case of folic acid) or of biliary acids to the polymer. This information is included in the SPC.

### Efficacy

- Patients on dialysis:

Two small trials compared the sevelamer hydrochloride formulation with the carbonate formulation. The studies GD3-163-201 (sevelamer carbonate tablets) and SVCARB00205 (sevelamer carbonate powder) were designed to demonstrate therapeutic equivalence, in terms of the control of serum phosphorus (time-weighted mean serum phosphorus), of sevelamer carbonate and sevelamer hydrochloride in CKD patients on haemodialysis. Study GD3-163-201 was a double-blind, randomized, crossover study whereas study SVCARB00205 was an open-label, randomized, crossover study. The results from these 2 studies indicate that sevelamer carbonate (powder and tablets) and sevelamer hydrochloride tablets, each dosed TID with meals, are equivalent in controlling serum phosphorus.

In addition, study GD3-199-301 (open label, randomised, parallel study to demonstrate non-inferiority of sevelamer carbonate powder once daily (QD) to sevelamer hydrochloride tablets three times daily (TID). Non-inferiority of sevelamer carbonate powder (QD) compared to sevelamer hydrochloride tablets (TID) was not demonstrated. Thus CHMP did not agree to the once daily administration.

No studies are submitted with sevelamer carbonate in peritoneal dialysis patients. The CHMP nevertheless agreed to peritoneal dialysis as part of the indication for sevelamer carbonate, based on the data available for sevelamer hydrochloride in this population, the demonstration of therapeutic equivalence of sevelamer hydrochloride and carbonate in haemodialysis and the scientific rationale

that use of the carbonate salt (instead of the hydrochloride salt) is not expected to impact negatively on patients' safety.

- Patients not on dialysis

Study SVCARB00105 was an open label, single arm, dose titration study (sevelamer carbonate tablets dosed TID) conducted in hyperphosphataemic CKD patients not on dialysis. The trial in itself was considered too small to support the large group of non-dialysis CKD patients. However, the majority of CHMP members concluded that although the database is very small, sevelamer carbonate is approvable for pre-dialysis CKD patients with serum phosphorus level  $\geq 1.78$  mmol/l (the population included in the study), as these patients are CKD patients with the same underlying disease as those patients on dialysis. The absolute decrease in serum phosphorus and the percentage of responders was similar to that observed in haemodialysis patients. Moreover, the type of AEs and the frequencies observed were in line with those observed in sevelamer-naïve patients in the sevelamer hydrochloride studies. Information on AEs in a larger population including drug interactions can be followed as part of the Risk Management Plan. CHMP found there is a need for regular monitoring of these patients, and this was added in the SPC. In addition, the applicant committed to perform a post-marketing surveillance trial in patients not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l to obtain additional safety data.

## Safety

The safety profile of sevelamer carbonate dosed three times per day in hyperphosphataemic CKD patients is similar to the established safety profile of the sevelamer hydrochloride. The AE profiles of sevelamer hydrochloride tablet, sevelamer carbonate tablet and sevelamer carbonate powder formulations are comparable when administered three times per day with meals to hyperphosphataemic CKD patients. The safety profiles of sevelamer hydrochloride and sevelamer carbonate were similar in hyperphosphataemic CKD patients on dialysis and not on dialysis. AEs for both sevelamer hydrochloride and sevelamer carbonate were distributed across similar system organ classes, and the majority of AEs were of mild or moderate intensity. The sevelamer safety profile was consistent with the non-absorbed nature of the product. The most common treatment emergent AEs observed across studies were gastrointestinal events, including nausea and vomiting. Overall, AEs seen during treatment with sevelamer carbonate powder and tablets in clinical studies were similar in nature to adverse drug reactions spontaneously received by Genzyme during sevelamer hydrochloride post-marketing surveillance. The most common all causality AEs during sevelamer carbonate treatment were nausea, vomiting, urinary tract infection, arteriovenous fistula operation, diarrhoea, muscle spasms and arteriovenous fistula complication.

In the peritoneal dialysis study with sevelamer hydrochloride, apart from peritonitis the reported AEs are consistent with the safety profile of sevelamer hydrochloride in haemodialysis patients. Peritonitis is a known risk of peritoneal dialysis and the SPC recommends that patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

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

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A cross bridging has been performed adequately referring to the sevelamer hydrochloride (Renagel) PIL (Patient Information Leaflet) for the items which are exactly the same, mainly the safety. In addition a new limited user test (four questions) has been performed only for the small differences with regard to the new population (for non dialysed patients).

The user testing report is in accordance with EU guidance on user testing of the PIL.

## Risk-benefit assessment

A routine EMEA GCP Inspection at the sponsor site and at one investigator site for the clinical study SVCARB00205 revealed critical and major issues, with regard to eligibility criteria, drug compliance, and adverse event reporting. Further to additional analyses and oral explanations by the applicant the data submitted were considered acceptable to support the current application.

The results from 2 small clinical studies in CKD patients on haemodialysis showed that sevelamer carbonate (powder and tablets) and sevelamer hydrochloride tablets (each dosed TID with meals) are equivalent in controlling serum phosphorus, and have a similar safety profile.

No studies are submitted with sevelamer carbonate in peritoneal dialysis patients. The CHMP nevertheless accepts this part of the indication for sevelamer carbonate, based on the data available for sevelamer hydrochloride in this population, the demonstration of therapeutic equivalence of sevelamer hydrochloride and carbonate in haemodialysis and the scientific rationale that use of the carbonate salt (instead of the hydrochloride salt) is not expected to impact negatively on patients' safety.

The database is very small for patients not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l, however as these patients are CKD patients with the same underlying disease as those patients on dialysis, the majority of CHMP members also endorsed the use of sevelamer carbonate in this group, provided that additional data are gathered in a post-marketing study to reinforce the safety data set (follow-up measure).

Based on the data available, no difference in terms of efficacy or safety profile has been shown as compared to sevelamer hydrochloride. The applicant's claim that sevelamer carbonate would have a lower risk for metabolic acidosis and therefore would be of particular benefit for the treatment of paediatric patients and non-dialysis CKD patients is not supported by data: (i) whether there is indeed a higher risk for metabolic acidosis in these patient groups is not discussed and no data for this claim are submitted; (ii) no data are submitted to support the better safety profile of sevelamer in reducing the appearance of metabolic acidosis in haemodialysis or pre-dialysis patients (although there is a small, statistically significant difference in plasma bicarbonate concentration at the end of the treatment period); (iii) currently, the use of sevelamer (either hydrochloride or carbonate) in paediatric patients would be off-label.

In conclusion, the claimed improved clinical benefit of sevelamer carbonate, as compared to sevelamer hydrochloride remains unsubstantiated both in clinical practice in CKD patients and in experimental animal settings.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see as detailed in section 2.3

## Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Renvela for the *control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis and in adult patients with chronic kidney disease not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l* was favourable and therefore recommended the granting of the marketing authorisation.

Divergent views were expressed, considering that:

- Efficacy and safety data submitted to support the “control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l are based on a very small clinical study.

- The follow-up of pre-dialysis patients is not the same as for dialysis patients. The latter are seen every other day and adverse events can be prevented by closely monitoring the blood lab values and adapting treatment given on this basis . This can not be done in the case of patients who are not on dialysis and who are seen at a much lower frequency.