



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Sevelamer Carbonate

Proprietary Product Name: Renvela, Sevelamer Carbonate Winthrop & Sevelamer Carbonate Sanofi

Sponsor: Sanofi-Aventis Australia Pty Ltd

First Round CER report: 1 July 2014

Second Round CER report: 2 December 2014

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About the Extract from the Clinical Evaluation Report

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
APD	Automated Peritoneal Dialysis
AV	Arteriovenous
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CER	Clinical Evaluation Report
CHMP	Committee on Human Medicinal Products
CKD	Chronic kidney disease
CMI	Consumer Medicines Information
EMA	European Medicines Agency
ESRD	End-stage renal disease
ET	Early termination
EU	European Union
FMD	Flow mediated dilation
GFR	Glomerular filtration rate
GI	Gastrointestinal
HCl	Hydrochloride
HDL	High density lipoprotein
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
LV	Left ventricular
MedDRA	Medical Dictionary of Regulatory Activities
mg	Milligram

Abbreviation	Meaning
ml	Milliliter
mmol	Millimol
NSAIDS	Non-steroidal Anti-inflammatory Drugs
PD	Peritoneal dialysis
PI	Product Information
PT	Preferred Term
PTH	Parathyroid hormone
QD	Once daily
RDPLF	French Peritoneal Dialysis Registry
RMP	Risk Management Plan
SAE	Serious adverse event
SCB	Sevelamer carbonate
SHC	Sevelamer hydrochloride
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
URR	Urea Reduction ratio

1. Background

1.1. Submission type

This is a Category 1 submission to register sevelamer carbonate, an alternative sevelamer salt to the currently registered sevelamer hydrochloride.

1.2. Drug class and therapeutic indication

1.2.1. Drug class

Sevelamer is a non-absorbed phosphate cross-linked polymer, free of metal and calcium.

1.2.2. Therapeutic indications (proposed)

Sevelamer carbonate is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and stage 5 chronic kidney disease.

Evaluator's Comment: The proposed indication is identical to the approved indication for sevelamer hydrochloride.

1.3. Dosage forms and strengths

The proposed dosage forms and strengths for sevelamer carbonate are: 800 mg film-coated tablets; 1.6 g and 2.4 g powder for solution, oral Sachet.

Evaluator's Comment: Sevelamer hydrochloride is registered as 400 mg and 800 mg tablets, but not as a powder for solution.

1.4. Dosage and administration

The following dosage and administration information has been taken directly from the proposed Product Information (PI) for Renvela (sevelamer carbonate). The sponsor is proposing three identical PI documents, one for each trade name. The following extract from the Renvela PI includes bracketed references to sevelamer carbonate to represent each of the three proposed trade names.

DOSAGE AND ADMINISTRATION

[Sevelamer Carbonate] is available as tablets or powder for oral suspension.

[Sevelamer Carbonate] 800 mg tablets must be taken three times per day with meals at a dosage based on individual patient requirements to control phosphate levels. Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Patients should swallow the tablets whole with water.

Starting dose

The recommended starting dose of [Sevelamer Carbonate] is 2.4 to 4.8 g per day based on clinical needs and phosphorus level (Table 3). [Sevelamer Carbonate] must be taken three times per day with meals.

Table 3 - Starting dose for patients not taking a phosphate binder

Serum Phosphorus	Total daily dose taken over three meals per day
> 1.78 and < 2.42 mmol/L	2.4 g
≥ 2.42	4.8 g

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), [Sevelamer Carbonate] should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses (Table 4).

Table 4 - Starting dose for patients switching from calcium acetate to Renvela

Calcium Acetate 667 mg (tablets per meal)	Renvela 800mg tablet (tablets per meal)	Renvela Powder (g per meal)
1 tablet	1	0.8
2 tablets	2	1.6
3 tablets	3	2.4

Titration and Maintenance

Serum phosphorus levels must be monitored and the dose of sevelamer carbonate titrated every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Patients taking [Sevelamer Carbonate] should adhere to their prescribed diets.

In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily dose is expected to be an average of approximately 6 g per day.

Evaluator's Comment: The approved sevelamer hydrochloride (Renagel) PI states that the 'recommended starting dose for patients not taking a phosphate binder is 800 to 1600 mg', which is lower than the recommended starting dose of sevelamer carbonate of '2.4 to 4.8 g per day based on clinical needs and phosphorus level'. The PI recommends that, for patients previously on phosphate binders (sevelamer hydrochloride or calcium based), sevelamer carbonate should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses. The approved sevelamer hydrochloride (Renagel) PI states that the 'average actual daily dose use in the chronic phase of a one year clinical study was 7 grams', while the sevelamer carbonate PI indicates that the average daily dose is 'expected to be an average of approximately 6 g per day' during 'continuous' treatment based on serum phosphorous levels.

2. Clinical rationale

Chronic kidney disease (CKD) is associated with serum phosphorous levels resulting in significant pathophysiology including secondary hyperparathyroidism, renal osteodystrophy, arterial calcification and increased mortality.^{1,2,3} The goal of therapy with sevelamer carbonate is to bind with phosphate in the intestinal tract in order to limit its absorption and prevent hyperphosphataemia in patients with Stage 4 and 5 CKD.

Sevelamer is an anion exchange resin with a polymeric structure of multiple amines separated by one carbon from the polymer backbone. Sevelamer salts become protonated in the stomach releasing the anions. The protonated amines of sevelamer bind negatively charged dietary phosphate ions in the intestine and the bound complex is passed out through the gut. The first salt of sevelamer developed for clinical purposes was sevelamer hydrochloride and the choice of salt was based on production considerations. However, data from clinical studies in CKD patients with hyperphosphataemia indicates that 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. Consequently, sevelamer carbonate was developed in order to mitigate the potential adverse effects on acid-base balance associated

with release of the chloride iron from sevelamer hydrochloride, while maintaining the same phosphate binding properties of the original product.

Sevelamer carbonate has been formulated as a tablet and as a powder for oral suspension. The sponsor states that the powder formulation will provide an alternative dosage form that could benefit those patients who dislike or have difficulties in swallowing tablets, or who have a high pill burden. The sponsor states that the powder formulation 'fulfils an unmet need for those hyperphosphataemic CKD patients unable to take tablets for any reasons' (letter of application).

Evaluator's Comment: The clinical rationale for development of sevelamer carbonate is considered to be acceptable.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The sponsor states that the '*clinical development program for sevelamer carbonate is a continuation of the development program for sevelamer hydrochloride. The two sevelamer salts have been shown to be therapeutically equivalent, in terms of control of serum phosphorus, and have a similar safety profile with the important distinction that the carbonate salt has reduced propensity for association with potentially adverse acid base changes. The demonstration of equivalence between the two salts allows the use of the sevelamer hydrochloride data to support the MAA for Renvela (sevelamer carbonate)*'.

The sponsor provided an abridged submission supporting the registration of sevelamer carbonate that included in vivo and in vitro data aimed at establishing the equivalence of sevelamer carbonate and sevelamer hydrochloride. Demonstration of therapeutic equivalence of the two sevelamer salts would allow the known efficacy and safety data for sevelamer hydrochloride to be extrapolated to sevelamer carbonate. The submission did not repeat all the studies which had been submitted for registration of sevelamer hydrochloride with sevelamer carbonate. However, the submission included clinical efficacy and safety study reports previously provided and evaluated to support registration of sevelamer hydrochloride.

The submission contained the following clinical information:

- 1 new in vitro bioequivalence study.
- 2 new drug-drug PK interaction studies (1 of which included PD data).
- 7 previously submitted PK studies.
- 4 new, clinical efficacy and safety studies considered to be key to the current submission to register sevelamer carbonate, including-one, 4 week, cross-over therapeutic equivalence study in patients on haemodialysis; one, 8 week, cross-over therapeutic study in patients on haemodialysis; one, 24 week, parallel group, non-inferiority study in patients on haemodialysis; one, open-label, single-arm, 12 week study in patients not on dialysis.
- 3 clinical efficacy and studies involving sevelamer carbonate not directly relevant to the current submission.
- 3 post-marketing reports relating to sevelamer carbonate.
- 17 previously submitted studies relating to sevelamer hydrochloride.
- 1 pooled safety analysis relating to sevelamer hydrochloride.
- Literature references.

3.2. Paediatric data

The proposed indication specifies that sevelamer carbonate is for the management of hyperphosphataemia in adult patients with Stage 4 and 5 CKD. The sponsor drew attention to an ongoing Phase II study in the US to evaluate the safety and tolerability of sevelamer carbonate in hyperphosphataemic paediatric patients aged < 18 years with CKD. The sponsor anticipates that a study report will be available by the middle of 2016.

3.3. Good clinical practice

The sponsor stated that the clinical studies were conducted in accordance with the principles of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The submission included 3 new studies providing PK data supporting the application to register sevelamer carbonate, and 7 previously submitted studies providing PK data supporting the application to register sevelamer hydrochloride. The approach adopted in this CER to the evaluation of the PK data has been to fully evaluate the 3 new studies and to briefly summarise the 7 previously submitted and evaluated studies.

The 3 new studies were:

- Study TR-2527-07-SC: an in vitro bioequivalence study of sevelamer hydrochloride (Renagel, 800 mg tablets) and sevelamer carbonate (800 mg tablets, 0.8, 1.6 and 2.4 g sachets).
- Study SVCARB01107: an open-label study to assess the potential pharmacokinetic interaction of a single dose of sevelamer carbonate with a single-dose of warfarin sodium in healthy volunteers.
- Study SVCARB03107: an open-label study to assess the potential pharmacokinetic interaction of a single dose of sevelamer carbonate with a single dose of oral digoxin and to investigate the pharmacodynamic effects of sevelamer carbonate on phosphorous absorption and excretion in healthy volunteers.

The 7 previously submitted and evaluated studies were:

- GTC-10-801: an open-label, parallel-dose study aimed to assess the non-absorbability of sevelamer hydrochloride.
- ICR013769: DDI study to assess the effect of sevelamer hydrochloride on the PKs of digoxin.
- ICR013281: DDI study to assess the effect of sevelamer hydrochloride on the PKs of warfarin.
- GTC-45-803: DDI study to assess the effect of sevelamer hydrochloride on the PKs of metoprolol.
- GTC-45-804: DDI study to assess the effect of sevelamer hydrochloride on the PKs of enalapril.
- GTC-45-807: DDI study to assess the effect of sevelamer hydrochloride on the PKs of ciprofloxacin.

- GTC-45-808: DDI study to assess the effect of sevelamer hydrochloride on the PKs of iron.

4.2. New studies

4.2.1. TR-2527-07-SC

In its letter of application, the sponsor stated that 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) was submitted, to compare sevelamer hydrochloride tablets, sevelamer carbonate tablets and sevelamer carbonate powder for oral suspension. The method used in the study was adapted from the FDA guidance for that used to determine the in vitro bioequivalence of cholestyramine powder.

Equilibrium binding studies were conducted under conditions of constant time and varying concentrations of phosphate on samples prior to and subsequent to acid pre-treatment. Eight different concentrations of phosphate salt solution were used with a fixed amount of sevelamer hydrochloride or sevelamer carbonate. The phosphate binding results were evaluated using the Langmuir approximation as outlined in the 'FDA Guidance', and a comparison of the capacity and the affinity constants was performed. The provided results were from a combination of three independent studies over the course of 1.5 years. The in vitro bioequivalence of sevelamer hydrochloride (Renagel, 800 mg tablets) and sevelamer carbonate (800 mg tablets, 0.8, 1.6, and 2.4g sachets) was demonstrated for phosphate binding with and without acid pre-treatment. The results of the study are briefly summarised below. However, it is recommended that definitive evaluation of this in vitro study be undertaken by the quality evaluator.

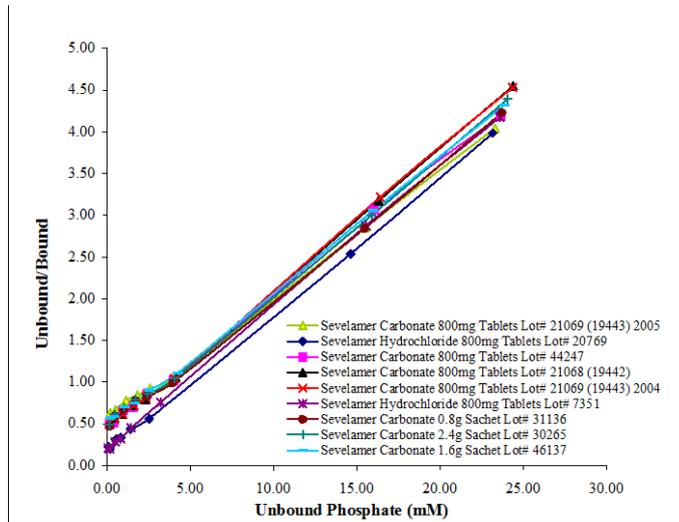
4.2.1.1. *Equilibrium study of phosphate binding*

4.2.1.1.1. *Equilibrium binding samples without acid pre-treatment*

The average amount of phosphate bound at each initial phosphate concentration, without acid pre-treatment, for each of the nine sevelamer test samples was summarised. Each value is the average of six independent preparations for sevelamer hydrochloride tablets lot #20769, sevelamer carbonate tablets lot #21069 (19443) from 2005, and lot #44247, and sevelamer carbonate sachets 0.8 g lot #31136, 1.6 g lot #46137, and 2.4 g lot #30265. Each value for sevelamer hydrochloride tablets lot #7351, sevelamer carbonate tablets lot #21068 (19442), and lot #21069 (19443) from 2004 is the average of two independent preparations.

The average values for the slope, intercept, and R-squared (RSQ) for each of the Langmuir isotherms and affinity constant (K1) and capacity constant (K2) values were summarised. For the tests samples without acid pre-treatment, the mean (SD) value for K1 was 0.450 (0.232), with a relative standard deviation (RSD) of 51.6%, and the mean (SD) value for K2 was 6.210 (0.262), with an RSD of 4.2%. The results for the Longmuir plots the nine samples without acid pre-treatment are summarised below in Figure 1.

Figure 1: TR-252707-07-SC-Langmuir plots for equilibrium binding samples without acid pre-treatment.

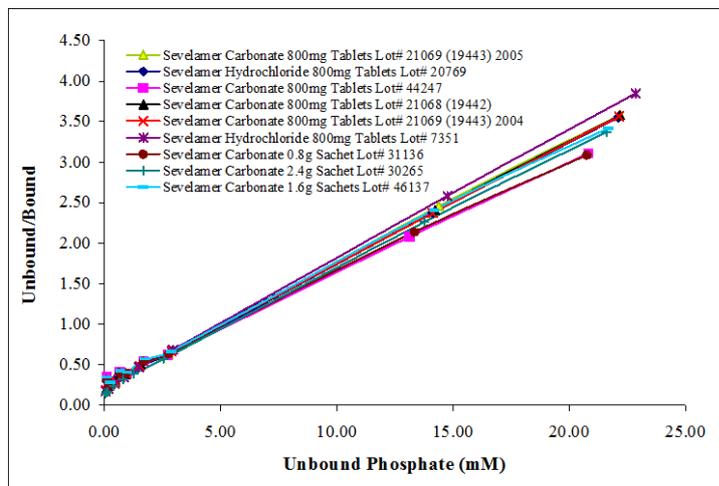


4.2.1.1.2. Equilibrium binding samples with acid pre-treatment

The average amount of phosphate bound at each initial phosphate concentration, with acid pre-treatment, for each of the nine sevelamer test samples was summarised. Each value is the average of six independent preparations for sevelamer hydrochloride tablets lot #20769, sevelamer carbonate tablets lot #21069 (19443) from 2005, and lot #44247, and sevelamer carbonate sachets 0.8 g lot #31136, 1.6 g lot #46137, and 2.4 g lot #30265. Each value for sevelamer hydrochloride tablets lot #7351, sevelamer carbonate tablets lot #21068 (19442), and lot #21069 (19443) from 2004 is the average of two independent preparations.

The average values for the slope, intercept, and RSQ for each of the Langmuir isotherms and affinity constant (K1) and capacity constant (K2) values with acid pre-treatment was summarised. For the tests samples with acid pre-treatment, the mean (SD) value for K1 was 0.654 (0.141), with an RSD of 21.6%, and the mean (SD) value for K2 was 6.70 (0.374), with an RSD of 5.5%. The results for the Longmuir plots the nine samples without acid pre-treatment are summarised below in Figure 2.

Figure 2: TR-252707-07-SC-Langmuir plots for equilibrium binding samples with acid pre-treatment.



4.2.1.1.3. *Comment:*

In the equilibrium binding study of phosphate with and without acid pre-treatment, sevelamer hydrochloride (800 mg tablets) and sevelamer carbonate (800 mg tablets, 0.8, 2.4, and 1.6 g Sachets) were demonstrated to be bioequivalent (in vitro). There were no marked differences in the phosphate binding capacity (k_1) characteristics in both acid pre-treated and non-acid pre-treated samples. The variation in the affinity constants (k_2) was reduced from 51.6% for the without acid pre-treated sevelamer samples to 21.6% for the with acid pre-treated samples. The range of %RSD for both the amount bound and the percent bound for the nine sevelamer test samples at each individual phosphate concentration dropped from approximately 2.8% to 6.3% for the samples without acid pre-treatment to approximately 0.9% to 4.0% for the samples with acid pre-treatment. The sponsor states that the difference in the variability of the affinity constants (k_2) between samples tested with and without acid pre-treatment is because under acidic conditions, both sevelamer hydrochloride and sevelamer carbonate will be similarly protonated salts of cross-linked poly(allylamine hydrochloride). Overall, the results suggest that differences in phosphate binding of the two salts of sevelamer are unlikely to be clinically significant over the dose and formulation range tested.

4.2.1.2. *Kinetic study of phosphate binding*

The purpose of the kinetic experiments was to show that phosphate is bound by sevelamer hydrochloride (800 mg tablets) and sevelamer carbonate (800 mg tablets, 0.8, 2.4, and 1.6 g Sachets) in a similarly rapid manner, independent of initial phosphate concentration. All nine sevelamer test samples exhibit similar kinetic behaviour. The binding of phosphate was fast and the equilibrium level of binding was reached at both initial phosphate (KH_2PO_4) concentrations (2.5 mM and 38.7 mM) in approximately 15 minutes.

4.2.2. **SVCARB01107**

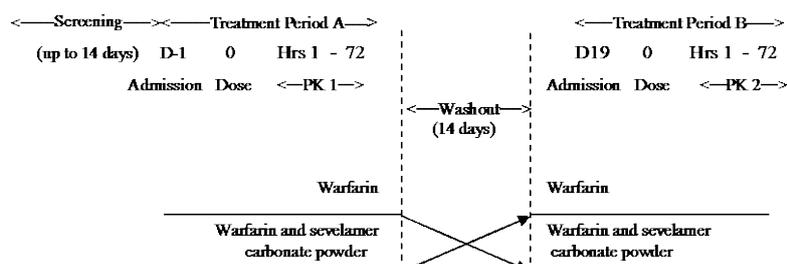
4.2.2.1. *Design and objectives*

The study was a Phase I, open-label, randomised, cross-over comparison of the pharmacokinetics of warfarin alone with warfarin plus sevelamer carbonate powder for oral suspension in healthy male volunteers aged 18 to 50 years. The primary objective was to investigate the effects of single-dose sevelamer carbonate powder for oral suspension (9.6 g) on the pharmacokinetics of single-dose warfarin sodium (20 mg). The secondary objective was to assess the safety/tolerability of the combination.

The study was undertaken at a single centre in the USA (Texas). The first subject was treated on 12 June 2007 and the last subject completed the study on 2 July 2007. The study report was dated 1 April 2008. The study was conducted in accordance with the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and the World Medical Association Declaration of Helsinki.

4.2.2.2. *Treatment*

During the two randomised treatment periods, eligible subjects received either warfarin alone followed by warfarin plus sevelamer carbonate powder (Sequence A) or warfarin plus sevelamer carbonate powder followed by warfarin alone (Sequence B). All study medication was taken orally, and subjects were required to fast overnight for at least 8 hours before dosing and for at least 4 hours after dosing. The study design is outlined below in Figure 3.

Figure 3: SVCARB01107-Phase I study design for each dosing cohort.

4.2.2.3. Sampling times

During each study session, blood samples for the analysis of plasma for warfarin were collected from each subject pre-dose and then post-dose at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours. The collection window was ± 5 minutes for the first 12 hours followed by ± 10 minutes to the end of treatment.

4.2.2.4. Statistical methods and sample size

PK parameters were calculated for plasma R- and S-warfarin and compared between treatments. The PK parameters of interest were C_{max} , T_{max} , AUC, $T_{1/2}$ and $AUC_{(0-\infty)}$. Analyses of variance (ANOVA) was performed on natural log transformed $AUC_{(0-\infty)}$, $AUC_{(0-\infty)}$, and C_{max} . The ANOVA model included sequence, regimen, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA was used to calculate least-squares means (LSM), the difference between regimen LSM, and the standard error associated with this difference. Exponentiation of the difference and associated 90% CI resulted in estimates of the ratio (warfarin+sevelamer)/(warfarin alone) and 90% CI. The Wilcoxon signed rank test was used for a nonparametric comparison of T_{max} values and a significant difference was defined a priori as $p < 0.05$.

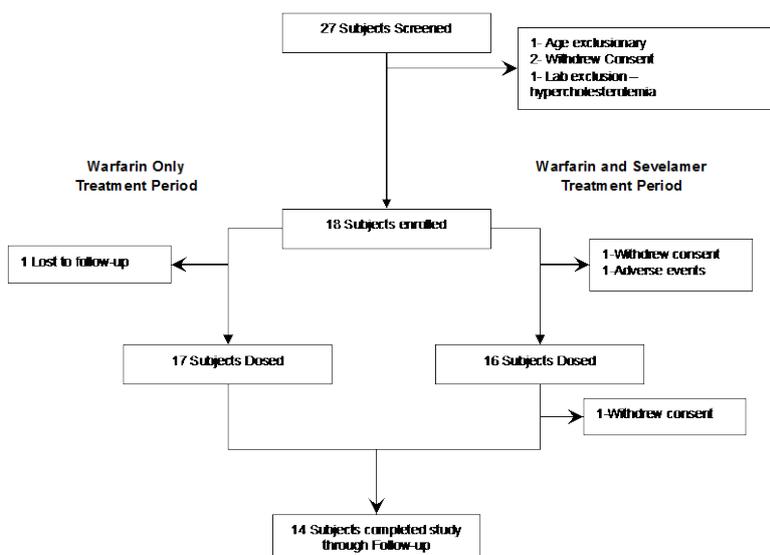
A sample size of 14 subjects provided 90% power for a 5% type I error rate two-one-sided test (TOST) with the 90% CI of the ratio (warfarin+sevelamer)/(warfarin alone) to be within the acceptance criteria of 0.80-1.25. A ratio of 1 and an intra-subject Coefficient of Variation (CV) of no more than 17% for C_{max} and AUC were assumed. To allow for the possibility of dropouts, 18 subjects were to be enrolled.

4.2.2.5. Changes in the conduct of the study or the planned analyses

There were no changes in the conduct of the study or the planned analyses.

4.2.2.6. Subject participation

The study enrolled healthy males aged 18 to 50 years, with body weight between 50 and 100 kg and BMI between 19 and 28 kg/m². The inclusion and exclusion criteria have been examined and are considered to be acceptable. The study enrolled and randomised 18 subjects, 15 (83.3%) completed all protocol required treatments over the two dosing period and 14 (77.8%) completed all study visits. In total, 17 subjects received warfarin alone and 16 subjects received warfarin in combination with sevelamer carbonate. The flow chart of study participation is summarised below in Figure 4.

Figure 4: SVCARB01107-Flow chart of subject participation.

There were protocol 27 deviations: 14 were due to procedures performed out of the time window, 12 were due to procedures not being done, and 1 related to lost ECG tracing. None of the deviations were considered to have significantly influenced the validity of the PK analysis.

4.2.2.7. Subject demographics

All subjects were male. The mean age of the cohort was 33.6 years, with a range of 21 to 49 years. The mean height was 177.4 cm (range: 160, 187 cm), the mean weight was 81.0 kg (range: 57.9, 95.5), and the mean BMI was 25.7 kg/m² (range: 20.5, 28.0 kg/m²). The ethnicity of the subjects was Caucasian (56%), Black (22%), and Hispanic (22%).

4.2.2.8. Pharmacokinetic results

The 90% CIs for the C_{max} and the $AUC_{(0-\infty)}$ ratios of the geometric means ([sevelamer+ warfarin]/[warfarin]) were within the standard bioequivalence interval of 80% to 125% for both R- and S- warfarin. The results indicate that the two treatments are bioequivalent in healthy male subjects, based on C_{max} and $AUC_{(0-\infty)}$ values. The results for R-warfarin are summarised below in Table 1, and the mean concentration time curves are provided in Figure 5. The results for S-warfarin are summarised below in Table 2 and the mean concentration time curves are provided in Figure 6.

Table 1: SVCARB01107-Summary of exposure parameters for R-warfarin; T = sevelamer carbonate + warfarin and R = warfarin alone.

a Geometric Mean for the Test Treatment (T) and Reference Treatment (R) based on Least Squares Mean of log-transformed parameter. b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref). c Post-hoc power was defined as the probability of having a 90% CI to a Test/Reference ratio within the acceptance criteria of 80-125% using a power of 90% and an alpha error of 5% based on the observed within-subject CV.

Table 2: SVCARB01107-Summary of exposure parameters for S-warfarin; T = sevelamer carbonate + warfarin and R = warfarin alone.

The notes are identical to those provided above for Table 1.

Figure 5: SVCARB01107 - R-warfarin concentration-time data after administration of sevelamer carbonate/warfarin (9.6 g/20 mg) and warfarin (20 mg) alone .

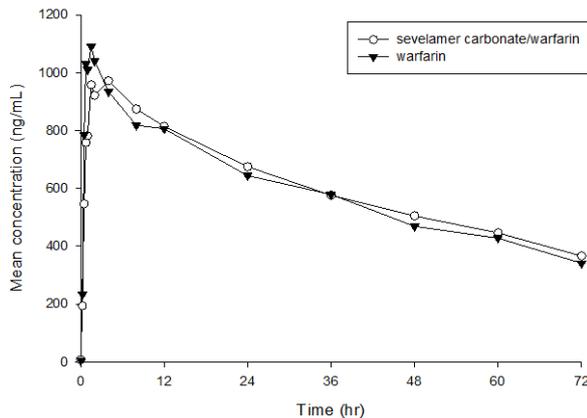
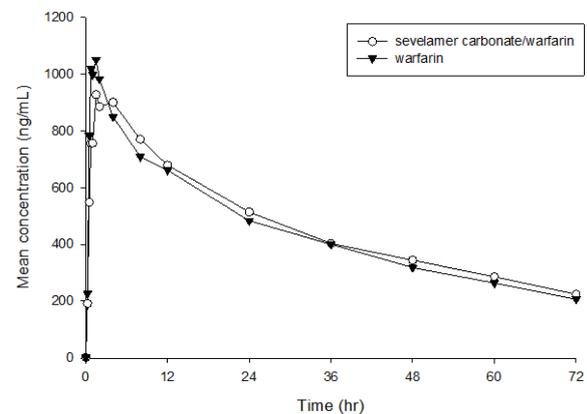


Figure 6: SVCARB01107 - S-warfarin concentration-time data after administration of sevelamer carbonate/warfarin (9.6 g/20 mg) and warfarin (20 mg) alone.



The mean (SD) T_{max} for R-warfarin was 2.59 (2.06) hours for sevelamer carbonate + warfarin and 1.42 (0.87) hours for warfarin alone; $p = 0.0449$. The mean (SD) T_{max} for S-warfarin was 2.40 (2.05) hours for sevelamer carbonate + warfarin and 1.33 (0.87) hours for warfarin alone; $p = 0.0549$. T_{max} values for R- and S-warfarin showed marked inter-subject variability following both treatments. The mean T_{max} for R- and S-warfarin was approximately 1 hour shorter when warfarin was administered alone compared with warfarin administered in combination with sevelamer carbonate, and this difference is unlikely to be clinically significant.

4.2.2.9. Safety results

Overall, 4 subjects reported a total of 5 AEs. Four (4) of the 5 AEs were assessed by the Investigator to be mild in intensity and not related to the study drugs. One (1) severe AE of prolonged prothrombin time (PT) occurred in 1 subject 1.5 days after dosing and was assessed by the Investigator to be related to warfarin. The subject was withdrawn from the study and

recovered without sequelae. There were no serious adverse events in this study. The AEs by subject and treatment are listed below in Table 3.

Table 3: SVCARB01107-Listing of adverse events by subject and treatment.*

Treatment	Subject Rand Number	MedDRA System Class	Organ	MedDRA Preferred Term	Description	Start Date Time	Stop Date Time	Duration	Severity	Relationship to Drug	Serious	Days Since First Dose
Warfarin Alone		Investigations		Prothrombin time prolonged	abnormally prolonged prothrombin time	20JUN07: 20:12:00	28JUN07: 08:21:00	7.5 days	Severe	Definite	No	1.5 days
		General disorders and administration site conditions		Pyrexia	fever	15JUN07: 08:43:00	27JUN07: 21:06:00	12.5 days	Mild	Remote/unlikely	No	3.0 days
Warfarin+ Sevelamer		Respiratory, thoracic and mediastinal disorders		Nasal oedema	Swollen right turbinate	14JUN07: 08:27:00	28JUN07: 06:29:00	13.9 days	Mild	Remote/unlikely	No	2.0 days
		Injury, poisoning and procedural complications		Heat stroke	Heat prostration	30JUN07: 17:00:00	02JUL07: 08:00:00	1.6 days	Mild	Unrelated	No	2.3 days
		Musculoskeletal and connective tissue disorders		Neck pain	neck pain	12JUN07: 22:00:00	13JUN07: 12:30:00	14.5 hrs	Mild	Unrelated	No	0.6 days

*Subject Rand Numbers have been redacted from this table.

4.2.3. SVCARB01307

4.2.3.1. Design and objectives

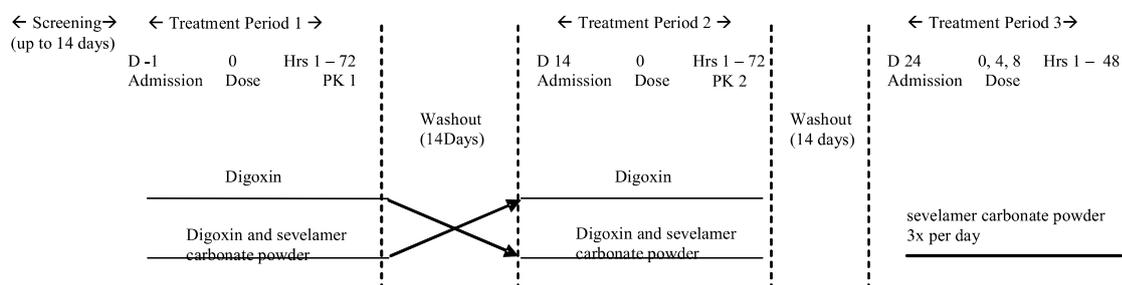
The primary objective of this Phase I, open-label, randomised, cross-over study was to investigate the effects of sevelamer carbonate powder for oral use on the pharmacokinetics of digoxin. The secondary objectives were to assess the safety/tolerability of the combination and to investigate the pharmacodynamic effects of sevelamer carbonate in healthy subjects on phosphorus absorption and excretion over time.

The study was undertaken at a single centre in the USA (Texas). The first subject was enrolled on 4 September June 2007 and the last subject completed the study on 30 November 2007. The study report was dated 19 November 2008. The study was conducted in accordance with the principles of GCP stated in the 'Guidance for Good Clinical Practice,' International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

4.2.3.2. Treatment

The study consisted of four periods: Screening period of up to 2 weeks; Treatment Period 1; Treatment Period 2; and Treatment Period 3. There was a 2 week washout between the three Treatment Periods. The PKs of the two treatments were analysed in Treatment Periods 1 and 2, and Treatment Period 3 was added to investigate the PDs of sevelamer carbonate on phosphorous absorption and excretion. The study is outlined below in Figure 7.

Figure 7: Source: SVCARB01307-Study design



In each dosing session, the subjects were confined to the clinical research unit for three nights and provided were standardised for phosphate content (1000 mg/day). Eligible subjects were randomised to one of two cohorts. The administered treatments included single-dose digoxin 1 mg alone in Treatment Periods 1 or 2, single-dose digoxin 1 mg in combination with single dose sevelamer carbonate powder 9.6 g (3 x 3.2 g sachets) in Treatment Periods 1 or 2, and three separate doses of sevelamer carbonate powder in Treatment Period 3 (3.2 g each at Hour 0,

Hour 4, and Hour 8). There was a 14 day washout between each treatment period. Subjects were discharged from the clinical research unit 48 hours following dosing in each treatment period. In Treatment Periods 1 and 2, subjects were required to return to the clinic as 'outpatients' 60 and 72 hours post-dose.

4.2.3.3. Sampling times

Plasma samples for digoxin were collected pre-dose and then post-dose at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 60 and 72 hours during Treatment Periods 1 and 2. No plasma samples were collected during Treatment Period 3.

Urine was collected for a urine phosphorus measurement pre-dose and in 4 hour intervals (0-4, 4-8, 8-12, 12-16, 16-20, 20-24, 24-28, 28-32, 32-36, 36-40, 40-44, and 44-48 hours) post-dose during each Treatment Period.

Serum inorganic phosphorus, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides were collected at Screening, pre-dose and then post-dose at 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours during each Treatment Period.

4.2.3.4. Statistical methods and sample size

PK parameters were calculated for plasma digoxin and compared between treatments. The PK parameters of interest were C_{max} , $AUC_{(0-72h)}$, and T_{max} . Since the effect of sevelamer carbonate on the absorption of digoxin was studied, and as digoxin has a long half-life, sampling was truncated to 72 hours. Therefore, $AUC_{(0-72h)}$ was used in place of $AUC_{(0-\infty)}$ for PK comparisons. Analyses of variance (ANOVA) was performed on the natural log transformed $AUC_{(0-72h)}$, $AUC_{(0-\infty)}$, and C_{max} parameters. The ANOVA model included sequence, regimen, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA was used to calculate least-squares means (LSM), the difference between regimen LSM, and the standard error associated with this difference. Exponentiation of the difference resulted in estimates of the ratio (digoxin+sevelamer)/(digoxin alone) ratio and 90% CI. Equivalence between treatments was to be declared if the entire 90% CI for the ratio of means of both $AUC_{(0-72h)}$ and C_{max} were entirely contained within the interval 80% to 125%. T_{max} was analysed using Wilcoxon signed-ranks test and statistical significance was declared if the p-value for the test was less than 0.05.

A sample size of 14 provided 90% powder for a 5% type I error rate two-one-sided test (TOST) for the 90% CI of the ratio (digoxin+sevelamer)/(digoxin alone) to be within the acceptance criteria of 80% to 125%. A ratio of 1 and an intra-subject Coefficient of Variance of no more than 17% for C_{max} and $AUC_{(0-\infty)}$ were assumed. To allow for the possibility of dropouts, 18 subjects were to be enrolled.

4.2.3.5. Changes in the conduct of the study or planned analyses

There were no changes in the conduct of the study. However, there were notable changes in the planned analyses. A total of 15 subjects were enrolled and administered Treatment Period 1 study medication. Due to a technical error during the preparation of the PK samples collected during Treatment Period 1 on 14 September 2007, the PK data could not be analysed and the subjects were not continued into Treatment Period 2. The 15 subjects that were dosed on 14 September 2007 were specified as the Non-Analyzable Group.

Following a 14 day washout, 10 of the subjects who participated in the 14 September 2007 dosing were re-consented and re-enrolled. Eight (8) additional subjects were enrolled. These 18 subjects make up the Analyzable Group and are included analyses comprising the summary of demographic and other baseline characteristics, all analyses of safety data and the pharmacokinetic analyses.

The C_{max} for one subject after administration of digoxin alone appeared to be anomalous compared to the C_{max} values for the other subjects. This C_{max} was identified as an outlier and PK and statistical analyses were performed with and without this subject.

4.2.3.6. Subject participation

The study enrolled healthy male and female subjects aged 18 to 50 years, with body weight between 50 and 100 kg and BMI between 19 and 28 kg/m². The inclusion and exclusion criteria have been examined and are considered to be acceptable.

In the Analyzable Group, a total of 18 subjects were screened and 17 (94.4%) subjects completed all protocol specified study procedures. One (1) subject discontinued during Treatment Period 3 due to 'illness/AE.'

4.2.3.7. Subject demographics

The baseline demographics of the 18 patients in the Analyzable group were: mean age 31.8 years (range: 18, 50 years); male 55.6% (n = 10), female 44.4% (n = 8); Black 22.2% (n = 4), Caucasian 72.2% (n = 13), Hispanic 5.6% (n = 1); mean weight 71.6 kg (range: 50.5, 93.5 kg); mean BMI 24.5 kg/m² (range: 19.1, 27.9 kg/mg²); never used tobacco 88.9% (n = 16); never used alcohol 44.4% (n = 8), currently using 55.6% (n = 10); all HIV negative; all hepatitis B surface antigen negative; all hepatitis C virus negative.

4.2.3.8. Pharmacokinetic results

The results of the ANOVA for the log-transformed values of C_{max} , $AUC_{(0-72h)}$, and $AUC_{(0-\infty)}$ for all subjects in the Analyzable Group (with outlier) are summarised below in Table 4. The mean digoxin concentration-time profile for the Analyzable Group (with outlier) are summarised in Figure 8.

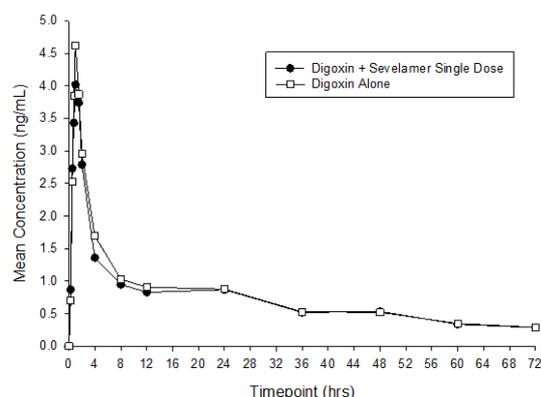
Table 4: SVCARB01307-Summary of exposure parameters; T = digoxin + sevelamer carbonate, R = digoxin alone Analyzable Group with outlier (n = 18).

Variable	Geometric Mean		Ratio (%) (Test/Reference)	90 % Confidence Interval	
	Test	Reference		Lower	Upper
$\ln(C_{max})$	4.32	4.57	94.35	79.73	111.64
$\ln(AUC_{0-72})$	50.30	53.05	94.83	87.64	102.60
$\ln(AUC_{0-\infty})$	67.97	67.58	100.58	88.66	114.10

Test: digoxin + sevelamer carbonate single dose

Reference: digoxin alone

Figure 8: SVCARB01307 - Mean digoxin concentration-time profile; Analyzable Group (all subjects).



With all subjects included, the mean ratios of log-transformed C_{max} , $AUC_{(0-72h)}$, and $AUC_{(0-\infty)}$ for the comparison of the two treatments were 94.4%, 94.8%, and 100.6%, respectively. The 90% CI for log-transformed $AUC_{(0-72h)}$, and $AUC_{(0-\infty)}$ were well within the standard bioequivalence interval of 80% to 125%. However, the lower boundary of the 90% CI for log-transformed C_{max}

(79.7%) was marginally below the lower limit, indicating a moderately decreased maximum concentration of digoxin in the presence of sevelamer carbonate. After excluding the C_{max} outlier, the geometric mean ratios (90%CI) for (digoxin + sevelamer)/digoxin were $C_{max} = 96.86\%$ (90%CI: 81.46, 115.17), $AUC_{(0-72h)} = 97.42$ (90%CI: 91.06, 104.23), and $AUC_{(0-\infty)} = 100.58\%$ (90%CI: 88.66, 114.10). The PK parameters for both treatment groups were similar in the Analyzable group with and without the outlier. Overall, it is considered that the results indicate that sevelamer carbonate is unlikely to have a clinically significant impact on the PKs of digoxin.

4.2.3.9. Pharmacodynamic results

The urine phosphorous results for 0-24 hours and 24-48 hours for the Analyzable Group (with outlier) are summarised below in Table 5. The highest urinary phosphorus excretion was seen during digoxin alone treatment with lower urinary phosphorus excretion during digoxin and sevelamer carbonate combination treatment and lowest excretion during sevelamer carbonate alone treatment.

Table 5: SVCARB01307-24-hour urine phosphorous levels.

Timepoint	Digoxin Alone (N=18) (mean ± SD)	Digoxin and Sevelamer Single Dose (N=18) (mean ± SD)	Sevelamer TID (N=18) (mean ± SD)
0-24 hours (mg)	623.3 ± 456.1	462.2 ± 233.7	377.3 ± 163.4
24-48 hour (mg)	652.7 ± 197.5	555.2 ± 166.4	435.0 ± 151.4

The mean serum phosphorus concentration was within the normal range at all time-points during all three treatment regimens. There were no notable differences between the treatments in serum phosphorus concentrations over time. The mean LDL cholesterol, total cholesterol, HDL cholesterol and triglyceride concentrations were within the normal range at all time-points during all three treatment regimens. There were no notable differences between the treatment regimens in LDL cholesterol, total cholesterol, HDL cholesterol or triglycerides.

4.2.3.10. Safety results

In the Analyzable Group (n = 13), TEAEs were reported in 9 (50.0%) patients with digoxin alone, 10 (55.6%) patients with digoxin + sevelamer carbonate, and 7 (38.9%) patients with sevelamer carbonate TDS (see Table 6, below). There were no severe TEAEs, no serious TEAEs, no deaths and 1 patient discontinued treatment in Period 3 (sevelamer carbonate TDS due to a TEAE). This subject experienced headache, nausea, vomiting and myalgia during sevelamer carbonate TDS treatment. All events were assessed as mild or moderate in intensity and remote/unlikely related to the study drug by the Investigator.

Table 6: SVCARB01307-TEAEs (all causality) occurring in ≥ 2 subjects during randomised period, by MedDRA preferred term.

System Organ Class	Digoxin Alone (N=18) n (%)		Digoxin and Sevelamer Single Dose (N=18) n (%)		Sevelamer TID [†] (N=18) n (%)	
	Events N	Subjects n (%)	Events N	Subjects n (%)	Events N	Subjects n (%)
Any AE	18	10 (55.6)	15	9 (50.0)	11	7 (38.9)
Blood and Lymphatic System Disorders						
Anaemia	2	2 (11.1)	0	0 (0)	0	0 (0)
Gastrointestinal Disorders						
Abdominal Distension	2	2 (11.1)	0	0 (0)	1	1 (5.6)
Abdominal Pain	2	2 (11.1)	0	0 (0)	0	0 (0)
Diarrhoea	1	1 (5.6)	2	2 (11.1)	0	0 (0)
Nausea	2	2 (11.1)	3	3 (16.7)	3	3 (16.7)
Vomiting	1	1 (5.6)	1	1 (5.6)	2	2 (11.1)
Investigations						
Electrocardiogram ST-T Change	2	2 (11.1)	2	2 (11.1)	0	0 (0)
Nervous System Disorders						
Headache	0	0 (0)	0	0 (0)	4	4 (22.2)

4.3. Evaluator's overall conclusions on pharmacokinetics

The submission included no clinical bioequivalence studies comparing sevelamer carbonate with sevelamer hydrochloride. The sponsor states that it is not possible to conduct conventional PK studies as sevelamer is not absorbed. The sponsor's justification is considered to be acceptable. The non-absorbability of sevelamer hydrochloride was confirmed in the previously evaluated Study GTC-10-801 in healthy young and elderly (> 65 years of age) male and female subjects (n = 20). On average, greater than 99% of the administered dose was recovered in the feces of each subject (n = 16). There was no detectable amount of sevelamer found in the blood of any subject at any time point (n = 16). The Renigel CER states that, based on the results of this study, 'conventional ADME studies were not conducted'.

In order to investigate the bioequivalence of the two sevelamer salts, the sponsor undertook an in vitro equilibrium and kinetic binding study [TR-2527-07-SC]. This study demonstrated that sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets (800 mg), and sevelamer carbonate powder (0.8 g, 1.6 g, and 2.4 g sachets) were equivalent based on phosphate binding, with and without acid pre-treatment. In particular, the Langmuir plots for the equilibrium binding samples (with and without acid pre-treatment) for the unbound phosphate concentration (mM) versus the ratio of unbound/bound phosphate were comparable for the sevelamer hydrochloride and carbonate formulations tested. In addition, kinetic binding experiments demonstrated that sevelamer hydrochloride and sevelamer carbonate bind phosphate in a similar rapid manner, independent of the initial phosphate concentration. The equilibrium level of binding was reached at both initial phosphate (KH_2PO_4) concentrations (2.5 mM and 38.7 mM) in approximately 15 minutes for the formulations tested. The results of the in vitro equilibrium and kinetic binding study suggest that sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets (800 mg), and sevelamer carbonate powder (0.8 g, 1.6 g, and 2.4 g sachets) formulations should bind phosphate in vivo in a similar manner.

The submission included two new drug-drug interaction (DDI) PK studies [SVCARB01107; SVCARB01307]. In SVCARB01107, single-dose sevelamer carbonate powder (9.6 g) administered in combination with single-dose warfarin (20 mg) had no significant effect on warfarin exposure in healthy male subjects. The 90% CIs for the C_{max} and the $\text{AUC}_{(0-\infty)}$ ratios of the geometric means ($[\text{sevelamer} + \text{warfarin}] / [\text{warfarin}]$) were all within the standard bioequivalence interval of 80% to 125% for both R- and S- warfarin. The results of this study were consistent with the previously submitted and evaluated DDI interaction PK study involving sevelamer hydrochloride and warfarin [ICR01382]. In SVCARB01307, single-dose sevelamer carbonate powder (9.6 g) administered in combination with single dose digoxin (1 mg) had no clinically significant effects on digoxin exposure in healthy subjects. The 90% CIs for the C_{max} , $\text{AUC}_{(0-72\text{h})}$, and $\text{AUC}_{(0-\infty)}$ ratios of the geometric means ($[\text{sevelamer} + \text{digoxin}] / [\text{digoxin}]$) were all within the standard bioequivalence interval of 80% to 125% for plasma digoxin in the all Analyzable Group (excluding 1 subject who was a C_{max} outlier). When the C_{max} outlier was included in the analysis, the lower bound 90% CI for the C_{max} ratio of 79.33% was marginally outside the lower bioequivalence interval of 80%, while the 90% CIs for the $\text{AUC}_{(0-72\text{h})}$, and $\text{AUC}_{(0-\infty)}$ ratios were within the standard bioequivalence interval of 80% to 125%. The results in this study were consistent with the previously submitted and evaluated DDI PK interaction study involving sevelamer hydrochloride and digoxin [ICR013769].

Previously submitted data included six DDI PK studies. These previously evaluated studies (Renigel CER) showed that sevelamer hydrochloride had no effect on the absorption of digoxin [ICR013769], warfarin [ICR013821], metoprolol [GTC-45-803], enalapril [GTC-45-804], and iron [GTC-45-808]. However, Study GTC-45-807 showed that the bioavailability of ciprofloxacin (750 mg) was statistically significantly ($p < 0.05$) decreased when co-administered with sevelamer hydrochloride (7x403 mg), based on reductions in C_{max} and $\text{AUC}_{(0-24\text{h})}$. Based on the new in vitro equilibrium and kinetic binding study [TR-2527-07-SC], and the two new in vivo drug-drug interaction PK studies [SVCARB01107; SVCARB01307], it can be reasonably inferred

that the results of the previously submitted and evaluated DDI PK studies relating to sevelamer hydrochloride can be extrapolated to sevelamer carbonate.

5. Pharmacodynamics

The submission included 1 study [SVCARB01307] providing new PD data. The PD data from this study has been reviewed above. The previously submitted and evaluated data included 2 studies with PD data in 44 healthy subjects [GTC-02-101; GTC-10-801]. In Study GTC-02-101 (randomised, placebo-controlled, parallel-group design), the evaluators comment that the prothrombin time was significantly decreased in all patients in the sevelamer hydrochloride group (n = 15), but there were no out of range values and no clinically significant changes in prothrombin time. The Clinical Overview included in the current submission states that Study GTC-02-101 'showed sevelamer hydrochloride decreased the urinary excretion of phosphorous in a dose related fashion'. In GTC-02-801, the evaluators comment that there were no clinically significant changes in laboratory values with the exception of 2 subjects who at the end of the study had increased ALT, AST, LDH and potassium levels and decreased carbon-dioxide levels that returned to normal within 1-2 months. No plausible explanation was provided for the abnormal values observed in these two subjects.

6. Dosage selection for the pivotal studies

In general, the sevelamer carbonate doses used in the new clinical efficacy and safety studies were based on the approved doses for sevelamer hydrochloride.

7. Clinical efficacy

7.1. Evaluable efficacy data

The submission included 4 new, previously unevaluated efficacy and safety studies in 294 patients treated with sevelamer carbonate. Each of these 4 studies has been fully evaluated and the results provided in the body of the text of this CER. The 4 studies are:

- GD3-163-201: Phase II, multicentre (USA), randomised, double-blind, cross-over, therapeutic equivalence study designed to compare the effects of sevelamer hydrochloride tablets TDS (n = 78) and sevelamer carbonate tablets TDS (n = 73) administered for 8 weeks on serum phosphorous levels in hyperphosphataemic patients with CKD on haemodialysis.
- SVCARB0005: Phase III, multicentre (UK), randomised, open-label, cross-over, therapeutic equivalence study designed to compare the effects of sevelamer carbonate powder TDS (n = 31) and sevelamer hydrochloride tablets TDS (n=28) administered for 4 weeks on serum phosphorous levels in hyperphosphataemic patients with CKD on haemodialysis.
- SVCARB00105: Phase III, multinational, multicentre, open-label, single-arm, dose-titration study designed to assess the effects of sevelamer carbonate TDS (n = 49) administered for 8 weeks on serum phosphorous levels in hyperphosphataemic CKD (Stage 4 and 5) patients not on dialysis.
- GD3-199-301: Phase III, multicentre (USA), randomised (2:1), parallel-group, open-label study designed to compare the effects of a once per day (QD) sevelamer carbonate powder regimen (n = 141) with the standard three times per days (TDS) sevelamer hydrochloride tablet regimen (n = 72) administered for 24 weeks on serum phosphorous levels in patients with CKD on haemodialysis.

In addition to the 4 key studies referred to above, the submission (Module 5) included information on 3 additional efficacy and safety studies involving sevelamer carbonate identified as EU post-approval commitment studies [SVCARB00606; SVCARB0308; APB00108]. Only the data from Study SVCARB0308 in Chinese patients with CKD who were hyperphosphataemic and on haemodialysis are considered to be relevant to the current submission. The data from this study have been reviewed and presented in Section 7.3 of this CER. Studies SVCARB00606 and APB00108 considered to be irrelevant as regards the evaluation of the efficacy of sevelamer carbonate for the purposes of this submission for the reasons presented in Section 7.3 of this CER.

In addition to the new studies relating to sevelamer carbonate, the submission included 17 studies that had been previously submitted to support the application to register sevelamer hydrochloride. These studies have been previously evaluated by the TGA, and have been reviewed in Section 7.4 of this CER.

7.2. Sevelamer carbonate-new studies not previously evaluated

7.2.1. Study GD3-163-201

7.2.1.1. Study design, objectives, locations and dates

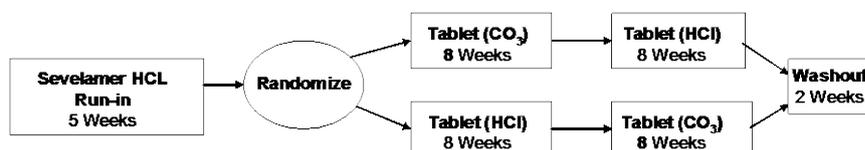
Study GD3-163-201 was a Phase II, randomised, double-blind, cross-over study designed to compare the effects on serum phosphorous levels of sevelamer hydrochloride (Renagel) and sevelamer carbonate in patients with chronic kidney disease (CKD) on haemodialysis.

The study was undertaken in 15 centres in the USA, and 13 of 15 sites enrolled patients. The first patient signed informed consent on 30 March 2005, and the last patient completed the study on 15 March 2006. The final CSR was dated 16 October 2006. The sponsor stated that study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP).

The primary objectives of the study were: (1) to compare the effects of sevelamer carbonate and sevelamer hydrochloride on the control of serum phosphorus in CKD patients on haemodialysis; and (2) to compare the safety and tolerability of the two treatments in the specified patient population. The secondary objective of the study was compare the effects of sevelamer carbonate and sevelamer hydrochloride on serum lipid profiles in CKD patients on haemodialysis.

The study consisted of five periods: a Screening Period of up to two weeks followed by a five-week Run-In Period, and two, eight-week study treatment periods followed by a two-week Washout Period. The study design is presented schematically in Figure 9, below.

Figure 9: GD3-163-201-Study design.



During the Screening Period, informed consent was obtained and patients were screened for eligibility. Eligible patients then entered a five-week Run-In Period in which all patients received sevelamer hydrochloride. The Investigator had one opportunity during the Run-In Period to titrate the sevelamer hydrochloride dose, cinacalcet hydrochloride (Sensipar) dose, vitamin D therapy and haemodialysis prescription (dialysate calcium level, dialysate bicarbonate level, treatment time). On the last day of the Run-In Period, eligibility criteria, adverse experiences and changes in concomitant medication were reviewed, and drug accountability was assessed.

Once the Run-In procedures were completed, 79 patients were randomised 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. The starting dose of sevelamer carbonate and sevelamer hydrochloride was individualised for each patient based on the most recently prescribed daily dose of sevelamer hydrochloride during the Run-In Period. Patients were instructed to maintain a fixed daily dose of sevelamer carbonate or sevelamer hydrochloride throughout both treatment periods.

During Treatment Period 1, patients were required to return for a study visit on Weeks 2, 4, 6 and 8. Blood samples were drawn and adverse events and changes in medications were assessed at each visit. Between Weeks 6 and 8, a 24-hour dietary recall was collected on three randomly selected days. At the Week 8 visit, a physical exam was performed, study drug was collected, Treatment Period 1 drug accountability was performed, and the study drug for Treatment Period 2 was dispensed. Patients who terminated early during Treatment Period 1 were asked to complete all of the assessments associated with Week 8.

During Treatment Period 2, patients were required to return for a study visit on Weeks 10, 12, 14 and 16. Blood samples were drawn and adverse events and changes in medications were assessed at each visit. Between Weeks 14 and 16, a 24-hour dietary recall was collected on three randomly selected days. At the Week 16 visit, a physical exam was performed, study drug was collected, Treatment Period 2 drug accountability was calculated, and the patient was instructed to discontinue all phosphate binders for the next two weeks. Patients who terminated early during Treatment Period 2 were asked to complete all of the assessments associated with Week 16.

During the Washout Period, patients were required to return for a study visit on Week 18. Blood samples were drawn and adverse events and changes in medications were assessed at this visit. Patients were instructed to resume their previously prescribed phosphate binders.

Evaluator's Comment: The randomised, double-blind design mitigates the chance of study bias. The cross-over design allowed each patient to act as his/her control. There was no washout period between the two treatment periods. Consequently, there was the chance of carry-over effects from one period to the next. The sponsor stated that no washout period occurred between treatment periods as 'carry over effects were not expected at the time of the efficacy measurements'. However, no data were provided supporting this supposition. All patients were on haemodialysis and, consequently, meet the criteria for stage 5 CKD.1

7.2.1.2. Inclusion and exclusion criteria

The key inclusion criteria are summarised briefly below. The study included patients who were at least 18 years of age with CKD on haemodialysis treatment three times per week and who had been on dialysis for three months or longer. Patients on phosphate binder therapy using sevelamer hydrochloride alone or patients on combination phosphate binder therapy were not to have exceeded a total daily binder dose of 13.6 g for at least 60 days prior to Screening.

Patients were also required to have the following documented local laboratory measurements:

- Two most recent consecutive serum phosphorus measurements ≥ 3.0 and ≤ 6.5 mg/dL within 60 days of Screening (that is, ≥ 1.0 and ≤ 2.1 mmol/L).
- Most recent iPTH measurement ≤ 600 pg/mL within 90 days of Screening (that is, ≤ 66 pmol/L); and
- Most recent serum calcium measurement within normal range provided by the local laboratory within 60 days of Screening.

In addition, patients were also required to have the following central laboratory measurements at randomization:

- Serum phosphorus measurement ≥ 3.0 and ≤ 6.5 mg/dL (that is, ≥ 1.0 and ≤ 2.1 mmol/L); and
- Intact PTH measurement ≤ 600 pg/mL (that is, ≤ 66 pmol/L).

The study also included procedures for Investigators to follow in cases where patients discontinued prematurely.

Evaluator's Comment: The inclusion criteria are considered to be satisfactory. The exclusion criteria included patients with 'active dysphagia, swallowing disorder, bowel obstruction, or severe gastrointestinal motility disorder', and patients with clinically significant, unstable medical conditions.

7.2.1.3. *Study treatments*

The study treatments consisted of sevelamer hydrochloride (Renagel) and sevelamer carbonate 800 mg tablets, with meals. Patients were eligible to participate in this study provided their total daily binder dose did not exceed 13.6 g (that is, equivalent to 17 x 800 mg tablets of sevelamer) for at least 60 days prior to screening. The maximum dose was selected for logistical reasons concerning supply of kits with enough study drugs for the duration of the trial. The sevelamer starting dose was individualised for each patient based on the last prescribed dose during the Run-In Period just prior to randomization. Patients were instructed to maintain a fixed daily dose throughout both randomised treatment periods.

All prior and concurrent medications taken within 30 days of Screening were documented on the Case Report Form (CRF). Patients were not to consume calcium, aluminum, or magnesium containing antacids throughout the duration of the study unless prescribed as an evening calcium supplement. If serum calcium (adjusted for albumin) fell below normal (defined by the central laboratory range) during the study, the Investigator could elect to prescribe an evening calcium supplement on an empty stomach starting with 0.6 grams of elemental calcium (3 x TUMS® Regular 500 mg tablets, containing 200 mg elemental calcium) and titrate the dose as necessary to return serum calcium to within the normal range.

If the patient was on Vitamin D replacement therapy, the Investigator was to maintain the dose recorded at randomization through the duration of the study, except for safety reasons. If the patient was taking a lipid-lowering medication, the patient was to maintain the dose recorded at Screening for the duration of the study, except for safety reasons. Otherwise, the patient was not to take these medications for the duration of the study.

The Investigator was to maintain a stable cinacalcet hydrochloride dose and haemodialysis regimen throughout the duration of the treatment periods, unless changes were needed for safety reasons.

7.2.1.4. *Efficacy variables and outcomes*

- The primary efficacy variable was serum phosphorous levels. Blood samples were measured for serum phosphorus at Weeks 4, 6, 8, 12, 14, and 16. The time-weighted mean of the measurements from the non-missing assessments from the last three visits in each treatment period were used for the analysis (that is, Weeks 4, 6, and 8 for Treatment Period 1 and Weeks 12, 14, and 16 for Treatment Period 2)
- The secondary efficacy variables were total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides measured at Weeks 4, 8, 12, and 16. The mean of the measurements from two visits in each treatment period (Weeks 4 and 8 for Treatment Period 1 and Weeks 12 and 16 for Treatment Period 2) were used for the analysis.

7.2.1.5. Randomisation and blinding methods

The patients were randomised in a 1:1 ratio 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. During the Run-In Period, patients were blinded to the study medication. For Treatment Periods 1 and 2, both Investigators and patients were blinded to the assigned treatment sequence. The sponsor also remained blinded to the assigned treatment sequence for the duration of the study and through the database lock. No patients were unblinded during the conduct of the study.

Evaluator's Comment: The method used to randomise patients 1:1 to one of the two treatment sequences could not be identified in the CSR or in the protocol.

7.2.1.6. Analysis populations

- The Full Analysis Set (FAS) included all randomised patients who were treated with at least one dose of randomised study medication and had at least one post-baseline assessment of serum phosphorus. Patients were analysed according to their randomised sequence. A confirmatory assessment of equivalence was conducted using the FAS.
- The Per-Protocol Set (PPS) included all FAS-evaluable patients who completed both treatment periods with no significant protocol deviations as determined by a blinded review prior to data analysis. Factors that were considered in determining PPS evaluability included: (1) greater than 15 percentage point difference in compliance between treatment periods was considered significant; (2) inclusion or exclusion criteria violation; (3) prohibited medication usage or significant change in Vitamin D/analogues use; (4) completed less than 6 weeks of treatment in either treatment period; (5) significant study medication interruption; and (6) other significant protocol deviations.
- The Safety Set included all randomised patients treated with at least one dose of randomised study medication. Patients who discontinued from the study during the Run-In Period were excluded from the Safety Set. Evaluable patients were analysed using their actual treatment sequence.

7.2.1.7. Sample size

Sample size calculations showed that 7 evaluable patients per sequence for a total of 14 patients were required to achieve 90% power to detect equivalence based on a 5% two, one-sided test (TOST) equivalence test, assuming that the expected ratio of means is 1 and the within subject mean square error from a cross-over ANOVA is 0.0265. Since no directly applicable data were available, the mean square error (MSE) used in this calculation was derived from a simulation based on serum phosphorus levels during a steady-state phase of a prior parallel arm study. A total of 80 patients were planned to be randomised to one of the two treatment sequences to account for dropouts and to expose additional patients to study treatment for the evaluation of safety.

7.2.1.8. Statistical methods

7.2.1.8.1. Primary efficacy endpoint analysis

The comparative effects of sevelamer hydrochloride and sevelamer carbonate on the control of serum phosphorus were determined using equivalence testing. The time-weighted mean of the measurements from the non-missing assessments from the last three visits in each treatment period were used for the analysis (that is, Weeks 4, 6, and 8 for Treatment Period 1 and Weeks 12, 14, and 16 for Treatment Period 2).

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 analysis of variance (ANOVA) with a random subject effect and fixed sequence, period, and treatment effects was used to derive the 90% CI 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% CI. If the 90% CI for the ratio was within the interval 0.80 to 1.25, then sevelamer carbonate and sevelamer hydrochloride were deemed to be equivalent. If the sequence effect was significant (p -value ≤ 0.05), then equivalence inferences were to be drawn from the Treatment Period 1 results.

7.2.1.8.2. Secondary efficacy endpoint analyses

To assess the differences between sevelamer carbonate and sevelamer hydrochloride on total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels, a 2x2 ANOVA model based on natural-log transformed data with a random subject effect and fixed sequence, period, and treatment effects was used. The mean of the measurements from two assessments in each treatment period were used in the analysis (that is, Weeks 4 and 8 for Treatment Period 1 and Weeks 12 and 16 for Treatment Period 2). Comparisons between the treatment regimens were tested at the 5% level.

7.2.1.8.3. Other matters relating to the statistical analyses

- Serum phosphorus at the end of Treatment Period 2, at the end of Washout, and the change from the end of Treatment Period 2 to the end of Washout were summarised overall and by treatment sequence for FAS patients with Washout visit data. The changes were assessed using Wilcoxon signed rank tests.
- No imputation or extrapolation was used to replace missing or invalid observations.
- No adjustments were made for multiplicity relating to the secondary efficacy endpoints.
- All data collected were documented using summary tables and patient data listings.
- All analyses were tested at the $\alpha = 0.05$ (2-tailed) level of significance unless otherwise specified.

7.2.1.9. Participant flow

Of the 101 patients screened for this study, 97 (96.0%) entered the Run-In Period and 79 (78.2%) were randomised. Of the 4 (4.0%) screened patients who did not enter the Run-In Period, 1 (1.0%) patient withdrew consent and 3 (3.0%) patients did not meet the inclusion/exclusion criteria. Of the 18 (17.8%) patients who entered the Run-In Period and were not randomised, 2 (2.0%) discontinued due to an AE, 7 (6.9%) withdrew consent, 4 (4.0%) did not meet the inclusion/exclusion criteria, 2 (2.0%) were discontinued for non-compliance to the study procedures, and 3 (3.0%) were discontinued due to Investigator's decision.

Of the 79 randomised patients, 40 were randomised to the sevelamer carbonate/sevelamer hydrochloride sequence and 39 to the sevelamer hydrochloride/sevelamer carbonate sequence. Of the 79 patients who entered the randomised treatment period, 5 (6.3%) discontinued during Treatment Period 1 (4 [5.1%] due to an AE; 1 [1.3%] due to non-compliance) and 1 discontinued between Treatment Period 1 and 2. Therefore, 74 (93.7%) completed Treatment Period 1.

Of the 73 (92.4%) randomised patients who entered Treatment Period 2, 4 (5.1%) discontinued during this period (1 [1.3%] due to an AE, 1 [1.3%] due to death, 1 [1.3%] lost to follow up, and 1 [1.3%] due to 'other' reasons.) Therefore, 69 (87.3%) patients completed Treatment Period 2.

The original study design did not include the two-week phosphate binder Washout Period following Treatment Period 2. This period was added to the study to confirm that the patients included in the study were hyperphosphataemic. As this change was implemented while the study was in progress, not all patients participated in the Washout Period. Twenty-two (22) patients did not enter the Washout Period after Treatment Period 2, all due to withdrawal of consent by the patients. A total of 47 patients entered the Washout Period. Seven (8.9%)

patients discontinued during the Washout Period: 1 was withdrawn for non-compliance with study procedures, 2 were withdrawn due to Investigator Decision, 1 due to 'other' reasons and 3 were missing Week 18 data. Forty (40) patients (50.6%) completed the study.

7.2.1.10. Major protocol violations/deviations

The sponsor stated that most protocol deviations were minor and were not expected to influence the scientific soundness of the study or the rights, safety or welfare of the patients. This conclusion is considered to be acceptable. Inspection of the listed protocol deviations identified major protocol deviations in 5 patients: 3 patients took drug for Treatment Period 2 rather than Treatment Period 1; 1 patient was hospitalised and missed study drug treatment; and 1 patient ran out of study drug and missed treatments. Overall, 22 patients 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 had a significant change to their Vitamin D medication; 1 patient had a significant study medication interruption; and 1 patient used a proscribed medication. Three patients (3) were treated in an opposite sequence to that specified by the randomization schedule. These patients were analysed according to their randomised sequence for the FAS analysis, but were analysed according to their actual sequence for the Safety Set and PPS analyses.

7.2.1.11. Baseline data

7.2.1.11.1. Demographics

In the Safety Set (n = 78), 40 (51%) patients were male and 38 (49%) patients were female, with a mean \pm SD age of 58 ± 12 years and a range of 29 to 88 years. Most patients were Black or African-American (67%), with Whites (27%), Others (5%) and American Indian or Alaskan Natives (1%) comprising the rest of the population. The mean \pm SD weight was 84 ± 25 kg, the mean \pm SD height was 170 ± 10 cm, and the mean \pm SD BMI was 29 ± 8 kg/m². There were no statistically significant differences between the treatment sequences in demographic characteristics. The baseline demographic data for the FAS and PPS were similar to those of the Safety Set.

7.2.1.11.2. History of renal disease

In the Safety Set (n = 78), the most commonly occurring primary cause of chronic renal failure was diabetes mellitus (n = 33, 42%) followed by hypertension (n = 18, 23%), 'other' (n = 16, 21%), glomerulonephritis (n = 7, 9%), polycystic kidneys (n = 2, 3%), hydronephrosis (n = 1, 1%) and interstitial nephritis (n = 1, 1%). The mean \pm SD time on dialysis was 4.4 ± 4.9 years, with a range of 0.3 to 23.4 years. Previous parathyroidectomy had been reported in 4 (5%) patients, and 67 (86%) patients were currently taking Vitamin D. The mean \pm SD dialysate bath calcium concentration was 2.4 ± 0.3 meq/L, with a range of 2.0 to 3.5 meq/L. The mean \pm SD urea reduction ratio (URR) was $74\% \pm 6\%$, with a range of 62% to 96%. Sevelamer hydrochloride had been used as the pre-study binder by 92% (n = 72) of the population, and sevelamer carbonate and calcium had been used by 8% (n = 6).

7.2.1.11.3. General medical history

More than 50% of patients reported prior or current disorders or abnormalities in the following body systems: cardiovascular (100%); surgical (99%); genitourinary/reproductive (94%); endocrine (92%); musculoskeletal (92%); haematologic (90%); gastrointestinal (89%); neurological (80%); respiratory (77%); HEENT (74%); other (62%); allergies (55%); and dermatologic (51%). In general, the prior and current disorders were similar between the two sequences.

7.2.1.11.4. Medications

All 78 patients (100%) had taken at least one medication within 30 days prior to Screening and during Screening. The most common classes of medication (> 25% of patients) were ACE inhibitors, plain (29.5%), analide analgesics such as doxyphene and paracetamol (55.1%), selective beta blocking agents such as atenolol and metoprolol (46.2%), dihydropyridine derivatives such as amlodipine, felodipine, and nifedipine (38.5%), electrolyte solutions (64.1%), heparin (94.9%), HMG CoA reductase inhibitors (46.2%), iron bivalent, oral preparations (33.3%), other anti-anaemic preparations such as erythropoietin and epoetin alpha (92.3%), platelet aggregation inhibitors excluding heparin such as acetylsalicylic acid and clopidogrel (47.4%), proton pump inhibitors (32.1%), vitamin D and analogues (88.5%).

During the Run-In Period, all (100%) patients in the Safety Set took a concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications during the Run-In Period were ACE inhibitors, plain (30.8%), analide analgesics (60.3%), selective beta blocking agents (42.3%), dihydropyridine derivatives (38.5%), electrolyte solutions (64.1%), H₂-receptor antagonists (25.6%), heparin (93.6%), HMG-CoA reductase inhibitors (47.4%), iron bivalent, oral preparations (29.5%), other anti-anaemic preparations such as erythropoietin and epoetin alpha (92.3%), platelet aggregation inhibitors excluding heparin (47.4%), proton pump inhibitors (34.6%), vitamin D and analogues (88.5%), and vitamin, other combinations (29.5%).

Overall, 70 (89.7%) patients began new medications or had changes in existing medications during the Run-In Period. The drug categories with the most frequent concomitant medication changes (> 10%) were influenza vaccines (16.7%), iron bivalent, oral preparations (14.1%), iron trivalent, oral preparations (16.7%), other anti-anaemic preparations (43.6%), and vitamin D and analogues (24.4%).

During the randomised treatment periods, all (100%) patients in the Safety Set took a concomitant medication. The drug categories with the most frequent (> 25%) concomitant medications were summarised. In the Safety Set, a total of 71 (97.3%) patients treated with sevelamer carbonate and 72 (92.3%) patients treated with sevelamer hydrochloride began new medications or had changes in existing medications during the randomised treatment periods. The drug categories with the most frequent concomitant medication changes (> 10%) were summarised. The concomitant medications changes were similar between treatment regimens and similar to the medication changes made during the Run-In Period.

7.2.1.11.5. Bicarbonate concentration of dialysate bath

There was no change in the bicarbonate concentration of the dialysate for either treatment in the safety set and no statistically significant difference in the change in this parameter between treatments. In the sevelamer carbonate group (n = 73), the mean±SD baseline and final concentrations were 34.21±7.98 mEq/L and in the sevelamer hydrochloride group (n = 78) the corresponding figure was 34.25±7.72 mEq/L.

7.2.1.11.6. Dietary intake

The dietary intake in the PPS during the randomised treatment period was similar for the sevelamer carbonate group (n = 56) and the sevelamer hydrochloride group (n = 56). In particular, there were no significant differences between the two treatment groups in dietary phosphorous, calcium, vitamin D, total energy, total protein, cholesterol and total carbohydrate.

7.2.1.12. Treatment compliance

During the Run-In Period, the mean percent compliance was 84% in both the Safety Set and the FAS, and was 86% in the PPS (that is, compliance = number of tablets taken/number of tablets prescribed x 100%). During the randomised treatment periods, mean percent compliance in the Safety Set and the FAS was similar for the sevelamer carbonate and sevelamer hydrochloride

regimens (82% and 83%, respectively, both analysis sets), and the corresponding results for the PPS were 85% and 86%.

7.2.1.13. Results for the primary efficacy outcome

The primary analysis was undertaken in the PPS and showed therapeutic equivalence of both treatments as regards mean serum phosphorous levels (see Table 7, below), and similar findings were observed in the confirmatory analysis in the FAS. The overall, Sequence 1, and Sequence 2 mean time weighted serum phosphorous levels (mg/dL) were similar for both treatment groups.

Table 7: GD3-163-201-Primary efficacy outcome serum phosphorous equivalence test; overall mean time weighted serum phosphorous in the PPS.

Serum phosphorous	Sevelamer carbonate (n=56)	Sevelamer hydrochloride (n=56)	Geometric LSM Ratio (Carb/HCl)	90% CI
Arithmetic mean \pm SD mmol/L	1.5 \pm 0.3	1.5 \pm 0.3	0.99	0.95, 1.03
Arithmetic mean \pm SD mg/dL	4.6 \pm 0.9	4.7 \pm 0.9	0.99	0.95, 1.03

In the PPS, the mean \pm SD prescribed dose was 7.2 \pm 3.1 g/day in both treatment groups, and the mean \pm SD actual dose in the randomised treatment periods was 6.0 \pm 2.8 g/day in both treatment groups. No patients in the PPS changed their prescribed dose during the randomised treatment periods. In the FAS, the mean \pm SD prescribed dose during the randomised treatment periods was 7.2 \pm 3.2 g/day of sevelamer carbonate and 7.1 \pm 3.3 g/day of sevelamer hydrochloride. The mean \pm SD actual dose during the randomised treatment periods was 5.8 \pm 2.8 g/day of sevelamer carbonate and 5.6 \pm 2.9 g/day of sevelamer hydrochloride. No patients in the FAS changed their prescribed dose during the randomised treatment periods. The mean number of weeks on study medication was similar for both treatment regimens (8.0 weeks on sevelamer carbonate treatment and 7.8 weeks on sevelamer hydrochloride treatment).

Post-hoc analyses were performed to understand the results across dose level as a marker for degree of underlying hyperphosphataemia. A regression analysis of the equivalence ratio (sevelamer carbonate/sevelamer hydrochloride) on prescribed dose was conducted. The flat regression line and non-significant p-value ($y=0.95 + 0.01 \cdot x$; $p=0.2745$) indicate that the equivalence ratio is invariant to prescribed dose.

As an alternative way to illustrate this relationship, an analysis of the geometric least squares mean ratio (sevelamer carbonate/sevelamer hydrochloride) was conducted by dose group. In the ≤ 4.8 g daily dose group ($n = 22$) the ratio was 0.97 (90% CI: 0.91, 1.04), in the > 4.8 to < 9.6 g daily dose group ($n = 14$) the ratio was 0.95 (90% CI: 0.85, 1.05), and in the ≥ 9.6 g daily dose group ($n = 20$) the ratio was 1.04 (90% CI: 0.98, 1.10). This analysis indicated that there was no relationship between the equivalence ratio and dose, and was consistent with the result of the regression analysis.

A two-week Washout Period was included following active treatment period to confirm that the patients enrolled in this trial were hyperphosphataemic. At the end of the treatment period the mean \pm SD serum phosphorus was 5.0 \pm 1.3 mg/dL in all FAS patients participating in the Washout Period. Following the two-week Washout Period, the mean \pm SD serum phosphorus level increased significantly (that is, $\Delta = 1.5 \pm 1.9$ mg/dL; $p < 0.001$). The increase in serum phosphorus during the Washout Period was seen regardless of sevelamer formulation prescribed immediately preceding the Washout Period. In patients treated with sevelamer carbonate prior to washout the mean \pm SD serum phosphorus increase was 1.3 \pm 2.2 mg/dL (from 5.3 \pm 1.4 mg/dL, $p=0.022$), and in patients treated with sevelamer hydrochloride

immediately preceding the washout the mean \pm SD serum phosphorus increase was 1.7 ± 1.5 mg/dL (from 4.6 ± 1.2 mg/dL, $p < 0.001$). The results for serum phosphorus before and after the end of washout are presented below in Table 8, overall and by treatment sequence.

Table 8: GD3-163-201-Serum phosphorous (mg/dL) before and after end of washout period; FAS with washout data.

	Overall (N=40) [mean \pm SD]	Sequence 1 (Carbonate/Hydrochloride) (N=19) [mean \pm SD]	Sequence 2 (Hydrochloride/Carbonate) (N=21) [mean \pm SD]
Week 16	5.0 \pm 1.3	4.6 \pm 1.2	5.3 \pm 1.4
Week 18	6.5 \pm 1.9	6.3 \pm 1.8	6.6 \pm 2.0
Change	1.5 \pm 1.9	1.7 \pm 1.5	1.3 \pm 2.2
P-Value	< 0.001	< 0.001	0.022

A regression analysis of the change in serum phosphorus during the Washout Period on prescribed dose was conducted. The regression line and significant p-value ($y=0.10+0.20*x$; $p=0.0296$) indicate that patients with a higher prescribed dose experienced greater increases in serum phosphorus during the Washout Period. This suggests that dose is a reasonable marker of the extent of hyperphosphataemia.

7.2.1.14. Results for the secondary efficacy outcomes

The results for the serum lipid levels in the FAS are summarised below in Table 9. The 90% CI for the geometric mean ratio for each of the lipid parameters was within the interval of 0.80 to 1.25, indicating that the effects of the two treatments are therapeutically equivalent.

Table 9: GD3-163-201-Serum lipids; FAS.

Laboratory Parameter	Sevelamer Carbonate (N=73) [mean \pm SD]	Sevelamer Hydrochloride (N=78) [mean \pm SD]	P-value	Geometric LS Mean Ratio	90% CI of Ratio
Total-C (mg/dL)	144.0 \pm 33.9	139.0 \pm 33.6	0.009	1.04	1.01 – 1.06
LDL-C (mg/dL)	59.5 \pm 24.9	56.0 \pm 23.3	0.035	1.07	1.01 – 1.12
HDL-C (mg/dL)	50.0 \pm 17.7	49.2 \pm 15.2	0.707	1.01	0.98 – 1.03
Triglycerides (mg/dL) [†]	176.0 \pm 109.5	169.1 \pm 104.1	0.243	1.03	0.99 – 1.07

7.2.2. SVCARB00205

7.2.2.1. Study design, objectives, locations and dates

Study SVCARB00205 was a Phase III, multicentre (UK), randomised, open-label, cross-over study designed to compare the effects of sevelamer carbonate powder and sevelamer hydrochloride tablets administered TDS with meals on serum phosphorous concentration in hyperphosphataemic patients with CKD on haemodialysis.

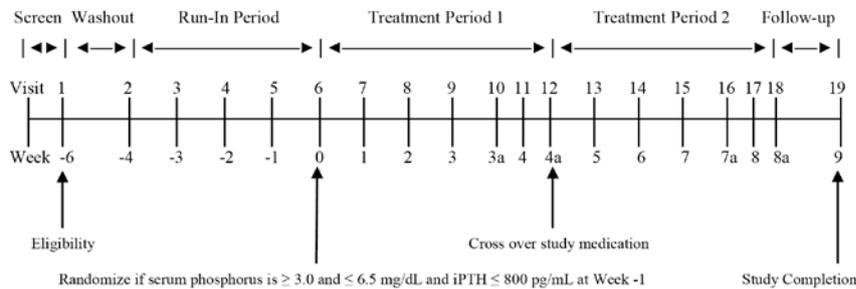
The study enrolled patients from 7 sites in the UK. The first patient was enrolled on 31 January 2006 and the last patient completed the study on 21 March 2007. The final CSR was dated 19 July 2007, and an amendment to the final report was dated 11 January 2008. The sponsor stated that study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP). The sponsor was Genzyme Europe Research, UK.

The primary objectives of the study were: (1) to demonstrate equivalence of sevelamer carbonate powder TDS to sevelamer hydrochloride tablets TDS with meals, on control of serum phosphorus levels; and (2) to compare the safety and tolerability of the two treatment regimens. The secondary objectives were to compare the effects of the two treatment regimens on (1) the serum calcium-phosphorous product and (2) the serum lipid profile.

The study consisted of 6 periods: a 2-week Screening and Washout Period; a 4 week sevelamer hydrochloride tablet Run-In Period; two, 4 week Treatment Periods; and a Follow-up visit 1

week after the last study treatment visit. The study is outlined schematically in Figure 10, below.

Figure 10: SVCARB00205-Study schematic.



At Screening, informed consent was obtained and patients were assessed for eligibility. Patients had to be taking sevelamer hydrochloride alone or as combination phosphate binding therapy. Patients who fulfilled the entry criteria were asked to discontinue their current phosphate binder and enter a 2-week Washout Period. At the end of the Washout Period, patients who were hyperphosphataemic (serum phosphorus ≥ 5.5 mg/dL or ≥ 1.76 mmol/L) continued in the 4 week Run-In Period. In the Run-In period, each binder dose taken prior to the Washout Period was replaced with an equivalent number of 800 mg tablets of sevelamer hydrochloride (not to exceed a total daily dose of 14.4 g or 18 x 800 mg tablets). In the Run-In Period, the dose of sevelamer hydrochloride tablets could be adjusted if necessary at Visits 3 and 4 to keep serum phosphorus levels within a target level of 3.5 and 5.5 mg/dL (1.12 and 1.76 mmol/L), inclusive, by increasing or decreasing by 1 x 800 mg tablet TDS (that is, 2.4 g/day).

Patients who were eligible to continue into the treatment period were to maintain the dose of study drug last prescribed during the Run-In Period for the remainder of the study. At Baseline, eligible patients were randomly assigned to 4 weeks treatment with sevelamer hydrochloride tablets or sevelamer carbonate powder during Treatment Period 1 (that is, Weeks 1, 2, 3, 4). During Treatment Period 2, patients previously assigned to sevelamer carbonate powder crossed-over to sevelamer hydrochloride tablets and those previously assigned to sevelamer hydrochloride tablets crossed-over to sevelamer carbonate powder for an additional 4 weeks of treatment (Weeks 5, 6, 7 and 8). At the end of Treatment Period 2, study medication was discontinued and patients were instructed to return to their pre-study phosphate binder medication. Patients returned for a Follow-up visit 7 days later.

Evaluator's Comment: The study is open-label in design. Consequently, it is subject to the well-known biases associated with studies of this nature. However, the potential biases are mitigated due to the efficacy endpoints being based on objective laboratory tests. The treatment cross-over allows each patient to act as his or her control. There was no washout period between the two, 4 week treatment periods. Therefore, there is the potential for carry-over effects from Treatment Period 1 to Treatment Period 2.

The submission included a final CSR for this study dated 19 July 2007 and an amendment to the final report dated 11 January 2008. The amendment included data from one site that had been identified by the sponsor subsequent to its approval of the original CSR. The sponsor states that the additional information had been identified by the sponsor during preparatory activities for a site inspection by the UK's Medicines and Healthcare products Regulatory Agency (MHRA). The sponsor stated that the additional information 'does not impact the

efficacy or safety conclusions described in the original CSR'. The original CSR had not been modified to reflect the changes.

Examination of the CHMP Assessment Report for Renvela (London. 19 March 2009; Doc.Ref.: EMEA/214544/2009), accessed from the European Medicines Agency (EMA) website, indicates that routine EMA GCP inspection at the sponsor site and one investigator site revealed 'critical and major issues, with regard to eligibility criteria, drug compliance, and adverse event reporting'. The assessment report stated that '[b]ased 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 Authorisation 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'. It appears that, in response to a list of outstanding issues raised by the inspection, the sponsor 'presented a sensitivity analysis [to the CHMP] and addressed the issue at the oral explanation'. Based on the presented data 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'.

The 'sponsor site' referred to in the CHMP assessment report was Genzyme Europe BV, The Netherlands, and is assumed to be the central co-ordination point for the study. However, the sponsor should confirm that the term 'sponsor site' refers to the central co-ordination point for the study (see Clinical Questions, Section 12). The investigator site that underwent routine EMA GCP Inspection was located in the UK. The sponsor should indicate the number of patients at both the 'sponsor site' and the 'investigator site' that gave rise to concern and the nature of these concerns (see Clinical Questions below). In addition, the sponsor should indicate the proportion of the total patient population that gave rise to concern (see Clinical Questions). Additional information relating to the EMA's concerns has been requested as have the results of the sensitivity analysis referred to in the CHMP assessment report (see Clinical Questions below).

The submission included an 'Addendum to the Clinical Overview for Renewal of Renvela 800 mg film-coated tablets 1.6 g & 2.4 g powder for oral suspension in the European Union' covering the period 10 June 2009 to 6 June 2013. This addendum included the results of an observational, open-label, post-marketing safety 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 ≥ 1.78 mmol/L. This study appears to have been undertaken by the sponsor as a post-approval commitment to the CHMP.

7.2.2.2. *Inclusion and exclusion criteria*

The study included men and women aged 18 years of age or older who had been receiving haemodialysis three times a week for three months or longer. Patients were required to have been taking sevelamer hydrochloride alone or in combination therapy, at a binder dose not exceeding 14.4 g/day, within 60 days prior to screening. In addition, patients were required to have had the following documented local laboratory measurements:

- Two most recent consecutive serum phosphorus measurements that were ≥ 3.0 and ≤ 7.0 mg/dL (≥ 0.96 and ≤ 2.26 mmol/L) within 60 days of screening.
- A most recent iPTH measurement ≤ 900 pg/mL (≤ 99 pmol/L) within 90 days of screening.

Furthermore, patients were required to have had the following central laboratory measurements:

- A serum phosphorus measurement ≥ 5.5 mg/dL (≥ 1.76 mmol/L) at Visit 2 (after Washout).
- A serum iPTH measurement ≤ 800 pg/mL (≤ 88 pmol/L) at Visit 5 (prior to randomization).
- A serum phosphorus measurement ≥ 3.0 and ≤ 6.5 mg/dL (≥ 0.96 and ≤ 2.08 mmol/L) at Visit 5.

The inclusion and exclusion criteria were summarised. The study also included criteria for withdrawing patients from therapy or assessment. Investigators were requested, wherever possible, to follow-up patients who had discontinued in order to obtain information about the reasons for discontinuation, collect data relating to AEs, and undertake an early termination assessment.

7.2.2.3. *Study treatments*

During the Run-In Period, patients received sevelamer hydrochloride at a dose based on their most recently prescribed phosphate binder dose prior to the Washout Period. During the Run-In Period, the sevelamer hydrochloride dose could be titrated to maintain control of phosphorous levels, but the total daily dose for each patient was not to exceed 14.4 g or 18 x 800 mg tablets. Dose titration, increasing or decreasing by 1 x 800 mg tablet TDS (2.4 g/day) was permitted during the Run-In Period at Visits 3 and 4 to keep serum phosphorus levels within a target range of 3.5 and 5.5 mg/dL (1.12 and 1.76 mmol/L), inclusive. The dose of study drug last taken during the Run-In Period was used throughout the randomised cross-over treatment periods. During the treatment periods, patients were randomised on a 1:1 basis to one of the following two oral treatment sequences:

- Sevelamer carbonate 800 mg powder TDS with meals for four weeks followed by sevelamer hydrochloride 800 mg tablets TDS for four weeks.
- Sevelamer hydrochloride 800 mg tablets TDS with meals for four weeks followed by sevelamer carbonate 800 mg powder TDS for four weeks.

Patients were instructed to thoroughly mix each individual sevelamer carbonate powder 800 mg sachet with 20 mL of water and to drink the mixture within 30 minutes of preparation. Multiple sachets may have been mixed at once, as long as 20 mL of water was used for each sachet. All medications taken by the patient within 30 days of signing the informed consent until study completion were recorded in the patient CRF. Patients were not to consume calcium, aluminium, or magnesium containing antacids throughout the duration of the study unless prescribed as an evening calcium supplement by the study physician. Calcium supplementation was permitted during the study if serum calcium (adjusted for albumin) fell below normal (defined by the central laboratory range). If the patient was on Vitamin D therapy, calcimimetics, or lipid-lowering medication, the investigator was to maintain the dose recorded at screening through the duration of the study, unless otherwise indicated for safety reasons. Patients not taking lipid-lowering medication at study entry were not to begin taking these

medications during study participation. During Treatment Periods 1 and 2, the investigator was to maintain the haemodialysis prescription regarding dialysate bicarbonate, calcium concentrations and treatment time, unless otherwise indicated for safety reasons. Instructions were provided to the investigator in cases where sevelamer was administered with medications known to alter the serum level of the drug.

7.2.2.4. Efficacy variables and outcomes

- The primary efficacy variable was serum phosphorous levels. Blood samples were measured for serum phosphorus at Weeks 3, 3a, 4, 4a (Treatment Period 1) and Weeks 7, 7a, 8, and 8a (Treatment Period 2).
- The secondary efficacy variables were serum calcium-phosphorous product and serum lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides). Blood samples were measured for serum calcium-phosphorus product at Weeks 3, 3a, 4, 4a (Treatment Period 1) and Weeks 7, 7a, 8, and 8a (Treatment Period 2). Blood samples for lipid parameters were measured at Week 4a for Treatment Period 1 and Week 8a for Treatment Period 2.

7.2.2.5. Randomisation and blinding methods

The study was open-label and blinding was not performed. Patients were randomised within each site on a 1:1 basis in blocks of 4 to one of the two treatment sequences.

7.2.2.6. Analysis populations

The Safety Set included all randomised patients who were treated with at least one dose of randomised study medication.

The Full Analysis Set (FAS) included the subset of Safety Set evaluable patients with at least one post-baseline assessment of serum phosphorus.

The Per Protocol Set (PPS) included all FAS evaluable patients with no significant protocol deviations, as determined by a blinded review by appropriate clinical and statistical personnel prior to data analysis.

The analysis populations are summarised below in Table 10.

Table 10: SVCARB00205-Analysis populations.

Analysis Set Reason for exclusion	Overall (N=31) n (%)	Sequence 1	Sequence 2
		Carbonate powder/ Hydrochloride tablets (N=17) n (%)	Hydrochloride tablets/Carbonate powder (N=14) n (%)
Randomised	31 (100)	17 (100)	14 (100)
Never received study medication	0	0	0
Included in the Safety Set	31 (100)	17 (100)	14 (100)
No post-baseline phosphorus assessments	1 (3)	1 (6)	0
Included in the Full Analysis Set	30 (97)	16 (94)	14 (100)
At least 30% difference in compliance between treatment periods	3 (10)	1 (6)	2 (14)
Entry criteria violation	0	0	0
Proscribed medication usage	0	0	0
Less than 3 weeks on study treatment in both treatment periods	6 (19)	2 (12)	4 (29)
Included in the Per Protocol Set	21 (68)	13 (77)	8 (57)

7.2.2.7. Sample size

Allowing for withdrawals, a sample size of 12 patients per sequence (powder/tablet versus tablet/powder; 24 patients in total) was required to be randomised to achieve 90% power to detect equivalence based on a 5% Two One-Sided Test (TOST) equivalence test, assuming that the expected ratio of means is 1 and the standard deviation of the difference between treatment

regimens on the log scale is 0.22 (derived from pilot data comparing once-a-day versus TDS dosing with sevelamer hydrochloride tablets).

7.2.2.8. Statistical methods

7.2.2.8.1. Primary efficacy endpoint analysis

The effects of powder and tablet dosing on the control of serum phosphorus were determined using equivalence testing. The time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen were used in the analysis (that is, mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2). Measurements prior to Week 3 for Treatment Period 1 and prior to Week 7 for Treatment Period 2 were not carried forward for efficacy assessment.

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 analysis of variance (ANOVA) with a random subject effect and fixed sequence, period, and treatment effects were used to derive the 90% CI for the difference between powder (test) and tablet (reference) data on the log scale. Back transformation to the original scale yielded an estimate of the ratio (test/reference) and corresponding 90% CI. The two treatments were deemed equivalent if the 90% CI of the ratio was within the interval 0.80 to 1.25. If the sequence effect was significant ($p\text{-value} \leq 0.05$), then equivalence inferences were to be drawn from the Treatment Period 1 results. The primary analysis was performed using the PPS to minimise the degree of bias in the equivalence testing, and a FAS analysis was performed as a confirmatory analysis.

7.2.2.8.2. Secondary efficacy analyses

To assess the differences between powder and tablet dosing on serum calcium-phosphorus product and serum lipid parameters, a 2x2 ANOVA model based on natural-log transformed data with a random subject effect and fixed sequence, period, and treatment effects was used. For calcium-phosphorus product, the time-weighted average was used for the analysis (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2). For the lipid parameters, the laboratory assessment at the end of each treatment period was used for the analysis. Measurements prior to Week 3 for Treatment Period 1 and prior to Week 7 for Treatment Period 2 were not carried forward for efficacy assessment. Comparisons between the treatment regimens were tested at the 5% level. In addition, the geometric LSM ratio and corresponding 90% CIs were derived as described for the primary efficacy parameter. The secondary efficacy analyses were undertaken using the FAS, with supporting analysis using the PPS.

7.2.2.8.3. Other matters relating to the statistical analyses

- Serum phosphorus, calcium (albumin-adjusted), and calcium-phosphorus product at Screening, at Week -4 (after the 2-week washout), change from Screening to Week -4, and at Week 0 were summarised overall and by treatment sequence for the PPS, FAS, and Safety Set. Within treatment regimen changes were assessed using the Wilcoxon signed rank test.
- No changes were made to the protocol defined analyses.
- Models adjusting for covariates were not part of the analysis plan for this study.
- Missing data were not imputed and measurements were not carried forward.
- No adjustment for multiplicity of secondary efficacy endpoint testing was undertaken.

7.2.2.9. Participant flow

Of the 76 screened patients, 75 unique patients were screened while 1 patient was re-screened and counted twice in prior to randomization data. Of the 76 screened patients, 42 (55.3%) patients entered the Run-In Period and 11 (14.5%) of these run-in patients were not randomised, and 34 (44.7%) patients did not enter the run-in. The disposition of all patients prior to randomization are summarised below in Table 11.

Table 11: SVCARB00205-Patient disposition prior to randomization; all screened patients.

Patient Category	Overall (N=76) n (%)
Screened Patients [1]	76
Patients Who Did Not Enter Run-in Period	34 (44.7%)
SCREEN FAILURE	26 (34.2%)
ADVERSE EVENT(S)	3 (3.9%)
NON-COMPLIANT	0
WISHES TO WITHDRAW	3 (3.9%)
LOST TO FOLLOW UP	0
OTHER	2 (2.6%)
Patients Entered Run-in Period	42 (55.3%)
Non-Randomized Patients Among Run-In Patients	11 (14.5%)
SCREEN FAILURE	7 (9.2%)
ADVERSE EVENT(S)	0
NON-COMPLIANT	1 (1.3%)
WISHES TO WITHDRAW	0
LOST TO FOLLOW UP	0
OTHER	3 (3.9%)
Randomized Patients	31 (40.8%)

1] = one patient screened twice and was counted twice. 75 unique patients were screened

A total of 31 patients were randomised to study treatment, 17 patients to Sequence 1 (sevelamer carbonate/hydrochloride) and 14 patients to Sequence 2 (sevelamer hydrochloride/carbonate) (see Table 12, below).

Table 12: SVCARB00205-Disposition of patients randomised to treatment.

Patient category	Sequence 1 (carbonate/hydrochloride)	Sequence 2 (hydrochloride/carbonate)
Randomised	17	14
Treatment Period 1		
Discontinued due to AE	1 (17.6%)	0
Elected to withdraw	2 (5.9%)	0
Completed	14 (82.4%)	14 (100%)
Treatment Period 2		
Discontinued due to AE	0	1 (7.1%)
Elected to withdraw	0	3 (21.4%)
Completed	14 (82.4%)	10 (71.4%)
Discontinued prior to follow up	0	0
Completed follow-up visit	14 (82.4%)	10 (71.4%)

7.2.2.10. Major protocol deviations

There were 7 major protocol deviations among 4 patients (Patients [information redacted]). Three (3) of the 4 patients were included in the PPS as the protocol deviations were not expected to influence the equivalence assessment between treatment regimens. The exception was Patient [information redacted] who was excluded from the PPS due to having failed to have at least 3 weeks of treatment in both randomised treatment periods. Patients [information

redacted] each had one major deviation relating to the dose of sevelamer hydrochloride during the Run-In Period. All 3 patients had serum phosphorus levels at Visit 3 which according to the study protocol required an increase in the dose of study medication. In each case, the investigator preferred that the patient remain on their existing dose of sevelamer hydrochloride, either because they had been on the dose for only 4 days before the Visit 3 sample was taken (Patients [information redacted]), or because the patient had experienced severe stomach cramps following previous dose escalations (Patient [information redacted]). Patient [information redacted] had 4 major protocol deviations, 3 relating to missed study visits and 1 relating to an error in study medication resulting in cross-over to sevelamer hydrochloride during Treatment Period 1 three weeks earlier than scheduled.

Evaluator's Comment: It is difficult to understand why Patient [information redacted] (4 major protocol deviations) was not excluded from the PPS, given that one of the major protocol deviations resulted in the patient being crossed-over to sevelamer hydrochloride in Treatment Period 1 three weeks earlier than scheduled (that is, at Visit 10 rather than Visit 13). This appears to be significant, given that the treatment period was only 4 weeks in duration. The sponsor should justify inclusion of this patient in the PPS (see Clinical Questions below).

7.2.2.11. Baseline data

7.2.2.11.1. Demographics

The safety set included 31 patients with mean \pm SD age 52.9 ± 13.2 years (range: 27, 80 years), 68% (n = 21) were male and 32% (n = 10) were female, 71% (n = 22) were Caucasian, 10% (n = 3) were Black and 19% (n = 6) were Asian, and 84% (n = 26) were non-smokers. The mean \pm SD values for other baseline characteristics were weight 75.9 ± 19.9 kg, height 170.3 ± 13.3 cm, and BMI 25.7 ± 5.8 kg/m². The results for the PPS and FAS were generally similar to those for the safety set, and the observed differences are unlikely to be significant.

7.2.2.11.2. Renal history

In the safety set (n = 31), the primary causes of ESRD in decreasing order of frequency were 'other' (n = 13, 42%), glomerulonephritis (n = 8, 26%), diabetes (n = 4, 13%), polycystic kidneys (n = 2, 7%), and n = 1 (3%) each for hypertension, pyelonephritis, interstitial nephritis, and congenital. The mean \pm SD time on dialysis was 7.2 ± 8.0 years (range: 0.2, 30 years), 8 (26%) patients had undergone a kidney transplant, and 4 (13%) patients had undergone a parathyroidectomy. Vitamin D was currently being taken by 25 (81%) patients, pre-study sevelamer hydrochloride had been taken by 18 (58%) patients, pre-study sevelamer hydrochloride and calcium by 11 (36%) patients, and other phosphate binders by 2 (7%) patients.

7.2.2.11.3. General medical history

More than half of the patients in safety set (n = 31) reported prior or current disorders or abnormalities in the following body systems: genitourinary/renal (n = 30, 97%); metabolic/endocrine/nutritional (n = 27, 87%); haematopoietic (n = 27, 87%); cardiovascular (n = 27, 87%); gastrointestinal/hepatic (n = 21, 68%); and musculoskeletal (n = 19, 61%).

7.2.2.11.4. Medications

All 31 patients (100%) in the safety set had taken at least one medication within 30 days prior to Screening and during Screening/Washout. Excluding the category of 'drugs for the treatment of hyperkalaemia and hyperphosphataemia', which were being taken by all patients prior to Screening due to existing sevelamer hydrochloride therapy, the most frequently used classes of medications (> 25% of patients) were other anti-anaemic preparations (94%), vitamin D and analogues (81%), platelet aggregation inhibitors excluding heparin (58%), HMG CoA reductase

inhibitors (42%), proton pump inhibitors (42%), beta blocking agents, selective (32%), calcium compounds (32%), dihydropyridine derivatives (32%), and plain ACE inhibitors (29%).

During the Run-In Period, all 31 (100%) patients in the safety set took a concomitant medication. The drug categories with the most frequent concomitant medications during the Run-In Period were consistent with those most frequently used in the period prior to and during Screening/Washout. Overall 20 (65%) patients in the safety set existing medications during the Run-In Period. The drug categories with the most frequent concomitant medication changes (>10%) were proton pump inhibitors (16%) and vitamin D and analogues (13%).

During the randomised treatment periods, 16 (52%) patients began new medications, or stopped or had changes in existing medications during treatment with sevelamer carbonate powder and 11 (39%) patients during treatment with sevelamer hydrochloride tablets. The concomitant medications changes were similar between treatment regimens and generally similar to the medication changes made during the Run-In Period. The results for the PPS were similar to those of the Safety Set.

7.2.2.12. Treatment compliance

During the Run-In Period, the mean percent compliance was 87% in both the safety set and the FAS, and 84% in the PPS (compliance was calculated as for Study GD3-163-201). During the randomised treatment periods, mean percent compliance in the Safety Set and the FAS was similar for the sevelamer carbonate and sevelamer hydrochloride regimens (81% and 83%, respectively). The mean percent compliance in the PPS during the randomised treatment period was also similar for the sevelamer carbonate and sevelamer hydrochloride regimens (86% and 84%, respectively).

7.2.2.13. Results for the primary efficacy outcome

The results for the analysis of the primary efficacy endpoint of serum phosphorous time weighted averages in the PPS and the FAS are summarised below in Table 13. In both the PPS and the FAS, the 90% CI of geometric LS mean ratio (sevelamer carbonate/hydrochloride) was enclosed entirely within the interval 0.85 to 1.25, indicating that that sevelamer carbonate was equivalent to sevelamer hydrochloride based on the serum phosphorous time weighted averages.

In the PPS, the mean \pm SD prescribed doses during the randomised treatment periods were 7.4 \pm 3.1 g/day of sevelamer carbonate powder and 7.5 \pm 3.1 g/day of sevelamer hydrochloride tablets, and the corresponding mean \pm SD actual doses were 6.0 \pm 3.1 g/day and 6.4 \pm 3.3 g/day, respectively. Patients with less than three weeks of exposure were excluded from the PPS, and the mean number of weeks on study medication was 4.3 weeks on sevelamer carbonate powder and 4.6 weeks on sevelamer hydrochloride tablets.

In the FAS, the mean \pm SD prescribed doses during the randomised treatment periods were 7.6 \pm 3.2 g/day of sevelamer carbonate powder and 7.8 \pm 3.0 g/day of sevelamer hydrochloride tablets, and the corresponding mean \pm SD actual doses were 5.9 \pm 2.8 g/day and 6.5 \pm 3.3 g/day, respectively. The mean number of weeks on study medication was 3.8 weeks on sevelamer carbonate powder and 4.6 weeks on sevelamer hydrochloride tablets.

Table 13: SVCARB00205-Serum phosphorous time weighted averages; PPS and FAS.

Analysis Set	Sevelamer Carbonate Powder mean ± SD	Sevelamer Hydrochloride Tablets mean ± SD	Geometric LS Mean Ratio	90% CI of Ratio
Serum phosphorus (mg/dL)				
Per Protocol Set (N=21)	5.0 ± 1.5 (n=21)	5.2 ± 1.1 (n=21)	0.95	0.87-1.03
Full Analysis Set (N=30)	5.0 ± 1.5 (n=25)	5.1 ± 1.1 (n=28)	0.96	0.88-1.05
Serum phosphorus (mmol/L)				
Per Protocol Set (N=21)	1.6 ± 0.5 (n=21)	1.7 ± 0.4 (n=21)	0.95	0.87-1.03
Full Analysis Set (N=30)	1.6 ± 0.5 (n=25)	1.7 ± 0.4 (n=28)	0.96	0.88-1.05

Prior to the randomised treatment periods, patients entered a 2-week Screening/Washout period followed by a 4 week sevelamer hydrochloride Run-In Period. The mean ± SD serum phosphorus at Screening in the PPS was 1.6 ± 0.3 mmol/L and at the end of the Washout period (Week -4) had increased significantly to 2.5 ± 0.6 mmol/L (mean change 0.9 ± 0.7 mmol/L, p<0.001). These results indicate that the patients in this study were hyperphosphataemic. Serum phosphorus levels subsequently decreased during the 4 week sevelamer hydrochloride Run-In Period and at the start of the randomised treatment period (Week 0), the mean ± SD value was 1.6 ± 0.4 mmol/L.

7.2.2.14. Results of the secondary efficacy outcomes

- No statistically significant differences were observed in the mean ± SD serum calcium (albumin adjusted)-phosphorous product between the sevelamer carbonate powder group (n = 30) and the sevelamer hydrochloride tablet group (n = 28) in the FAS: 3.7 ± 1.1 versus 3.7 ± 0.8 mmol²/L²; LS mean ratio = 0.98 (90% CI: 0.88, 1.09), p = 0.749. The 90% CI was enclosed entirely within the interval 0.8 to 1.25. In the FAS, the mean serum calcium (albumin-adjusted)-phosphorus product at Screening was 3.8 ± 0.9 mmol²/L² and at the end of the Washout period (Week -4), had increased significantly to 5.4 ± 1.5 mmol²/L² (mean change 1.6 ± 1.8 mmol²/L², p < 0.001).
- No statistically significant differences were observed in the FAS between the two treatment groups in the mean serum lipid parameters for the changes from Baseline (Week 0) to the end of the treatment period. The 90% CI for the geometric LS mean ration was within the 0.80 to 1.25 interval (see Table 14, below).

Table 14: SVCARB00205-Analysis of serum lipids; FAS.

Laboratory Parameter	Sevelamer Carbonate Powder (N=30) mean ± SD	Sevelamer Hydrochloride Tablets (N=28) mean ± SD	P-value	Geometric LS Mean Ratio	90% CI of Ratio
mmol/L	(n=22)	(n=27)			
Total Cholesterol	3.5 ± 0.7	3.3 ± 0.8	0.218	1.02	0.99-1.06
LDL Cholesterol	1.8 ± 0.5	1.8 ± 0.7	0.109	1.05	1.00-1.10
HDL Cholesterol	1.2 ± 0.5	1.1 ± 0.4	0.537	0.98	0.93-1.04
Triglycerides	2.2 ± 1.6	2.1 ± 1.5	0.992	1.0	0.89-1.12

7.2.3. Study SVCARB00105

7.2.3.1. Study design, objectives, locations and dates

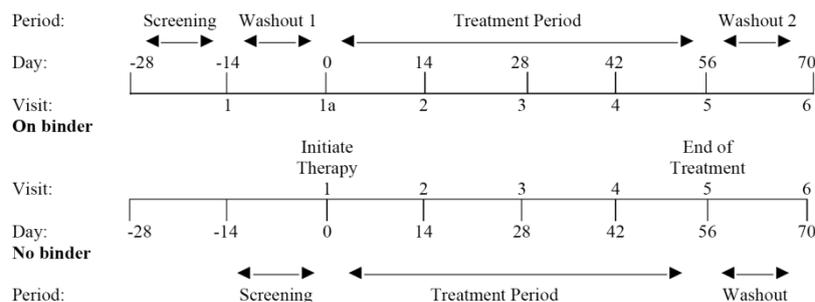
Study SVCARB00105 was a Phase III, multinational, multicentre, open-label, dose titration study of sevelamer carbonate administered TDS in hyperphosphataemic CKD patients not on dialysis.

The primary objectives of the study were: (1) to evaluate the efficacy of sevelamer carbonate tablets administered TDS with meals in controlling serum phosphorus levels; and (2) to evaluate the safety and tolerability of the treatment regimen. The secondary objectives were to evaluate the effects of the treatment regimen on: (1) serum calcium-phosphorous product; (2) serum lipids; and (3) percent responders (serum phosphorous between 0.86 and 1.47 mmol/L, inclusive, at Day 56/early termination [ET]); 'Day 56/ET' was defined as the 'study visit for Day 56 among completers, or the last on treatment visit for patients who terminated sevelamer carbonate early'.

The study included 25 sites, and 19 of these sites enrolled patients (15 in Europe [UK, Germany, France, Denmark] and 4 in Australia). The first patient was enrolled on 14 February 2007, the last patient completed the study on 23 January 2007 and the study report was dated 30 May 2007. The sponsor stated that the study was designed, conducted, recorded and reported in compliance with the principles of Good Clinical Practice (GCP). The study was sponsored by Genzyme Europe Research, UK.

The study consisted of four periods: a 2-week screening period; a 2-week washout period; an 8 week treatment period; a second 2-week washout period. The initial 2-week washout period was only applicable to those patients taking phosphate binders at screening. Patients not taking phosphate binders at screening proceeded directly to the start of the 8 week treatment period. The outline of the study is provided schematically in Figure 11 below.

Figure 11: SVCARB00105-Schematic of study.



In the 2-week screening period, eligibility criteria were assessed and patients with serum phosphate levels < 1.76 mmol/L either at screening or after washout and meeting all eligibility criteria entered the study. Patients started treatment with sevelamer carbonate at a dose of 4.8 g daily (2 x 800 mg tablets TDS). Blood samples were obtained every 2 weeks for the 8 week treatment period beginning at baseline (that is, Days 0, 14, 28, 42, and 56). The sevelamer carbonate dose was titrated to a maximum 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 TDS at visits on Days 14, 28, and 42) to reach a target serum phosphorus level ≥ 0.86 and ≤ 1.47 mmol/L. At Day 56/ET blood samples were taken, sevelamer carbonate was stopped and patients entered a second washout phase. At Day 70, after the second washout period, a final blood sample was obtained and patients were returned to their pre-treatment phosphate binders, if applicable.

7.2.3.2. Inclusion and exclusion criteria

The study included men and women aged 18 years or older with the following central laboratory assessments:

1. if not on a phosphate binder, serum phosphorus ≥ 1.76 mmol/L) at screening (Visit 1);
2. if taking a phosphate binder at screening, serum phosphorus ≥ 1.76 mmol/L after the 2-week washout period at Visit 1a (Day 0).

In addition, at screening (Visit 1) patients were required to have the following central laboratory measurements: (a) 25-hydroxyvitamin D \geq 10 ng/mL; and (b) iPTH \leq 800 pg/mL (\leq 88 pmol/L).

All inclusion and exclusion criteria were provided. Patients who were screened and failed to fulfil the inclusion or exclusion criteria could be re-screened if their screening central laboratory results were: (a) serum phosphorus level $>$ 1.5 mmol/L; or (b) serum 25-OH vitamin D level $>$ 7 ng/mL. Re-screening was not advised within 1 month of the previous screening attempt. The number of re-screening attempts was not limited, but consideration was given to the appropriateness of multiple re-screening attempts.

The study also included appropriate criteria for discontinuing patients from therapy or assessment. These included discontinuation of patients requiring dialysis or admitted for renal transplantation at any time during the study.

7.2.3.3. Study treatments

During the 8 week treatment period, all patients received sevelamer carbonate 800 mg tablets. The starting dose for all patients was 4.8 g/day, and the dose could be titrated to a maximum dose of 12 g/day during the Treatment Period. Dose titration occurred as necessary to maintain serum phosphorous levels \geq 0.86 mmol/L and \leq 1.47 mmol/L.

The starting dose in this study was based on data from a Phase II study [GTC-45-204] in hyperphosphataemic patients not on dialysis, where a statistically significant reduction in serum phosphate was demonstrated with an average dose of sevelamer hydrochloride of 3.53 g/day. However, this study showed that the number of patients attaining serum phosphorus within the target range and the magnitude of reduction in serum phosphorus was lower than previously seen in clinical trials involving patients on haemodialysis where average doses of approximately 6 g/day were used. Consequently, a starting dose of 4.8 g/day was selected to allow more rapid control of serum phosphorus levels.

All medications taken by the patient within 30 days of signing the informed consent until study completion were recorded in the CRF. Patients were not to consume calcium, aluminium, or magnesium containing antacids throughout the duration of the study, unless prescribed as an evening calcium supplement by the study physician. Calcium supplementation was permitted during the study if serum calcium (adjusted for albumin) fell below normal (defined by the central laboratory range). If the patient was on Vitamin D therapy, cinacalcet therapy, or lipid-lowering medication, the investigator was to maintain the dose recorded at screening through the duration of the study, unless otherwise indicated for safety reasons. Patients not taking lipid-lowering medication at study entry were not to begin taking these medications during study participation.

To minimise the effects of dietary absorption of vitamin D that may occur with treatment with sevelamer carbonate, all patients were supplemented with a daily dose of 400 IU. This supplement was given in addition to any ongoing active vitamin D therapy routinely prescribed. Instructions were provided to the investigator in cases where sevelamer was administered with medications known to alter the serum level of the drug.

7.2.3.4. Efficacy variables and outcomes

- The primary efficacy variable was the change in serum phosphorous from baseline to Day 56/ET. Baseline was defined as screening (Visit 1) for patients not on phosphate binders at study entry and Day 0 (Visit 1a) for patients on phosphate binders at study entry.
- The secondary efficacy endpoints include the changes from baseline to Day 56/ET in: (1) serum phosphorous-calcium product; (2) serum lipids (total, LDL, and HDL cholesterol); and (3) percent serum phosphorous responders. Baseline was defined as for analysis of serum phosphorous levels.

7.2.3.5. Randomisation and blinding methods

Not applicable. The study was open-label with all treated patient receiving sevelamer carbonate.

7.2.3.6. Analysis populations

- The Safety Set included all patients who received at least one dose of sevelamer carbonate.
- The Full Analysis Set (FAS) included the subset of the Safety Set with a baseline and at least one post-baseline serum phosphorus measure during treatment (± 5 days). The FAS is considered to be the primary efficacy population.
- The Per Protocol Set (PPS) included the subset of the FAS with no significant protocol violations. All exclusions from the PPS were identified before database lock. Significant protocol violations included, but were not limited to the following: (1) study drug compliance $< 75\%$; (2) inclusion or exclusion criteria violation; (3) < 42 days on sevelamer carbonate; (4) proscribed medication usage; and (5) protocol deviations.

7.2.3.7. Sample size

Statistical power calculations aimed 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, with a standard deviation for the change from baseline of 0.45 mmol/L. Given these assumptions, 23 evaluable (FAS) patients were required. Therefore, to account for a possible 20% dropout rate, a minimum of 28 were planned.

7.2.3.8. Statistical methods

7.2.3.8.1. Primary efficacy endpoint analysis

The primary efficacy variable was the change in serum phosphorous from baseline to Day 56/ET. Baseline was defined as screening (Visit 1) for patients not on phosphate binders at study entry and Day 0 (Visit 1a) for patients on phosphate binders at study entry. Standard descriptive statistics were presented for serum phosphorus at all study visits and for the changes between screening and baseline, baseline and Day 56/ET, and Day 56 to Day 70 (the end of the second washout). A Wilcoxon signed rank test was used to assess the changes (significance $p < 0.05$).

7.2.3.8.2. Secondary efficacy endpoint analyses

The secondary efficacy endpoints include the changes from baseline to Day 56/ET in: (1) serum phosphorous-calcium product; (2) serum lipids; and (3) percent serum phosphorous responders. Baseline was defined as for the serum phosphorous analysis. Standard descriptive statistics were presented for lipid parameters and calcium-phosphorus product at all study visits and for the changes between screening and baseline, baseline and Day 56/ET, and Day 56 to Day 70 (end of the second washout). A Wilcoxon signed rank test was used to assess the changes (significance $p < 0.05$). The percent responders (serum phosphorus ≥ 0.86 mmol/L and ≤ 1.47 mmol/L) were calculated for each post-baseline study visit during the treatment period and for Day 56/ET.

7.2.3.8.3. Other matters relating to statistical methods

- Additional post hoc analyses performed in the FAS included: (1) serum phosphorus over time by CKD Stage (4 versus 5); (2) serum phosphorus over time in the subset of patients who were on phosphate binders at study entry; (3) serum phosphorus over time by investigative site; and (4) compliance, dosing, and baseline serum phosphorus by serum phosphorus responder status at Day 56/ET.
- Models adjusting for covariates were not part of the statistical plan. For laboratory data, the last non-missing post-baseline on-treatment 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 visit. Otherwise no extrapolation or imputation procedures were performed for missing or invalid observations for any other measurement.

7.2.3.9. Participant flow

A total of 129 patients were screened and 12 were re-screened. A total of 49 patients were treated and 41 (84%) completed the study. Of the 8 treated patients who were treated but did not complete the study, 4 discontinued due to AEs, 2 withdrew consent, and 2 withdrew for 'other' reasons (1 on medical advice, 1 due to starting dialysis).

7.2.3.10. Major protocol violations/deviations

There were four major protocol deviations in four patients: 1 patient took the dose twice a day rather than three times a day; 1 patient was missing the required label on one blood sample, and re-sample was outside the time interval; 1 patient's required dose increase was not undertaken; 1 patient's dose was titrated downwards instead of upwards. The four major protocol deviations are considered unlikely to have invalidated the efficacy analysis. The sponsor comments that most protocol deviations were minor and had no influence on the scientific soundness of the study or the rights, safety or welfare of the patients.

7.2.3.11. Baseline data

7.2.3.11.1. Demographics

In the Safety Set (n=49), the mean \pm SD age of the population was 62.0 \pm 12.1 years, 32 (65%) patients were male and 17 (35%) patients were female. Most patients were Caucasian (45, 92%), with 1 Black patient (2%), 2 Asian patients (4%) and 1 patient (2%) listed as Other (Indian) comprising the rest of the population. The mean \pm SD BMI was 27.8 \pm 5.94 kg/m² and the mean \pm SD height was 169.5 \pm 9.37 cm. Results for the FAS and PPS were similar to those of the Safety Set.

7.2.3.11.2. Renal history

In the Safety Set (n=49), 17 (35%) patients had Stage 4 CKD (GFR 15-29 mL/min/1.73m²) and 32 (65%) patients had Stage 5 CKD (GFR < 1.73 mL/min/1.73m²). There were no patients with CKD Stages 1, 2, or 3. The estimated mean \pm SD GFR was 13.14 \pm 4.76 mL/min/1.73m². The primary causes of ESRD reported in \geq 10% (n=5 patients) were 'other' (22%), diabetes (18%), polycystic kidneys (16%), glomerulonephritis (16%), and hypertension (14%). Other causes of ESRD reported in < 10% of patients were pyelonephritis (8%), hydronephrosis (2%), and interstitial nephritis (2%). No patients had undergone renal transplantation or parathyroidectomy. Pre-study phosphate binders had been used by 30 (61%) patients, with the majority having used calcium carbonate (23 [47%]). Pre-study Vitamin D had been taken by 24 (49%) patients.

7.2.3.11.3. General medical history

In the Safety Set (n=49), the most commonly reported medical conditions (other than genitourinary/renal) occurring in \geq 50% of patients were cardiovascular (44 [89.8%]), metabolic/endocrine/nutritional (41 [83.7%]), and haematopoietic (31 [63.3%]). The general medical history profile was consistent with a patient population with Stage 4 or 5 CKD with a mean age of 62 years.

7.2.3.11.4. Medications

All patients in the Safety Set (n=49) had taken prior medications within 30 days of screening and/or during screening. The most frequently prescribed prior medications reported to have been taken by \geq 50% of patients included: plain sulfonamides (69.4%); vitamin D preparations (59.2%); HMG CoA reductase inhibitors (57.1%); and dihydropyridine derivatives (51.0%). During the treatment period, all patients in the Safety Set (n=49) took concomitant medication.

The most frequently administered concomitant medications reported in $\geq 50\%$ of patients were vitamin D preparations (38 [77.6%]), plain sulfonamides (33 [67.3%]), other anti-anaemic preparations not including iron preparations (30 [61.2%]), HMG co-reductase inhibitors (28 [57.1%]), and dihydropyridine inhibitors (25 [51.0%]). Changes (started, stopped or changed) in concomitant medications after the start of the treatment phase were most frequent for vitamin D preparations (46.9%). The patterns of prior and concomitant medication use were not unexpected.

7.2.3.12. Treatment compliance

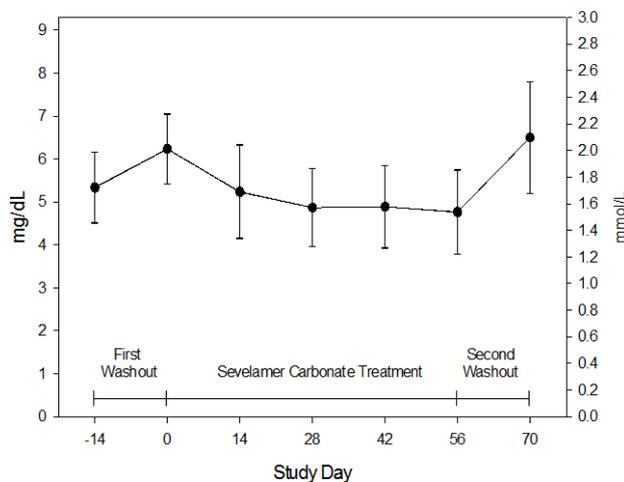
Percent compliance was calculated as the number of tablets taken in the period divided by the total number of tablets prescribed in the period, and multiplied by 100. During the treatment period, mean percent compliance for the Safety Set and the FAS were similar (87.7% and 89.1%, respectively), and mean percent compliance for the PPS was 94.9%.

7.2.3.13. Results for the primary efficacy outcome

The primary analysis was in the FAS (n=46). The mean \pm SD baseline serum phosphorus level (n=46) was 2.0 ± 0.3 mmol/L, and the corresponding mean \pm SD level (n=46) at Day 56/ET was 1.6 ± 0.3 mmol/L. The mean \pm SD decrease in serum phosphorus level from baseline to Day 56/ET was statistically significant ($\Delta = -0.5 \pm 0.3$ mmol/L, $p < 0.001$). There was a statistically significant ($p < 0.001$) increase in mean \pm SD levels (n=40) from Day 56 to Day 70 of 0.6 ± 0.3 mmol/L, indicating that the patient population was hyperphosphataemic. The results were similar in the PPS. The results for change in serum phosphorous levels in the FAS are summarised in Table 15, and the serum phosphorous levels over time are provided in Figure 12. The mean \pm SD actual daily dose of sevelamer carbonate was 5.38 ± 1.69 g for the Safety Set, 5.52 ± 1.62 g for the FAS, and 5.93 ± 1.42 g for the PPS.

Table 15: SVCARB00105 - Change in serum phosphorous; FAS.

Timepoint statistics	Sevelamer Carbonate mmol/L	Sevelamer Carbonate mg/dL
Pre-Washout (n=27)		
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)
Baseline (n=46)		
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)
Day 56/ET (n=46)		
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)
Day 70 (n=40)		
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)
Change from Pre-washout to Baseline (n=27)		
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)
Change from Baseline to Day 56/ET (n=46)		
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
Change from Day 56 to Day 70 (n=40)		
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		

Figure 12: SVCARB00105 - Serum phosphorous levels over time.

7.2.3.14. Results for the secondary efficacy outcomes

- In the FAS, the mean \pm SD level of serum calcium (albumin-adjusted)-phosphorus product at Baseline (n=44) was 4.3 ± 0.57 mmol²/L², and the corresponding mean \pm SD level at Day 56/ET (n=45) was 3.4 ± 0.65 mmol²/L². There was a statistically significant ($p < 0.001$) decrease in levels from Baseline to Day 56/ET of -0.8 (0.73) mmol²/L². There was a statistically significant ($p < 0.001$) increase in mean \pm SD levels (n=40) from Day 56 to Day 70 of 1.1 ± 0.77 mmol²/L². The corresponding measurements for the PPS were comparable. The results for change calcium (albumin-adjusted)-phosphorus product in the FAS are summarised in Table 16.

Table 16: SVCARB00105 - Change in calcium (albumin-adjusted)-phosphorous product; FAS.

Timepoint statistics	Sevelamer Carbonate mmol ² /L ²	Sevelamer Carbonate mg ² /dL ²
Baseline (n=44)		
Mean \pm SD	4.3 \pm 0.57	53.07 \pm 7.03
Median (Range)	4.2 (3.0-5.8)	51.76 (37.82-71.25)
Day 56/ET (n=45)		
Mean \pm SD	3.4 \pm 0.65	42.20 \pm 8.06
Median (Range)	3.3 (1.9-4.9)	40.85 (23.66-60.59)
Day 70 (n=40)		
Mean \pm SD	4.5 \pm 0.91	55.71 \pm 11.21
Median (Range)	4.6 (2.5-6.9)	57.12 (31.68-85.26)
Change from Baseline to Day 56/ET (n=43)		
Mean \pm SD	-0.8 \pm 0.73	-10.39 \pm 8.99
Median (Range)	-0.9 (-2.3-0.5)	-10.62 (-28.62-5.92)
P value	< 0.001	< 0.001
Change from Day 56 to Day 70 (n=40)		
Mean \pm SD	1.1 \pm 0.77	13.77 \pm 9.52
Median (Range)	1.1 (-0.7-3.0)	13.78 (-8.10-38.04)
P value	<0.001	<0.001

P values determined using Wilcoxon signed rank tests
SD= Standard deviation

- In the FAS, there were statistically significant ($p < 0.001$) reductions from Baseline to Week 56/ET in total cholesterol and LDL-cholesterol, but not in HDL-cholesterol or triglycerides. The results for the lipid parameters are summarised in Table 17.

Table 17: SVCARB00105 - Change in serum lipids; FAS.

	Sevelamer Carbonate mmol/L	Sevelamer Carbonate mg/dL
Total Cholesterol (n=44)		
Baseline	4.5 ±1.08	173.2 ±42.00
Day 56/ET	3.5 ±0.94	137.2 ±36.36
Change from Baseline to Day 56 /ET (p value) n=42	-0.9 ±0.79 (p < 0.001)	-35.8 ±30.60 (p < 0.001)
Percent Change from Baseline to Day 56/ET (p value) n=42	-19.5 ±17.02 (p < 0.001)	-19.5 ±17.10 (p < 0.001)
LDL Cholesterol (n=44)		
Baseline	2.7 ±0.87	104.7 ±33.64
Day 56/ET	1.8 ±0.65	69.7 ±25.17
Change from Baseline to Day 56 /ET (p value) n=42	-0.9 ±0.58 (p < 0.001)	-35.1 ±22.26 (p < 0.001)
Percent Change from Baseline to Day 56/ET (p value) n=42	-31.8 ±18.16 (p < 0.001)	-31.9 ±18.14 (p < 0.001)
HDL Cholesterol (n=44)		
Baseline	1.2 ±0.45	47.7 ±17.38
Day 56/ET	1.2 ±0.42	48.3 ±16.12
Change from Baseline to Day 56 /ET (p value) n=42	0.0 ±0.19 (p = 0.183)	1.3 ±7.40 (p = 0.162)
Percent Change from Baseline to Day 56/ET (p value) n=42	4.1 ±15.16 (p = 0.145)	4.4 ±15.30 (p = 0.139)
Triglycerides (n=44)		
Baseline	2.1 ±0.98	182.2 ±86.88
Day 56/ET	2.1 ±1.27	184.6 ±112.38
Change from Baseline to Day 56 /ET (p value) n=42	0.0 ±0.72 (p = 0.694)	-3.2 ±63.45 (p = 0.680)
Percent Change from Baseline to Day 56/ET (p value) n=42	3.8 ±38.28 (p = 0.956)	3.8 ±38.46 (p = 0.956)
P values determined using Wilcoxon signed rank tests SD = Standard deviation		

- By the end of study treatment (Day 56/ET), 50% of patients in the FAS reached the titration target level of serum phosphorus ≥ 0.86 mmol/L and ≤ 1.47 mmol/L following treatment with sevelamer carbonate.

7.2.3.15. Results for the subgroup analysis

Analyses in the FAS were performed to compare the primary endpoint results for patients with CKD Stages 4 and 5. The mean \pm SD serum phosphorus levels for Stage 4 CKD patients (n=16) were 1.95 ± 0.29 mmol/L at Baseline and 1.44 ± 0.26 mmol/L at Day 56 ET, with a mean reduction of 0.50 mmol/L (p<0.001) The mean + SD baseline serum phosphorus levels for stage 5 CKD patients (n=30) were 2.05 ± 0.25 mmol/L at Baseline and 1.62 ± 0.34 mmol/L at Day 56/ET, with mean \pm SD reduction of -0.43 (p<0.001). mmol/L from baseline to Day 56/ET. There was a statistically significant decrease from baseline to Day 56/ET in serum phosphorus levels for both CKD Stage 4 and Stage 5 patients (p values for both subgroups < 0.001).

7.2.4. Study GD3-199-301

7.2.4.1. Study design, objectives, locations and dates

Study GD3-199-301 was a Phase III, multicentre (USA), randomised (2:1), parallel-group, open-label study designed to compare once per day (QD) sevelamer carbonate powder dosing with three times per day (TDS) sevelamer hydrochloride tablet dosing on serum phosphorous levels in patients with chronic kidney disease (CKD) on haemodialysis.

The study was undertaken at 29 sites centres in the USA, and 1 site screened but did not randomise any patients. The first patient signed informed consent on 27 January 2006, and the last patient completed the last visit on 19 March 2007. The final CSR was dated 9 November 2007. The sponsor stated that study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP). The sponsor was Genzyme Corporation, USA.

The primary objectives of the study were: (1) to evaluate the efficacy of sevelamer carbonate powder QD with the largest meal compared with sevelamer hydrochloride tablets TDS with meals on the control of serum phosphorus; and (2) to evaluate the safety and tolerability of the two treatment regimens. The secondary objectives of the study were to evaluate the effects of the two treatment regimens on (1) serum calcium adjusted for albumin-phosphorous product and (2) serum lipids.

The study consisted of three periods: a two-week screening period; a two-week phosphate binder washout period; and a 24 week randomised treatment period. The study is presented schematically below in Figure 13.

Figure 13: GD3-199-301-Study schematic.



During the Screening Period, informed consent was obtained and patients were screened for eligibility. Eligible patients entered a two-week phosphate binder washout period. At Week 0, eligibility was assessed again. Patients whose serum iPTH was ≤ 800 pg/mL (88 pmol/L) at screening and whose serum phosphorus was > 5.5 mg/dL (1.78 mmol/L) following washout (Week 0) were randomised (stratified by screening iPTH ≤ 400 or > 400 pg/mL [≤ 42 or ≥ 42 pmol/L]) and cinacalcet treatment at baseline [Week 0]) to one of two treatment groups in a 2:1 fashion to sevelamer carbonate powder QD with largest meal or sevelamer hydrochloride tablets (TDS) with meals. During the 24 week randomised treatment period, patients were required to return for a study visit every two weeks for the first eight weeks on treatment (Weeks 2, 4, 6, and 8), and every four weeks thereafter (Weeks 12, 16, 20 and 24).

The treatment starting dose was 4.8 g daily for both treatment groups. The dose was to be titrated up or down in increments of 2.4 g daily at each visit to reach a target serum phosphorus ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.78 mmol/L). Therapy for hyperparathyroidism was to be started, stopped, or titrated every four weeks to reach a target serum iPTH of ≥ 150 and ≤ 300 pg/mL (≥ 16 and ≤ 32 pmol/L). Cinacalcet was to be initiated or the dose increased if the PTH and calcium (adjusted for albumin)-phosphorus product remained above target levels after maximum titration of vitamin D and phosphate binding therapy. At Week 24 or early termination study treatment was stopped, and patients returned to their usual phosphate binders.

Evaluator's Comment: This was an open-label study and potentially subject to the well-known biases associated with studies of this type. However, the potential biases in this study are mitigated by the objective determination of the primary and secondary efficacy laboratory endpoints. All patients were on haemodialysis and, consequently, meet the criteria for stage 5 CKD.1

7.2.4.2. Inclusion and exclusion criteria

The key inclusion criteria are summarised briefly below and the complete inclusion and exclusion criteria were provided. The study included patients who were at least 18 years of age with CKD who were on haemodialysis three times per week and had been on dialysis for three months or longer and were on phosphate binders.

Patients were required to have the following documented local laboratory measurements:

- Two most recent consecutive serum phosphorus measurement ≥ 3.0 and ≤ 6.5 mg/dL (that is, ≥ 0.96 and ≤ 2.10 mmol/L) within 60 days of Screening.
- Most recent iPTH measurement ≤ 800 pg/mL within 90 days of Screening (that is, ≤ 88 pmol/L).

In addition, patients were also required to have the following central laboratory measurements:

- Serum phosphorus measurement > 5.5 mg/dL (that is, > 1.76 mmol/L) at randomization.
- Intact iPTH measurement ≤ 600 pg/mL (that is, ≤ 66 pmol/L) at screening.

The study also included procedures for Investigators to follow in cases where patients discontinued prematurely.

7.2.4.3. Study treatments

The two treatments were:

- Sevelamer hydrochloride (Renagel®) 800 mg tablets
- Sevelamer carbonate powder supplied as 2.4 g sachets. Patients were instructed to thoroughly mix each individual sevelamer carbonate powder 2.4 g packet with cold water. Patients were instructed to drink the mixture immediately, and not longer than 30 minutes after preparation. If the mixture was not taken immediately after preparation, the patients were instructed to stir the mixture again prior to drinking.

The starting dose of 4.8 g/day for both sevelamer carbonate powder and sevelamer hydrochloride tablets was selected based on the approved dosing instructions for sevelamer hydrochloride tablets. The sevelamer dose was to be titrated up or down in increments of 2.4 g/day at Visits 4, 5, 6, 7, 8, 9 and 10 (that is, Weeks 2, 4, 6, 8, 12, 16, 20) to reach a target serum phosphorus level of ≥ 3.5 and ≤ 5.5 mg/dL (≥ 1.13 and ≤ 1.78 mmol/L).

Patients were not to consume calcium, aluminium, magnesium, or lanthanum containing antacids or phosphate binders throughout the duration of the study, unless prescribed as an evening calcium supplement. The therapy administered for hyperparathyroidism may have been started, stopped or titrated every four weeks (Weeks 4, 8, 12, 16, and 20) to reach a target serum iPTH of ≥ 150 and ≤ 300 pg/mL. Cinacalcet may have been initiated or the dose increased if the iPTH and calcium-phosphorus product remained above target levels after maximum titration of vitamin D and phosphate binding therapy. If the patient was on lipid-lowering medication, the Investigator was to maintain the dose recorded at screening through the duration of the study. The Investigator was to maintain a stable cinacalcet hydrochloride dose, sodium bicarbonate dose and haemodialysis regimen recorded at randomization through the duration of the treatment periods.

Once the Week 0 baseline laboratory assessments were available, eligible patients were randomised and stratified by screening iPTH ≤ 400 or > 400 pg/mL and cinacalcet treatment at Week 0 baseline (yes/no) to 2:1 to sevelamer carbonate powder administered QD with the largest meal or sevelamer hydrochloride tablets administered TDS with meals. Patients with higher iPTH levels are likely to have higher levels of phosphorus and can be more difficult to treat. Cinacalcet treatment may result in more effective treatment of hyperparathyroidism and be associated with lower serum phosphorus levels. Therefore, the stratification by iPTH and cinacalcet was an attempt to balance the number of patients with severe hyperparathyroidism and cinacalcet use in each group.

7.2.4.4. Efficacy variables and outcomes

- The primary efficacy variable was the change from baseline (Week 0) to Week 24/End of Treatment (ET) in serum phosphorus.

- The secondary efficacy variables were: (a) the time-weighted average of serum phosphorous; (b) percent responders for serum phosphorous at each time point (that is, serum phosphorus between 3.5 and 5.5 mg/dL [1.13 and 1.78 mmol/L], inclusive); (c) serum calcium (albumin-adjusted)-phosphorous product; and (d) serum lipids change from baseline (Week 0) to Week 24/ET.

7.2.4.5. Randomisation and blinding methods

The study was open-label.

7.2.4.6. Analysis populations

- The Safety Set consisted of all randomised patients who took at least one dose of study treatment.
- The Full Analysis Set (FAS) consisted of a subset of the Safety Set with any post-dose phosphorous assessments.
- The Per-Protocol Set (PPS) consisted of a subset of the FAS with no significant protocol deviations. Factors considered in determining PPS evaluability included: (1) less than 8 weeks treatment; (2) compliance; (3) inclusion or exclusion violation; (4) use of proscribed medications, including additional phosphate binders beyond study assigned treatment; and (5) other significant protocol deviations. Prior to finalizing and locking the database, all decisions concerning exclusion of patients from analysis populations were made by appropriate statistical and clinical personnel.

7.2.4.7. Sample size

The sample size was determined with respect to the primary efficacy parameter of change from baseline to Week 24/ET in serum phosphorus. A total of 165 evaluable patients (2:1 randomisation: 110 sevelamer carbonate QD powder, 55 sevelamer hydrochloride TDS tablet) were required to achieve 90% power based on a two-group student's t-test with a one-sided 2.5% type I error rate for a non-inferiority margin of 1 mg/dL (0.32 mmol/L). Approximately 207 patients were to be randomised to one of the two treatment groups to account for anticipated exclusions from the per-protocol population.

Evaluator's Comment: No justification could be identified for the non-inferiority margin of 1 mg/dL. However, the margin is considered to be clinically acceptable. Nevertheless, the sponsor should justify the margin (see Clinical questions below).

7.2.4.8. Statistical methods

7.2.4.8.1. Primary efficacy analysis

The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/ET in the PPS. Specifically, a two-sided 95% confidence interval was estimated for the difference in serum phosphorus change between treatment groups (sevelamer carbonate powder QD minus sevelamer hydrochloride tablets TDS). If the one sided 97.5% upper confidence bound was less than 1 mg/dL (0.32 mmol/L), then non-inferiority was concluded. In addition to the primary analysis in the PPS, a confirmatory analysis was undertaken in the FAS.

Sub-group analyses for the primary efficacy endpoint were also performed separately within the following randomisation strata: (1) serum iPTH \leq 400 and $>$ 400 pg/mL [\leq 44 and $>$ 44 pmol/L]; and (2) cinacalcet use at Week 0. No non-inferiority assessment was made among these sub-groups.

Evaluator's Comment: The use of the PPS for the primary efficacy endpoint is considered appropriate for non-inferiority testing. The non-inferiority level for

serum phosphorous of 1 mg/dL (0.32 mmol/L) is considered to be clinically acceptable.

7.2.4.8.2. Secondary efficacy analyses

- Time-weighted average of serum phosphorus (excluding the first month of therapy) was summarised for the PPS and the FAS using the formula indicated below in Figure 14. For this analysis, Weeks 2 and 4 were considered as the first month of therapy and excluded from this time-weighted analysis. In the following formula, the serum phosphorus value from blood specimen i is denoted by $C[i]$ and the corresponding time is denoted by $t[i]$ (i indexes the assessment number, not a fixed time point). There are up to six blood specimens. Actual blood draw dates were used for calculation. Wilcoxon rank sum tests were used to compare the two treatment groups.

Figure 14: GD3-199-301-Time weighted average formula.

$$\text{Time weighted average} = \frac{\sum \{(C[i] + C[i+1])/2 \times (t[i+1] - t[i])\}}{(t[6] - t[1])} \quad \text{for } i=1,2,3,4,5, 6$$

- Percent responders (serum phosphorus between 3.5 and 5.5 mg/dL [1.13 and 1.78 mmol/L], inclusive) were summarised for the PPS and the FAS at each assessment time point. Fisher's exact test was used to compare the two treatment groups.
- The change from baseline to Week 24/ET in serum calcium (albumin-adjusted)-phosphorus product was analysed for the PPS and FAS. The Wilcoxon signed rank test was used to assess the within treatment group changes, while the Wilcoxon rank sum test was used to assess the between treatment group differences.
- The change from baseline to Week 24/ET in serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides) was analysed for the PPS and the FAS. The Wilcoxon signed rank test was used to assess the within treatment group changes, while the Wilcoxon rank sum test was used to assess the between treatment group differences.

7.2.4.8.3. Other matters relevant to the statistical analyses

- All statistical tests used a significance level of $\alpha = 0.05$ and were two sided.
- Standard statistical descriptive methods were used to summarise the results.
- The SAP states that one of the factors to be considered in determining PPS evaluability was that the patient had completed 12 weeks of treatment. During the evaluability meeting, all patients with less than 12 weeks of treatment were considered for exclusion, but the cu-off was set at 8 weeks because that provided enough time for the patient to be titrated to an effective dose.
- A post-hoc analysis was performed to understand the serum phosphorus results across dose level. The change from baseline to Week 24/ET in serum phosphorus was analysed by average prescribed dose for the PPS.
- Models adjusting for covariates were not part of the analysis plan for this study.
- The last on treatment efficacy measure was carried forward to represent the Week 24/ET measurement for patients who had no Week 24 measurement due to discontinuation and/or missing values and had at least one post-washout efficacy measurement.
- No interim analyses were planned or performed.
- No adjustments were made for the multiple secondary endpoints.

7.2.4.9. Participant flow

A total of 396 patients were screened for this study and 179 patients were screen failures. A total of 217 patients were randomised to treatment, 144 to sevelamer carbonate QD powder and 73 to sevelamer hydrochloride TDS tablet. A total of 155 randomised patients completed treatment, 93 in the sevelamer carbonate QD powder group and 62 in the sevelamer hydrochloride TDS tablet group. Patient disposition is summarised below in Table 18.

Table 18: GD3-199-301-Patient disposition by treatment group.

	Overall	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablet TID
Screened	396		
Screen Failures			
Withdrawal of Consent Prior to Visit 2 or Visit 3	12 (6.7)		
Exclusionary Medical or Medication History	17 (9.5)		
Exclusionary Laboratory Measurement	130 (72.6)		
Adverse Experience	5 (2.8)		
Other	15 (8.4)		
Randomised Patients	217	144	73
Never Received Study treatment	4 (1.8)	3 (2.1)	1 (1.4)
Discontinued Prematurely			
Adverse Experience	22 (10.1)	18 (12.5)	4 (5.5)
Failure to Comply with Protocol Requirements	4 (1.8)	4 (2.8)	0 (0)
Withdrew Consent	20 (9.2)	18 (12.5)	2 (2.7)
Lost to Follow-up	2 (0.9)	1 (0.7)	1 (1.4)
Death	3 (1.4)	1 (0.7)	2 (2.7)
Other	11 (5.1)	9 (6.3)	2 (2.7)
Completed Study	155 (71.4)	93 (64.6)	62 (84.9)

Evaluator's Comment: The percentage of randomised patients completing treatment was notably greater in the sevelamer hydrochloride TDS tablet group than the sevelamer carbonate QD powder group (84.9% versus 64.6%). The main differences between the two treatment groups were the higher incidences of premature discontinuation due to AEs and withdrawn consent in the sevelamer carbonate group than in the sevelamer hydrochloride group. The sponsor should comment on the reasons for the discrepancy between the two treatment arms relating to the proportion of patients withdrawing consent (*Clinical questions*).

7.2.4.10. Major protocol violations/deviations

There were 5 major protocol deviations in 4 patients. One patient experienced prolonged hospitalization (approximately 6 weeks), during which the patient did not take sevelamer hydrochloride and resulted in the final study visit being more than 5 weeks delayed. One patient had their dose of sevelamer hydrochloride increased to 16.8 g/day (greater than allowed per protocol) and the dose was reduced to within protocol specifications (14.4 g/day) approximately 8 weeks later. One patient returned 519 sevelamer hydrochloride tablets at the end of study visit, believed to be due to the nursing home giving her their supply of sevelamer hydrochloride instead of the provided study treatment. One patient received haemodialysis four times per week rather than three times per week as specified by the protocol due to weight gain between dialyses.

7.2.4.11. Baseline data

7.2.4.11.1. Demographics

There were no significant differences between the two treatment groups as regards baseline demographic characteristics. The mean age of each of the two groups was between 55 and 60 years, and patient age ranged between 20 and 85 years. Approximately 60% of patients in each of the two groups were male, and approximately 55% of the population was African American while approximately 45% were 'White'. Approximately 55% of patients in both treatment groups had a history of diabetes mellitus.

7.2.4.11.2. *History of renal disease*

The renal disease characteristics were similar for the two treatment groups. The four most common causes of chronic renal failure reported with an incidence of $\geq 10\%$ in at least one of the treatment groups (sevelamer carbonate versus sevelamer hydrochloride, respectively) were diabetes (n=57, 40.4% versus n=25, 34.7%), hypertension (n=41, 29.1% versus n=24, 33.3%), other causes (n=23, 16.3% versus n=15, 20.8%) and glomerulonephritis (n=15, 10.6% versus n=4, 5.6%). Other primary causes of renal failure occurring in $\leq 5\%$ of patients in each treatment group were pyelonephritis, polycystic kidneys, hydronephrosis and interstitial nephritis. Other characteristics of renal disease in the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride, respectively) were mean \pm SD time on dialysis 44.4 \pm 45.0 versus 52.6 \pm 43.9 months, vitamin D use at screening 85.1% (n=120) versus 84.7% (n=61), and previous parathyroidectomy (total or partial) 3.5% (n=5) versus 1.4% (n=1).

7.2.4.11.3. *General medical history*

More than half of the patients in the safety set reported clinically significant history in the following body systems: cardiovascular (98.6%); renal (97.7%); endocrine/metabolic (95.3%); haematological conditions (92.5%); gastrointestinal (85.9%); musculoskeletal (83.6%); respiratory (66.7%); head, eyes, ears, nose, and throat (HEENT) (66.2%); neurological (58.7%), urological/reproductive (55.9%); allergies (51.2%), and dermatologic (50.2%). There were no statistically significant differences between the two treatment groups in medical history. Results for the FAS and PPS were similar to those for the Safety Set.

7.2.4.11.4. *Medications*

All patients (100%) had taken at least one prior medication. The most common classes of prior medication ($> 50\%$ of patients) were vitamins (98%), anti-anaemic preparations (97%), antithrombotic agents (81%), all other therapeutic products (68%), antacids (55%), beta blockers (52%), lipid reducing agents (52%), and agents acting on the renin-angiotensin system (50%).

During the randomised treatment period, all (100%) patients in the Safety Set took at least one concomitant medication. The pattern of concomitant medications was similar to the pattern of prior medications. In the Safety Set, a total of 129 (91.5%) patients in the sevelamer carbonate group and 67 (93.1%) patients in the sevelamer hydrochloride group began new medications or had changes in existing medications during the randomised treatment period. New medications reported in $\geq 20\%$ of patients in at least one of the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride, respectively) were anti-anaemic preparations (64% versus 71%), vitamins (60% versus 67%), antibacterials (33% versus 44%), analgesics (30% versus 24%), vaccines (29% versus 38%), psycholeptics (20% versus 17%), antithrombotic agents (17% versus 25%), and antacids (16% versus 22%).

7.2.4.11.5. *Dialysate bicarbonate concentration*

In the Safety Set, the mean \pm SD baseline bicarbonate concentration in the dialysate was 37.0 \pm 2.49 mEq/L and 36.7 \pm 3.23 mEq/L for the sevelamer carbonate group and the sevelamer hydrochloride group, respectively. The mean \pm SD bicarbonate concentration at Week 24/ET was 36.9 \pm 2.53 mEq/L and 36.8 \pm 2.90 mEq/L for the sevelamer carbonate group and the sevelamer hydrochloride group, respectively. There was no statistically significant change in dialysate bicarbonate concentration within groups and no statistically significant difference in the change in bicarbonate concentration between groups.

7.2.4.11.6. *Dietary intake*

In the PPS, there were differences between the two treatment groups in dietary intake from pre-treatment to late treatment, with most dietary intake parameters being marginally lower in late treatment compared with pre-treatment in the sevelamer hydrochloride group and most late treatment dietary intake parameters being marginally higher or unchanged in the sevelamer

carbonate group. However, in the PPS there were no statistically significant changes from baseline in dietary intake within treatment groups and no statistically significant differences in the change in dietary intake between treatment groups.

7.2.4.12. Treatment compliance

During the randomised treatment periods, mean percent treatment compliance in the Safety Set and the FAS was similar in the sevelamer carbonate and sevelamer hydrochloride groups (86% and 85%, respectively, both analysis sets), and the corresponding results for the PPS were 90% and 91%. Patients with < 70% compliance during the treatment period were excluded from the PPS.

7.2.4.13. Results for the primary efficacy outcome

The primary analysis of the primary efficacy endpoint, non-inferiority in serum phosphorus, was undertaken in the PPS, and the FAS was used for confirmation. The results are summarised below in Table 19. In the PPS, non-inferiority of sevelamer carbonate powder QD compared with sevelamer hydrochloride tablets TDS was not demonstrated as the upper bound 2-sided, 95% CI of 1.50 mg/dL (0.48 mmol/L) was greater than the pre-specified non-inferiority margin of 1 mg/dL (0.32 mmol/L). The results of the analysis in the FAS confirmed this finding.

A post-hoc analysis was performed in the PPS to understand the serum phosphorus results across dose levels (Table 20). The change in serum phosphorus in the 2.4 to 4.8 g group was similar for both sevelamer carbonate QD powder and sevelamer hydrochloride TDS tablet groups. In the sevelamer hydrochloride tablet TDS group, the change in serum phosphorus was greater at higher doses. In the sevelamer carbonate powder QD group there was no dose response.

Table 19: GD3-199-301-Change in serum phosphorous; PPS and FAS.

	Sevelamer Carbonate Powder QD [mean ± SD]	Sevelamer Hydrochloride Tablets TID [mean ± SD]	2-sided 95% CI†
Serum Phosphorus (mg/dL)			
Per Protocol Set	N=97	N=51	
Pre-washout	5.2 ± 1.1	5.3 ± 1.0	
Baseline	7.3 ± 1.3	7.6 ± 1.3	
Week 24/ET	5.3 ± 1.4	4.6 ± 1.0	
Change	-2.0 ± 1.8	-2.9 ± 1.3	0.39, 1.50
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	5.3 ± 1.1	5.3 ± 1.0	
Baseline	7.3 ± 1.4	7.4 ± 1.3	
Week 24/ET	5.4 ± 1.4	4.9 ± 1.2	
Change	-1.9 ± 1.7	-2.5 ± 1.6	0.19, 1.12
P-value [^]	< 0.001	< 0.001	
Serum Phosphorus (mmol/L)			
Per Protocol Set	N=97	N=50	
Pre-washout	1.68 ± 0.37	1.72 ± 0.32	
Baseline	2.36 ± 0.43	2.45 ± 0.41	
Week 24/ET	1.71 ± 0.45	1.50 ± 0.32	
Change	-0.66 ± 0.57	-0.96 ± 0.42	0.12, 0.48
P-value [^]	< 0.001	< 0.001	
Full Analysis Set	N=141	N=72	
Pre-washout	1.70 ± 0.36	1.72 ± 0.31	
Baseline	2.34 ± 0.44	2.39 ± 0.41	
Week 24/ET	1.73 ± 0.46	1.58 ± 0.38	
Change	-0.61 ± 0.54	-0.82 ± 0.50	0.06, 0.36
P-value [^]	< 0.001	< 0.001	

[^]P-value is from Wilcoxon Signed Rank Test

† 95% CI on difference = sevelamer carbonate powder QD – sevelamer

Table 20: GD3-199-301 - Serum phosphorous by average prescribed dose; PPS

Dose Groups (g/day)	Sevelamer Carbonate Powder QD	Sevelamer Hydrochloride Tablet TID
Serum Phosphorus (mg/dL)		
2.4-4.8		
N	23	10
Mean Change	-2.13	-2.18
≥ 4.8-9.6		
N	44	25
Mean Change	-2.09	-2.93
>9.6		
N	29	13
Mean Change	-1.75	-3.51
Serum Phosphorus (mmol/L)		
2.4-4.8		
N	23	10
Mean Change	-0.69	-0.70
≥ 4.8-9.6		
N	44	25
Mean Change	-0.68	-0.95
>9.6		
N	29	13
Mean Change	-0.56	-1.13

Evaluator's Comment: In the PPS, the mean \pm SD actual dose in sevelamer carbonate powder QD group was 6.9 ± 2.7 g/day compared with 7.3 ± 3.0 g/day in the sevelamer hydrochloride tablet TDS group, and the mean \pm SD treatment duration was 22.0 ± 3.8 weeks and 23.3 ± 0.6 weeks, respectively. The sevelamer carbonate group was not non-inferior to the sevelamer hydrochloride group, based on the change from baseline to Week 24/ET in serum phosphorous concentration in either the primary analysis (PPS) or the confirmatory analysis (FAS). Reductions in serum phosphorous concentration from baseline to Week 24/ET were greater in the sevelamer hydrochloride group compared with the sevelamer carbonate group in both the PPS and the FAS analyses.

7.2.4.14. Results for other efficacy outcomes

7.2.4.14.1. Results for the secondary efficacy outcomes

- In both the PPS and the FAS, time weighted average values were statistically significantly lower in the sevelamer hydrochloride tablets TDS group than in the sevelamer carbonate powder QD group. In the PPS, the mean \pm SD time weighted (excluding the first month of treatment) serum phosphorus was 5.3 ± 0.9 mg/dL (1.70 ± 0.30 mmol/L) for the sevelamer carbonate powder QD group and 4.9 ± 0.7 mg/dL (1.59 ± 0.24 mmol/L) for the sevelamer hydrochloride tablet TDS group; $p=0.021$.
- In the PPS, the proportion of serum phosphorous responders at each time-point from Week 6 through Week 24/ET was greater in the sevelamer hydrochloride tablets TDS group than in the sevelamer carbonate powder QD group. At Week 24/ET, the percentage of serum phosphorus responders in the sevelamer hydrochloride tablet TDS group (73%) was higher than in the sevelamer carbonate powder QD group (56%); $p=0.052$. The results in the FAS were similar to the results in the PPS.
- In the FAS, there were statistically significant reductions from baseline to Week 24/ET in serum calcium-phosphorus product in both the sevelamer carbonate powder QD group and the sevelamer hydrochloride tablet TDS group. Between group comparison showed that the decrease in serum calcium-phosphorus product from baseline to Week 24/ET was significantly greater in the sevelamer hydrochloride tablets TDS group than in the sevelamer carbonate QD powder group.
- In the FAS, there were statistically significant reductions from baseline to Week 24/ET in serum total cholesterol, LDL cholesterol and non-HDL cholesterol in both the sevelamer

carbonate powder QD group and the sevelamer hydrochloride tablets TDS group. Between group comparisons for each of these three lipid parameters showed statistically significantly greater reductions from baseline to Week 24/ET in the sevelamer hydrochloride tablets TDS group than in the sevelamer carbonate powder QD group. There were no within group or between group statistically significant changes from baseline to Week 24/ET in HDL cholesterol or triglycerides.

7.2.4.14.2. Results for the subgroup efficacy analyses

- In the subgroup analysis based on baseline iPTH level (≤ 400 pg/mL and > 400 pg/mL), reductions from baseline to Week 24/ET in serum phosphorous were statistically significant within both treatment groups in both iPTH subgroups. The results for the PPS are summarised in Table 21.

Table 21: GD3-199-301 - Change in serum phosphorous (mmol/L) by iPTH subgroup; PPS.

	Sevelamer Carbonate Powder QD [mean \pm SD]	Sevelamer Hydrochloride Tablets TID [mean \pm SD]
Serum Phosphorus (mmol/L)		
iPTH ≤ 400 pg/mL Patients	N=79	N= 39
Baseline	2.34 \pm 0.42	2.47 \pm 0.44
Week 24/ET	1.66 \pm 0.40	1.50 \pm 0.32
Change	-0.68 \pm 0.52	-0.97 \pm 0.42
P-value [^]	< 0.001	< 0.001
iPTH > 400 pg/mL Patients	N=18	N=12
Baseline	2.48 \pm 0.42	2.38 \pm 0.25
Week 24/ET	1.91 \pm 0.61	1.48 \pm 0.33
Change	-0.57 \pm 0.75	-0.91 \pm 0.43
P-value [^]	0.006	< 0.001

Data source: Table 14.2.3.1; Table 14.2.3.2; Table 14.2.3.3; Table 14.2.3.4; Listing 16.2.6.1
[^]P-values are from Wilcoxon Signed Rank Test

- In the subgroup analysis based on baseline (Week 0) cinacalcet use (used versus not used), reductions from baseline to Week 24/ET in serum phosphorous were statistically significant within both treatment groups in both cinacalcet subgroups. The results for the PPS are summarised in Table 22.

Table 22: GD3-199-301 - Change in serum phosphorous (mmol/L) by cinacalcet subgroup; PPS.

	Sevelamer Carbonate Powder QD [mean \pm SD]	Sevelamer Hydrochloride Tablets TID [mean \pm SD]
Serum Phosphorus (mmol/L)		
Cinacalcet Used	N=30	N=16
Baseline	2.42 \pm 0.36	2.41 \pm 0.43
Week 24/ET	1.80 \pm 0.45	1.46 \pm 0.29
Change	-0.63 \pm 0.46	-0.94 \pm 0.51
P-value [^]	< 0.001	< 0.001
Cinacalcet Not Used	N=67	N=35
Baseline	2.33 \pm 0.45	2.47 \pm 0.40
Week 24/ET	1.67 \pm 0.45	1.51 \pm 0.33
Change	-0.67 \pm 0.61	-0.96 \pm 0.38
P-value [^]	< 0.001	< 0.001

Data source: Table 14.2.4.1; Table 14.2.4.2; Table 14.2.4.3; Table 14.2.4.4; Listing 16.2.6.1
[^]P-values are from Wilcoxon Signed Rank Test

7.3. Additional studies with sevelamer carbonate

7.3.1. SVCARB03808

- Study SVCARB03808 was identified as an 'Import Registration Trial' undertaken at 18 sites in the People's Republic of China between 20 March 2010 and 13 September 2010, with a report date of January 2011. This randomised, double-blind, placebo-controlled, Phase III study was designed to evaluate the efficacy of sevelamer carbonate tablets TDS (taken with

meals) in Chinese patients with CKD and hyperphosphataemia being treated with phosphate binders and on haemodialysis. The study was undertaken in accordance with standard and acceptable ethical procedures. The study was sponsored by Genzyme (Shanghai).

2. The inclusion and exclusion criteria have been examined and are considered to be appropriate. Eligible patients entered a 2-week phosphate binder Washout Period, and mean serum phosphorous levels increased from Screening to the end of the Washout Period indicating that the patients were hyperphosphataemic. At the end of the Washout Period, patients whose serum phosphorus was > 1.78 mmol/L at Visit 1a were randomised in a 2:1 (active: placebo) fashion, stratified by Visit 1a serum phosphorus result (>1.78 - 2.10 mmol/L; >2.10 mmol/L) and investigative site to sevelamer carbonate or placebo. The starting dose of treatment drug sevelamer was 1 x 800 mg tablet TDS with meals or matching placebo. If the serum phosphorus was >1.78 mmol/L at Visits 3, 4 or 5, the patient was to be instructed at the next haemodialysis session to increase their dose by 1 x 800 mg tablet per meal. At Week 8 or early termination (ET), study treatment was stopped and patients returned to their usual phosphate binder.
3. The primary efficacy endpoint was change from Baseline to Day 57/ET in serum phosphate. The endpoint was compared between sevelamer carbonate and placebo using Wilcoxon rank sum tests, with a 5% type 1 error rate. The mean difference and 95% CI of the mean difference in change from Baseline for serum phosphorous values were calculated (sevelamer carbonate-placebo). The secondary efficacy endpoint was change from Baseline to Day 57/ET in serum lipids (total cholesterol and LDL cholesterol). The statistical methods used to analyze the secondary efficacy endpoint were the same as used for the primary efficacy endpoint analysis.
4. The efficacy analyses were conducted using the FAS and PPS populations. The Safety Set included all randomised patients who received at least 1 dose of Investigational Product. The FAS included the subset of Safety Set evaluable patients with a Baseline phosphorus measure and at least one post Day 1 phosphorous measured ≤ 3 days after date of last study treatment. The PPS included all FAS evaluable patients with no significant protocol deviations, as determined and documented by a blinded data review prior to database lock.
5. A total of 72 evaluable patients (48 active and 24 placebo) were required in order to have 90% power to detect a 0.40 mmol/L difference in change from Baseline phosphorus levels between treatment groups based on a 2-group, t-test with a 2-sided Type I error rate of 0.05, assuming a standard deviation for the change from Baseline of 0.49 mmol/L. Approximately 180 patients (120 active and 60 placebo) were planned to be randomised to meet the regulatory requirement of 100 active patients, assuming a 17% withdrawal rate.
6. A total of 205 patients were randomised, 135 to sevelamer carbonate and 70 to placebo and were included in the Safety Set. The FAS included 204 patients (134 sevelamer carbonate; 70 placebo), and the PPS included 190 patients (124 sevelamer carbonate; 66 placebo). The mean \pm SD age of the 205 randomised patients was 48 ± 13 years (range: 20, 80), 60.5% (n=124) were male, 39.5% (n=81) were female and the mean \pm SD BMI was 22.9 ± 3.6 kg/m². The basic demographic factors were well balanced between the two treatment groups. The most common primary causes of CKD reported in $\geq 10\%$ of patients were glomerulonephritis (111 [54.1%]), 'other' (29 [14.1%]), hypertension (26 [12.7%]), and diabetes (21 [10.2%]). The mean \pm SD duration of dialysis was 4.4 ± 4.4 years (range: 0.1, 21.6 years), and 96% (n=197) of patients had not undergone a parathyroidectomy.
7. The primary efficacy endpoint was the change from Baseline to Day 57/ET in serum phosphorus for the FAS. The mean \pm SD reduction in this parameter was significantly greater in the sevelamer carbonate group compared with the placebo group ($\Delta = -0.69 \pm 0.64$ versus $\Delta = -0.06 \pm 0.57$ mmol/L; $p < 0.0001$). In the sevelamer carbonate group

(n=134), the mean \pm SD serum phosphorous Baseline and Day 57/ET levels were 2.57 ± 0.625 mmol/L and 1.88 ± 0.503 mmol/L, respectively. In the placebo group (n=70), the mean \pm SD serum phosphorous Baseline and Day 57/ET levels were 2.52 ± 0.579 mmol/L and 2.46 ± 0.577 mmol/L, respectively. The results for the secondary efficacy endpoint of change from Baseline to Day 57/ET in total cholesterol and LDL cholesterol levels were consistent with the results for the primary efficacy endpoint.

8. In the Safety Set, the mean \pm SD actual dose was 5.03 ± 0.76 g/day (range: 2.4, 6.0 g/day) in the placebo group (n=70) and 4.32 ± 1.15 g/day (range: 0.6, 6.1 g/day) in the sevelamer carbonate group (n=135). The most frequently prescribed maximum daily dose was 9.6 g/day in both the placebo and sevelamer carbonate groups (74.3% and 40.0% of patients, respectively). The median duration of treatment was 57.0 days for both groups. The CSR stated that the exposure results for the FAS and PPS were similar to those for the Safety Set.

7.3.2. APB00108 (LEAP Study)

1. Study APB00108 was a multicentre (USA), randomised, double-blind, placebo-controlled Phase II study designed to compare Genz-644470 (a new phosphate binder not being proposed for registration) and sevelamer carbonate in patients with CKD with hyperphosphataemia on haemodialysis. The study was conducted from 11 February 2009 (first patient enrolled) to 20 August 2009 (last patient completed), and the study report was dated 11 February 2011. The study was undertaken in accordance with standard and acceptable ethical procedures. The study was sponsored by Genzyme (USA).
2. The primary efficacy endpoint compared the effects of Genz-64470 TDS versus placebo TDS on reducing serum phosphate levels. The secondary efficacy endpoints were: (1) comparison of the effects of Genz-64470 versus placebo on reducing serum calcium-phosphate product and serum lipids; and (2) comparison of the relative potency of Genz-64470 versus sevelamer carbonate on reducing serum phosphorous, serum calcium-phosphorous product, and serum lipids. The relevant efficacy endpoints related to change from baseline to Visit 7 (Day 22)/ET in the relevant parameters. This study has not been evaluated as the efficacy data are considered not to be relevant to the submission to register sevelamer carbonate. However, the relevant safety data from this study have been summarised under *Supportive data for sevelamer carbonate from 2 studies* in this CER.

7.3.3. SVCARB00606 (ASPIRE STUDY)

1. SVCARB00606 was a multinational, multicentre, randomised, double-blind, placebo-controlled Phase III study designed to investigate the efficacy and safety of sevelamer carbonate tablets TDS in hyperphosphataemic patients not on dialysis. The study was conducted from 8 January 2009 (first patient enrolled) to 8 September 2009 (last patient completed), and the study report was dated 16 March 2010. The study was undertaken in accordance with standard and acceptable ethical procedures. The study was sponsored by Genzyme (USA).
2. The study was planned to compare the efficacy and safety of sevelamer carbonate and placebo in hyperphosphataemic (serum phosphorous ≥ 1.49 and ≤ 1.76 mmol/L) patients with CKD not on dialysis. However, due to difficulty enrolling eligible patients, it was not possible to complete this study in an appropriate time frame. Consequently, the study was terminated prematurely by the sponsor. The sponsor states that the decision was reached after an extensive review of the study and its benefits, as well as possible changes to the study and operational factors. A total of 5 patients were randomised (2 sevelamer carbonate; 3 placebo). As a result of the small number of study patients the data from SVCARB00606 were presented in an abbreviated CSR format. However, the number of patients is considered too small to allow clinically meaningful conclusions to be drawn. Consequently, the limited efficacy data from this study have not been evaluated, but the

safety data have been summarised under *Supportive data for sevelamer carbonate from 2 studies* in this CER.

7.4. Sevelamer hydrochloride studies

7.4.1. CKD patients on haemodialysis dialysis

The RenaGel CER identified six Phase II/III studies supporting treatment with sevelamer hydrochloride in CKD patients on haemodialysis. All six studies enrolled patients with end stage renal disease (ESRD) on stable haemodialysis regimens, who were also on phosphorous restricted diets and who needed phosphate binders to control serum phosphorous levels. In addition, patients were either on a stable dose of Vitamin D or were not taking Vitamin D.

The duration of the six Phase II/III studies was 2 weeks in GTC-10-201, 8 weeks in Studies GTC-10-202, GTC-36-301, and GTC-36-302, 12 weeks in Studies GTC-36-203 and 44 weeks in Study GTC-45-901 (also identified as GTC-36-901). In the five Phase II/III short-term studies (2-12 weeks), a total of 392 patients had been treated with sevelamer hydrochloride alone or in combination with calcium, while in the extension study 192 patients had been treated with sevelamer. In addition to the six Phase II/III studies previously referred to, the RenaGel CER also included evaluation of Study GTC-49-301, which was designed to compare acute (first 12 weeks) and chronic (12-52 weeks) treatment with sevelamer and calcium acetate/carbonate on patients with CKD on haemodialysis. The seven previously evaluated studies were:

- GTC-10-201: A randomised, double-blind, placebo-controlled, parallel design evaluation of Renagel (sevelamer hydrochloride) in lowering serum phosphorus in haemodialysis patients.
- GTC-10-202: An open-label dose titration study of Renagel (sevelamer hydrochloride) in Haemodialysis Patients.
- GTC-36-203: A randomised, open-label, dose titration study of Renagel phosphate binder (sevelamer hydrochloride) versus Renagel phosphate binder (sevelamer hydrochloride) with calcium carbonate in haemodialysis patients.
- GTC-36-301: An open-label, cross-over study of Renagel (sevelamer hydrochloride) and calcium acetate in haemodialysis patients.
- GTC-36-302: An open-label, dose titration study of Renagel (sevelamer hydrochloride) in haemodialysis patients.
- GTC-49-301/ GTC-36-901: An extended use study of Renagel (sevelamer hydrochloride) in haemodialysis patients.
- GTC-49-301: A randomised, open-label, parallel design study of sevelamer hydrochloride (Renagel) and calcium-based phosphate binders in haemodialysis patients.

The primary efficacy endpoint for the clinical efficacy studies was the change in serum phosphorous level from the end of the phosphate binder washout period (Baseline) to the end of the treatment (EOT) period. The results of the primary efficacy endpoint for the seven previously referred to and evaluated studies in CKD patients on haemodialysis are summarised immediately below in Table 23.

The secondary efficacy endpoints included effects on serum calcium and incidence of hypercalcaemic episodes, effects on serum calcium-phosphorous product (only in studies GTC-36-203, -301 and -302), effects on iPTH levels and effects on lipid profile. Perusal of the results for these parameter provided in the Renagel CER and in the current submission raise no concerns about the efficacy of sevelamer hydrochloride.

Table 23: Phase II/III short-term studies-Mean serum phosphorous levels (mmol/L), change from Baseline (1st washout) to end of treatment (EOT) in patients on haemodialysis.

Study	Treatment	N	Weeks	Screen	Base-line/ Washout	EOT	Change (Δ)	Change (Δ)	Washout
							EOT-Baseline	p-value	
GTC-10-201	Placebo	12	2	1.49	2.16 →	2.26 mmol/L	+0.10 mmol/L	0.43	NA
	Renagel	24	2	1.84	2.00 →	1.78 mmol/L	-0.23 mmol/L	0.05	NA
GTC-10-202	Renagel	48	8	2.23	2.62 →	2.20 mmol/L	-0.45 mmol/L	0.0001	2.65
GTC-36-203	Renagel	36	12	2.20	2.87 →	2.07 mmol/L	-0.77 mmol/L	<0.0001 **	2.39
	Renagel/Ca	36	12	2.20	2.62 →	1.87 mmol/L	-0.74 mmol/L	< 0.0001	2.49
GTC-36-301 ***	Renagel	80	8	2.13	2.71 →	2.10 mmol/L	-0.65 mmol/L	<0.0001	2.52
	Ca Acetate	80	8	2.13	2.58 →	1.91 mmol/L	-0.68 mmol/L	< 0.0001	2.58
GTC-36-302	Renagel	168	8	2.20	2.94 →	2.13 mmol/L	-0.81 mmol/L	<0.0001	2.58
GTC-45-901	Renagel	192	44	2.03	2.81 →	2.07 mmol/L	-0.71 mmol/L	<0.0001	2.52
GTC-49-301	Renagel	76	52	1.81	2.39 →	1.68 mmol/L	-0.71 mmol/L	<0.0001	NA
	Calcium	81	52	1.81	2.32 →	1.68 mmol/L	-0.64 mmol/L	<0.0001	NA

* Median (mean) change is derived from the median or mean of individual patient changes. ** n=35 for mean change and p-value. *** Cross-over data presented combined.

Evaluator's Comment: The results for the primary efficacy endpoint of change from Baseline to EOT for CKD patients on haemodialysis were consistent for sevelamer hydrochloride over the time-period from 2 to 52 weeks. In those studies in which there was a sevelamer hydrochloride washout period following treatment, serum phosphorous levels increased once sevelamer hydrochloride treatment was stopped indicating that the patients were hyperphosphataemic. It is considered that the results observed for sevelamer hydrochloride observed in these studies in patients with CKD on haemodialysis can be unreservedly extrapolated to sevelamer carbonate.

7.4.2. CKD patients on peritoneal dialysis

7.4.2.1. PB006JP

The Renegel CER reviewed one Phase III, open-label study of the effects of sevelamer hydrochloride (8 weeks treatment) in Japanese patients (n=33) with CKD on peritoneal dialysis [PB006JP]. The mean \pm SD baseline and EOT serum phosphorous levels were 7.4 ± 1.1 and 5.93 ± 0.16 mg/dL, respectively, and the mean \pm SD change from baseline was -1.52 ± 0.22 mg/dL (95% CI: -1.95, -1.08 mg/dL). Overall, 54.5% (18/33) of the patients achieved the target serum phosphorous levels of 4 to 6 mg/dL following 8 weeks treatment.

7.4.2.2. REN-003-04

The current submission included further data on patients with CKD on peritoneal dialysis from Study REN-003-04. A review of this study could not be identified in the Renegel CER. The study was multi-national (7 Western European countries), multi-centre (17 sites), open-label, randomised, and parallel-group in design. The primary efficacy objective was to compare the effects of sevelamer hydrochloride 800 mg tablets TDS with meals and calcium acetate 538 mg tablets TDS with meals on serum phosphorous levels in patients with CKD on peritoneal dialysis. Treatment was initiated in both groups with a total daily dose of 4.8 g/d, and the mean \pm SD actual doses received were sevelamer hydrochloride 5.9 ± 2.6 g/day and calcium acetate 4.3 ± 1.5 g/day.

The study included men and women aged 18 years and older diagnosed with CKD, and receiving peritoneal dialysis (continuous ambulatory [CAPD], automated [APD], or continuous cyclical [CCPD]) that was expected to continue for the duration of the study. In addition, patients were required to have a serum phosphorous level of > 1.77 mmol/L and a serum calcium level (adjusted for albumin) of 2.10-2.60 mmol/L following 2 weeks washout from their usual phosphate binder. The first patient was enrolled on 23 December 2003 and the last patient completed on 6 March 2006. The original study report was dated 11 July 2006 and an amendment to this report was dated 6 November 2006. The study was conducted in accordance with the principles of Good Clinical Practice (GCP/ICH guidelines), and was sponsored by Genzyme (USA).

The study screened 253 patients, and 143 were randomised 2:1 to sevelamer hydrochloride (n=97) and calcium acetate (n=46). Of the 143 randomised patients, 73% (n=104) completed the study, including 76% (n=74) in the sevelamer hydrochloride group and 65% (n=30) in the calcium acetate group. The mean \pm SD age of the 143 randomised patients was 54 ± 16 years (range: 20, 91 years), 65% (n=93) were male, 35% (n=50) were female and 90% (n=129) were Caucasian with the ethnicity of the remaining patients being Asian (n=7, 5%), other (n=4, 3%), and Black (n=3, 2%). The primary causes of ESRD reported in $\geq 10\%$ of patients were 'other' (n=46, 32%), glomerulonephritis (n=28, 18%), diabetes (n=26, 18%), and polycystic kidneys (n=18, 13%). Hypertension was the primary cause of ESRD in 7% (n=10) of patients. The mean \pm SD duration of peritoneal dialysis was 26 ± 34 months (range: 2, 255 months), and 80% of patients were non-anuric (urine output > 200 mL). The majority of patients had not undergone

renal transplantation (n=119, 83%) or total or partial thyroidectomy (n=136, n=95%). All patients were taking pre-study phosphate binder.

The primary efficacy endpoint was the change in serum phosphorous level from the end of washout (Baseline) to Week 12/Final in the PPS (with a confirmatory analysis in the FAS). Specifically, a one-sided 97.5% upper confidence bound was estimated for the difference in serum phosphorus change between treatment groups (difference = sevelamer-calcium). If this confidence bound was less than 0.3 mmol/L, then non-inferiority was concluded. If non-inferiority was established and this confidence bound was less than 0 mmol/L, then superiority would be concluded. The one-sided 97.5% upper confidence bound serum phosphorous level for the difference between sevelamer hydrochloride and calcium acetate was 0.237 mmol/L in the PPS, demonstrating that sevelamer hydrochloride was non-inferior to calcium acetate (see Table 24, below). However, as the one-sided upper 97.5% confidence bound serum phosphorous level for the difference between the two treatments was not less than 0 mmol/L superiority of sevelamer hydrochloride over calcium acetate was not demonstrated. The results observed in the PPS were confirmed in the FAS, with the difference between the two treatments being 0.012 mmol/L, and the one-sided 97.5% upper confidence bound serum phosphorous level being 0.163 mmol/L.

Table 24: REN-003-04 (amendment)-Change from Baseline to Week 12/Final in serum phosphorous (mmol/L); PPS.

Statistic	sevelamer (N=95)	calcium (N=44)
Per Protocol Set		
N	72	31
Mean	-0.522	-0.583
Median	-0.54	-0.56
Std Dev	0.3750,487	
Min-Max	-1.76, 0.35	-1.95, 0.33
95% CI	-0.61, -0.43	-0.76, -0.40
Wilcoxon Signed Rank Test (p-value)	<0.001	<0.001
Difference in change (sevelamer - calcium Acetate) (97.5% Upper CI)		0.061 (0.237)

Secondary efficacy endpoints included the change from Baseline to Week 12/Final for the following endpoints: serum calcium-phosphate product, total cholesterol, LDL cholesterol, non-HDL cholesterol, HDL cholesterol, triglycerides and plasma biomarkers (CRP, BSAP, random blood glucose, HbA1C, and uric acid). The secondary endpoint comparisons between treatment groups were assessed using a two-sided Wilcoxon rank sum test and changes within treatment groups were assessed using Wilcoxon sign rank test. All these analyses were tested at the alpha = 0.05 (2-tailed) level of significance, and p-values <0.05 were considered statistically significant. The secondary efficacy endpoint analyses were undertaken in the FAS.

There was a statistically significant change from Baseline to Week 12/Final in the calcium-phosphorous product in both treatment groups (p<0.001). However, there was no statistically significant difference between sevelamer hydrochloride (n=95) and calcium acetate (n=44) in change from Baseline to Week 12/Final in calcium-phosphorous product in the FAS.

There was a statistically significant decrease (p<0.001) from baseline to Week 12/Final for total-, LDL-, and non-HDL cholesterol in the sevelamer group, but not in the calcium acetate group. These changes were statistically significantly different between treatment groups (p<0.001), with reductions in total-, LDL-, and non-HDL cholesterol levels being greater in the sevelamer hydrochloride group compared with the calcium acetate group. No statistically significant changes occurred in HDL cholesterol in either treatment group. There was a statistically significant increase in percentage change from baseline to Week 12/Final in triglyceride levels in both the sevelamer hydrochloride group (p=0.009) and the calcium acetate group (p=0.007). A statistically significant increase from baseline to Week 12/Final in serum triglyceride level was seen in the calcium acetate group (p=0.036), but not in the sevelamer hydrochloride group. There was no difference between the treatment groups for the change

from baseline to Week 12/Final in serum triglyceride levels. The results for the lipid profile (mg/dL) in the FAS are summarised in Table 25. Similar results were observed in the PPS.

Table 25: REN-003-04 (amendment to the CSR) - Mean serum lipid levels (mg/dL); FAS.

Parameter	sevelamer (N=95)	calcium (N=44)	Wilcoxon Rank Sum Test p-value
Total Cholesterol			
Baseline	183.5	180.2	0.729
Week 12/Final	152.2	180.1	0.001
Wilcoxon Signed Rank Test p-value	<0.001	0.445	
Percent Change	-15.20	0.96	<0.001
Wilcoxon Signed Rank Test p-value	<0.001	0.412	
LDL Cholesterol			
Baseline	120.6	118.5	0.659
Week 12/Final	90.0	117.1	<0.001
Wilcoxon Signed Rank Test (p-value)	<0.001	0.805	
Percent Change	-23.15	0.27	<0.001
Wilcoxon Signed Rank Test p-value	<0.001	0.742	
HDL Cholesterol			
Baseline	46.8	42.5	0.504
Week 12/Final	46.7	42.1	0.370
Wilcoxon Signed Rank Test (p-value)	0.830	0.456	
Percent Change	0.72	-1.17	0.529
Wilcoxon Signed Rank Test p-value	0.756	0.517	
Non-HDL Cholesterol			
Baseline	136.8	137.6	0.851
Week 12/Final	105.5	138.0	<0.001
Wilcoxon Signed Rank Test (p-value)	<0.001	0.458	
Percent Change	-19.69	2.23	<0.001
Wilcoxon Signed Rank Test p-value	<0.001	0.308	
Triglycerides			
Baseline	155.6	173.1	0.415
Week 12/Final	162.6	197.2	0.092
Wilcoxon Signed Rank Test (p-value)	0.089	0.036	
Percent Change	17.76	21.38	0.410
Wilcoxon Signed Rank Test p-value	0.009	0.007	

Uric acid serum concentrations showed a statistically significant decrease from baseline to Week 12/Final in the sevelamer hydrochloride group. A statistically significant increase ($p < 0.001$) in BSAP was seen during treatment with sevelamer hydrochloride only. There was no within or between treatment group difference for change from baseline to end of study in random blood sugar, CRP or HbA1C. Albumin-adjusted serum calcium concentration increased in a statistically and clinically significant manner in the calcium acetate group, but not in the sevelamer group. Serum iPTH decreased in a statistically significant manner in the both the sevelamer hydrochloride and calcium groups, with no difference in change from baseline between the two groups.

Evaluator's Comment: The available clinical trial data demonstrate that sevelamer hydrochloride results in statistically significant and clinically meaningful reductions in serum phosphorous levels in patients with CKD on peritoneal dialysis. It is considered that the results observed for sevelamer hydrochloride in patients with CKD on peritoneal dialysis can be unreservedly extrapolated to sevelamer carbonate.

7.4.3. CKD patients not on dialysis

The Renagel submission included two studies in CKD patients not on dialysis [GTC-45-204; GTC-68-208]. Study GTC-68-208 was listed in the Renagel CER, but not evaluated presumably because it was undertaken in non-hyperphosphataemic patients. Furthermore, in this uncontrolled study evaluating three doses of sevelamer hydrochloride the primary efficacy variables were change in serum iPTH and LDL-cholesterol from Baseline (Week 0) to endpoint (Week 6), with change in serum phosphorous being a secondary efficacy variable. The study included a total of 53 patients with Stage 4 disease ($15 \leq \text{GFR mL/min} < 30$) and 24 patients

with Stage 3 disease ($30 \leq \text{GFR mL/min} \leq 59$), and no patients had GFR values $< 15 \text{ mL/min}$. The data from this study are considered to be not relevant to the current submission.

Study GTC-45-204 was evaluated in the Renagel CER. The study was a Phase II, multinational, multicentre (8 centres in the USA, 4 in Europe) open-label dose titration study in patients with CKD not requiring dialysis. The primary efficacy objective was to determine the effect of Renagel in lowering serum phosphorous levels following 12 weeks treatment in patients with hyperphosphataemia (serum phosphorous $\geq 1.61 \text{ mmol/L}$) following a 4 week phosphate binder washout period. The dose was titrated during the treatment period to achieve a serum phosphorus level between 0.81 and 1.45 mmol/L. After 12 weeks of sevelamer hydrochloride treatment, patients entered a second 4 week phosphate binder washout period. A total of 79 patients entered the study and 44 completed the study, and the mean estimated GFR at baseline was $9.5 \text{ mL/min}/1.73 \text{ m}^2$.

In GTC-45-204, a statistically significant mean \pm SD decrease in serum phosphorus level was noted during the 12 week treatment period of $-0.26 \pm 0.24 \text{ mmol/L}$ ($p < 0.001$) in the ITT population ($n=78$), with mean \pm SD serum phosphorous levels at Baseline and Week 12 being 1.95 ± 0.29 and $1.69 \pm 0.38 \text{ mmol/L}$, respectively. Consistent with the serum phosphorus results, there were statistically significant reductions in urinary phosphorus excretion ($\Delta = -0.17 \text{ g/day}$; $p < 0.001$) and calcium-phosphorus product ($\Delta = -0.54 \text{ mmol}^2/\text{L}^2$; $p < 0.001$), but not serum iPTH. Sevelamer hydrochloride treatment was also associated with statistically significant reductions in total cholesterol ($\Delta = -1.05 \text{ mmol/L}$; $p < 0.001$) and LDL-cholesterol ($\Delta = -1.04 \text{ mmol/L}$; $p < 0.001$). No changes in mean serum calcium, HDL-cholesterol, or triglycerides levels were observed over the 12 weeks treatment.

Evaluator's Comment: It is considered that the efficacy data from the sevelamer hydrochloride clinical program in hyperphosphataemic patients with CKD not on dialysis is of no support to the current submission to register sevelamer carbonate. In the one study with relevant data [GTC-45-204], the serum phosphate level at the end of the 4 week phosphate binder washout period triggering treatment with sevelamer hydrochloride was $\geq 1.61 \text{ mmol/L}$. This level is lower than the serum phosphorous level proposed in the Dosage and Administration section of the PI for starting sevelamer carbonate treatment in patients not taking phosphate binder (that is, $> 1.78 \text{ mmol/L}$). However, it is possible that some patients treated in Study GTC-45-204 had serum phosphorous levels $> 1.78 \text{ mmol/L}$ and might have benefited from treatment with sevelamer hydrochloride. No information on the proportion of the 79 patients in this study with serum phosphorous levels $> 1.78 \text{ mmol/L}$ could be identified. The sponsor will be requested to comment on outcomes in patients in Study GTC-45-204 with serum phosphorous levels $> 1.78 \text{ mmol/L}$ (see *Clinical questions*, Question 6).

7.5. Evaluator's conclusions on clinical efficacy

7.5.1. Overview

The submission included 4 key, previously unevaluated clinical efficacy and safety studies supporting the application to register sevelamer carbonate (tablets and powder) for the treatment of hyperphosphataemia in adult patients with CKD Stage 4 and 5. The data from these 4 studies are summarised below.

In two, short-term equivalence studies of 4 and 8 weeks duration in a total of 77 hyperphosphataemic patients with CKD on haemodialysis, sevelamer carbonate TDS was demonstrated to be equivalent to sevelamer hydrochloride TDS, based on reductions in time weighted serum phosphorous levels in the PP Sets [GD3-163-201; SVCARB00205]. In both

equivalence studies, the 90% CIs for the geometric LS mean ratios (carbonate/hydrochloride) were within the pre-specified equivalence interval of 0.80 to 1.25. Support for the efficacy of sevelamer carbonate for the treatment of hyperphosphataemic patients with CKD on haemodialysis is provided by the previously unevaluated study undertaken exclusively in Chinese patients (FAS [Day 57/ET]: n=134, sevelamer carbonate; n=70, placebo) [SVCARB03808].

In an open-label, single-arm key study, sevelamer carbonate TDS statistically significantly lowered serum phosphorous levels from Baseline to Day 56/ET in the FAS (n=46) in patients with CKD (Stage 4 or 5) not on dialysis [SVCARB00105]. In an open-label key study, a sevelamer carbonate QD regimen (n=97) was not non-inferior to the standard sevelamer hydrochloride TDS regimen (n=51) in patients with CKD on haemodialysis [GD3-199-301].

7.5.2. Equivalence studies-hyperphosphataemic patients on haemodialysis

7.5.2.1. Study GD3-163-201

In the Phase II, multicentre (US), randomised, double-blind, cross-over study in patients with CKD on haemodialysis and taking phosphate binders [GD3-163-201], sevelamer carbonate was equivalent to sevelamer hydrochloride as regards reduction in serum phosphorous levels following 8 weeks treatment (n=56; PPS). In both treatment groups, the target dose was achieved using 800 mg tablets administered TDS with meals.

In both treatment groups (PPS), the mean \pm SD prescribed sevelamer dose was 7.2 ± 3.1 g/day and the mean \pm SD actual dose in the randomised treatment periods was 6.0 ± 2.8 g/day. No patients in the PPS changed their prescribed dose during the randomised treatment periods. The mean duration of treatment was similar for both treatment regimens; 8.0 weeks in the sevelamer carbonate group and 7.8 weeks in the sevelamer hydrochloride group.

The primary efficacy endpoint of mean \pm SD serum phosphorous time weighted averages (mmol/L) was identical for treatment with sevelamer carbonate and sevelamer hydrochloride in the PPS (that is, 1.5 ± 0.3 mmol/L). The geometric least square mean ratio between the two treatments (sevelamer carbonate/hydrochloride) was 0.99 (90% CI: 0.95, 1.03), and the two treatments were declared to be equivalent as the 90% CI of the ratio was enclosed completely within the prespecified equivalence interval of 0.80 to 1.25. The results of the confirmatory analysis in the FAS (n=73 [carbonate]; n=78 [hydrochloride]) for the primary efficacy endpoint were similar to the results for the primary analysis in the PPS. The results for the secondary efficacy endpoints relating to serum lipid parameters also demonstrated that the two sevelamer treatment regimens were therapeutically equivalent.

7.5.2.2. Study SVCARB00205

In the Phase III, multicentre (UK), randomised, open-label, cross-over study in hyperphosphataemic patients with CKD on haemodialysis [SVCARB00205], sevelamer carbonate powder for oral solution was equivalent to sevelamer hydrochloride tablets as regards reduction in serum phosphorous levels following 4 weeks treatment (n=21; PPS). The target dose of sevelamer carbonate was administered TDS with meals using 800 mg sachets (powder) and the target dose of sevelamer hydrochloride was administered TDS with meals using 800 mg tablets. The study was open-label and would have required a double-dummy technique in order for it to have been blinded. The use of objective, laboratory determined endpoints mitigated the potential for bias associated with open-label studies.

In the PPS, the mean \pm SD prescribed dose during the randomised treatment periods was 7.4 ± 3.1 g/day of sevelamer carbonate powder and 7.5 ± 3.1 g/day of sevelamer hydrochloride tablets, and the corresponding mean \pm SD actual doses were 6.0 ± 3.1 g/day of sevelamer carbonate powder and 6.4 ± 3.3 g/day of sevelamer hydrochloride tablets. The mean duration of treatment was 4.3 weeks on sevelamer carbonate powder and 4.6 weeks on sevelamer

hydrochloride tablets. Patients with less than three weeks of exposure were excluded from the PPS,

In the PPS, the primary efficacy endpoint of mean \pm SD serum phosphorous time weighted average for treatment with sevelamer carbonate powder was 1.6 ± 0.5 mmol/L compared with 1.7 ± 0.4 mmol/L for treatment with sevelamer hydrochloride tablets. The geometric least square mean ratio between the two treatments (sevelamer carbonate/hydrochloride) was 0.95 (90% CI: 0.87, 1.03) and the two treatments were declared equivalent as the 90% CI was enclosed completely within the pre-specified equivalence interval of 0.80 to 1.25. The results for the primary efficacy endpoint confirmatory analysis in the FAS (n=30) were almost identical to the results for the primary analysis of this endpoint in the PPS. The results for the secondary efficacy endpoints relating to serum calcium (albumin adjusted)-phosphorous product and serum lipids in the FAS (n=25 [carbonate]; n=28 [hydrochloride]) also demonstrated that the two sevelamer treatment regimens were therapeutically equivalent.

7.5.3. Hyperphosphataemic patients not on dialysis

The submission included one Phase III, multinational, multicentre, open-label, sevelamer carbonate single-arm study in hyperphosphataemic CKD patients not on dialysis [SVCARB00105]. The sevelamer carbonate treatment regimen used 800 mg tablets and the dose was administered TDS. The primary analysis of change from Baseline to Day 56/ET in the serum phosphorous level was in the FAS (n=46), and the mean \pm SD actual daily dose of sevelamer carbonate administered to patients in the FAS was 5.52 ± 1.62 g. In the FAS, the mean \pm SD Baseline serum phosphorus level was 2.0 ± 0.3 mmol/L and decreased to 1.6 ± 0.3 mmol/L at Day 56/ET ($\Delta = -0.5 \pm 0.3$ mmol/L, $p < 0.001$). There was a statistically significant ($p < 0.001$) increase in mean \pm SD levels (n=40) following post-treatment wash-out from Day 56 to Day 70 of 0.6 ± 0.3 mmol/L, indicating that the patient population was hyperphosphataemic. The results for the secondary efficacy endpoint analyses in the FAS for change from Baseline to Day 56/ET in serum calcium (albumin adjusted)-phosphorous product and serum lipids were consistent with the results for the primary efficacy endpoint analysis. By the end of study treatment (Day 56/ET), 50% of patients in the FAS had reached the titration target serum phosphorus level of ≥ 0.86 mmol/L and ≤ 1.47 mmol/L. In the subgroup analyses (FAS) in patients with Stage 4 (n=16) or Stage 5 (n=30) CKD, the reductions from Baseline to Day 56/ET were similar for both subgroups and were statistically significant ($p < 0.001$).

7.5.4. Sevelamer carbonate QD versus sevelamer hydrochloride TDS

The submission included one Phase III, multisite (USA), parallel group, open-label study of 24 weeks duration comparing the effects of sevelamer carbonate QD and sevelamer hydrochloride TDS on serum phosphorous levels in patients with CKD on haemodialysis [GD3-199-301]. In this study, the sevelamer carbonate dose was administered QD as a powder for oral solution using 2.4 g sachets and the sevelamer hydrochloride dose was administered TDS as tablets using the 800 mg formulation. In the primary efficacy analysis in the PPS, sevelamer carbonate powder QD (n=97) was not non-inferior to sevelamer hydrochloride tablets TDS (n=51) as regards change from Baseline to Week 24/ET in serum phosphorous levels. In the PPS, the 2-sided 95% CI for the difference between the two treatments (change from Baseline) was 0.12 to 0.48 mmol/L. The upper bound 95% CI for the difference of 0.48 mmol/L was greater than the pre-specified non-inferiority margin of 0.32 mmol/L and, consequently, sevelamer carbonate QD was declared to be not non-inferior to sevelamer hydrochloride. Therefore, this study does not support a QD dosing regimen for sevelamer carbonate.

7.5.5. Limitations of the efficacy data

There were a total of 294 CKD patients treated with sevelamer carbonate in the four previously unevaluated studies, including 245 on haemodialysis and 49 not on dialysis. There were no therapeutic equivalence studies longer than 8 weeks duration in CKD patients comparing sevelamer carbonate at the proposed dose (TDS) with sevelamer hydrochloride at the approved

(TDS) dose in patients on haemodialysis. There was one 24 week study showing that sevelamer carbonate powder administered QD (non-proposed dosing interval) was not non-inferior to sevelamer hydrochloride tablets administered TDS (approved dosing interval) in patients on haemodialysis, and that the hydrochloride regimen was more efficacious than the carbonate regimen. There were limited, 8 week data in patients with CKD Stage 4 and 5 not on dialysis treated with sevelamer carbonate, but no long-term data with this formulation in this patient group. There were no data in patients on peritoneal dialysis treated with sevelamer carbonate.

7.5.6. Extrapolation of the sevelamer hydrochloride efficacy data to sevelamer carbonate

It is considered that the limitations of the submitted efficacy data relating to sevelamer carbonate can be addressed by extrapolating the previously evaluated efficacy data relating to sevelamer hydrochloride for the treatment of CKD Stage 4 and 5. In the sevelamer hydrochloride clinical trial program, a total of 607 unique patients on dialysis (haemodialysis or peritoneal dialysis) have been treated with sevelamer hydrochloride in 8 key efficacy and safety studies (7 previously evaluated Studies [GTC-10-201, GTC10-202, GTC-36-203, GTC-36-301, GTC-36-302, GTC-45-901, and GTC-49-301] and 1 [REN-003-04] study evaluated in this CER). It should be noted that the 607 unique patients do not include the patients from long-term extension Study GTC-45-901 who were required to have participated in an earlier sevelamer trial in order to gain entry in to this study. However, the long-term extension Study GTC-45-901 did include 7 patients who were naïve to sevelamer treatment. In addition, the current submission includes 106 CKD patients on haemodialysis treated with sevelamer hydrochloride and with sevelamer carbonate in the two cross-over therapeutic equivalence studies [GD3-163-201, SVCARB00205]. Therefore, 713 unique patients with CKD on dialysis in total have been treated with sevelamer hydrochloride, while 106 patients have been treated with sevelamer carbonate. The 10 key studies in patients on dialysis are listed below in Table 26 and it should be noted that only 1 study [REN-003-04] included patients on peritoneal dialysis while all of the other 9 studies included patients on haemodialysis.

Table 26: Overview of 10 key efficacy and safety studies in patients on dialysis treated with sevelamer hydrochloride and/or sevelamer carbonate.

Protocol Number	Patients Treated with Sevelamer Hydrochloride	Patients Treated with Sevelamer Carbonate
GTC-10-201	24	
GTC-10-202	48	
GTC-36-203	75	
GTC-36-301	84	
GTC-36-302	172	
GTC-45-901	192 [†]	
GTC-49-301	100	
REN-003-04	97	
GD3-163-201	78	78 [‡]
SVCARB00205	28	31 [‡]

[†] 7 patients were naïve to sevelamer; all other study participants took part in a previous sevelamer hydrochloride study.

[‡] 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.

The demographic and renal history of the dialysis treated patients in the 8 key studies in the sevelamer hydrochloride clinical program are summarised in Table 27.

Table 27: Summary of demographics in 8 key studies in the sevelamer hydrochloride clinical program in hyperphosphataemic CKD patients on dialysis.

Variable	GTC-10-201 (n=24)	GTC-10-202 (n=48)	GTC-36-203 (n=75)	GTC-36-301 (n=82)	GTC-36-302 (n=172)	GTC-45-901 (n=192)	GTC-49-301 (n=99)	REN-003-04 (n=97)
Sex: M/F (%)	46/54	62/38	67/33	54/46	64/36	62/38	64/36	67/33
Race: B/C/O (%)	67/21/12	42/50/8	39/57/4	56/31/13	52/34/14	54/35/11	17/71/12	2/90/8
Mean age (yrs)	58.8	52.0	58.7	54.6	53.4	56.1	57.0	54.6
Primary Cause of CKD (%):								
hypertension	ND	29	29	36	30	34	16	7
diabetes		35	37	29	23	30	23	18
other		36	34	35	47	36	61	75
Previous Phosphate Binder: (%)								
calcium carbonate	42	42	43	44	36	12	38	46
calcium acetate	50	50	47	37	48	19	33	6
aluminium	NA	8	1	8	9	1	6	1
sevelamer	NA	NA	NA	NA	NA	53	3	14
combination	8	NA/	5	6	4	1	19	31
other	NA	NA	4	5	3	14	1	0
none	NA	NA	NA	NA	NA	NA	NA	NA
Parathyroidectomy: yes/no (%)	ND	2/98	1/99	13/87	8/92	7/93	11/89	4/96
Vitamin D therapy: yes/no (%)	ND	60/40	51/49	67/33	52/48	74/26	56/44	45/55
Mean Duration of Dialysis (yrs)	ND	3.9	3.0	4.3	3.6	3.8	5.1	2.3
Mean Kt/V	ND	ND	1.5	1.4	1.4	1.5	ND	ND

NA: not applicable, ND: not done. B/C/O= Black, Caucasian, Other

In these 8 studies, the average age of the patients ranged from 52 to 59 years, females represented 33% to 54% of patients, Caucasians 21% to 90%, and Black 2% to 67%. The majority of patients had been using calcium carbonate or calcium acetate as their previous phosphate binder, except for the long-term extension study [GTC-45-901] where previous sevelamer hydrochloride use was required by the protocol. The majority of patients had not undergone parathyroidectomy, and were using vitamin D replacement therapy. The most common primary causes of CKD were hypertension, diabetes, glomerulonephritis and unspecified other causes. The demographic and renal history of the dialysis treated patients in 8 key studies in the sevelamer hydrochloride clinical program were consistent with those treated with sevelamer carbonate in the 2 therapeutic equivalence studies in the current submission.

It is considered that the data from 8 key studies from the sevelamer hydrochloride clinical trial program in hyperphosphataemic CKD patients on dialysis are consistent with the 2 key equivalence studies from the sevelamer carbonate clinical trial program. Consequently, it can be reasonably inferred that the efficacy data for sevelamer hydrochloride relating to hyperphosphataemic patients with Stage 4 and 5 CKD on haemodialysis can be safely extrapolated to sevelamer carbonate.

In the sevelamer hydrochloride clinical trial program there were 79 hyperphosphataemic patients with CKD not on dialysis treated with sevelamer hydrochloride [GTC-45-204]. However, the serum phosphate levels of ≥ 1.61 mmol/L in this study (following 4 weeks phosphate buffer wash-out) determining whether patients were treated with sevelamer hydrochloride was lower than the PI recommended level of > 1.78 mmol/L for initiating sevelamer carbonate treatment in patients not taking a phosphate binder. Therefore, it is considered that the data from Study GTC-45-204 is of limited support for sevelamer carbonate for hyperphosphataemic CKD patients not on dialysis.

8. Clinical safety

8.1. Studies providing evaluable safety data

The safety profile of sevelamer hydrochloride for the treatment of hyperphosphataemia in patients with CKD Stage 4 and 5 has been well characterised, based on the previously evaluated

data from the Renagel submission and the 14 years of post-marketing data following first approval in the USA. The data provided in the current submission demonstrate sevelamer hydrochloride and sevelamer carbonate are therapeutically equivalent as regards the proposed indication. Consequently, it is considered that the known safety profile of sevelamer hydrochloride can be extrapolated to sevelamer carbonate. However, there are likely to be differences between the two sevelamer salts relating to adverse gastrointestinal and metabolic effects based on the different physiological properties of the hydrochloride and carbonate moieties. In particular, the sponsor states that the carbonate salt has a reduced propensity for association with potentially adverse acid-base changes compared with the hydrochloride salt and mitigates metabolic acidosis that can occur in hyperphosphataemic CKD patients.

The evaluation of the clinical safety data in this CER centres on sevelamer carbonate, and includes reference to relevant differences between the carbonate and hydrochloride formulations. The approach adopted to evaluate the safety of sevelamer carbonate for the proposed indications is outlined below:

1. The safety data from the four new sevelamer carbonate studies submitted to support registration have been evaluated [GD3-163-201; SVCARB00205; SVCARB0015; GD3-199-201]. In patients with CKD on haemodialysis, sevelamer was administered TDS and compared with sevelamer hydrochloride TDS in Studies GD3-163-201 and SVCARB00205, and sevelamer carbonate was administered QD and compared with sevelamer hydrochloride TDS in Study GD3-199-301. In patients with CKD not on dialysis, single-arm sevelamer carbonate was administered TDS in Study SVCARB00105.
2. The data from the Phase IV Post Authorisation Safety Study (PASS/SVCARB06009) have been reviewed in the Postmarketing experience section of this CER. This observational, postmarketing study was designed to monitor the clinical use of sevelamer carbonate (Renvela) in adult hyperphosphataemic CKD patients with serum phosphorous ≥ 1.78 mmol/L who were not on dialysis. The sponsor was requested by the EU Committee for Medicinal Products for Human Use (CHMP) to undertake this study as a post-approval safety commitment.
3. The new safety data relating to sevelamer carbonate from the two studies that are not directly relevant to the proposed indication have also been briefly summarised (APB00108 [LEAP]; SVCARB00606 [ASPIRE])
4. The submission included an Addendum to Clinical Overview for Renewal of Renvela 800 mg Film-Coated Tablets, 1.6 g and 3.4 g Powder for Oral Suspension in the European Union covering the period from 10 June 2009 to 06 June 2013. The objective of this report was to support the renewal of the EU marketing authorisation of sevelamer carbonate following its first EU marketing authorisation on 10 June 2009. This report has been reviewed in the Post-marketing experience section of this CER.

8.2. Safety data from the 4 new studies with sevelamer carbonate

8.2.1. Patient exposure

The 4 new studies included a total of 294 hyperphosphataemic patients with CKD exposed to at least one dose of sevelamer carbonate (245 on haemodialysis, 49 not on haemodialysis). Based on the data for the 294 patients included in safety set, the estimated exposure was 69.4 patient-years. The exposure relating to the sevelamer carbonate safety set are summarised below in Table 28.

Table 28: Sevelamer carbonate exposure in the 4 new studies.

Study	N	Duration	Mean \pm SD treatment	Patient-years of exposure	Mean \pm SD actual daily dose
GD3-163-201	73	8 weeks	8.0 \pm 0.4 weeks	11.1	5.8 \pm 2.8 g/day
SVCARB00105	49	8 weeks	7.4 \pm 2.4 weeks	6.9	5.4 \pm 1.7 g/day
SVCARB00205	31	4 weeks	3.7 \pm 1.3 weeks	2.2	5.9 \pm 2.7 g/day
GD3-199-301	141	24 weeks	18.4 \pm 7.9 weeks	49.2	6.2 \pm 2.6 g/day

Note: The mean \pm SD actual daily dose relates to the randomised treatment period for the safety set for studies GD3-163-2012, SVCARB00205, and GD4-199-301.

Sevelamer carbonate exposure by maximum duration of treatment in the 4 new studies is summarised below in Table 29.

Table 29: Sevelamer carbonate maximum duration of exposure in the 4 new studies.

Cumulative	GD3-199-301		SVCARB00105		GD3-163-201		SVCARB00205	
	N	Person-time	N	Person-time	N	Person-time	N	Person-time
Up to 4 weeks	13	23.3 weeks	6	8.0 weeks	0	0	1	25.7 weeks
Up to 8 weeks	26	97.5 weeks	23	137.4 weeks	36	281.1 weeks	3	114.1 weeks
Up to 12 weeks	32	151.9 weeks	49	361.0 weeks	72	575.3 weeks	3	114.1 weeks
Up to 16 weeks	38	234.5 weeks	49	361.0 weeks	72	575.3 weeks	3	114.1 weeks
Up to 24 weeks	139	2557 weeks	-	-	-	-	-	-

Sevelamer carbonate exposure by average actual daily dose is summarised below in Table 30.

Table 30: Sevelamer carbonate exposure by average actual daily dose in the 4 new studies.

Dose g/day	GD3-199-301		SVCARB00105		GD3-163-201		SVCARB00205	
	N	Person-time	N	Person-time	N	Person-time	N	Person-time
Unknown	-	-	1	9.1 weeks	1	5.1 weeks	5	13.4 weeks
\leq 4.8	4	757.4 weeks	20	119.1 weeks	30	240.7 weeks	12	46.4 weeks

	GD3-199-301		SVCARB00105		GD3-163-201		SVCARB00205	
> 4.8 to < 9.6	7 2	1392.7 weeks	27	225.1 weeks	34	273.6 weeks	12	46.0 weeks
≥ 9.6	1 8	406.9 weeks	1	7.6 weeks	7	55.9 weeks	2	8.3 weeks

Evaluator's Comment: None of the 294 patients in the sevelamer carbonate safety set were exposed to the formulation for more than 24 weeks. The majority of patients in the safety set were treated with sevelamer carbonate at a total daily dose of > 4.8 to < 9.6 g.

8.2.2. Adverse events

8.2.2.1. Overview of adverse events

The adverse event profiles associated with treatments occurring in the randomised treatment periods of the three controlled studies in patients on haemodialysis, and in the treatment period in the single-arm study in patients not on dialysis are summarised below in Table 31.

Table 31: Safety profiles in the safety sets occurring in the treatment periods in patients on haemodialysis; mean actual dose refers to dose in the safety set during treatment.

	GD3-163-201		SVCARB00205		GD3-199-301		SVCARB00105
Parameter	SCB (n=73)	SHC (n=78)	SCB (n=31)	SHC (n=28)	SCB (n=141)	SHC (n=72)	SCB (n=49)
Mean±SD actual daily dose	5.8 ± 2.8 g/d	5.6 ± 2.9 g/d	5.9 ± 2.7	6.5 ± 3.3 g/d	6.2 ± 2.6 g/d	6.7 ± 3.0 g/d	5.4 ± 1.7 g/d
Any TEAEs	60 (82.2%)	65 (83.3%)	10 (32.3%)	12 (42.9%)	124 (87.9%)	66 (91.7%)	44 (89.8%)
Related TEAEs	12 (16.4%)	15 (19.2%)	3 (9.7%)	0	43 (30.5%)	13 (18.1%)	19 (38.8%)
Severe TEAEs	5 (6.8%)	6 (7.7%)	1 (3.2%)	0	22 (15.6%)	19 (26.4%)	2 (4.1%)
SAEs	8 (11.0%)	11 (14.1%)	2 (6.5%)	1 (3.6%)	33 (23.4%)	28 (38.9%)	11 (22.4%)
Discontinuations due to AEs	0 (0.0%)	6 (7.7%)	3 (9.7%)	0	17 (12.1%)	4 (5.6%)	4 (8%)
Deaths	1 (1.4%)	1 (1.3%)	1 (3.2%)	0	3 (2.1%)	4 (5.6%)	1 (2%)

Evaluator's Comment: In the two cross-over equivalence studies, the overall adverse event profiles were similar in the sevelamer carbonate and sevelamer hydrochloride treatment groups. In these two studies, TEAEs occurred

more frequently in GD3-163-201 compared with SVCARB00205. However, this difference is most likely to be due to the longer mean duration of exposure in GD3-163-201 compared with SVCARB00205 (that is, 8 weeks versus 3.7 weeks). In Study GD3-199-301, there were some differences in the adverse event profiles between sevelamer carbonate QD and sevelamer hydrochloride TDS treatment groups, with a greater proportion of TEAEs being treatment-related in the carbonate group and a greater proportion of severe TEAEs and SAEs being reported in the hydrochloride group. In all 4 studies, the majority of TEAEs reported with sevelamer carbonate were considered to be unrelated to treatment.

8.2.2.2. Adverse events (all causality) by MedDRA SOC

In the 8 week cross-over study [GD3-163-201], in the randomised treatment periods, AEs by MedDRA SOC occurring in $\geq 10\%$ of patients in either of the two treatment groups in descending order of frequency in the sevelamer carbonate tablet TDS group (n=73) versus the sevelamer hydrochloride tablet TDS group (n=78), respectively, were: 'infections and infestations' (26.0% versus 23.1%); 'injury poisoning and procedural complications' (21.9% versus 20.5%); 'gastrointestinal disorders' (20.5% versus 35.9%); 'investigations' (19.2% versus 16.7%); 'musculoskeletal and connective tissue disorders' (16.4% versus 20.5%); 'metabolism and nutrition disorders' (16.4% versus 17.9%); 'nervous system disorders' (16.4% versus 16.7%); 'respiratory, thoracic, and mediastinal disorders' (16.4% versus 16.7%); and 'general disorders and administration site conditions' (13.7% versus 16.7%). The most notable difference between the two treatment groups was the higher incidence of 'gastrointestinal disorders' in the sevelamer hydrochloride group than in the sevelamer carbonate group.

In the 4 week, cross-over study [SVCARB00205], in the randomised treatment periods, AEs by MedDRA SOC occurring in $\geq 10\%$ of patients in either of the two treatment groups in descending order of frequency in the sevelamer carbonate powder TDS group (n=31) versus the sevelamer hydrochloride tablet TDS group (n=28), respectively, were: 'gastrointestinal disorders' (12.9% versus 10.7%); 'general disorders and administration site conditions' (3.2% versus 14.3%); 'musculoskeletal and connective tissue disorders' (3.2% versus 10.7%); and 'surgical and medical procedures' (3.2% versus 10.7%).

In the 24 week, parallel group study [GD3-199-301], AEs by MedDRA SOC occurring in $\geq 10\%$ of patients in either of the two treatment groups in descending order of frequency in the sevelamer carbonate powder QD group (n=141) versus the sevelamer hydrochloride tablet TDS group (n=72), respectively, were: 'gastrointestinal disorders' (46.8% versus 48.6%); 'infections and infestations' (30.5% versus 38.9%); 'injury poisoning and procedural complications' (31.2% versus 44.4%); 'musculoskeletal and connective tissue disorders' (33.3% versus 29.2%); 'nervous system disorders' (20.6% versus 25.0%); 'respiratory, thoracic, and mediastinal disorders' (20.6% versus 25.0%); 'general disorders and administration site conditions' (26.2% versus 37.5%); 'metabolism and nutrition disorders' (17.0% versus 22.2%); 'vascular disorders' (15.6% versus 27.8%); 'skin and subcutaneous tissue disorders' (14.9% versus 19.4%); 'cardiac disorders' (13.5% versus 16.7%); and 'investigations' (7.8% versus 16.7%).

In the 8 week, single-arm, sevelamer carbonate tablet TDS study in patients not on haemodialysis [SVCARB00105], AEs (all causality) occurring in $\geq 10\%$ of randomised patients by MedDRA SOC in descending order of frequency were: 'gastrointestinal disorders' (46.9%); 'general disorders and administration site conditions' (20.4%); 'infections and infestations' (14.3%); 'metabolism and nutrition disorders' (14.3%); 'surgical and medical procedures' (14.3%); 'nervous system disorders' (10.2%); 'respiratory, thoracic, and mediastinal disorders' (10.2%); 'skin and subcutaneous tissue disorders' (10.2%); and 'musculoskeletal and connective tissue disorders' (10.2%).

8.2.2.3. Adverse events (all causality) by preferred term (PT)

Adverse events (all causality) by PTs occurring in $\geq 5\%$ of patients of patients in the randomised treatment periods at least one of the two treatment groups in the three controlled studies were summarised.

In the 8 week cross-over study [GD3-163-201], in the randomised treatment periods:

- AEs (all causality) were reported in 60 (82.2%) patients (195 events) in the sevelamer carbonate tablet TDS group (n=73) and in 65 (83.3%) patients (226 events) in the sevelamer hydrochloride tablet TDS group (n=78). There were no statistically significant differences between the two treatment groups in the incidences of any AE (all causality/PT).
- The most commonly reported AEs (all causality) occurring in $\geq 5\%$ of patients in the sevelamer carbonate tablet group (n=73) versus the sevelamer hydrochloride group (n=78), in decreasing order of frequency were: nausea (9.6% versus 12.8%); vomiting (8.2% versus 10.3%); hypercalcaemia (8.2% versus 3.8%); AV fistula site complications (6.8% versus 1.3%); cough (5.5% versus 3.8%); AV fistula site haemorrhage (5.5% versus 2.6%); carbon dioxide decreased (5.5% versus 5.1%); and muscle spasms (5.5% versus 3.8%). AEs occurring in $\geq 5\%$ of patients in the sevelamer carbonate group and $\geq 2\%$ more frequently than in the sevelamer hydrochloride group were hypercalcaemia, dizziness, urinary tract infection, AV fistula site complications, and AV fistula site haemorrhage.
- AEs (all causality) occurring in $\geq 5\%$ of patients in the sevelamer hydrochloride group and $\geq 2\%$ more frequently than in the sevelamer carbonate group were nausea (12.8% versus 9.6%), AV fistula thrombosis (11.5% versus 4.1%), vomiting (10.3% versus 8.2%), pain in extremity (7.7% versus 4.1%), diarrhoea (6.4% versus 2.7%), GORD (5.1% versus 1.4%), and fatigue (5.1% versus 1.4%).

In the 4 week cross-over study [SVCARB00205], AEs (all causality) were reported in 10 (32.3%) patients (21 events) in the sevelamer carbonate powder TDS group (n=31) and 12 (42.9%) patients (26 events) in the sevelamer hydrochloride tablet TDS group (n=28). The only AEs (all causality) reported in $\geq 5\%$ of patients in the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride, respectively) were nausea (6.5% versus 0%), AV fistula operation (3.2% versus 7.1%) and fatigue (0% versus 7.1%).

In the 24 week, parallel-group study [GD3-163-201]:

- AEs (all causality) were reported in 124 (87.9%) patients (723 events) in the sevelamer carbonate powder QD group (n=141) and in 66 (91.7%) patients (430 events) in the sevelamer hydrochloride tablet TDS group (n=72).
- The most commonly reported AEs (all causality) occurring in $\geq 5\%$ of patients in the sevelamer carbonate group (n=141) versus the sevelamer hydrochloride group (n=72), in decreasing order of frequency were: nausea (21.3% versus 11.1%); diarrhoea (17.7% versus 18.1%); vomiting (17.0% versus 8.3%); muscle spasms (14.2% versus 5.6%); AV fistula site complication (12.8% versus 6.9%); headache (10.6% versus 11.1%); pain in extremity (8.5% versus 9.7%); urinary tract infection (7.1% versus 2.8%); upper respiratory infection (6.4% versus 6.9%); dizziness (6.4% versus 11.1%); cough (6.4% versus 5.6%); pruritus (6.4% versus 4.2%); hypotension (6.4% versus 11.1%); AV fistula thrombosis (5.7% versus 18.1%); back pain (5.7% versus 4.2%); and dyspnoea (5.7% versus 6.9%). AEs occurring in $\geq 5\%$ of patients in the sevelamer carbonate group and $\geq 2\%$ more frequently than in the sevelamer hydrochloride group were nausea, vomiting, muscle spasms, AV fistula site complications, urinary tract infection, and pruritus.
- AEs (all causality) occurring in $\geq 5\%$ of patients in the sevelamer hydrochloride group and $\geq 2\%$ more frequently than in the sevelamer carbonate group were: AV fistula thrombosis (18.1% versus 5.7%); constipation (11.1% versus 4.3%); dizziness (11.1% versus 6.4%);

hypotension (11.1% versus 6.4%); pyrexia (8.3% versus 2.8%); cardiac failure congestive (6.9% versus 3.5%); oedema peripheral (6.9% versus 4.3%); AV fistula site haemorrhage (6.9% versus 2.1%); abdominal pain upper (5.6% versus 3.5%); AV fistula site infection (5.6% versus 1.4%); hypocalcaemia (5.6% versus 2.1%); heart rate irregular (5.6% versus 1.4%); and arthralgia (5.6% versus 2.8%).

In the single-arm sevelamer carbonate tablet TDS study [SVCARB00105] in patients not on haemodialysis (n=49), AEs (all causality/PT) following 8 weeks treatment occurred in 44 (89.8%) patients (137 events). The most frequently reported events occurring in $\geq 10\%$ of patients by descending order of frequency were (number of patients, percentage of patients; number of events): nausea (11, 22.4%; 12); AV fistula operation (7, 14.3%; 7); constipation (6, 12.2%; 7); diarrhoea (5, 10.2%; 8); vomiting (5, 10.2%; 6); flatulence (3, 6.1%; 3); oedema peripheral (3, 6.1%; 4); pyrexia (3, 6.1%; 4); lower respiratory tract infection (3, 6.1%; 5); headache (3, 6.1%; 6); and pruritus (3, 6.1%; 3).

8.2.2.4. Adverse events (treatment related)

Adverse events (treatment related) occurring in $\geq 5\%$ of patients of randomised patients by MedDRA SOC in $\geq 2\%$ of randomised patients by PT in at least one of the two treatment groups in the three controlled studies in patients on haemodialysis are summarised below in Table 32.

Table 32: Sevelamer carbonate (SCB) and sevelamer hydrochloride (SHC)-Adverse events (treatment related) in $\geq 5\%$ of randomised patients on haemodialysis by MedDRA SOC and $\geq 2\%$ of patients by PT in the three controlled studies by patient number (%); number of events

	GD3-163-201		SVCARB00205		GD3-199-301	
	SCB (n=73)	SHC (n=78)	SCB (n=31)	SHC (n=28)	SCB (n=141)	SHC (n=72)
Mean \pm SD actual daily dose	5.8 \pm 2.8 g/d	5.6 \pm 2.9 g/d	5.9 \pm 2.7	6.5 \pm 3.3 g/d	6.2 \pm 2.6 g/d	6.7 \pm 3.0 g/d
Adverse event (SOC and PT)						
Any	12 (16.4%); 20	15 (19.2%); 33	3 (9.7%); 4	0	43 (30.5%); 72	13 (18.1%)
Gastrointestinal	6 (8.2%); 9	8 (10.3%); 14	3 (9.7%); 4	0	32 (22.7%); 58	8 (11.1%); 18
Nausea	2 (2.7%); 2	2 (2.6%); 5	2 (6.5%); 2	0	12 (8.5%); 17	4 (5.6%); 5
Vomiting	2 (2.7%); 2	1 (1.3%); 1	1 (3.2%); 1	0	8 (5.5%); 8	1 (1.4%); 1
GORD	1 (1.4%); 1	3 (3.8%); 4	0	0	0	0
Constipation	0	0	1 (3.2%); 1	0	1 (0.7%); 1	4 (5.6%); 4
Stomach discomfort	0	1 (1.3%); 1	0	0	3 (2.1%); 5	1 (1.4%); 1

	GD3-163-201		SVCARB00205		GD3-199-301	
Investigations	7 (9.6%); 9	7 (9.0%); 10	0	0	2 (1.4%)	2 (2.8%); 3
Carbon dioxide decreased	4 (5.5%); 4	4 (5.1%); 5	0	0	1 (0.7%); 1	2 (2.8%); 3
Blood triglycerides increased	2 (2.7%); 2	1 (1.3%); 1	0	0	0	0
Blood bicarbonate decreased	1 (1.4%); 1	2 (2.6%); 10	0	0	0	0
Blood PTH increased	1 (1.4%); 1	2 (2.6%); 2	0	0	1 (0.7%); 1	0
Metabolism and nutrition	2 (2.7%); 2	4 (5.1%); 4	0	0	5 (3.5%); 5	3 (4.2%); 4
Decreased appetite	0	2 (2.6%); 2	0	0	2 (1.4%); 2	0
Hypocalcaemia	0	0	0	0	1 (0.7%); 1	2 (2.8%); 3

In the single-arm sevelamer carbonate tablet TDS study [SVCARB00105] in patients not on haemodialysis (n=49), AEs (treatment related/PT) following 8 weeks treatment occurred in 19 (38.8%) patients (44 events). The most frequently reported events occurring in $\geq 2\%$ of patients by descending order of frequency were (number of patients, percentage of patients; number of events): nausea (8, 32.7%; 35); constipation (5, 10.2%; 6); diarrhoea (3, 6.1%; 6); abdominal pain upper (2, 4.1%; 2); abdominal distension (2, 4.1%; 2); and 1, 2.0% (1 event) each for bowel sounds abnormal; dyspepsia; epigastric discomfort; frequent bowel movements; decreased appetite; hypocalcaemia; increased appetite; blister; pruritus; malaise; lethargy; sleep disorder; and hot flush.

8.2.3. Deaths and other serious adverse events (SAEs)

8.2.3.1. Deaths

In the 8 week, cross-over study in patients on haemodialysis [GD3-163-201], 2 patients died during the study, 1 in the sevelamer carbonate tablet TDS group (n=73) and 1 in the sevelamer hydrochloride tablet TDS group (n=78). Both deaths were considered by Investigators to be unrelated to treatment with sevelamer. In the sevelamer carbonate group, one 73 year old female patient with a history of type II diabetes and significant cardiovascular disease (myocardial infarction, angina, stroke, peripheral vascular disease) died of complications of worsening coronary artery disease approximately 1 month after starting treatment. In the sevelamer hydrochloride group, one 40 year old female patient with a history of diabetes, hyperlipidaemia, and kidney transplant discontinued 1 month after starting treatment with sevelamer due to a renal transplant and died 3 weeks after receiving the transplant due to complications of diabetes.

In the 4 week, cross-over study in patients on haemodialysis [SVCARB00205], no patients died during Screening through to the end of one week of follow-up. During the 30-day post completion period, 1 patient who had been in the sevelamer carbonate powder TDS group experienced a SAE of brain stem haemorrhage resulting in death considered to be unrelated to sevelamer carbonate treatment.

In the 24 week, parallel-group study in patients on haemodialysis [GD3-163-301], 2 (1.4%) patients in the sevelamer carbonate powder QD group (n=141) and 4 (5.6%) patients in the sevelamer hydrochloride tablet TDS group (n=72) died during the randomised treatment period. In the sevelamer carbonate group, the 2 deaths were due to cardiac arrest (unknown cause) in 1 patient and withdrawal of renal replacement therapy in 1 patient. In the sevelamer hydrochloride group, the 4 deaths were due to cardiac arrest (unknown cause) in 1 patient; septic shock, staphylococcal pneumonia, and hypertensive cardiovascular disease in 1 patient; septicaemia in 1 patient; and intracranial bleed in 1 patient. All the deaths in the randomised treatment period were considered by Investigators to be unrelated to treatment with sevelamer.

In the single-arm sevelamer carbonate tablet TDS study [SVCARB00105] in patients not on haemodialysis (n=49), 1 patient died during the course of the study due to bronchopneumonia approximately 1 month after prematurely terminating the study due to a pleural effusion (SAE). The SAE and the cause of death were considered by the Investigator to be unrelated to sevelamer carbonate treatment.

8.2.3.2. Other serious adverse events (SAEs)

In the 8 week cross-over study in patients on haemodialysis [GD3-163-201], in the randomised treatment periods 8 (11.0%) patients in the sevelamer carbonate group (n=73) experienced 17 SAEs, and 11 (14.1%) patients in the sevelamer hydrochloride group (n=78) experienced 17 SAEs. The only SAEs reported in $\geq 2\%$ of patients in either of the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride) were coronary artery disease (2.7% versus 2.6%) and renal transplant (0% versus 2.6%). All SAEs in the randomised treatment periods were assessed by the Investigator as being unrelated to treatment. All SAEs reported as starting or worsening during randomised treatment in the safety set are summarised in Table 33.

Table 33: GD3-163-201 - SAEs starting or worsening during randomised treatment; safety set.

System Organ Class/ Adverse Event	Sevelamer Carbonate (N=73)		Sevelamer Hydrochloride (N=78)		McNemar's Test P-value
	Patients n (%)	Events N	Patients n (%)	Events N	
Any	8 (11.0%)	17	11 (14.1%)	17	1.000
CARDIAC DISORDERS	3 (4.1%)	5	2 (2.6%)	3	0.655
BRADYCARDIA	1 (1.4%)	1	0	0	0.317
CARDIAC ARREST	1 (1.4%)	1	1 (1.3%)	1	1.000
CORONARY ARTERY DISEASE	2 (2.7%)	2	2 (2.6%)	2	1.000
NODAL ARRHYTHMIA	1 (1.4%)	1	0	0	0.317
EYE DISORDERS	1 (1.4%)	1	0	0	0.317
EYE HAEMORRHAGE	1 (1.4%)	1	0	0	0.317
IMMUNE SYSTEM DISORDERS	0	0	1 (1.3%)	1	0.317
KIDNEY TRANSPLANT REJECTION	0	0	1 (1.3%)	1	0.317
INFECTIONS AND INFESTATIONS	3 (4.1%)	3	2 (2.6%)	2	0.655
ENDOCARDITIS	0	0	1 (1.3%)	1	0.317
GASTROENTERITIS VIRAL	1 (1.4%)	1	0	0	0.317
LOBAR PNEUMONIA	1 (1.4%)	1	0	0	0.317
LOCALISED INFECTION	1 (1.4%)	1	0	0	0.317
PNEUMONIA	0	0	1 (1.3%)	1	0.317
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (1.3%)	1	0.317
ARTERIOVENOUS FISTULA THROMBOSIS	0	0	1 (1.3%)	1	0.317
INVESTIGATIONS	0	0	2 (2.6%)	2	0.157
INTERNATIONAL NORMALISED RATIO DECREASED	0	0	1 (1.3%)	1	0.317
INTERNATIONAL NORMALISED RATIO INCREASED	0	0	1 (1.3%)	1	0.317
METABOLISM AND NUTRITION DISORDERS	1 (1.4%)	1	2 (2.6%)	3	1.000
DIABETIC COMPLICATION	0	0	1 (1.3%)	1	NC
DIABETIC KETOACIDOSIS	0	0	1 (1.3%)	1	0.317
HYPERGLYCAEMIA	0	0	1 (1.3%)	1	0.317
HYPERKALAEMIA	1 (1.4%)	1	0	0	0.317
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.4%)	5	1 (1.3%)	1	0.317
INTERVERTEBRAL DISC DEGENERATION	1 (1.4%)	1	0	0	0.317
MUSCULAR WEAKNESS	0	0	1 (1.3%)	1	NC
OSTEOARTHRITIS	1 (1.4%)	1	0	0	0.317
OSTEOPENIA	1 (1.4%)	1	0	0	0.317
PAIN IN EXTREMITY	1 (1.4%)	2	0	0	0.317
NERVOUS SYSTEM DISORDERS	1 (1.4%)	1	1 (1.3%)	1	1.000
CAROTID ARTERY STENOSIS	0	0	1 (1.3%)	1	0.317
GRAND MAL CONVULSION	1 (1.4%)	1	0	0	0.317
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (1.3%)	1	0.317
PULMONARY OEDEMA	0	0	1 (1.3%)	1	0.317
SURGICAL AND MEDICAL PROCEDURES	0	0	2 (2.6%)	2	NC
RENAL TRANSPLANT	0	0	2 (2.6%)	2	NC
VASCULAR DISORDERS	1 (1.4%)	1	0	0	0.317
HYPERTENSION	1 (1.4%)	1	0	0	0.317

In the 4 week cross-over study in patients on haemodialysis [SVCARB00205], SAEs in the randomised treatment period were reported in 2 (6.5%) patients in the sevelamer carbonate powder TDS group (n=31) and 1 (3.6%) patient in the sevelamer hydrochloride tablet TDS group (n=28). In the sevelamer carbonate group, the SAEs were chest pain in 1 patient (remote/unlikely related to treatment) and 1 patient with catheter sepsis (not related to treatment). In the sevelamer hydrochloride group, the SAE was catheter related complication in 1 patient (not related to treatment).

In the 24 week, parallel-group study in patients on haemodialysis [GD3-199-301], 33 (23.4%) patients in the sevelamer carbonate QD powder group (n=141) experienced 85 SAEs, and 28 (38.9%) patients in the sevelamer hydrochloride tablet TDS group (n=72) experienced 72 SAEs. SAEs reported in $\geq 2\%$ of patients in either of the two treatment groups and by decreasing order of frequency in the sevelamer carbonate group (versus the sevelamer hydrochloride group) were: pneumonia (4.3% versus 4.2%); cardiac failure congestive (3.5% versus 5.6%); hyperkalaemia (2.8% versus 2.8%); atrial fibrillation (2.1% versus 1.4%); pulmonary oedema (2.1% versus 1.4%); AV fistula thrombosis (1.4% versus 5.6%); hypoglycaemia (0.7% versus 2.8%); coronary artery disease (0.7% versus 4.2%); hypertension (0.7% versus 2.8%); and AV fistula operation (0% versus 2.8%). The majority of SAEs were considered by the Investigator to be unrelated to treatment with sevelamer. In one patient treated with sevelamer hydrochloride a SAE of probable faecal impaction presenting approximately 15 weeks after start of treatment

was reported by the investigator as being possibly related to treatment with sevelamer. Treatment emergent SAEs reported in the safety set are summarised in Table 34.

Table 34: GD3-199-301 - Treatment-emergent serious adverse events; safety set.

Body System Preferred Term	Sevelamer Carbonate Powder QD (n=141)		Sevelamer Hydrochloride Tablet TID (n=72)	
	Events	Subjects (%)	Events	Subjects (%)
Number of Events/Subjects with at Least One Event	85	33 (23.4)	72	28 (38.9)
Blood and lymphatic system disorders	2	2 (1.4)	1	1 (1.4)
Anaemia	1	1 (0.7)	1	1 (1.4)
Splenic infarction	1	1 (0.7)	0	0 (0.0)
Cardiac disorders	17	9 (6.4)	16	9 (12.5)
Acute myocardial infarction	0	0 (0.0)	1	1 (1.4)
Atrial fibrillation	3	3 (2.1)	1	1 (1.4)
Atrial flutter	1	1 (0.7)	0	0 (0.0)
Bradycardia	1	1 (0.7)	0	0 (0.0)
Cardiac arrest	1	1 (0.7)	1	1 (1.4)
Cardiac failure congestive	7	5 (3.5)	7	4 (5.6)
Cardio-respiratory arrest	1	1 (0.7)	0	0 (0.0)
Coronary artery disease	1	1 (0.7)	3	3 (4.2)
Hypertensive heart disease	0	0 (0.0)	1	1 (1.4)
Myocardial infarction	0	0 (0.0)	1	1 (1.4)
Pericarditis	1	1 (0.7)	0	0 (0.0)
Tachyarrhythmia	0	0 (0.0)	1	1 (1.4)
Tachycardia	1	1 (0.7)	0	0 (0.0)
Congenital, familial and genetic disorders	1	1 (0.7)	0	0 (0.0)
Congenital cystic kidney disease	1	1 (0.7)	0	0 (0.0)
Gastrointestinal disorders	1	1 (0.7)	5	4 (5.6)
Diarrhoea	0	0 (0.0)	1	1 (1.4)
Duodenal ulcer haemorrhage	0	0 (0.0)	1	1 (1.4)
Faecaloma	0	0 (0.0)	1	1 (1.4)
Gastrointestinal haemorrhage	0	0 (0.0)	1	1 (1.4)
Ileus	1	1 (0.7)	0	0 (0.0)
Inguinal hernia	0	0 (0.0)	1	1 (1.4)
General disorders and administration site conditions	3	3 (2.1)	4	3 (4.2)
Catheter related complication	0	0 (0.0)	1	1 (1.4)
Catheter site haemorrhage	1	1 (0.7)	1	1 (1.4)
Impaired healing	0	0 (0.0)	1	1 (1.4)
Ischaemic ulcer	1	1 (0.7)	0	0 (0.0)
Pyrexia	1	1 (0.7)	1	1 (1.4)
Hepatobiliary disorders	0	0 (0.0)	1	1 (1.4)
Cholelithiasis	0	0 (0.0)	1	1 (1.4)
Infections and infestations	19	15 (10.6)	12	11 (15.3)
Arteriovenous fistula site infection	1	1 (0.7)	1	1 (1.4)
Bacteraemia	1	1 (0.7)	0	0 (0.0)
Bronchitis	1	1 (0.7)	1	1 (1.4)
Catheter related infection	1	1 (0.7)	0	0 (0.0)
Catheter sepsis	2	2 (1.4)	1	1 (1.4)
Cellulitis	1	1 (0.7)	1	1 (1.4)
Enterococcal infection	1	1 (0.7)	0	0 (0.0)
Gangrene	1	1 (0.7)	0	0 (0.0)
Incision site infection	0	0 (0.0)	1	1 (1.4)
Pneumonia	6	6 (4.3)	3	3 (4.2)
Pneumonia staphylococcal	0	0 (0.0)	1	1 (1.4)
Sepsis	2	2 (1.4)	1	1 (1.4)
Septic shock	0	0 (0.0)	1	1 (1.4)
Staphylococcal bacteraemia	2	2 (1.4)	0	0 (0.0)
Staphylococcal sepsis	0	0 (0.0)	1	1 (1.4)
Injury, poisoning and procedural complications	5	4 (2.8)	7	6 (8.3)
Arteriovenous fistula site complication	1	1 (0.7)	0	0 (0.0)
Arteriovenous fistula thrombosis	3	2 (1.4)	5	4 (5.6)
Femur fracture	0	0 (0.0)	1	1 (1.4)

Table 34 continued: GD3-199-301 - Treatment-emergent serious adverse events; safety set.

Fibula fracture	1	1 (0.7)	0	0 (0.0)
Wound dehiscence	0	0 (0.0)	1	1 (1.4)
Investigations	1	1 (0.7)	1	1 (1.4)
Arteriogram carotid	0	0 (0.0)	1	1 (1.4)
Cardioactive drug level increased	1	1 (0.7)	0	0 (0.0)
Metabolism and nutrition disorders	12	8 (5.7)	5	3 (4.2)
Diabetic foot	1	1 (0.7)	0	0 (0.0)
Diabetic ketoacidosis	2	2 (1.4)	0	0 (0.0)
Fluid overload	2	2 (1.4)	1	1 (1.4)
Hyperkalaemia	5	4 (2.8)	2	2 (2.8)
Hypoglycaemia	1	1 (0.7)	2	2 (2.8)
Hyponatraemia	1	1 (0.7)	0	0 (0.0)
Musculoskeletal and connective tissue disorders	1	1 (0.7)	0	0 (0.0)
Lumbar spinal stenosis	1	1 (0.7)	0	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2 (1.4)	0	0 (0.0)
Breast cancer	1	1 (0.7)	0	0 (0.0)
Thymoma	1	1 (0.7)	0	0 (0.0)
Nervous system disorders	3	3 (2.1)	3	3 (4.2)
Cerebrovascular accident	1	1 (0.7)	1	1 (1.4)
Haemorrhage intracranial	0	0 (0.0)	1	1 (1.4)
Spinal cord infarction	1	1 (0.7)	0	0 (0.0)
Syncope	1	1 (0.7)	0	0 (0.0)
Transient ischaemic attack	0	0 (0.0)	1	1 (1.4)
Psychiatric disorders	1	1 (0.7)	0	0 (0.0)
Depression	1	1 (0.7)	0	0 (0.0)
Renal and urinary disorders	1	1 (0.7)	0	0 (0.0)
Renal failure chronic	1	1 (0.7)	0	0 (0.0)
Respiratory, thoracic and mediastinal disorders	8	8 (5.7)	3	3 (4.2)
Chronic obstructive pulmonary disease	1	1 (0.7)	0	0 (0.0)
Dyspnoea	2	2 (1.4)	0	0 (0.0)
Interstitial lung disease	1	1 (0.7)	0	0 (0.0)
Pleural effusion	1	1 (0.7)	0	0 (0.0)
Pulmonary hypertension	0	0 (0.0)	1	1 (1.4)
Pulmonary oedema	3	3 (2.1)	1	1 (1.4)
Sleep apnoea syndrome	0	0 (0.0)	1	1 (1.4)
Skin and subcutaneous tissue disorders	2	2 (1.4)	0	0 (0.0)
Decubitus ulcer	1	1 (0.7)	0	0 (0.0)
Skin ulcer	1	1 (0.7)	0	0 (0.0)
Surgical and medical procedures	2	2 (1.4)	3	3 (4.2)
Arteriovenous fistula operation	0	0 (0.0)	2	2 (2.8)
Nephrectomy	1	1 (0.7)	0	0 (0.0)
Renal transplant	0	0 (0.0)	1	1 (1.4)
Therapy cessation	1	1 (0.7)	0	0 (0.0)
Vascular disorders	4	4 (2.8)	11	7 (9.7)
Aneurysm arteriovenous	0	0 (0.0)	1	1 (1.4)
Aortic aneurysm	0	0 (0.0)	1	1 (1.4)
Aortic stenosis	0	0 (0.0)	1	1 (1.4)
Hypertension	1	1 (0.7)	2	2 (2.8)
Hypertensive emergency	1	1 (0.7)	2	1 (1.4)
Hypotension	2	2 (1.4)	0	0 (0.0)
Peripheral arterial occlusive disease	0	0 (0.0)	1	1 (1.4)
Peripheral artery aneurysm	0	0 (0.0)	1	1 (1.4)
Superior vena caval occlusion	0	0 (0.0)	1	1 (1.4)
Venous stenosis	0	0 (0.0)	1	1 (1.4)

In the single-arm sevelamer carbonate tablet TDS study [SVCARB00105] in patients not on haemodialysis (n=49), 11 (22.4%) patients (n=49) experienced 19 treatment-emergent SAEs during the study. SAEs occurring in > 1 patient (> 2.0%) were: AV fistula operation (8.2%, n=4) lower respiratory tract infection (4.1%, n=2); and fluid overload (4.1%, n=2). SAEs each occurring in 1 (2.0%) patient were: coronary artery disease; bronchopneumonia; gastroenteritis clostridial; fall; fractured humerus; hyperkalaemia; chronic renal failure; pleural effusion; insertion of ambulatory peritoneal catheter; and hypertension. All SAEs were assessed as not related to sevelamer carbonate treatment.

8.2.4. Discontinuations due to adverse events

In the 8 week cross-over study in patients on haemodialysis [GD3-163-201], 6 (7.7%) patients discontinued treatment due to AEs in the sevelamer hydrochloride tablet TDS group (n=78) compared with no patients in the sevelamer carbonate tablet TDS group (n=73). In the sevelamer hydrochloride group, 2 patients discontinued due to renal transplant, 1 patient discontinued due to AV fistula thrombosis and hepatic ischaemia, and 1 patient each discontinued due to allergic dermatitis, asthenia, and muscular weakness.

In the 4 week cross-over study in patients on haemodialysis [SVCARB00205], 3 (9.7%) randomised patients in the sevelamer carbonate TDS powder group (n=31) discontinued treatment due to AEs (4 events) compared with no randomised patients in the sevelamer hydrochloride tablet TDS group (n=28). The AEs leading to treatment discontinuation were nausea (1 event) and vomiting (1 event) in 1 patient, nausea (1 event) in 1 patient, and chest pain (1 SAE) in 1 patient.

In the 24 week, parallel-group study in patients on haemodialysis [GD3-199-301], 17 (12.0%) patients in the sevelamer carbonate QD powder group (n=141) discontinued treatment due to AEs compared with 3 (4.2%) patients in the sevelamer hydrochloride tablet TDS group (n=72). In the sevelamer carbonate powder group, 5 patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), 8 patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and 4 patients discontinued due to other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders leading to discontinuation in the sevelamer carbonate group were classified as related to study treatment by the Investigators. All 4 patients in the sevelamer hydrochloride tablets group who discontinued did so due to a SAE (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which were classified as related to study treatment by the Investigators.

In the single-arm sevelamer carbonate tablet TDS study [SVCARB00105] in patients not on haemodialysis (n=49), 5 (10.2%) patients discontinued due to AEs. In 4 of the 5 patients, AEs leading to treatment discontinuation were treatment-related gastrointestinal events, including nausea (2 patients), diarrhoea (2 patients), constipation (2 patients), stomach discomfort (1 patient), and vomiting (1 patient). The majority of events leading to treatment discontinuation were assessed as mild or moderate in intensity, except for 3 events in one patient (diarrhoea, nausea and vomiting), which were assessed as severe. One patient discontinued due to serious pleural effusion, which was assessed as not related to sevelamer carbonate.

8.2.5. Laboratory tests

Abnormal laboratory values were not analysed in the new, clinical sevelamer carbonate studies due to the high frequency of chronically abnormal laboratory parameters in dialysis patients. However, changes in laboratory measures that were considered by the Investigators to be clinically significant, and for which medical intervention was indicated were categorised as AEs. The mean changes in laboratory values are summarised below for the 4 new clinical studies. The results for the individual studies are presented in non-SI and/or SI units, as reporting varied not only between studies but also within studies.

8.2.5.1. Serum chemistry

8.2.5.1.1. Serum calcium, iPTH, albumin

Study GD3-163-201

In the 8 week cross-over study in patients on haemodialysis, median iPTH increased significantly from Baseline in the randomised treatment periods in both the sevelamer carbonate (n=68) group ($\Delta = 38$ pg/mL; $p < 0.001$) and the sevelamer hydrochloride (n=72) group ($\Delta = 25$ pg/mL; $p = 0.024$), and the difference between the two treatment groups was statistically significant ($p = 0.020$). There were no statistically significant differences between the two treatment groups in mean change from Baseline in serum phosphorous, albumin, calcium, or calcium-phosphorous product.

Study SVCARB00205

In the 4 week, cross-over study in patients on haemodialysis, there were no statistically significant differences between the sevelamer carbonate and sevelamer hydrochloride groups

in mean change from Baseline in serum calcium or albumin or median change from Baseline in serum iPTH.

Study GD3-199-301

In the 24 week, parallel-group study in patients on haemodialysis, there were no statistically significant differences between the sevelamer carbonate and sevelamer hydrochloride groups in mean change from Baseline in serum calcium or albumin or median change from Baseline in serum iPTH.

Study SVCARB00105

In the single-arm sevelamer carbonate tablet TDS study in patients not on haemodialysis (n=49), there was no statistically significant change from baseline to Day 56/ET in serum albumin and there were statistically significant changes from baseline to Day 56/ET in serum iPTH, calcium (adjusted) and uric acid levels (see Table 35).

Table 35: SVCARB00105 - Serum laboratory parameters; safety set n=49.

Laboratory Parameter	Baseline mean \pm SD	Day 56/ET mean \pm SD	Day 70 mean \pm SD	Change from baseline to Day 56/ET mean \pm SD	Change from Day 56 to Day 70 mean \pm SD	Change from baseline to Day 56 / ET P-value [†]
iPTH (pg/mL) [‡]	341	319	362	-39	63	0.013
Albumin (g/dL)	4.28 \pm 0.34	4.24 \pm 0.33	4.24 \pm 0.33	-0.03 \pm 0.26	0.01 \pm 0.22	0.338
Calcium (albumin adjusted) (mg/dL)	8.52 \pm 0.86	8.80 \pm 0.76	8.60 \pm 0.57	0.31 \pm 0.50	-0.23 \pm 0.52	< 0.001
Uric acid mg/dL	7.98 \pm 1.87	7.49 \pm 1.56	8.22 \pm 1.88	-0.47 \pm 1.10	0.78 \pm 1.10	0.006

[†] iPTH presented as median values

[‡] Wilcoxon signed rank test

8.2.5.1.2. Other serum chemistry parameters

Study GD3-163-201

In the 8 week cross-over study in patients on haemodialysis, there was a statistically significant decrease from baseline in the randomised treatment period in mean \pm SD serum chloride (n=78) in the sevelamer carbonate (n=73) group ($\Delta = -2.6 \pm 3.6$ mEq/L; p<0.001), but not in the sevelamer hydrochloride (n=78) group ($\Delta = 0.0 \pm 4.1$ mEq/L; p=0.733). The change in serum chloride was statistically significant between the two treatment groups at each week and at the end of treatment (p<0.001). There was a statistically significant increase in mean \pm SD serum carbon dioxide in the sevelamer carbonate (n=73) group ($\Delta = 1.3 \pm 4.1$ mEq/L; p<0.001), but not in the sevelamer hydrochloride (n=78) group ($\Delta = -0.3 \pm 3.6$ mEq/L; p=0.833). The change in mean serum carbon dioxide was statistically significant between the two treatment groups at each week and at the end of treatment (p<0.001). There were no statistically significant changes in the other serum chemistry parameters within or between the two treatment groups (that is, ALT, AST, alkaline phosphatase, glucose, potassium).

Study SVCARB00205

In the 4 week, cross-over study in patients on haemodialysis, there was a statistically significant decrease in mean \pm SD serum chloride in the sevelamer carbonate powder (n=25) group ($\Delta = -2.7 \pm 2.7$ mEq/L; p<0.001), but not in the sevelamer hydrochloride tablet (n=26) group ($\Delta = -0.4 \pm 2.7$ mEq/L; p=0.337). The change in mean serum chloride was statistically significantly different between the two treatment groups (p<0.001). There was a statistically significant increase in mean \pm SD serum bicarbonate in the sevelamer carbonate powder (n=25) group ($\Delta = 2.7 \pm 3.7$ mEq/L; p=0.001), but not in the sevelamer hydrochloride tablet (n=26)

group ($\Delta = 0.1 \pm 3.3$ mEq/L; $p=0.791$). The change in mean serum bicarbonate was statistically significantly different between the two treatment groups ($p=0.001$). There were no statistically significant changes in other serum chemistry parameters within or between treatment groups (that is, glucose, AST, ALT, sodium, potassium).

Study GD3-199-301

In the 24 week, parallel-group study in haemodialysis patients, there was a statistically significant increase from baseline to Week 24/ET in mean \pm SD serum chloride in the sevelamer hydrochloride tablet ($n=72$) TDS group ($\Delta = 2.4 \pm 3.85$ mmol/L; $p<0.001$), but not in the sevelamer carbonate powder ($n=141$) QD group ($\Delta = 0.5 \pm 3.71$ mmol/L; $p=0.084$). The difference in mean change from baseline in serum chloride between the two treatment groups was statistically significant ($p=0.001$). There was a statistically significant decrease from baseline in mean \pm SD serum carbon dioxide in the sevelamer hydrochloride ($n=71$) tablet TDS group ($\Delta = -1.0 \pm 3.62$ mmol/L; $p<0.008$), but not in the sevelamer carbonate powder ($n=141$) QD group ($\Delta = 0.1 \pm 3.42$ mmol/L; $p=0.532$). The difference in mean change from baseline in serum bicarbonate between the two treatment groups was statistically significant ($p<0.006$).

There was a statistically significant decrease from baseline in mean serum glucose in the sevelamer carbonate ($n=125$) powder QD group ($\Delta = -0.88 \pm 3.02$ mmol/L, $p=0.001$), but not in the sevelamer hydrochloride ($n=64$) tablet TDS group ($\Delta = -0.23 \pm 2.28$ mmol/L, $p=0.518$). There was no statistically significant difference in the change in serum glucose between the two treatment groups ($p=0.176$). There was a statistically significant increase from baseline in mean \pm SD ALT in the sevelamer carbonate ($n=141$) powder QD group ($\Delta = 1.8 \pm 37.7$ U/L, $p=0.006$), but not in the sevelamer hydrochloride ($n=64$) tablet TDS group ($\Delta = 0.3 \pm 17.9$ U/L, $p=0.654$). There was no statistically significant difference in the change in ALT between the two treatment groups ($p=0.292$).

There was a statistically significant decrease from baseline in mean \pm SD serum uric acid in the sevelamer hydrochloride tablet ($n=64$) TDS group ($\Delta = -4.67 \pm 12.59$ μ mol/L, $p=0.002$), but not in the sevelamer carbonate ($n=124$) powder QD group ($\Delta = -1.31 \pm 8.51$ μ mol/L, $p=0.101$). There was a statistically significant difference in the change in serum uric acid between the two treatment groups ($p=0.008$). There was a statistically significant decrease from baseline in mean \pm SD CRP in the sevelamer hydrochloride ($n=63$) tablet TDS group ($\Delta = -0.7 \pm 1.8$ mg/dL, $p<0.001$), but not in the sevelamer carbonate ($n=125$) powder QD group ($\Delta = 0.2 \pm 2.6$ mg/dL, $p=0.325$). There was a statistically significant difference in the change in CRP between the treatment groups ($p=0.008$). There were no statistically significant changes in the other serum chemistry parameters within or between the two treatment groups (that is, AST, sodium, potassium).

Study SVCARB00105

In the single-arm sevelamer carbonate tablet TDS study in patients not on haemodialysis, there were no statistically significant changes from baseline to Day 56/ET in serum glucose, CRP, AST, ALT, chloride, sodium, and potassium. There were statistically significant increases from baseline to Day 56/ET in mean \pm SD serum bicarbonate ($\Delta = 1.3 \pm 2.9$ mmol/L, $p=0.005$; $n=40$), and in mean \pm SD serum alkaline phosphatase ($\Delta = 9.5 \pm 15.7$ IU/L, $p<0.001$; $n=42$).

8.2.5.1.3. Serum creatinine

Study GD3-163-201

In the 8 week cross-over study in patients on haemodialysis, in the sevelamer carbonate ($n=73$) group the mean \pm SD serum creatinine increased from 9.06 ± 2.73 mg/dL at baseline ($n=73$) to 9.43 ± 2.72 mg/dL ($n=68$) at endpoint ($\Delta = 0.33 \pm 1.09$ mg/dL; $p=0.001$), and in the sevelamer hydrochloride group the corresponding increase was from 8.91 ± 2.74 mg/dL ($n=78$) at baseline to 9.19 ± 2.66 mg/dL ($n=71$) at endpoint ($\Delta = 0.26 \pm 1.34$ mg/dL; $p=0.008$). There was no statistically significant difference between the two treatment groups ($p=0.513$).

Study SVCARB00205

In the 4 week cross-over study in patients on haemodialysis, in the sevelamer carbonate powder group the mean \pm SD serum creatinine decreased from 11.38 ± 3.31 mg/dL at baseline (n=30) to 10.67 ± 3.13 mg/dL (n=25) at study endpoint ($\Delta = -0.86 \pm 1.47$ mg/dL; p=0.002), and in the sevelamer hydrochloride tablet group the corresponding decrease was from 11.70 ± 3.33 mg/dL (n=27) to 11.27 ± 2.98 mg/dL (n=26) ($\Delta = -0.41 \pm 1.77$ mg/dL; p=0.142). There was no statistically significant difference between the two treatment groups in mean change from baseline (p=0.388).

Study GD3-199-301

In the 24 week, parallel group study in patients on haemodialysis, in the sevelamer carbonate powder QD group (n=125) the mean \pm SD serum creatinine was similar at baseline (828 ± 246 μ mol/L) and study endpoint (833 ± 258 μ mol/L) ($\Delta = 5 \pm 126$ μ mol/L; p=0.715), and a similar result was seen for the sevelamer hydrochloride tablet TDS group (n=64) with the mean \pm SD baseline value being 864 ± 213 μ mol/L and the study endpoint value being 840 ± 235 μ mol/L ($\Delta = -24 \pm 129$ μ mol/L; p=0.078). There was no statistically significant difference between the two treatment groups in mean change from baseline (p=0.076).

Study SVCARB00105

In the single-arm sevelamer carbonate tablet TDS study in patients not on haemodialysis, there was a statistically significant increase in mean \pm SD serum creatinine from baseline to Day 56/ET (585 ± 151 μ mol/L [n=49] \rightarrow 611 ± 177 μ mol/L [n=46]; $\Delta = 27 \pm 69$ μ mol/L; p=0.005).

8.2.5.2. Haematology

8.2.5.2.1. Study GD3-163-201

In the 8 week, cross-over study in patients on haemodialysis, there were no statistically significant differences between sevelamer carbonate and sevelamer hydrochloride groups in change from Baseline for any of the haematological parameters.

8.2.5.2.2. Study SVCARB00205

In the 4 week, cross-over study in patients on haemodialysis, there were statistically significant differences between sevelamer carbonate and sevelamer hydrochloride in change from baseline for haemoglobin, monocytes, and eosinophils. However, the differences are unlikely to be clinically meaningful. There were no statistically significant differences between the two treatment groups in change from baseline for and of the other haematological parameters.

8.2.5.2.3. Study GD3-199-301

In the 24 week, parallel group study in patients on haemodialysis, except for monocytes there were no statistically significant differences between the sevelamer carbonate and sevelamer hydrochloride groups in change from baseline for any of the haematological parameters. In addition, there were no statistically significant differences between the two treatment groups in change from baseline in the clotting factors aPPT and PT.

8.2.5.2.4. Study SVCARB00105

In the single-arm sevelamer carbonate tablet TDS study in patients not on haemodialysis, there was a statistically significant decrease in mean \pm SD eosinophils from baseline to Day 56/ET ($\Delta = -0.07 \pm 0.16$ GI/L, p=0.015; n=38) and a statistically significant decrease in mean \pm SD PT from baseline to Day 56/ET ($\Delta = -0.97 \pm 3.13$ seconds, p=0.029; n=35). There were no statistically significant changes from baseline to Day 56/ET in haemoglobin, haematocrit, WBC, RBC, platelets, or basophils.

8.2.5.2.5. *Vitamin D*

- In neither the 4 week nor the 8 week cross-over studies in patients on haemodialysis were the changes in the vitamin D parameters (25-hydroxyvitamin D; 1,25 dihydroxyvitamin D) statistically significant either within or between the sevelamer treatment groups [SVCARB00205, GD3-163-201].
- In the 24 week, parallel group study [GD3-199-301], there was a statistically significant decrease from baseline in mean \pm SD 25-hydroxyvitamin D in both the sevelamer carbonate powder QD group ($\Delta = -2.5 \pm 9.22$ ng/mL, $p=0.001$; $n=125$) and the sevelamer hydrochloride tablet TDS group ($\Delta = -5.5 \pm 8.3$ ng/mL, $p<0.001$; $n=64$). There was a statistically significant difference in the change in 25-hydroxyvitamin D between the treatment groups ($p=0.041$). There was no statistically significant changes from baseline in 1,25 dihydroxyvitamin D within or between the two treatment groups.
- In the single-arm sevelamer carbonate tablet TDS study [SVCARB00105] in patients not on haemodialysis, there was statistically significant increase in mean \pm SD serum 1,25-hydroxyvitamin D from baseline to Day 56/ET ($\Delta = 12.8 \pm 35.6$ pmol/L, $p=0.026$; $p=37$), but not in serum 25-hydroxyvitamin D.

8.2.5.3. *Clinically significant laboratory abnormalities*

8.2.5.3.1. *Study GD3-163-201*

In the 8 week cross-over study in patients on haemodialysis, during the randomised treatment periods the frequency of patients experiencing AEs in the SOC 'investigations' was similar for the two treatment regimens: 19 AEs in 14 (19.2%) patients in the sevelamer carbonate group ($n=73$) and 17 AEs in 13 (16.7%) patients in the sevelamer hydrochloride group ($n=78$). In the SOC 'investigations', AEs (PT) assessed as treatment-related by the Investigators included (sevelamer carbonate versus sevelamer hydrochloride): carbon dioxide decreased (4 events in 4 [5.5%] patients versus 5 events in 4 [5.1%] patients); triglycerides increased (2 events in 2 [2.7%] patients versus 1 event in 1 [1.3%] patient); bicarbonate decreased (1 event in 1 [1.4%] patient versus 2 events in 2 [2.6%] patients); iPTH increased (1 event in 1 [1.4%] patient versus 2 events in 2 [2.6%] patients).

8.2.5.3.2. *Study SVCARB00205*

In the 4 week cross-over study in patients on haemodialysis, during the randomised treatment periods there were 4 AEs in 4 patients reported as clinically significant laboratory abnormalities in the safety set: in the sevelamer carbonate powder group-1 event of haemoglobin decreased in 1 (3.2%) patient; and in the sevelamer hydrochloride group-1 event of anaemia in 1 (3.6%) patient, 1 event of blood calcium decreased in 1 (3.6%) patient, and 1 event of hypocalcaemia in 1 (3.6%) patient.

8.2.5.3.3. *Study GD3-199-301*

In the 24 week, parallel group study, 11 (7.8%) patients in the sevelamer carbonate powder QD group experienced a clinically significant laboratory AE coded to the SOC 'investigations' compared with 12 (16.7%) patients in the sevelamer hydrochloride tablet TDS group. Treatment emergent AEs (PTs) in the SOC 'investigations' by PT assessed as treatment-related by the Investigators included iPTH increased (sevelamer carbonate powder QD in 1 [0.7%] patient; sevelamer hydrochloride tablet TDS in no [0%] patients) and carbon dioxide decreased (sevelamer carbonate powder QD in 1 [0.7%] patient; sevelamer hydrochloride tablet TDS in 2 [2.8%] patients).

8.2.5.3.4. *Study SVCARB00105*

In the single-arm sevelamer carbonate tablet TDS study in patients not on haemodialysis ($n=49$), clinically significant laboratory abnormalities were reported by the Investigators for blood triglycerides increased (1 event) and 2 events each for hypokalaemia, hyperkalaemia, and

hypocalcaemia. Only one case of hypocalcaemia was rated by the Investigators as being treatment-related.

8.2.6. Vital signs

Vital signs assessed in the 4 new studies included pulse rate (bpm), post-dialysis weight (kg), and systolic and diastolic blood pressure (mmHg). There were no statistically significant changes in vital signs within or between the sevelamer carbonate and sevelamer hydrochloride treatment groups in the three studies in patients on haemodialysis [SVCARB002005; GD3-163-201; GD3-199-301]. There were no clinically significant changes in vital signs in the single-arm, sevelamer carbonate study in patients not on haemodialysis [SVCARB00105].

8.2.7. Safety in special groups

8.2.7.1. Age

8.2.7.1.1. Study GD3-163-201

In the 8 week cross-over study in patients on haemodialysis a similar proportion of patients aged < 65 years and ≥ 65 years experienced an AE during the randomised treatment period in the sevelamer carbonate group (83.3% [45/54] versus 78.9% [15/19], respectively). Overall, there were no notable differences in the sevelamer carbonate AE profiles between the two age groups, and no differences in each group between the AE profiles of sevelamer carbonate and sevelamer hydrochloride.

In the < 65 year old group, drug-related AEs in the randomised treatment periods were reported in 13.0% (7/54) of patients (14 events) in the sevelamer carbonate group and 14.3% (8/56) of patients in the sevelamer hydrochloride group. Drug-related AEs reported in ≥ 2 patients in either of the two treatment groups were carbon dioxide increased (3, 5.6%), nausea (2, 3.7%), and vomiting (2, 3.7%) in the sevelamer carbonate group, and nausea (2, 3.6%) and carbon dioxide increased (3, 5.4%) in the sevelamer hydrochloride group.

In the ≥ 65 year old group, drug-related AEs in the randomised treatment periods were reported in 26.3% (5/19) of patients (6 events) in the sevelamer carbonate group and 31.8% (7/22) of patients (12 events) in the sevelamer hydrochloride group. All drug-related AEs (PTs) in both treatment groups were reported in 1 patient only.

A similar proportion of patients aged < 65 years and patients aged ≥ 65 years experienced SAEs during sevelamer carbonate treatment (11.1% [6/54] versus 10.5% [2/54], respectively). All SAEs were assessed by the investigator as not related to study treatment, and in both treatment regimens no SAEs occurred in more than one patient. A similar proportion of patients aged < 65 years experienced SAEs during sevelamer carbonate treatment (11.1% [6/54], 7 events) and sevelamer hydrochloride treatment (14.3% [8/56], 11 events). Nearly all SAEs experienced by patients < 65 years old occurred as single events in individual patients. Two (2) SAEs of renal transplant were experienced by 2 patients in the sevelamer carbonate group, and both events were assessed by the Investigator as being not related to study treatment.

Overall, a similar proportion of patients aged ≥ 65 years experienced SAEs in the sevelamer carbonate group (10.5% [2/19], 10 events) and the sevelamer hydrochloride group (13.6% [3/22], 6 events). Nearly all SAEs experienced by patients aged ≥ 65 years occurred as single events in individual patients. Among patients on sevelamer carbonate, 2 SAEs of pain in extremity were experienced by 1 patient. In addition, 1 patient on sevelamer carbonate experienced 5 SAEs in the SOC 'musculoskeletal and connective tissue disorders' (intervertebral disc degeneration, osteoarthritis, and osteopenia, and 2 events of pain in extremity). All SAEs were assessed by the investigator as not related to study treatment.

8.2.7.1.2. Study SVCARB00205

It is considered that no meaningful AE or SAE comparisons can be between patients aged < 65 years and ≥ 65 years due to the small total number of patients in the study (n=31) and the imbalance between the two groups (that is, < 65 years, n=25 and ≥ 65 years, n=6).

8.2.7.1.3. Study GD3-199-301

In the 24 week, parallel group study, in patients aged < 65 years AEs were reported in 88.4% (84/95) of patients (450 events) in the sevelamer carbonate powder QD group and 93.5% (43/46) of patients (277 events) in the sevelamer hydrochloride tablet TDS group. In patients aged ≥ 65 years, AEs were reported in 87.0% (40/46) of patients (273 events) in the sevelamer carbonate powder QD group and 88.5% (23/26) of patients (153 events) in the sevelamer hydrochloride tablet TDS group.

In patients aged < 65 years, drug-related AEs were reported in 32.6% (31/95) of patients (44 events) in the sevelamer carbonate powder QD group and 13.0% (6/46) of patients (11 events) in the sevelamer hydrochloride tablet TDS group. Drug-related AEs (PTs) reported in ≥ 2 patients in either of the two treatment groups were diarrhoea (8, 8.4%), nausea (8, 8.4%), oral administration complication (5, 5.3%), stomach discomfort (2, 2.1%), vomiting (2, 2.1%), and decreased appetite (2, 2.1%) in the sevelamer carbonate powder QD group, and diarrhoea (3, 6.5%) and carbon dioxide decreased (2, 4.3%) in the sevelamer hydrochloride tablet TDS group.

In patients aged ≥ 65 years, drug-related AEs were reported in 26.1% (12/46) of patients (28 events) in the sevelamer carbonate powder QD group and 26.9% (7/26) of patients (15 events) in the sevelamer hydrochloride tablet TDS group. Drug-related AEs (PTs) reported in ≥ 2 patients in either of the two treatment groups were nausea (6, 13.0%), vomiting (6, 13.0%), and diarrhoea (4, 8.7%) in the sevelamer carbonate powder QD group, and diarrhoea (3, 11.5%) and hypocalcaemia (2, 7.7%) in the sevelamer hydrochloride tablet TDS group.

In patients aged < 65 years, SAEs were reported in 16.8% (16/95) of patients (43 events) in the sevelamer carbonate powder QD group and 41.3% (19/46) of patients (49 events) in the sevelamer hydrochloride tablet TDS group. SAEs reported in ≥ 2 patients in either of the two treatment groups were hyperkalaemia (3, 3.2%), atrial flutter (2, 2.1%), congestive cardiac failure (2, 2.1%), pneumonia (2, 2.1%), staphylococcal bacteraemia (2, 2.1%), diabetic ketoacidosis (2, 2.1%) and fluid overload (2, 2.1%) in the sevelamer carbonate powder QD group, and congestive cardiac failure (2, 4.3%), coronary artery disease (2, 4.3%), AV fistula thrombosis (2, 4.3%), hyperkalaemia (2, 4.3%) and hypoglycaemia (2, 4.3%) in the sevelamer hydrochloride tablet TDS group.

In patients aged ≥ 65 years, SAEs were reported in 37.0% (17/46) of patients (42 events) in the sevelamer carbonate powder QD group and 34.6% (9/26) of patients (23 events) in the sevelamer hydrochloride tablet TDS group. SAEs reported in ≥ 2 patients in either of the two treatment groups were pneumonia (4, 8.7%), congestive cardiac failure (3, 6.5%), catheter sepsis (2, 4.3%), AV fistula thrombosis (2, 4.3%), pulmonary oedema (2, 4.3%) and hypotension (2, 4.3%) in the sevelamer carbonate powder QD group, and congestive cardiac failure (2, 7.7%) and pneumonia (2, 7.7%) in the sevelamer hydrochloride tablet TDS group.

8.2.7.2. Gender

8.2.7.2.1. Study GD3-163-201

In the 8 week cross-over study in patients on haemodialysis, in the randomised treatment periods AEs were reported in 79.5% (31/39) of males (87 events) in the sevelamer carbonate group compared with 82.5% (33/40) of males (108 events) in the sevelamer hydrochloride group, and in 85.3% (29/34) of females (108 events) in the sevelamer carbonate group compared with 84.2% (32/38) of females (118 events) in the sevelamer hydrochloride group.

Drug-related AEs were reported in 20.5% (8/39) of male patients (11 events) in the sevelamer carbonate group and 22.5% (9/40) of male patients (21 events) in the sevelamer hydrochloride group. Drug-related AEs (PTs) reported in ≥ 2 male patients in either of the two treatment groups were GORD (2, 5.0%), nausea (2, 5.0%) and carbon dioxide decreased (2, 5.0%) in the sevelamer hydrochloride group. Drug-related AEs were reported in 11.8% (4/34) of female patients (9 events) in the sevelamer carbonate group and 15.8% (6/38) of female patients (12 events) in the sevelamer hydrochloride group. The only drug-related AE (PT) reported in ≥ 2 female patients in either of the two treatment groups was carbon dioxide increased (3 [5.8%] in the sevelamer carbonate group and 2 [5.3%] in the sevelamer hydrochloride group).

SAEs were reported in 12.8% (5/39) of males (9 events) in the sevelamer carbonate group and 12.5% (5/8) of males (8 events) in the sevelamer hydrochloride group, and in 8.8% (3/34) of females (8 events) in the sevelamer carbonate group and 15.8% (6/38) of females (9 events) in the sevelamer hydrochloride group.

8.2.7.2.2. Study SVCARB00205

In the 4 week cross-over study in patients on haemodialysis, in the randomised treatment period AEs were reported in 33.3% (7/21) of male patients (14 events) in the sevelamer carbonate group and 40.0% (8/20) of male patients (16 events) in the sevelamer hydrochloride group. In female patients, AEs were reported in 30.0% (3/10), 4 events, in the sevelamer carbonate group and 37.5% (3/8), 8 events, in the sevelamer hydrochloride group.

Drug-related AEs were reported in 14.3% (3/21) of male patients (4 events) in the sevelamer carbonate group and no male patients in the sevelamer hydrochloride group. The only drug-related AE (PT) reported in ≥ 2 male patients was nausea (2, 9.5%) in the sevelamer carbonate group. There were no SAEs reported in female patients in either of the two treatment groups.

8.2.7.2.3. Study GD3-199-301

In the 24 week, parallel group study, AEs were reported in 83.9% (73/87) of male patients (400 events) in the sevelamer carbonate powder QD group and 95.2% (40/42) of male patients (223) events in the sevelamer hydrochloride tablet TDS group. In female patients, AEs were reported in 94.4% (51/54) of patients (321 events) in the sevelamer carbonate powder QD group and 86.7% (26/30) of patients (207 events) in the sevelamer hydrochloride tablet TDS group.

Drug-related AEs were reported in 26.4% (23/87) of male patients (33 events) in the sevelamer carbonate powder QD group and 16.7% (7/42) of male patients (11 events) in the sevelamer hydrochloride tablet TDS group. Drug-related AEs (PTs) reported in ≥ 2 male patients in either of the two treatment groups were diarrhoea (7, 8.0%), nausea (7, 8.0%), stomach discomfort (3, 3.4%), vomiting (3, 3.4%), abdominal distension (2, 2.3%) and oral complications (2, 2.3%) in the sevelamer carbonate powder QD group, and diarrhoea (3, 7.1%) in the sevelamer hydrochloride tablet TDS group.

Drug-related AEs were reported in 37.0% (20/54) of female patients (39 events) in the sevelamer carbonate powder QD group and 20.0% (6/30) of female patients (15 events) in the sevelamer hydrochloride tablet TDS group. Drug-related AEs (PTs) reported in ≥ 2 female patients in either of the two treatment groups were nausea (7, 13.0%), diarrhoea (5, 9.3%), vomiting (5, 9.3%), oral complications (4, 7.4%) and decreased appetite (2, 3.7%) in the sevelamer carbonate powder QD group, and constipation (4, 13.3%) and nausea (2, 6.7%) in the sevelamer hydrochloride tablet TDS group.

8.2.7.3. Race

8.2.7.3.1. Study GD3-163-201

In the 8 week, cross-over study in patients on haemodialysis, the majority of the 78 patients in the safety set were Black or African American (52, 67%) with the remainder of the patients being White (21, 27%), Other (4, 5%) or American Indian/Alaska native (1, 1%). Overall, the AE

and SAE profiles in Black/African American and Non-Black/African American patients were similar.

In Black/African Americans, AEs in the randomised treatment periods were reported in 83.7% (41/49) of patients (110 events) in the sevelamer carbonate group and 82.7% (43/52) of patients (137 events) in the sevelamer hydrochloride group. In Non-Black/African Americans, AEs in the randomised treatment periods were reported in 79.2% (19/24) of patients (85 events) in the sevelamer carbonate group and 84.6% (22/26) of patients (89 events) in the sevelamer hydrochloride group.

In the Black/African American group, AEs considered by Investigators to be related to the study drug were reported in 18.4% (9/49) of patients (10 events) in the sevelamer carbonate group and 11.5% (6/52) of patients (12 events) in the sevelamer hydrochloride group. The only treatment related AE reported in ≥ 2 patients in either of the two treatment groups in Black/African American patients was carbon dioxide decreased in 2 (4.1%) patients in the sevelamer carbonate group and 3 (5.8%) patients in the sevelamer hydrochloride group.

In the Non-Black/African American group, AEs considered by Investigators to be related to the study drug were reported in 12.5% (3/24) of patients (10 events) in the sevelamer carbonate group and 34.6% (9/26) of patients (21 events) in the sevelamer hydrochloride group. Treatment related AEs reported in ≥ 2 patients in either of the two treatment groups in Non-Black/African American patients were vomiting (2, 8.3%) and carbon dioxide decreased (2, 8.3%) in the sevelamer carbonate group and GORD (3, 11.5%), blood bicarbonate decreased (2, 7.7%), iPTH increased (2, 7.7%) and decreased appetite (2, 7.7%) in the sevelamer hydrochloride group.

In Black/African Americans, SAEs in the randomised treatment periods were reported in 10.2% (5/49) of patients (10 events) in the sevelamer carbonate group and 13.5% (7/52) of patients (10 events) in the sevelamer hydrochloride group. In Non-Black/African Americans, SAEs in the randomised treatment periods were reported in 12.5% (3/24) of patients (7 events) in the sevelamer carbonate group and 15.4% (4/26) of patients (7 events) in the sevelamer hydrochloride group. No SAEs in either of the two racial groups were assessed by the Investigators as being related to sevelamer carbonate or sevelamer hydrochloride.

8.2.7.3.2. Study SVCARB00205

It is considered that no meaningful AE or SAEs comparisons can be made based on race due to the imbalance in the small number of patients in the racial groups (that is, Caucasian 71% [22/31]; Black 10% [3/31]; Asian 19% [6/31]).

8.2.7.3.3. Study GD3-199-301

In the 24 week, parallel group study, AEs in African Americans were reported in 92.1% (70/76) of patients (356 events) in the sevelamer carbonate powder QD group and 89.7% (35/39) of patients (238 events) in the sevelamer hydrochloride tablet TDS group. AEs in non-African Americans were reported in 83.1% (54/65) of patients (367 events) in the sevelamer carbonate powder QD group and 93.9% (31/33) of patients (192 events) in the sevelamer hydrochloride tablet TDS group.

Drug-related AEs in African Americans were reported in 30.3% (23/76) of patients (34 events) in the sevelamer carbonate powder QD group and 20.5% (8/39) of patients (18 events) in the sevelamer hydrochloride tablet TDS group. Drug-related AEs (PTs) reported in ≥ 2 patients in African American patients in either of the two treatment groups were diarrhoea (6, 7.9%), oral administration complications (6, 7.9%), nausea (5, 6.6%), stomach discomfort (2, 2.6) and decreased appetite in the sevelamer carbonate powder QD group, and constipation (4, 10.3%), diarrhoea (2, 5.1%), nausea (2, 5.1%) and carbon dioxide decreased (2, 5.1%) in the sevelamer hydrochloride tablet TDS group.

Drug-related AEs in non-African Americans were reported in 30.8% (20/65) of patients (38 events) in the sevelamer carbonate powder QD group and 15.2% (5/33) of patients (8 events) in the sevelamer hydrochloride tablet TDS group. Drug-related AEs (PTs) reported in ≥ 2 patients in African American patients in either of the two treatment groups were nausea (9, 13.8%), vomiting (7, 10.8%) and diarrhoea (6, 9.2%) in the sevelamer carbonate powder QD group, and diarrhoea (2, 6.1%) and hypocalcaemia (2, 6.1%) in the sevelamer hydrochloride tablet TDS group.

SAEs in African Americans were reported in 19.7% (15/76) of patients (28 events) in the sevelamer carbonate powder QD group and 38.5% (14/39) of patients (31 events) in the sevelamer hydrochloride tablet TDS group. SAEs reported in ≥ 2 patients in African American patients in either of the two treatment groups were AV fistula thrombosis (2, 2.6%) and hyperkalaemia (2, 2.6%) in the sevelamer carbonate powder QD group, and AV fistula thrombosis (2, 5.1%) and hypertension (2, 5.1%) in the sevelamer hydrochloride tablet TDS group.

SAEs in non-African Americans were reported in 27.7% (18/65) of patients (57 events) in the sevelamer carbonate powder QD group and 39.4% (13/33) of patients (41 events) in the sevelamer hydrochloride tablet TDS group. SAEs reported in ≥ 2 patients in non-African American patients in either of the two treatment groups were pneumonia (5, 7.7%), congestive cardiac failure (4, 6.2%), pulmonary oedema (3, 4.6%), atrial fibrillation (2, 3.1%), sepsis (2, 3.1%) and hyperkalaemia (2, 3.1%) in the sevelamer carbonate powder QD group, and congestive cardiac failure (4, 12.1%), pneumonia (2, 6.1%), AV fistula thrombosis (2, 6.1%), hyperkalaemia (2, 6.1%) and hypoglycaemia (2, 6.1%) in the sevelamer hydrochloride tablet TDS group.

8.3. Supportive safety data for sevelamer carbonate from 2 studies

8.3.1. APB00108 [LEAP]

This study has been briefly outlined under Efficacy in this CER. The safety data included a comparison between placebo, Genz-644470 and sevelamer carbonate. In the Safety Set, the mean \pm SD actual active dose was 2.2 ± 0.3 g/day for the 2.4 g/day Genz-644470 group, 4.3 ± 0.8 g/day for the 4.8 g/day Genz-644470 group, 6.4 ± 1.1 g/day for the 7.2 g/day Genz-644470 group, 2.1 ± 0.4 g/day for the 2.4 g/day sevelamer carbonate group, 4.3 ± 0.9 g/day for the 4.8 g/day sevelamer carbonate group, and 6.5 ± 1.1 g/day for the 7.2 g/day sevelamer carbonate group. The median duration of treatment was 22.0 days for all treatment groups. An overview of treatment-emergent AEs in the safety set are summarised below in Table 36.

Table 36: LEAP-Overview of treatment emergent adverse events in the safety set.

	Placebo (N=50) n (%)	Genz-644470			Sevelamer Carbonate		
		2.4 g/day (N=49) n (%)	4.8 g/day (N=48) n (%)	7.2 g/day (N=50) n (%)	2.4 g/day (N=50) n (%)	4.8 g/day (N=51) n (%)	7.2 g/day (N=48) n (%)
Any Treatment-Emergent AE	18 (36.0)	18 (36.7)	22 (45.8)	27 (54.0)	27 (54.0)	26 (51.0)	26 (54.2)
Treatment-Emergent Related AEs	2 (4.0)	5 (10.2)	3 (6.3)	9 (18.0)	7 (14.0)	3 (5.9)	8 (16.7)
Treatment-Emergent Severe AEs	3 (6.0)	0 (0.0)	2 (4.2)	1 (2.0)	2 (4.0)	2 (3.9)	1 (2.1)
Treatment-Emergent SAEs	4 (8.0)	2 (4.1)	6 (12.5)	6 (12.0)	8 (16.0)	5 (9.8)	5 (10.4)
Discontinuations Due to AE	0 (0.0)	1 (2.0)	1 (2.1)	0 (0.0)	3 (6.0)	1 (2.0)	1 (2.1)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)

The treatment-emergent AEs of interest in this study relate to the placebo and the sevelamer carbonate groups. Treatment-emergent AEs (all causality) occurred more frequently in each of the three sevelamer carbonate groups than in the placebo group. No dose-response relationship for treatment-emergent AEs was seen among the three sevelamer carbonate groups. The most commonly reported treatment-emergent AEs (all causality) occurring in the sevelamer carbonate groups were 'gastrointestinal disorders' (SOC). These disorders were reported more

frequently in patients in each of the sevelamer carbonate groups than in the placebo group (14.0% [n=7], 2.4 g/day versus 21.6% [n=11], 4.8 g/day versus 22.9% [n=11], 7.2g/day versus 10.0% [n=5], placebo). Treatment-emergent AEs (PT) reported in $\geq 5\%$ of patients in the placebo and/or the sevelamer carbonate groups and more commonly in one or more of the sevelamer groups than in the placebo group were (2.4 g/day versus 4.8 g/day versus 7.2 g/day versus placebo): nausea (4.0% versus 5.9% versus 14.6% versus 4.0%); diarrhoea (2.0% versus 7.8% versus 8.3% versus 4.0%); and vomiting (2.0% versus 3.9% versus 6.3% versus 2.0%).

Treatment-related AEs occurred more frequently in each of the three sevelamer carbonate groups than in the placebo group. No dose-response relationship for treatment-related AEs was seen among the three sevelamer carbonate groups. Treatment-related 'gastrointestinal disorders' (SOC) were reported notably more frequently in the sevelamer carbonate groups than in the placebo group. There were no marked differences between the sevelamer carbonate groups and the placebo group for other treatment-related AEs. All treatment-related AEs occurring in the study were reported as mild or moderate in intensity. Treatment-related AEs (SOC or PT) occurring in ≥ 2 patients in any of the treatment groups are summarised below in Table 37.

Table 37: LEAP-Treatment-related adverse events (SOC or PT) occurring in ≥ 2 patients in any treatment group.

	Placebo (N=50)		Genz-644470						Sevelamer Carbonate					
			2.4 g/day (N=49)		4.8 g/day (N=48)		7.2 g/day (N=50)		2.4 g/day (N=50)		4.8 g/day (N=51)		7.2 g/day (N=48)	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Any AE	3	2 (4.0)	7	5 (10.2)	5	3 (6.3)	11	9 (18.0)	13	7 (14.0)	4	3 (5.9)	18	8 (16.7)
Endocrine disorders	1	1 (2.0)	0	0 (0)	0	0 (0)	1	1 (2.0)	0	0 (0)	0	0 (0)	0	0 (0)
Hyperparathyroidism secondary	1	1 (2.0)	0	0 (0)	0	0 (0)	1	1 (2.0)	0	0 (0)	0	0 (0)	0	0 (0)
Gastrointestinal disorders	0	0 (0)	4	3 (6.1)	2	1 (2.1)	7	6 (12.0)	8	5 (10.0)	3	2 (3.9)	13	5 (10.4)
Nausea	0	0 (0)	0	0 (0)	1	1 (2.1)	1	1 (2.0)	2	2 (4.0)	1	1 (2.0)	5	3 (6.3)
Diarrhoea	0	0 (0)	1	1 (2.0)	0	0 (0)	2	2 (4.0)	1	1 (2.0)	1	1 (2.0)	2	2 (4.2)
Constipation	0	0 (0)	1	1 (2.0)	0	0 (0)	1	1 (2.0)	2	2 (4.0)	1	1 (2.0)	0	0 (0)
Dyspepsia	0	0 (0)	1	1 (2.0)	0	0 (0)	1	1 (2.0)	0	0 (0)	0	0 (0)	1	1 (2.1)
Vomiting	0	0 (0)	0	0 (0)	1	1 (2.1)	0	0 (0)	1	1 (2.0)	0	0 (0)	1	1 (2.1)
Gastroesophageal reflux disease	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (2.0)	0	0 (0)	3	1 (2.1)
Metabolism and nutrition disorders	2	2 (4.0)	0	0 (0)	0	0 (0)	0	0 (0)	2	2 (4.0)	1	1 (2.0)	4	4 (8.3)
Hyperphosphataemia	1	1 (2.0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (2.0)	1	1 (2.0)	1	1 (2.1)
Decreased appetite	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (2.0)	0	0 (0)	1	1 (2.1)
Hypocalcaemia	1	1 (2.0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (2.1)
Nervous system disorders	0	0 (0)	1	1 (2.0)	2	1 (2.1)	0	0 (0)	1	1 (2.0)	0	0 (0)	0	0 (0)
Dizziness	0	0 (0)	0	0 (0)	2	1 (2.1)	0	0 (0)	1	1 (2.0)	0	0 (0)	0	0 (0)
Skin and subcutaneous tissue disorders	0	0 (0)	2	2 (4.1)	0	0 (0)	2	2 (4.0)	1	1 (2.0)	0	0 (0)	1	1 (2.1)
Pruritus	0	0 (0)	1	1 (2.0)	0	0 (0)	2	2 (4.0)	1	1 (2.0)	0	0 (0)	1	1 (2.1)

There was one treatment-emergent death reported in the study in a patient randomised to sevelamer carbonate 2.4 g/day. The patient had a significant medical history of recurrent toe cellulitis and recurrent antibiotic induced *Clostridium difficile* colitis. Recent *Clostridium difficile* treatment had been completed ten days prior to study dosing. The patient remained asymptomatic during the blinded study drug period. However, following completion of the treatment period the patient developed sudden onset of abdominal pain, septic shock, possible perforated viscus, and fatal cardiopulmonary arrest. This event was assessed as severe in intensity and was considered by the Investigator to be remotely or unlikely to be related to the study drug.

Treatment-emergent SAEs occurred more frequently in each of the sevelamer carbonate groups than in the placebo group. No dose-response relationship for treatment-emergent SAEs was seen among the three sevelamer carbonate groups. No treatment-emergent SAEs (PT) were reported in ≥ 2 patients in the sevelamer carbonate groups or in the placebo group. Treatment-emergent SAEs (SOC or PT) occurring in ≥ 2 patients in any of the treatment groups are summarised below in Table 38.

Table 38: LEAP-Treatment emergent serious adverse events (SOC or PT) occurring in ≥ 2 patients in any treatment group.

	Placebo (N=50)		Genz-644470						Sevelamer Carbonate					
			2.4 g/day (N=49)		4.8 g/day (N=48)		7.2 g/day (N=50)		2.4 g/day (N=50)		4.8 g/day (N=51)		7.2 g/day (N=48)	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Any SAE	10	4 (8.0)	2	2 (4.1)	9	6 (12.5)	7	6 (12.0)	16	8 (16.0)	14	5 (9.8)	5	5 (10.4)
Cardiac disorders	0	0 (0.0)	0	0 (0.0)	2	2 (4.2)	3	3 (6.0)	1	1 (2.0)	2	2 (3.9)	0	0 (0.0)
Coronary artery disease	0	0 (0.0)	0	0 (0.0)	1	1 (2.1)	1	1 (2.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)
Gastrointestinal disorders	3	1 (2.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	3	2 (4.0)	2	2 (3.9)	0	0 (0.0)
Colitis	1	1 (2.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)	0	0 (0.0)
General disorders and administration site conditions	1	1 (2.0)	1	1 (2.0)	0	0 (0.0)	1	1 (2.0)	1	1 (2.0)	2	2 (3.9)	0	0 (0.0)
Non-cardiac chest pain	1	1 (2.0)	1	1 (2.0)	0	0 (0.0)	1	1 (2.0)	1	1 (2.0)	1	1 (2.0)	0	0 (0.0)
Infections and infestations	1	1 (2.0)	0	0 (0.0)	3	1 (2.1)	1	1 (2.0)	6	3 (6.0)	3	2 (3.9)	2	2 (4.2)
Bacteraemia	1	1 (2.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)
Catheter bacteraemia	0	0 (0.0)	0	0 (0.0)	3	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.2)
Injury, poisoning and procedural complications	1	1 (2.0)	1	1 (2.0)	1	1 (2.1)	0	0 (0.0)	2	1 (2.0)	1	1 (2.0)	1	1 (2.1)
Procedural nausea	0	0 (0.0)	0	0 (0.0)	1	1 (2.1)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)	0	0 (0.0)
Metabolism and nutrition disorders	0	0 (0.0)	0	0 (0.0)	1	1 (2.1)	1	1 (2.0)	1	1 (2.0)	1	1 (2.0)	1	1 (2.1)
Fluid overload	0	0 (0.0)	0	0 (0.0)	1	1 (2.1)	1	1 (2.0)	0	0 (0.0)	1	1 (2.0)	1	1 (2.1)
Musculoskeletal and connective tissue disorders	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (4.0)	0	0 (0.0)	0	0 (0.0)
Nervous system disorders	2	1 (2.0)	0	0 (0.0)	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)
Pleural effusion	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)	1	1 (2.0)	0	0 (0.0)
Vascular disorders	1	1 (2.0)	0	0 (0.0)	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

No patients discontinued prematurely due to AEs in the placebo group, while 5 patients in the sevelamer carbonate groups discontinued prematurely due to AEs (3 [6.0%] in the 2.4 g/day group [1 x somnolence, unrelated to treatment; 1 x hyperphosphataemia, definitely related to treatment; 1 x upper abdominal pain, possibly related to treatment]; 1 [2.0%] in the 4.8 g/day group [1 x diarrhoea, possibly related to treatment]; 1 [2.1%] in the 7.2 g/day group [1 x hyperphosphataemia, definitely related to treatment]).

There were no clinically meaningful differences in clinical chemistry parameters, haematology parameters or vital signs among the treatment groups. In particular, there were no clinically significant differences in these measures between the placebo and the sevelamer carbonate groups.

Evaluator's Comment: Overall, the treatment-emergent AE profile of sevelamer carbonate in this study was consistent with the treatment-emergent profiles of the drug from the four studies providing the key efficacy and safety data supporting approval of sevelamer carbonate for the proposed indication described above. Most of the treatment-emergent AEs reported in all treatment groups were mild or moderate in intensity. The most frequently reported treatment-related AEs were gastrointestinal disorders, particularly nausea and diarrhoea.

8.3.2. SVCARB00606 [ASPIRE]

This study has been briefly outlined under Efficacy in this CER. There were 5 patients randomised to treatment (3 to placebo and 2 to sevelamer carbonate). Of the 5 randomised patients, 4 experienced 7 AEs (2 events in 1 patient in the sevelamer carbonate group and 5 events in 3 patients in the placebo group). The 2 treatment-emergent AEs (PT) in the 1 patient randomised to sevelamer carbonate were vomiting and nausea (both considered by the Investigator to be mild in severity and probably related to the study drug). The 5 treatment-emergent AEs (PT) in the placebo group were diarrhoea and vomiting in 1 patient (both considered by the Investigator to be moderate in intensity and definitely related to the study drug), peripheral oedema in 2 patients (both considered by the Investigator to be mild in intensity and not related to the study drug), and chronic renal failure in 1 patient (considered by the Investigator to be moderate in intensity and not related to the study drug). There were no deaths or other SAEs reported in the study.

Evaluator's Comment: It is not possible to draw meaningful safety conclusions from this study due to the small number of patients with relevant data.

8.4. Post-marketing experience

8.4.1. Post Authorisation Safety Study (PASS) [SVCARB006009]

8.4.1.1. Overview of the study

The submission included one post-marketing observational study designed to monitor the clinical use of sevelamer carbonate (Renvela®) in adult hyperphosphataemic CKD patients not on dialysis with serum phosphorous levels ≥ 1.78 mmol/L. This study was requested by the CHMP (European Medicines Agency) as a post-approval commitment by the marketing authorisation holder (Genzyme Europe BV) to assess the safety profile of sevelamer carbonate in the specified patient population in a clinical setting. The study was undertaken in 27 sites in Austria (2 sites), Germany (5 sites), Denmark (1 site), France (4 sites), the Netherlands (4 sites), Italy (8 sites) and Spain (3 sites). The first patient signed informed consent on 15 September 2010 and the last patient completed on 5 October 2012. The study report was dated 23 April 2013.

The study included patients in the EU who met the following criteria:

1. Adult CKD patients not on dialysis with serum phosphorus ≥ 1.78 mmol/L.
2. Prescribed Renvela (800 mg tablets or 2.4 g powder for oral suspension) in accordance with the Renvela SmPC.
3. Provided signed informed consent (patient or their legally authorised representative).

The patients were followed for up to 12 months or up to the time dialysis was started, whichever occurred first. The Investigators were required to assess the patients during clinical visits according to standard clinical practice. No study specific visits were defined, but data points of interest occurring between the date of consent and the end of the 12 month observation period as documented in the patient charts were collected. Nephrologists who cared for CKD patients not on dialysis were invited to include all of their eligible patients in this study.

Safety was documented and assessed by collecting reports of adverse drug reactions (ADRs). An ADR was defined as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. ADRs also included adverse clinical consequences associated with use of the product outside the terms of the SmPC or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

It was estimated that no more than 5,000 patients in the EU would be hyperphosphataemic due to CKD with serum phosphorous ≥ 1.78 mmol/L, and PASS planned to enrol 200 patients. In the clinical study with Renvela in adult hyperphosphataemic CKD patients not on dialysis with serum phosphorus ≥ 1.78 mmol/L [SVCARB00105], AEs considered by the investigator to be related to study treatment were most frequently reported for the 'gastrointestinal disorders' SOC (32.7%). If the observed incidence rate for related gastrointestinal events is 32.7%, with a sample size of 200 patients, an incidence rate $>39.2\%$ can be ruled out with 95% confidence. With a sample size of 200 patients, the smallest ADR which can be excluded with 95% confidence if no case is observed is an ADR occurring at a rate of approximately 1.5%.

8.4.1.2. Results

8.4.1.2.1. Disposition

The Safety Set included all patients who were treated with at least one dose of Renvela during the study, from the time of signing informed consent until ending study participation. A patient was considered treated if they had Renvela prescribed during the study. A total of 212 patients signed informed consent; full case report data were collected on 210 of these patients and 2 patients were lost to follow-up. Of the 210 patients treated patients, 192 (91.4%) completed the study and 18 (8.6%) discontinued prematurely. Of the 18 (8.6%) patients prematurely discontinuing, the most frequent cause was 'other' (12 patients, 5.7%), while 'wishes to withdraw' and 'lost to follow-up' were each reported as the cause in 3 (1.4%) patients. Of the 12 discontinuations due to 'other', all but one was deaths assessed as being unrelated to treatment with Renvela. Of the 192 (91.4%) patients who completed the study, 74 (35.2%) started dialysis.

8.4.1.2.2. Demographics

The mean \pm SD age of the total population (n=210) was 63.6 \pm 14.3 years (range: 19, 91), and the majority of patients were male (65.2%, n=137). Most patients (79.0%, n=166) had used a phosphate binder in the 30 days prior to signing informed consent, and sevelamer carbonate was the most frequently used phosphate binder (47.6%, n=100).

8.4.1.2.3. Extent of exposure

All patients in the Safety Set were prescribed Renvela, and most took the drug TDS (70.5%, n=148). The mean \pm SD prescribed starting dose was 3.4 \pm 1.9 g/day, and the mean \pm SD prescribed ending dose was 3.8 \pm 2.1 g/day. The mean \pm SD prescribed dose was 3.7 \pm 1.9 g/day (range: 0.8, 12 g/day). The median duration of study treatment was 312 days (range: 5, 373 days).

8.4.1.2.4. Protocol deviations

There were 7 protocol deviations in this study. Four (4) were minor protocol deviations relating to signing of the consent form and not expected to effect the scientific soundness of the study or the rights, safety or welfare of the patients. Three (3) were major protocol deviations in 3 patients: 2 patients did not meet the inclusion criteria of phosphate level of \geq 1.78 mmol/L; 1 patient was on Renagel at time of study start and changed to Renvela approximately 6 months later. The 3 patients with major protocol deviations were included in the analysis set since the objective of the study was safety and these patients had been exposed to Renvela.

8.4.1.2.5. Adverse drug reactions

Overall, there were 46 ADRs in 33 (15.7%) patients: 26 mild ADRs in 21 (10.0%) patients; 13 moderate ADRs in 9 (4.3%) patients; and 3 severe ADRs in 3 (1.4%) patients. There were 19 ADRs in 16 (7.6%) patients leading to treatment discontinuation (6 events of constipation in 6 patients, 2 events in 2 patients each for nausea, diarrhoea, abdominal pain upper, and all other events occurred in one patient each). There were no serious ADRs reported in this study. There were 12 deaths and all were reported as being unrelated to Renvela.

The most commonly reported AEs (\geq 10% of patients) occurred in the SOC of 'gastrointestinal disorders' (14.3%, n=30, 41 reactions). No other AEs grouped by SOC occurred in \geq 10% of patients. ADRs (PTs) reported in \geq 1% of patients were nausea (4.3%), constipation (3.8%), diarrhoea (1.9%), dyspepsia (1.9%), vomiting (1.4%), abdominal distension (1.0%), abdominal pain (1.0%), and upper abdominal pain (1.0%). The severe ADRs reported in 3 patients were constipation in 2 patients and vomiting in 1 patient.

ADRs were reported in 12.4% (17/137) of male patients (25 ADRs) and 21.9% (16/73) of female patients (21 ADRs). ADRs (PTs) reported in \geq 2 patients in either male or females were constipation (7, 5.1%), nausea (5, 3.6%) and dyspepsia (2, 1.5%) in males, and nausea (4, 5.5%),

diarrhoea (4, 5.5%), abdominal distension (2, 2.7%), dyspepsia (2, 2.7%) and vomiting (2, 2.7%) in females.

ADRs were reported in 9.1% (9/99) of patients aged < 65 years (12 reactions) and 21.6% (24/111) of patients aged ≥ 65 years (34 reactions). ADRs (PTs) reported in ≥ 2 patients the two age groups were abdominal distension (2, 2.0%), constipation (2, 2.0%), and nausea in patients < 65 years, and nausea (7, 6.3%), constipation (6, 5.4%), diarrhoea (4, 3.6%), dyspepsia (4, 3.6%) and vomiting (2, 1.8%) in patients aged ≥ 65 years.

8.5. Addendum to clinical overview

The submission included a document titled '*Addendum to Clinical Overview for Renewal of Renvela 800 mg Film-Coated Tablets, 1.6 g & 2.4 g Powder for Oral Suspension in the European Union*'. The objective of the Addendum was to provide consolidated safety and efficacy data for the renewal of the centralised EU marketing authorisation for Renvela (sevelamer carbonate) since its first Marketing Authorisation on 10 June 2009. The period covered by the renewal application was 10 June 2009 to 06 June 2013. The Addendum reviewed the relevant published literature relating to sevelamer carbonate in adults and children, and to the safety data from clinical studies undertaken by the Marketing Authorisation Holder [LEAP (APB00108), ASPIRE (SVCARB00606), SVCARB03808, SVCARB06009 (PASS), Registre de Dialyse Peritoneale de Langue Francais].

The Addendum noted that sevelamer carbonate 800 mg tablets are currently approved for marketing in 62 countries worldwide, and sevelamer carbonate for oral suspension is currently approved for marketing in 43 countries worldwide. On the basis of information available during the period from 10 June 2009 to 06 June 2013, no actions relating to sevelamer carbonate were taken for safety reasons by regulatory authorities or the sponsor. The estimated exposure to sevelamer carbonate tablets and powder over the reporting interval was 1,495,673 patients, corresponding to 440,489 total patient-years for sevelamer carbonate.

The Addendum noted the following safety concerns: important identified risks-intestinal obstruction/ileus and intestinal perforation; important potential risks-peritonitis in peritoneal disease patients, AV fistula site complications in haemodialysis patients, difficulty swallowing Renvela tablets, off-label use in children, drug interactions with ciprofloxacin, cyclosporin, mycophenolate mofetil, levothyroxine and tacrolimus, vitamin deficiency; and important missing information-data on use of in hyperphosphataemic patients on CKD patients on peritoneal dialysis, data on use in hyperphosphataemic CKD patients not on dialysis with serum phosphorous ≥ 1.78 mmol/L, use in pregnancy and lactation, use in hepatic impairment and immunocompromised patients.

The addendum concluded that no new nonclinical or clinical data were available which changed or resulted in a new risk-benefit evaluation from that provided 5 years previously.

8.6. Evaluator's overall conclusions of clinical safety

In the sevelamer carbonate and sevelamer hydrochloride clinical trial programs, a total of 1093 individual patients received at least one dose of sevelamer during the investigative study treatment period (that is, excluding any run-in period). A total of 900 patients received at least one dose of sevelamer hydrochloride and 294 patients received at least one dose of sevelamer carbonate, with some patients receiving both sevelamer hydrochloride and sevelamer carbonate in the cross-over studies and being counted once within each treatment group [GD3-163-201; SVCARB00205].

Of the 1093 patients individual CKD patients treated with sevelamer carbonate and/or sevelamer hydrochloride, 969 were on haemodialysis (724 patients received at least one dose of sevelamer hydrochloride; 245 patients received at least one dose of sevelamer carbonate), 97

were on peritoneal dialysis (all 97 patients received at least one dose of sevelamer hydrochloride; no patients received sevelamer carbonate), and 128 were not on dialysis (79 patients received at least one dose of sevelamer hydrochloride; 49 patients received at least one dose of sevelamer carbonate). The mean treatment duration in the studies ranged from approximately 4 to 50 weeks, and the mean actual dose of sevelamer varied across studies from 3.6 to 6.7 g/day.

The four new clinical studies presented in this submission included clinical safety data on a total of 249 adult hyperphosphataemic patients with CKD Stage 4 and 5 treated with at least one dose of sevelamer carbonate (245 patients on haemodialysis, 49 patients not on dialysis). The estimated exposure for the 294 patients was 69.4 patient-years. Of the 249 patients, 141 [Study GD3-199-301] had been treated for 24 weeks, but no patients had been treated for more than 24 weeks. The majority of the 249 patients were treated with sevelamer carbonate at a dose of > 4.8 to < 9.6 g/day.

8.6.1. CKD patients on haemodialysis-sevelamer carbonate versus sevelamer hydrochloride

In the two, cross-over equivalence studies in patients on haemodialysis involving 4 weeks treatment [SVCARB00205] and 8 weeks treatment [GD3-163-201], the safety profiles of sevelamer carbonate TDS and sevelamer hydrochloride TDS were similar. The key safety conclusions from the 8 week cross-over study [GD3-163-201] comparing sevelamer carbonate tablets TDS and sevelamer hydrochloride tablets TDS are reviewed below.

In the 8 week, cross-over study comparing sevelamer carbonate tablets TDS (n=73) and sevelamer hydrochloride tablets TDS (n=78) [GD3-163-201], most patients (82.2% and 83.3%, respectively) experienced at least one AE (all causality). Most of the AEs in both treatment groups were considered unrelated to sevelamer by the Investigators, with treatment-related events being reported in 16.4% of patients in the sevelamer carbonate tablet TDS group and 19.2% of patients in the sevelamer hydrochloride tablet TDS group.

In Study GD3-163-201, the most commonly reported AEs (all causality) reported in $\geq 5\%$ of patients in either of the two treatment groups and in decreasing order of frequency in the sevelamer carbonate tablet TDS group versus the sevelamer hydrochloride tablet TDS group were nausea (9.6% versus 12.8%), vomiting (8.2% versus 10.3%), hypercalcaemia (8.2% versus 3.8%), AV fistula site complications (6.8% versus 1.3%), cough (5.5% versus 3.8%), AV fistula site haemorrhage (5.5% versus 2.6%), carbon dioxide decreased (5.5% versus 5.1%), muscle spasms (5.5% versus 3.8%), AV-fistula thrombosis (4.1% versus 11.5%), pain in extremity (4.1% versus 7.7%), diarrhoea (2.7% versus 6.4%), GORD (1.4% versus 5.1%), and fatigue (1.4% versus 5.1%). The two most commonly reported AEs in both treatment groups were nausea and vomiting. Overall, there were no marked differences in the AE (all causality) profiles between the two sevelamer formulations.

In Study GD3-163-201, treatment-related AEs were reported in 16.4% (n=12) of patients in the sevelamer carbonate tablet TDS group and 19.2% (n=15) of patients in the sevelamer hydrochloride tablet TDS group. The most commonly reported treatment-related AEs reported in ≥ 2 patients in either of the two treatment groups and in decreasing order of frequency in the sevelamer carbonate tablet TDS group versus the sevelamer hydrochloride tablet TDS group were carbon dioxide decreased (4, 5.5% versus 4, 5.1%), nausea (2, 2.7% versus 2, 2.6%), vomiting (2, 2.7% versus 1, 1.3%), blood triglycerides increased (2, 2.7% versus 1, 1.3%), GORD (1, 1.4% versus 3, 3.8%), blood bicarbonate decreased (1, 1.4% versus 2, 2.6%) and blood iPTH increased (1, 1.4% versus 2, 2.6%). Overall, there were no marked differences in the treatment-related AE (drug-related) profiles between the two sevelamer salts.

In Study GD3-163-201, 2 patients died during the study, 1 in the sevelamer carbonate tablet TDS group (worsening of coronary artery disease) and 1 in the sevelamer hydrochloride tablet TDS group (diabetic complications following renal transplant). Both deaths were considered by

Investigators to be unrelated to treatment. Overall, SAEs were reported in 11.0% (n=8) of patients in the sevelamer carbonate group and 14.1% (n=11) of patients in the sevelamer hydrochloride group. The only SAEs reported in $\geq 2\%$ of patients in either of the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride) were coronary artery disease (2.7% versus 2.6%) and renal transplant (0% versus 2.6%). All SAEs in the randomised treatment periods were assessed by the Investigator as being unrelated to treatment.

In Study GD3-163-201, 6 (7.7%) patients discontinued treatment due to AEs in the sevelamer hydrochloride tablet TDS group compared with no patients in the sevelamer carbonate tablet TDS group. In the sevelamer hydrochloride tablet TDS group, 2 patients discontinued due to renal transplant, 1 patient discontinued due to AV fistula thrombosis and hepatic ischaemia, and 1 patient each discontinued due to allergic dermatitis, asthenia, and muscular weakness.

The safety profiles of sevelamer carbonate tablet TDS and sevelamer hydrochloride tablet TDS in the 8 week cross-over study [GD3-163-201] were not markedly different from the safety profiles of sevelamer carbonate powder TDS and sevelamer hydrochloride tablet TDS in the 4 week cross-over study [SVCARB00205]. However, AEs were reported less frequently in the 4 week compared with the 8 week study, which is likely to be a function of the shorter duration of exposure.

In the 24 week, parallel-group study in patients on haemodialysis [GD3-199-301] comparing sevelamer carbonate powder QD (n=141) with sevelamer hydrochloride tablet TDS (n=72), the total daily dose was similar in the two treatment groups (6.2 and 6.7 g, respectively), while the mean duration of treatment was approximately 4 weeks longer in the sevelamer hydrochloride tablet TDS group compared with the sevelamer carbonate powder QD group (22.1 versus 18.4 weeks; p=0.008).

In Study GD3-199-301, AEs (all causality) occurred in 87.9% of patients in the sevelamer carbonate powder QD group and 91.1% of patients in the sevelamer hydrochloride tablet TDS group. The majority of AEs in both treatment groups were considered to be unrelated to treatment, with treatment-related AEs being reported in 30.5% of patients in the sevelamer carbonate powder QD group and 18.1% of patients in the sevelamer hydrochloride tablet TDS group. The QD treatment regimen used for sevelamer carbonate powder in the 24 week, parallel-group study differs from the TDS regimen proposed by the sponsor for approval.

In Study GD3-199-301, the most commonly reported AEs (all causality) occurring in $\geq 5\%$ of patients in decreasing order of frequency in the sevelamer carbonate powder QD group versus the sevelamer hydrochloride tablet TDS group were nausea (21.3% versus 11.1%), diarrhoea (17.7% versus 18.1%), vomiting (17.0% versus 8.3%), muscle spasms (14.2% versus 5.6%), AV fistula site complication (12.8% versus 6.9%), headache (10.6% versus 11.1%), pain in extremity (8.5% versus 9.7%), urinary tract infection (7.1% versus 2.8%), upper respiratory infection (6.4% versus 6.9%), dizziness (6.4% versus 11.1%), cough (6.4% versus 5.6%), pruritus (6.4% versus 4.2%), hypotension (6.4% versus 11.1%), AV fistula thrombosis (5.7% versus 18.1%), back pain (5.7% versus 4.2%), dyspnoea (5.7% versus 6.9%), and constipation (4.3% versus 11.1%). Of note, nausea and vomiting occurred more commonly in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group. This might be a function of the QD dosing regimen in the sevelamer carbonate powder group compared with the TDS dosing regimen in the sevelamer hydrochloride group.

In Study GD3-199-301, AEs (all causality) occurring in $\geq 5\%$ of patients in the sevelamer carbonate powder QD group and $\geq 2\%$ more frequently than in the sevelamer hydrochloride tablet TDS group were nausea, vomiting, muscle spasms, AV fistula site complications, urinary tract infection, and pruritus. AEs (all causality) occurring in $\geq 5\%$ of patients in the sevelamer hydrochloride tablet TDS group and $\geq 2\%$ more frequently than in the sevelamer carbonate powder QD group were AV fistula thrombosis, constipation, dizziness, hypotension, pyrexia,

cardiac failure congestive, oedema peripheral, AV fistula site haemorrhage, abdominal pain upper, AV fistula site infection, hypocalcaemia, heart rate irregular, and arthralgia.

In Study GD3-199-301, treatment-related AEs notably occurred more frequently in patients in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group (30.5% versus 18.1%). The major difference between the two treatment groups was the two-fold greater frequency of treatment-related 'gastrointestinal disorders' (SOC) in the sevelamer carbonate powder QD group (22.7%) than in the sevelamer hydrochloride tablet TDS group (11.1%). This difference was primarily due the greater incidence of both treatment-related nausea and vomiting in the sevelamer carbonate powder QD group compared with the sevelamer hydrochloride tablet TDS group.

In Study GD3-199-301, during the 24 week treatment period there were 2 (1.4%) deaths in the sevelamer carbonate powder QD group (1 x cardiac arrest [unknown cause], 1 x withdrawal of renal replacement therapy), and 4 deaths (5.6%) in the sevelamer hydrochloride tablet TDS group (cardiac arrest [unknown cause] in 1 patient; septic shock, staphylococcal pneumonia and hypertensive cardiovascular disease in 1 patient; septicaemia in 1 patient; and intracranial bleed in 1 patient). All 6 treatment-emergent deaths in the study were assessed by the Investigators as not related to the study treatment.

In Study GD3-199-301, SAEs occurred notably less frequently in patients in the sevelamer carbonate powder QD group than in patients in the sevelamer hydrochloride tablets TDS group (23.4% versus 38.9%, respectively). SAEs reported in $\geq 2\%$ of patients in either of the two treatment groups and by decreasing order of frequency in the sevelamer carbonate powder QD group versus the sevelamer hydrochloride tablet TDS group were pneumonia (4.3% versus 4.2%), cardiac failure congestive (3.5% versus 5.6%), hyperkalaemia (2.8% versus 2.8%), atrial fibrillation (2.1% versus 1.4%), pulmonary oedema (2.1% versus 1.4%), AV fistula thrombosis (1.4% versus 5.6%), hypoglycaemia (0.7% versus 2.8%), coronary artery disease (0.7% versus 4.2%), hypertension (0.7% versus 2.8%), and AV fistula operation (0% versus 2.8%). The majority of SAEs were considered by the Investigator to be not treatment-related.

In Study GD3-199-301, discontinuations due to AEs occurred notably more frequently in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group (12.0% versus 4.2%, respectively). In the sevelamer carbonate powder QD group, 5 patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), 8 patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and 4 patients discontinued due to other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders leading to discontinuation in the sevelamer carbonate group were classified by the Investigators as treatment-related. All 4 patients in the sevelamer hydrochloride tablet TDS group who discontinued did so due to a SAE (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which were classified as treatment-related by the Investigators.

8.6.2. CKD patients not on dialysis-sevelamer carbonate

The submission included 1, single-arm Phase III study assessing the safety of sevelamer carbonate tablet TDS in hyperphosphataemic patients (n=49) not on dialysis following 8 weeks treatment [SVCARB00105]. The safety profile of sevelamer carbonate in patients not on haemodialysis was similar to the safety profile of the drug in patients on dialysis. All causality AEs occurred in 89.8% (n=44) of patients, and events reported in $\geq 10\%$ of patients were nausea (22.4%), AV fistula operation (14.3%), constipation (12.2%), diarrhoea (10.2%), vomiting (10.2%), flatulence (6.1%), oedema peripheral (6.1%), pyrexia (6.1%), lower respiratory tract infection (6.1%), headache (6.1%) and pruritus (6.1%). Treatment-related AEs occurred in 38.8% of patients, and events reported in $\geq 5\%$ of patients were nausea (32.7%), constipation (10.2%) and diarrhoea (6.1%).

In Study SVCARB00105, 1 patient died due to bronchopneumonia considered by the Investigator to be unrelated to treatment with sevelamer carbonate. SAEs were reported in 22.4% of patients, and events occurring in > 1 patient (> 2.0%) were AV fistula operation (8.2%, n=4), lower respiratory tract infection (4.1%, n=2) and fluid overload (4.1%, n=2). Treatment discontinuations due to AEs were reported in 10.2% of patients (n=5). AEs leading to discontinuation in 4 of the 5 patients were treatment-related gastrointestinal events, including nausea (2 patients), diarrhoea (2 patients), constipation (2 patients), stomach discomfort (1 patient), and vomiting (1 patient). The remaining patient discontinued due to serious pleural effusion (followed by death due to bronchopneumonia), which was assessed as not treatment-related.

In addition to the pre-authorisation Phase III study in 49 CKD patients, not on haemodialysis treated with sevelamer carbonate tablets TDS for 8 weeks [SCVCARB00105], the submission also included a post-authorisation safety study [PASS] in adult CKD patients not on dialysis with serum phosphorous levels ≥ 1.78 mmol/L. In PASS, 210 patients took Renvela for a median duration of 312 days (range: 5, 373 days), at a mean \pm SD prescribed dose of 3.7 ± 1.9 g/day (range: 0.8, 12 g/day), and 148 (70.5%) took the drug TDS. Overall, in PASS 15.7% of patients experienced ADRs and the most commonly reported events occurred in the SOC of 'gastrointestinal disorders' (14.3%). ADRs (PTs) reported in $\geq 1\%$ of patients were nausea (4.3%), constipation (3.8%), diarrhoea (1.9%), dyspepsia (1.9%), vomiting (1.4%), abdominal distension (1.0%), abdominal pain (1.0%), and upper abdominal pain (1.0%). Overall, the post-marketing ADR profile observed in PASS in patients with CKD not on dialysis was similar to the pre-marketing safety profile observed in patients in the Phase III Study SVCARB00105.

8.6.3. Other safety aspects -sevelamer carbonate

The three new studies in the submission comparing sevelamer carbonate with sevelamer hydrochloride in patients on haemodialysis showed not marked differences in mean changes in clinical laboratory parameters (haematology and clinical biochemistry) in patients treated with the two formulations [GD3-163-201, SVCARB00205, GD3-199-301]. Similarly, there were no notable differences in changes in vital signs between sevelamer carbonate and sevelamer hydrochloride in the three new comparative studies in patients on haemodialysis.

In the three new studies in the submission comparing sevelamer carbonate with sevelamer hydrochloride in patients on dialysis showed no marked difference between the two formulations based on patient age (< 65 versus ≥ 65 years), gender (male versus female), and race (non-Black/African American versus Black/African American).

8.6.4. Long-term safety-sevelamer carbonate

There were no pre-authorisation clinical study safety data in patients on haemodialysis treated with sevelamer carbonate for more than 6 months. However, data from the Renagel CER indicates that long-term safety was demonstrated in > 200 patients on haemodialysis [Study GTC-45-901; Study GTC-49-301]. In addition, the current submission included 54 week data from Study GTC-68-402 on 71 hyperphosphataemic CKD patients on haemodialysis (sevelamer hydrochloride [n=39], calcium carbonate [n=32]) showing that the long-term safety profile of sevelamer hydrochloride was consistent with the known safety profile of the formulation. In addition, the study found no detrimental effects of Renagel compared with calcium carbonate on bone turnover and mineralization.

8.6.5. Post-marketing-sevelamer carbonate

Reassurance concerning the long-term safety of sevelamer carbonate is provided by the data in the *Addendum to the Clinical Overview* noting that sevelamer carbonate 800 mg tablets are currently approved for marketing in 62 countries worldwide, and sevelamer carbonate for oral suspension is currently approved for marketing in 43 countries worldwide. On the basis of information available during the period from 10 June 2009 to 06 June 2013, no actions for safety reasons relating to sevelamer carbonate were taken in the reporting interval by

regulatory authorities or the sponsor. The estimated exposure to sevelamer carbonate tablets and powder over the reporting interval was 1,495,673 patients, corresponding to 440,489 total patient-years for sevelamer carbonate.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The submitted data have satisfactorily demonstrated the benefits of sevelamer carbonate administered TDS for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD. The data showed that the benefits of sevelamer carbonate for the proposed indication are consistent with those of sevelamer hydrochloride, the approved product. Furthermore, it is considered that the submission has satisfactorily established that the known benefits of sevelamer hydrochloride for the treatment of hyperphosphataemic patients with Stage 4 and 5 CKD can be satisfactorily extrapolated to sevelamer carbonate for the same indication.

In the two, small, short-term, cross-over studies of 4 and 8 weeks duration in hyperphosphataemic patients with CKD on haemodialysis, sevelamer carbonate was shown to be therapeutically equivalent to sevelamer carbonate based on reductions in time weighted serum phosphorous levels in the PPS [GD3-163-201; SVCARB00205]. In Study GD3-163-201, sevelamer carbonate tablet TDS was compared with sevelamer hydrochloride tablet TDS. The mean \pm SD actual sevelamer dose over the 8 week randomised treatment periods in the PPS (n=56) was 7.2 ± 3.1 g/day for both sevelamer carbonate and sevelamer hydrochloride. In Study SVCARB00205, sevelamer carbonate powder TDS was compared with sevelamer hydrochloride tablet TDS. The mean \pm SD actual doses over the 4 week randomised treatment periods in the PPS (n=21) was 7.4 ± 3.1 g/day for the sevelamer carbonate regimen and 7.5 ± 3.1 g/day for the sevelamer hydrochloride regimen. In addition, the benefits of sevelamer carbonate and sevelamer hydrochloride in the FAS were equivalent as assessed by change in lipid parameters in both studies and change in serum calcium-phosphorous product in Study SVCARB00205. However, while the two, cross-over equivalence studies support the benefits of sevelamer carbonate TDS compared with sevelamer hydrochloride TDS, the 24 week parallel group study [GD3-199-301] did not establish the non-inferiority of sevelamer carbonate powder QD compared with sevelamer hydrochloride tablet TDS. Therefore, the benefits of sevelamer carbonate tablet and powder for the proposed indication relate only to TDS regimens.

In an open-label, single-arm study in hyperphosphataemic patients with CKD not on dialysis, sevelamer carbonate tablets TDS showed a benefit in reducing serum phosphate levels from baseline over the 8 week treatment period in 46 patients in the FAS [SVCARB00105]. In this study, benefits relating to change in serum lipid levels and change in serum calcium-phosphorous product were also observed. There were no data in the submission comparing the treatment benefits of sevelamer carbonate and sevelamer hydrochloride on serum phosphorous reduction in hyperphosphataemic patients with CKD not on dialysis.

There were no data exploring the benefits of sevelamer carbonate in hyperphosphataemic patients with CKD on peritoneal dialysis. However, it is considered reasonable to extrapolate the data from Study REN-003-04 demonstrating the non-inferiority of sevelamer hydrochloride tablets TDS (n=95) to calcium carbonate (n=44), as regards reduction in serum phosphorous levels from baseline over 12 weeks treatment.

9.2. First-round assessment of risks

The submission has satisfactorily characterised the risks of sevelamer carbonate for the treatment of hyperphosphataemia in adults patients with CKD Stage 4 and 5. Furthermore it is considered that the submission has demonstrated that the known risks of sevelamer

hydrochloride for the proposed indication can be extrapolated to sevelamercarbonate. In the Clinical Overview (Module 2), the sponsor comments that the risks of sevelamer carbonate are similar to the risks of sevelamer hydrochloride, with the exception of the inherent risk hyperchloraemic acidosis with sevelamer hydrochloride.

The main risks of treatment with sevelamer carbonate relate to 'gastrointestinal' disorders. In the two, cross-over studies of 4 weeks and 8 weeks duration [SVCARB00205 and GD3-163-201, respectively], the risks of 'gastrointestinal disorders' were similar for the sevelamer carbonate TDS and sevelamer hydrochloride TDS treatment regimens. However, in the 24 week non-inferiority study [GD3-199-301], the risks of 'gastrointestinal disorders' were notably greater in the sevelamer carbonate powder QD regimen than in the sevelamer tablet TDS regimen. The increased risk is likely to be a function of the QD dosing regimen for sevelamer carbonate powder compared with the TDS dosing regimen for sevelamer hydrochloride tablets. Both sevelamer carbonate and sevelamer hydrochloride should be used with caution in patients with severe gastrointestinal motility disorders including severe constipation, active inflammatory bowel disease, or major gastrointestinal tract surgery. In addition, the hygroscopic characteristics of sevelamer carbonate (and sevelamer hydrochloride) present a risk of oesophageal and intestinal obstruction due to swelling of the drug when it comes into contact fluid in the bowel.

In the two, small, short-term, cross-over studies of 4 and 8 weeks duration in hyperphosphataemic patients with CKD on haemodialysis, the safety profiles of sevelamer carbonate and sevelamer hydrochloride were shown to be similar [SVCARB00205 and GD3-163-201, respectively]. Furthermore, the qualitative features of the safety profiles of the two formulations were similar in the two cross-over studies, but the frequency of AEs was lower in the 4 week, cross-over study than the 8 week, cross-over study.

In the 8 week, cross-over study comparing sevelamer carbonate tablets TDS (n=73) and sevelamer hydrochloride tablets TDS (n=78) [GD3-163-201], most patients (82.2% and 83.3%, respectively) experienced at least one AE (all causality). However, most of the AEs in both treatment groups were considered unrelated to sevelamer by the Investigators, with treatment-related events being reported in 16.4% of patients treated with the sevelamer carbonate tablet TDS and 19.2% of patients treated with sevelamer hydrochloride tablet TDS. The most commonly reported drug-related AEs reported in ≥ 2 patients with either of the two treatments and in decreasing order of frequency with sevelamer carbonate tablet TDS versus sevelamer hydrochloride tablet TDS treatment were carbon dioxide decreased (4, 5.5% versus 4, 5.1%), nausea (2, 2.7% versus 2, 2.6%), vomiting (2, 2.7% versus 1, 1.3%), blood triglycerides increased (2, 2.7% versus 1, 1.3%), GORD (1, 1.4% versus 3, 3.8%), blood bicarbonate decreased (1, 1.4% versus 2, 2.6% and blood iPTH increased (1, 1.4% versus 2, 2.6%). Overall, there were no marked differences in the treatment-related AE profiles between the two sevelamer formulations.

In the 24 week, parallel-group, non-inferiority study in patients on haemodialysis comparing sevelamer carbonate powder QD (n=141) with sevelamer hydrochloride tablet TDS (n=72), AEs (all causality) occurred in 87.9% and 91.1% of patients in the two treatment groups, respectively [GD3-199-301]. However, although a similar proportion of patients in both treatment groups experienced AEs (all causality), treatment-related AEs were reported notably more frequently in the sevelamer carbonate powder QD group than in the sevelamer hydrochloride tablet TDS group (30.5% versus 18.1%). The major difference between the two treatment groups was the two-fold greater frequency of 'gastrointestinal disorders' (SOC) in the sevelamer carbonate powder QD group (22.7%) than in the sevelamer hydrochloride tablet TDS group (11.1%).

In the two, cross-over equivalence studies of 4 weeks [SVCARB00205] and 8 weeks duration [GD3-199-201, and the one, 24 week non-inferiority study [GD3-199-301], sevelamer carbonate was not associated with an increased risk of death compared with sevelamer hydrochloride. In

the 8 week, cross-over equivalence study [GD3-199-201], the risks of experiencing SAEs were similar in patients in the sevelamer carbonate tablet TDS group and the sevelamer hydrochloride tablet TDS group (11.0% [n=8] versus 14.1% [n=11], respectively). The only SAEs reported in $\geq 2\%$ of patients in either of the two treatment groups (sevelamer carbonate versus sevelamer hydrochloride) were coronary artery disease (2.7% versus 2.6%) and renal transplant (0% versus 2.6%). All SAEs in the randomised treatment periods were assessed by the Investigator as being un-related to treatment with sevelamer.

In the 24 week, parallel-group, non-inferiority study [GD3-199-301], the risk of experiencing an SAE was notably lower in patients in the sevelamer carbonate powder QD group than in patients in the sevelamer hydrochloride tablets TDS group (23.4% [n=33] versus 38.9% [n=28], respectively). SAEs reported in $\geq 2\%$ of patients in either of the two treatment groups and by decreasing order of frequency in the sevelamer carbonate powder QD group versus the sevelamer hydrochloride tablet TDS group were pneumonia (4.3% versus 4.2%), cardiac failure congestive (3.5% versus 5.6%), hyperkalaemia (2.8% versus 2.8%), atrial fibrillation (2.1% versus 1.4%), pulmonary oedema (2.1% versus 1.4%), AV fistula thrombosis (1.4% versus 5.6%), hypoglycaemia (0.7% versus 2.8%), coronary artery disease (0.7% versus 4.2%), hypertension (0.7% versus 2.8%), and AV fistula operation (0% versus 2.8%). The majority of SAEs were considered by the Investigator to be un-related to treatment with sevelamer.

In the 8 week, cross-over, equivalence study [GD3-163-201], 6 (7.7%) patients discontinued treatment due to AEs in the sevelamer hydrochloride tablet TDS group compared with no patients in the sevelamer carbonate tablet TDS group. In the sevelamer hydrochloride tablet TDS group, 2 patients discontinued due to renal transplant, 1 patient discontinued due to AV fistula thrombosis and hepatic ischaemia, and 1 patient each discontinued due to allergic dermatitis, asthenia, and muscular weakness. In the 24 week, parallel-group study [GD3-199-201], the risk of discontinuation from the study due to AEs was notably greater in the sevelamer carbonate tablet TDS group (12.0% [n=17]) than in the sevelamer hydrochloride table TDS group (5.6% [n=4]). In the sevelamer carbonate powder QD group, 5 patients discontinued due to oral administration complications (bad taste of study drug, gagging when taking study drug), 8 patients discontinued due to gastrointestinal disorders (nausea, vomiting, bloatedness, diarrhoea and rectal bleeding), and 4 patients discontinued due to other events (worsening hyperphosphataemia, renal transplant, cerebrovascular accident, and central line infection). All of the oral administration complications and 7 of the 8 gastrointestinal disorders leading to discontinuation in the sevelamer carbonate group were classified as related to the study drug by the Investigators. All 4 patients in the sevelamer hydrochloride tablet TDS group who discontinued did so due to a SAE (cardiac arrest, myocardial infarction, septic shock, intracranial bleed), none of which were classified as related to the study drug by the Investigators.

There were no studies comparing the risks of sevelamer carbonate with sevelamer hydrochloride for the treatment of hyperphosphataemia in adult patients with CKD Stage 4 and 5 not on dialysis. However, in the 8 week, open-label, single-arm study [SVCARB00105] in patients with these characteristics (n=49), the safety profile of sevelamer carbonate tablets TDS was consistent with the safety profiles of this formulation observed in the controlled studies in patients with hyperphosphataemia on haemodialysis [GD3-163-201, SVCARB00205, GD3-199-301]. In addition, the safety profile in the post-marketing study [PASS] in 210 adult patients with CKD not on dialysis with serum phosphate concentrations ≥ 1.78 mmol/L treated for up to 12 months was consistent with the Phase III study [SVCARB00105].

There were no studies assessing the risks of sevelamer carbonate for the treatment hyperphosphataemia in adult patients with CKD Stage 4 and 5 on peritoneal dialysis. However, it is considered reasonable to extrapolate the safety data from the 12 week study [REN-003-04] in patients treated with sevelamer hydrochloride. The safety data from Study REN-003-04 relating to sevelamer hydrochloride were generally consistent with the known safety data for

this formulation. However, in contrast to the studies in patients on haemodialysis or not on dialysis the most frequently occurring SAE in Study REN-003-04 was peritonitis (8 events in 8 patients [8.2%] in the sevelamer hydrochloride group and 2 events in 2 [4.3%] patients in the calcium acetate group). Peritonitis is a common complication in patients on peritoneal dialysis, and it is likely that the difference in incidence of this AE between the sevelamer hydrochloride and calcium acetate groups is due to chance.

There were no long-term (> 24 weeks), safety data from pre-authorisation studies in adult patients with hyperphosphataemia and CKD Stage 4 and 5 treated with sevelamer carbonate. However, reassurance concerning the long-term safety of sevelamer carbonate for the proposed indication is provided by: (1) the long-term (> 52 weeks), clinical studies with sevelamer hydrochloride in approximately 250 hyperphosphataemic CKD patients on haemodialysis; (2) the 12-month post-authorisation study [PASS] referred to above in hyperphosphataemic CKD patients not on dialysis; (3) the 5-year post-marketing (EU) data for sevelamer carbonate (10 June 2009 to 06 June 2013) indicating that the estimated exposure to sevelamer carbonate tablets and powder over this interval was 1,495,673 patients, corresponding to 440,489 total patient-years, and that no significant regulatory and/or sponsor initiated actions relating to the safety of sevelamer carbonate have been required over this interval; and (4) satisfactory long-term safety of sevelamer hydrochloride demonstrated since its initial approval in the USA on 30 October 1998.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of sevelamer carbonate, given the proposed usage, is favourable. The benefits of sevelamer carbonate powder and tablets administered TDS in adult hyperphosphataemic patients with CKD Stage 4 and 5 have been satisfactorily established. The two cross-over studies demonstrated that sevelamer carbonate and sevelamer hydrochloride were equivalent in adult hyperphosphataemic CKD patients on haemodialysis as regards reduction of time weighted serum phosphorous concentration over 4 weeks (sevelamer carbonate powder TDS versus sevelamer hydrochloride tablets TDS) and over 8 weeks (sevelamer carbonate tablets TDS versus sevelamer hydrochloride tablets TDS). In addition, the benefits of sevelamer carbonate in the open-label, single-arm study in adult hyperphosphataemic patients with CKD not on dialysis were consistent with the benefits observed with sevelamer carbonate in the cross-over, equivalence studies in hyperphosphataemic adult CKD patients on haemodialysis. Overall, based on the in vivo therapeutic equivalence studies [GD3-163-201, SVCARB00205] and the in vitro bioequivalence study [TR-2527-07-SC] it is considered that the known benefits of sevelamer hydrochloride for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD can be extrapolated to sevelamer carbonate. The risks of sevelamer carbonate have been well characterised in the 4 new clinical efficacy and safety studies, and in the post-marketing safety sevelamer carbonate data over the 5-year interval from 10 June 2009 to 06 June 2013. It is considered that the extensive and well known safety data for sevelamer hydrochloride can be extrapolated to sevelamer carbonate.

10. First round recommendation regarding authorisation

It is recommended that sevelamer carbonate 800 mg tablets and 1.6 g and 2.4 g powder for oral solution, with trade names Renvela, Sevelamer Carbonate Winthrop, and Sevelamer Carbonate Sanofi, be approved for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.

11. Clinical questions

11.1. Efficacy

1. The submission included a final report for Study SVCARB002005 dated 19 July 2007 and an amendment to this report dated 11 January 2008. The sponsor states that the additional information had been identified by the sponsor during preparatory activities for a site inspection by the UK's Medicines and Healthcare products Regulatory Agency (MHRA). Examination of the CHMP Assessment Report for Renvela (London, 19 March 2009; Doc.Ref.: EMEA/214544/2009), accessed from the European Medicines Agency (EMA) website, indicates that routine inspection EMA GCP inspection at the sponsor site and one investigator site revealed 'critical and major issues, with regard to eligibility criteria, drug compliance, and adverse event reporting'. It appears that, in response to a list of outstanding issues raised by the inspection, the sponsor 'presented a sensitivity analysis [to the CHMP] and addressed the issue at the oral explanation'. Based on the presented data 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'. It is noted the *Addendum to the Clinical Overview* includes an observational, post-marketing safety study. Please provide the following information:
 - a. The list of outstanding issues raised by the MHRA following routine GCP inspection of the sponsor site and one investigator site.
 - b. The sponsor's response to each of the outstanding issues raised by the MHRA, including the sensitivity analysis referred to in the CHMP Assessment Report for Renvela.
 - c. Clarification of the status of the post-marketing study report provided in the addendum to the clinical overview. Was this, or any other study, undertaken to meet the requirement of the CHMP for additional post-marketing data to reinforce the safety set?
 - d. Has the CHMP raised concerns about any other studies submitted to the EU in support of the marketing approval of sevelamer carbonate? If so, please provide all details.
 - e. Have any other regulatory agencies raised concerns about any of the studies submitted to support the marketing approval of sevelamer carbonate in their country? If so, please provide all details.
 - f. The term 'sponsor site' referred to in the CHMP assessment report was Genzyme Europe BV, The Netherlands, and is assumed to be the central co-ordination point for the study. Does the term 'sponsor site' refer to the central co-ordination point for the study?
 - g. How many patients at the 'sponsor site' and the 'investigator site' gave rise to concern and what was the nature of these concerns? What was the proportion of the total patient population that gave rise to concern?
2. Please justify why Patient [information redacted] (4 major protocol deviations) from Study SVCARB002005 was not excluded from the PPS, given that one of the major protocol deviations resulted in the patient being crossed-over to sevelamer hydrochloride in Treatment Period 1 three weeks earlier than scheduled (that is, at Visit 10 rather than Visit 13). This appears to be significant, given that the treatment period was only 4 weeks in duration.
3. Was the formula used to calculate the time-weighted average serum phosphorous level in Studies GD3-163-201 and SVCARB002005 the same as that used to calculate this parameter

in Study GD3-199-301? Have the formulas used in the studies been validated? Were the formulas used to calculate the time-weighted serum phosphorous level in the sevelamer carbonate studies the same as the formulas used to calculate this parameter in the sevelamer hydrochloride studies?

4. Please provide a justification for the non-inferiority margin of 1 mg/dL for serum phosphorous used in Study GD3-199-301.
5. In Study GD3-199-301, please account for the greater proportion of patients in the sevelamer carbonate powder QD group compared with the sevelamer hydrochloride tablet TDS group discontinuing prematurely because of withdrawn consent (12.5% [18/144] versus 5.5% [4/73], respectively).
6. In Study GTC-45-204, patients who developed hyperphosphataemia (serum phosphorous > 1.61 mmol/L) were treated with sevelamer hydrochloride for 12 weeks. What proportion of the 79 treated patients had serum phosphorous levels > 1.78 mmol/L prior to treatment and what were the efficacy outcomes for these patients?

12. Second round evaluation of clinical data submitted in response to questions

12.1. Efficacy

12.1.1. Question 1

See above for more details on background to this question.

12.1.1.1. The list of outstanding issues raised by the MHRA following routine GCP inspection of the sponsor site and one investigator site.

12.1.1.1.1. Sponsor's Response:

The list of outstanding issues raised by the MHRA following routine GCP inspection of the sponsor site and one investigation site is provided in Appendix 5 [of the sponsor's s31 Response].

12.1.1.1.2. Clinical Evaluator's Comment:

Appendix 5 was a letter to Genzyme (the sponsor) from the site inspection team (on behalf of the EMA) relating to the routine GCP inspection of sites for Study SCVCARB002005. The inspected sites were an investigator site, [information redacted] (inspected 16 to 18 June 2006) and the sponsor site, Genzyme Europe [information redacted] (inspected 21 to 23 July 2008). The inspection team's letter included the team's observations and summaries of the sponsor's responses to the observations. In addition, Appendix 6 and Appendix 7 of the sponsor's s31 Response (referred to below in the sponsor's response to Question 1b) provided detailed tabulations of the inspection team's findings and Genzyme's response and proposed undertakings to prevent recurrence of the identified failures to comply with GCP.

The inspection team found numerous instances of non-compliance with GCP. In particular, the inspection team identified non-compliance with the protocol for Study SVCARB002005 in relation to patient eligibility, monitoring of compliance with study medication, and SAE recording. The inspection team was concerned that non-compliance with the protocol might have compromised the 'integrity of the statistical analysis of the PPS and the extrapolation of the conclusion to the population as a whole.'

The inspection team identified 1 critical, 3 major and several minor deviations from GCP in the conduct of the clinical study at the RLH site. The critical observation was that the RLH site was

persistently non-compliant with the study protocol and GCP. The protocol deviations identified at the RLH were of particular concern as this site contributed 13 (42%) of the 31 patients randomised to the study and 10 (48%) of the 21 patients who completed the study.

The inspection team identified 1 critical and 9 major deviations from GCP at the sponsor's site. The critical observation was that the 'trial management' allowed study sites to be persistently non-compliant with the protocol. Based on the findings from the sponsor's site the inspection team concluded that the study was not (fully) compliant with GCP.

12.1.1.2. The sponsor's response to each of the outstanding issues raised by the MHRA, including the sensitivity analysis referred to in the CHMP Assessment Report for Renvela.

12.1.1.2.1. Sponsor's Response:

The sponsor's responses to each outstanding issue raised by the MHRA during the routine GCP inspection are attached in Appendices 6 and 7 [of the sponsor's s31 Response].

Concerning the sensitivity analysis, this was discussed in responses to the CHMP List of Outstanding Issues at Day 180. This sensitivity analysis is detailed in response to question 25 in pages 3, 7, 8 and 11 of the responses to CHMP LoOI [that is, List of Outstanding Issues = LoOI] attached in Appendix 8 [of the sponsor's s31 Response].

12.1.1.2.2. Clinical Evaluator's Comment:

Appendix 6 and Appendix 7 have been examined as part of the sponsor's response to Question 1a (see immediately above).

The information in Appendix 8 relating to the sensitivity analysis has been examined. In Genzyme's response to the CHMP Day 180 List of Outstanding Issues (Clinical Aspects) provided in Appendix 8, the sponsor draws attention to the inspection team's recommendation to the EMA that 'the assessors should carefully look into the non-compliances with the protocol (especially eligibility criteria, drug compliance, adverse event reporting) and 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.'

In response to this recommendation Genzyme state that: (a) review of the nature of protocol non-compliance (that is, eligibility criteria deviations, compliance with study medication, site monitoring and SAE reporting) confirm no impact on the safety of the patients, nor on the scientific validity of Study SVCARB00205; (b) independent QA audits in December 2008 of all other recruiting sites in SVCARB00205 confirm data integrity; and (c) sensitivity analysis excluding data from the RLH site confirms the robustness of results from Study SVCARB00205.

The sponsor undertook a sensitivity analysis of the primary efficacy endpoint for Study SVCARB002005, excluding 7 patients from the RLH site who had been included in the PPS analysis. The primary efficacy endpoint for this study was serum phosphorous levels. The time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen were used in the analysis (that is, mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2). Measurements prior to Week 3 for Treatment Period 1 and prior to Week 7 for Treatment Period 2 were not carried forward for efficacy assessment. The sponsor notes that ICH E9 (Statistical Principles for Clinical Trial) states that, '[I]n some cases, it may be desirable to plan further exploration of the sensitivity of conclusions to the choice of the set of subjects analysed'.

The RLH site recruited 7 of the 21 patients in the Per Protocol Set (PPS) in SVCARB00205. The results for the PPS sensitivity analysis without the RLH were comparable to the PPS analysis with the RLH site, indicating that addition of the 7 patients from the RLH site had no detrimental effect on the protocol specified PPS analysis. The results for the ad hoc sensitivity analysis

without the RLH site and the analysis with the site in the PPS rare summarised in LoOI 25 Table 39 below.

LoOI 25 Table 39: Serum phosphorous time-weighted averages for the PPS in study SCVARB00205 with and without patients from the RLH site.

	Test Arm (sevelamer carbonate powder TID) mean \pm SD	Reference Arm (sevelamer hydrochloride tablets TID) mean \pm SD	Geometric Least Square Mean Ratio	90% CI Ratio	95% CI Ratio
Serum Phosphorus (mmol/L)					
With site (N=21)	1.6 \pm 0.5	1.7 \pm 0.4	0.95	0.87, 1.03	0.85, 1.05
Without site (N=14)	1.6 \pm 0.6	1.6 \pm 0.3	0.96	0.87, 1.07	0.85, 1.10
Serum Phosphorus (mg/dL)					
With site (N=21)	5.0 \pm 1.5	5.2 \pm 1.1	0.95	0.87, 1.03	0.85, 1.05
Without site (N=14)	4.8 \pm 1.7	4.9 \pm 1.1	0.96	0.87, 1.07	0.85, 1.09

The sponsor also conducted a sensitivity analysis of the primary efficacy endpoint for Study SVCARB00105, excluding the 9 patients from the RLH site who had been included in the primary analysis population (FAS). Study SVCARB00105 was a Phase III, multinational, multicentre, open-label dose titration study of sevelamer carbonate administered TDS in hyperphosphataemic CKD patients not on dialysis. The primary efficacy variable for this study was the change in serum phosphorous from baseline to Day 56/ET. Baseline was defined as screening (Visit 1) for patients not on phosphate binders at study entry and Day 0 (Visit 1a) for patients on phosphate binders at study entry. The total number of patients (FAS) in the primary analysis was 46 (including 9 from the RLH site). The sponsor stated that, even allowing for exclusion of the 9 patients from the RLH site from the analysis, the FAS still includes 37 evaluable patients, which exceeds the pre-specified sample size of 23 evaluable FAS patients defined in the study protocol for SVCARB00105. The results for the sensitivity analysis without the RLH site patients were comparable to the results for the analysis with the RLH site patients. The results are summarised below in LoOI 25 Table 40.

LoOI 25 Table 40: Change in serum phosphorous for the FAS in Study SVCARB00105 with and without patients from the RLH site.

Timepoint	mean \pm SD serum phosphorus, mmol/L (mg/dL)	
	Full Analysis Set (all patients) N=46	Full Analysis Set (excluding patients from The Royal London Hospital site) N=37
Pre-washout	1.72 \pm 0.26 (5.3 \pm 0.8) (n=27)	1.76 \pm 0.27 (5.4 \pm 0.8) (n=19)
Baseline	2.01 \pm 0.26 (6.2 \pm 0.8) (n=46)	2.02 \pm 0.26 (6.3 \pm 0.8) (n=37)
Day 56/ET	1.56 \pm 0.32 (4.8 \pm 1.0) (n=46)	1.56 \pm 0.33 (4.8 \pm 1.0) (n=37)
Day 70	2.10 \pm 0.42 (6.5 \pm 1.3) (n=40)	2.11 \pm 0.43 (6.5 \pm 1.3) (n=33)
Change from Pre-washout to Baseline	0.36 \pm 0.30 (1.1 \pm 0.9) p<0.001 (n=27)	0.37 \pm 0.31 (1.1 \pm 1.0) p<0.001 (n=19)
Change from Baseline to Day 56/ET	-0.45 \pm 0.34 (-1.4 \pm 1.0) p<0.001 (n=46)	-0.46 \pm 0.30 (-1.4 \pm 0.9) p<0.001 (n=37)
Change from Day 56 to Day 70	0.55 \pm 0.35 (1.7 \pm 1.1) p<0.001 (n=40)	0.55 \pm 0.36 (1.7 \pm 1.1) p<0.001 (n=33)

Note: P-values from Wilcoxon Signed Rank Test. Pre-washout is only applicable for patients taking phosphate binders at study entry.

Overall, the sponsor's response to Questions 1a and 1b have been satisfactorily addressed by the comprehensive data provided in in Appendices 5, 6, 7, and 8 of the s31 Response.

12.1.1.3. Clarification of the status of the post-marketing study report provided in the addendum to the clinical overview. Was this, or any other study, undertaken to meet the requirement of the CHMP for additional post-marketing data to reinforce the safety set?

12.1.1.3.1. Sponsor's Response:

The post-marketing report provided in the Module 2.5 addendum to the Clinical Overview refers to the completed Study SVCARB06009. This was an observational study undertaken upon request by the CHMP during the marketing authorization application as a post-approval commitment to assess in a clinical setting the safety profile of Renvela in adult hyperphosphataemic CKD patients not on dialysis with serum phosphorus ≥ 1.78 mmol/L. This study satisfied the agreed follow-up measures in Europe. No other clinical studies were requested to meet the requirement of the CHMP for additional post-marketing data to reinforce the safety set.

12.1.1.3.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.1.1.4. Has the CHMP raised concerns about any other studies submitted to the EU in support of the marketing approval of sevelamer carbonate? If so, please provide all details.

12.1.1.4.1. Sponsor's Response:

CHMP raised GCP concerns about Study SVCARB002005 and Study SVCARB00105 due to findings in a routine EMA GCP inspection. As described in response to b) above, the sensitivity analysis and agreement to conduct one further study (SVCARB06009) satisfied the CHMP concerns. There were no other follow-up measures requiring a clinical trial beyond the FUM 004 which was met through the conduct of Study SVCARB06009.

12.1.1.4.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.1.1.5. Have any other regulatory agencies raised concerns about any of the studies submitted to support the marketing approval of sevelamer carbonate in their country? If so, please provide all details.

12.1.1.5.1. Sponsor's Response:

Sevelamer carbonate has been registered in 99 countries globally. The clinical data set supporting the majority of these global registrations was based on the same clinical data set as that provided in Europe, where the initial concerns were addressed and subsequently satisfied. During the global registration process there were no applications deferred, withdrawn or rejected. The efficacy and overall safety of sevelamer carbonate have been well documented. There are more than 440,000 patient-years of experience over the 4-year period since first marketing approval with the active moiety sevelamer carbonate as 2 formulations (tablets and powder).

12.1.1.5.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.1.1.6. The term 'sponsor site' referred to in the CHMP assessment report was Genzyme Europe BV, The Netherlands, and is assumed to be the central co-ordination point for the study. Does the term 'sponsor site' refer to the central co-ordination point for the study?

12.1.1.6.1. Sponsor's Response:

SVCARB00205 CSR (Clinical Study Report) Section 6.2 describes the administrative structure of the study sponsor, Genzyme. The term 'sponsor site' referred to in the CHMP assessment report does refer to Genzyme Europe [information redacted]. This is the only Genzyme location visited as part of the CHMP inspection. Activities carried out at this location included pharmacovigilance (responsible for receiving and processing all Serious Adverse Event reports from the investigators), data management, and clinical pharmacy services (co-ordination and distribution of study drug to the sites and return and destruction of any unused study medication). The only other Genzyme location involved in the study was Genzyme Europe Research, UK which was not visited as part of the CHMP inspection. Activities carried out at the UK location include medical monitoring, study management, and site monitoring. These activities and those conducted at Genzyme Europe Research, UK together constitute the central coordinating center for the study.

12.1.1.6.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.1.1.7. How many patients at the 'sponsor site' and the 'investigator site' gave rise to concern and what was the nature of these concerns? What was the proportion of the total patient population that gave rise to concern?

12.1.1.7.1. Sponsor's Response:

There were no patients at the 'sponsor site.' As discussed above, the sponsor site conducted only administrative activities. With regard to the patients at the 'investigator site,' the findings do not always specifically apply to selected patients but rather to the overall study. Please refer to Appendix 5, 6, 7 and 8 for detailed findings and responses. There were 31 patients randomised overall and 13 at the investigative site inspected. This represents 42% of the patients randomised into Study SVCARB00205.

12.1.1.7.2. Clinical Evaluator's Comment:

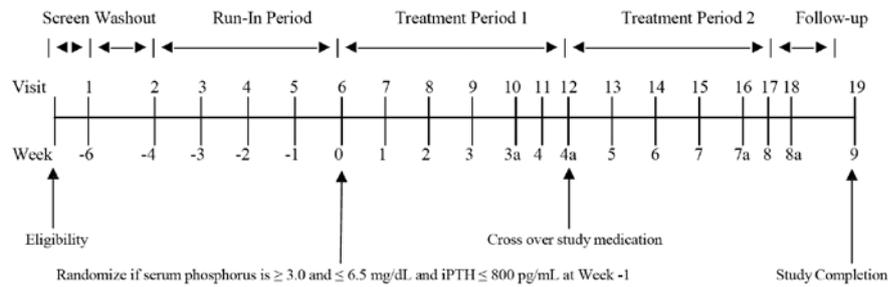
The sponsor's response is satisfactory.

12.1.2. Question 2

Please justify why Patient [information redacted] (4 major protocol deviations) from Study SVCARB00205 was not excluded from the PPS, given that one of the major protocol deviations resulted in the patient being crossed-over to sevelamer hydrochloride in Treatment Period 1 three weeks earlier than scheduled (that is, at Visit 10 rather than Visit 13). This appears to be significant, given that the treatment period was only 4 weeks in duration.

12.1.2.1. Sponsor's Response:

The primary efficacy measure is a time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and mean of non-missing assessments from Weeks 7, 7a, 8, and 8a for Treatment Period 2). See the study diagram below for reference (Figure 15).

Figure 15: SVCARB00205 Study Diagram

From SVCARB00205 CSR Listing 16.2.2.1 (Protocol Deviations) for Patient [information redacted]: 'Patient was randomised to receive Sevelamer Powder sachets on 06 April 06 for Treatment Period 1. However, on 4 May 06 (Visit 10) instead of being given more powder sachets, the patient was prescribed Renagel tablets [sevelamer hydrochloride]. Therefore the cross-over occurred 3 weeks early (instead of at Visit 13 on 27 May 06).' However, it turns out this entry is in error and that the crossover occurred 2 weeks early per the Drug Accountability Listing (Listing 16.2.5.1.3) which states the patient started sevelamer carbonate on 06 April 2006 and started sevelamer hydrochloride on 04 May 2006. Of note, the patient had an assessment on 27 April 2006 which was taken ≥ 3 weeks after starting sevelamer carbonate and this was the only value was used per protocol for the efficacy analysis. No earlier values were included.

The time-weighted average for each period was calculated using the actual study drug start and stop date for the period. For Patient [information redacted], the efficacy analysis dataset has the phosphorus time-weighted average for Period 1 = 2.3 mg/dL (0.74 mmol/L) and for Period 2 = 3.668421 mg/dL (1.17 mmol/L). [The response then included a Tabulated summary of the results for patient 0101].

12.1.2.2. *Clinical Evaluator's Comment:*

The sponsor's response is satisfactory. The provided data relating to Patient [information redacted] indicates that the result for Period 1 (sevelamer powder) was calculated from one observation taken at the end of three weeks of treatment, and that the result for Period 2 (sevelamer hydrochloride) was calculated from four observations taken after 16, 21, 29, and 32 days of treatment.

12.1.3. **Question 3**

Was the formula used to calculate the time-weighted average serum phosphorous level in studies GD3-163-201 and SVCARB00205 the same as that used to calculate this parameter in Study GD3-199-301? Have the formulas used in the studies been validated? Were the formulas used to calculate the time-weighted serum phosphorous level in the sevelamer carbonate studies the same as the formulas used to calculate this parameter in the sevelamer hydrochloride studies?

12.1.3.1. *Sponsor's Response:*

For Study GD3-199-301, the primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/final among the Per Protocol Set. This study did not use a time-weighted average serum phosphorous level, since the study treatment was titrated over time to reach goal. Rather, the last efficacy measurement on study was considered to be the most representative for efficacy.

For Study GD3-163-201, the primary efficacy measure was the time-weighted mean calculated based on the serum phosphorus measurements from the last three visits of each treatment regimen (mean of non-missing assessments from Weeks 4, 6, and 8 for Treatment Period 1 and Weeks 12, 14, and 16 for Treatment Period 2). Similarly for Study SVCARB00205, the primary

efficacy measure was the time-weighted average of the serum phosphorus assessments during the last two weeks of each treatment regimen (mean of non-missing assessments from Weeks 3, 3a, 4, and 4a for Treatment Period 1 and Weeks 7, 7a, 8, and 8a for Treatment Period 2). The time weighted mean approach provides an assessment of phosphorous control over time and is less subject to intra-patient variability than a single time point (e.g., Weeks 8 and 16 for Study GD3-163-201 and Weeks 4a and 8a for Study SVCARB00205). The time-weighted mean accounts for the difference in time between measurements and is proportional to the area under the curve (AUC) calculated using the trapezoidal rule. Studies of both sevelamer hydrochloride and sevelamer carbonate included in this dossier show that, when stopped, the effect of phosphate binders are no longer evident in serum phosphorus levels following a two-week washout. The serum phosphorus levels used for the calculation of the time weighted mean are taken more than two weeks following cessation of prior phosphate binders and, as such, are each fully representative of the effect of the treatment assigned during a given treatment interval.

The MAH is not aware of any validation of the time weighted mean or AUC approach per se, but it has been utilised in drug approvals, particularly in the studies assessing non-inferiority a generic versus a brand for regulatory approval for marketing.

12.1.3.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.1.4. Question 4

Please provide a justification for the non-inferiority margin of 1 mg/dL for serum phosphorous used in Study GD3-199-301.

12.1.4.1. Sponsor's Response:

Study GD3-199-301 was designed to show non-inferiority of sevelamer carbonate powder dose QD versus sevelamer hydrochloride dosed TDS. The primary efficacy analysis was an assessment of non-inferiority with respect to change from baseline in serum phosphorus levels at Week 24/ET among the Per Protocol Set. Specifically, a two-sided 95% confidence interval was estimated for the difference in mean serum phosphorus change between treatment groups (diff = sevelamer carbonate powder QD – sevelamer hydrochloride tablets TID). If the upper confidence bound (one sided 97.5% upper confidence bound) was less than 1 mg/dL (0.32 mmol/L), then non-inferiority was to be concluded.

The non-inferiority margin of 1 mg/dL was chosen as it was felt that a 1 mg/dL or less difference between the two treatments' effect in lowering of serum phosphorus was believed not to be clinically meaningful; however, since the Study GD3-199-301 failed to meet its primary endpoint (that is, demonstrate that sevelamer carbonate powder dosed QD is non-inferior to sevelamer hydrochloride tablet dosed TDS with respect to lowering serum phosphorus in haemodialysis patients), this study is not considered supportive of QD dosing. Study GD3-199-301 is included in our analysis of safety for the purpose of completeness. The Dosing and Administration Instructions within the proposed product label state that sevelamer carbonate tablets and powder must be taken TID.

12.1.4.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.1.5. Question 5

In Study GD3-199-301, please account for the greater proportion of patients in the sevelamer carbonate powder QD group compared with the sevelamer hydrochloride tablet TDS group discontinuing prematurely because of withdrawn consent (12.5% [18/144] versus 5.5% [4/73], respectively).

12.1.5.1. Sponsor's Response:

Sevelamer hydrochloride tablet TDS group discontinued prematurely because of withdrawn consent (12.5% [18/144] versus 2.7% [2/73], respectively). [Please see CSR Section 10.1 and CSR Table 3 for the percentage of patients who withdrew consent.] CSR Patient Data Listing 16.2.1 titled 'Discontinued Patients' lists the reason for discontinuation and includes additional detail for most cases of patient withdrawn consent. A total of 3.5 % (5/144) of sevelamer carbonate powder QD patients withdrew consent for reasons related to dislike of product taste, and a total of 2.8% (4/144) of this same group withdrew consent for reasons related to dissatisfaction with serum phosphorus levels. A total of 2.8% (4/144) of the sevelamer carbonate powder QD patients and 1.4% (1/73) of the sevelamer hydrochloride tablet TDS patients withdrew consent for reasons related to a perceived association of the study product with an adverse event. A total of 2.1% (3/144) of sevelamer carbonate powder QD patients withdrew consent with no further detail provided, and total of 1.4% (2/144) of this same group withdrew consent for other reasons (1 patient did not like bringing her study medication back to the site each visit and 1 patient felt she had too much going on in her life to start something new.)

Since Study GD3-199-301 failed to meet its primary endpoint (that is, demonstrate that sevelamer carbonate powder dosed QD is non-inferior to sevelamer hydrochloride tablet dosed TDS with respect to lowering serum phosphorus in haemodialysis patients), this study is not considered to be a pivotal study for the proposed indication. GD3-199-301 is included in our analysis of safety for the purpose of completeness. The Dosing and Administration Instructions within the proposed product label state that sevelamer carbonate tablets and powder must be taken TID.

12.1.5.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory. The data in Table 3 referred to in the sponsor's response has been re-examined. The table indicates that premature discontinuations due to withdrawn consent were reported in 12.5% (18/144) of randomised patients in the Sevelamer Carbonate Powder QD group and 2.7% (2/73) randomised patients in the Sevelamer Hydrochloride Tablet TDS group (not 5.5% [4/73] as inadvertently stated in the question).

12.1.6. Question 6

In Study GTC-45-204, patients who developed hyperphosphataemia (serum phosphorous > 1.61 mmol/L) were treated with sevelamer hydrochloride for 12 weeks. What proportion of the 79 treated patients had serum phosphorous levels > 1.78 mmol/L prior to treatment and what were the efficacy outcomes for these patients?

12.1.6.1. Sponsor's Response:

In Study GTC-45-204, there are 53/78 (68%) of the ITT patients with serum phosphorus levels >1.78 mmol/L prior to treatment and 25/78 (32%) with serum phosphorus levels ≤ 1.78 mmol/L prior to treatment. Provided in Appendix 9 are the efficacy tables [serum phosphorus, serum calcium adjusted for albumin, 24 hour urinary phosphorus excretion, calcium-phosphorus product adjusted for albumin, serum intact parathyroid hormone, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides] subsetted by patients with serum phosphorus levels >1.78 mmol/L prior to treatment, and patients with serum phosphorus levels ≤ 1.78 mmol/L prior to treatment.

The efficacy results for the subset of patients with serum phosphorus levels >1.78 mmol/L prior to treatment are the same as for the overall ITT population; the means are numerically different (for the subset, n=53 of the 78 ITT patients), but the p-values for the statistical comparisons are consistent with those obtained for the ITT population.

12.1.6.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory. Of note, in patients (n=53) with serum phosphorous levels > 1.78 mmol/L prior to treatment, the reduction in mean serum phosphorous level from Week 0 to Week 12 was 0.32 mmol/L (14.7% reduction), p<0.001, while in patients (n=25) with serum phosphorous levels ≤ 1.78 mmol/L prior to treatment, the reduction in mean serum phosphorous level from week 0 to week 12 was 0.12 mmol/L (6.7% reduction), p=0.012.

12.2. Product information**12.2.1. Question 1**

Please explain why the proposed Renvela PI includes a mixture of SI and non-SI units for biochemical parameters. It is recommended that all biochemical parameters be consistently expressed in SI units.

12.2.1.1. Sponsor's Response:

The sponsor has amended the Clinical Trials section of the Renvela PI fully in line with the recommendation of the Clinical Evaluator. Several study descriptions were incorporated into the draft AU Product Information using the US Prescribing Information as a reference, hence the mg/dL common units were used. These have been converted to the SI unit, mmol/L and revisions to the PI made accordingly.

12.2.1.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.2.2. Question 2

Pharmacodynamics (Mechanism of Action)-The last paragraph of this section in the Renagel PI has not been included in the Renvela PI. Please account for the difference between the two documents.

12.2.2.1. Sponsor's Response:

The Pharmacodynamics section of the Renvela PI has been amended and is identical to that of the Renagel PI.

12.2.2.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

12.2.3. Question 3

Adverse effects-Please explain why the information relating to treatment-related effects reported in clinical trials refers only to gastrointestinal disorders. It is considered that this section should include information on all drug-related adverse reactions (very common, common, uncommon, rare, very rare) for events (PT) grouped by SOC. It is suggested that the sponsor should format the Adverse effects section of the PI in accordance with the TGA's guidance document provided at <http://www.tga.gov.au/industry/legislation-pi-form.htm>.

12.2.3.1. Sponsor's Response

The Renvela PI document has been updated to include information on all drug-related adverse reactions for event grouped by the System Organ Class, in accordance with the TGA's guidance document.

12.2.3.2. Clinical Evaluator's Comment:

The sponsor's response is satisfactory.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the s31 responses to the clinical questions, the benefits of sevelamer carbonate administered TDS for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD are unchanged from those identified in Section 9.1

13.2. Second round assessment of risks

After consideration of the s31 responses to the clinical questions, the risks of sevelamer carbonate administered TDS for the treatment of hyperphosphataemia in adult patients with Stage 4 and 5 CKD are unchanged from those identified in Section 9.2.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of sevelamer carbonate, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

It is recommended that sevelamer carbonate 800 mg tablets and 1.6 g and 2.4 g powder for oral solution, with trade names Renvela, Sevelamer Carbonate Winthrop, and Sevelamer Carbonate Sanofi, be approved for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.

15. References

1. Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis.* 1992;19(4):303-17.
2. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int.* 2005;67(3):1179-87.
3. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol.* 2005;16(6):1788-93.
4. Johnson DW et al. KHA-CARI Guidelines: Early chronic kidney disease: Detection, prevention and management. *Nephrology.* 2013; 18:340-350.

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