European Medicines Agency
Evaluation of Medicines for Human Use

London, 30 May 2008
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WITHDRAWAL ASSESSMENT REPORT FOR Kiacta

International Nonproprietary Name:
eprodisate disodium

Procedure No. EMEA/H/C/779

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

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Neurochem Luco II SARL submitted on 30 August 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Kiacta, which was designated as an orphan medicinal product EU/3/01/051 on 31 July 2001. Kiacta was designated as an orphan medicinal product in the following indication "Treatment of Systemic Secondary Amyloidosis". The calculated prevalence of this condition was at most 1.68 per 100,000 EU population.

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

The applicant applied for the following indication treatment of amyloid A (AA) amyloidosis.

Information relating to Orphan Market Exclusivity

Not applicable

Scientific Advice:
The applicant received Scientific Advice (Protocol Assistance) from the CHMP on 11 May 2004 and on 17 February 2005. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status:
A new application (NDA) was filed in the following countries: United States of America and is currently pending.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Pierre Demolis Co-Rapporteur: Ian Hudson

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 30 August 2006.
- The procedure started on 27 September 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 December 2006.
- During the meeting on 22-24 January 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 Janaury 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 May 2007.
- The inspection report of the inspection carried out at the following site: Quintiles Canada, Inc. 100 Alexis-Nihon, suite 800 Ville St-Laurent Quebec Canada H4M 2P4 between 03/04/07 and 05/04/07 was issued on 22 May 2007.
  The inspection report of the inspection carried out at the following site: Dr. Irena Butrimiene Vilnius University Hospital, "Santariskiu Hospital", Santariskiu 2, LT-08661-Vilnius, Lithuania between 20/03/07 and 23/03/07 was issued on 15 may 2007.
  The integrated inspection report was issued on 25 May 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 14 June 2007.

- During the CHMP meeting on 16-19 July 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 September 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 22 October 2007.
- During the CHMP meeting on 15 November 2007, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 10-13 December 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Kiacta on 13 December 2007.

2 GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

Not applicable

3 SCIENTIFIC DISCUSSION

3.1 Introduction

Amyloidosis refers to a group of diseases related by extracellular deposition of insoluble fibrillar proteins (amyloid) in specific organs, which eventually leads to the failure of the involved. These amyloid deposits can remain limited to one organ (localized amyloidosis) or may be more broadly distributed (systemic amyloidosis).
Systemic amyloidosis is classified into four types based on the nature of the fibrillar deposits:
1) Amyloid "light chain" (AL) amyloidosis (formerly known as idiopathic primary amyloidosis) is caused by a plasma cell dyscrasia (i.e. monoclonal immunoglobulin light chain);
2) Amyloid A (AA) amyloidosis (formerly known as reactive or secondary amyloidosis) is caused by longstanding inflammation, with the production of a precursor serum amyloid A protein (SAA), and its subsequent cleavage into AA protein;
3) Familial amyloidosis (formerly known as familial amyloidotic polyneuropathy) is caused by various autosomal dominant hereditary point mutations of the precursor protein transthyretin (TTR); and
4) Chronic dialysis-associated amyloidosis (β2M protein, beta-2 microglobulin).

NC-503 (Kiacta) is intended for the treatment of AA amyloidosis. This rare disease is due to AA protein formed from the precursor SAA, an acute phase protein produced and secreted by hepatocytes in response to inflammation.
AA amyloidosis is associated with chronic inflammatory conditions (rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease), chronic infections (tuberculosis, osteomyelitis), and hereditary fevers (familial Mediterranean fever, Muckle-Wells syndrome). Rheumatoid arthritis is the major underlying inflammatory condition leading to AA amyloidosis in Western Europe and North America.
There are no epidemiological studies of patients with AA amyloidosis currently available. The absence of epidemiological data is indicative of the rarity of the disease and the difficulty to diagnose it.

AA amyloidosis mainly affects parenchymal organs, such as, kidneys, spleen, liver, gastrointestinal (GI) tract and adrenal glands. The most common clinical feature of AA amyloidosis is renal dysfunction manifested as nephrotic-range proteinuria and/or renal insufficiency at the time of diagnosis. It has also been estimated that approximately 5% of AA amyloidosis patients with renal insufficiency do not have proteinuria. End-stage renal disease (ESRD) is the cause of death in 40-60% of cases**.**

Gastrointestinal involvement is also frequent and is usually manifested as chronic diarrhea, body weight loss and malabsorption. Enlargement of the liver and spleen may also occur in some patients. Cardiac involvement is rare and occurs late in the disease. The median survival time from diagnosis varies from 2 to 10 years depending on the stage of the disease at time of diagnosis**.**

The renal involvement is then the dominating and most life-threatening feature of AA amyloidosis. Indeed renal failure is the major cause of death.

It is thought that treatment that suppresses the inflammation will also decrease the liver production of SAA precursor and slow the progression of AA amyloidosis. The current treatment options for patients with AA amyloidosis are limited to the control of the underlying inflammatory condition (e.g. use of immunosuppressive agents or anti-TNF-antagonist therapy in rheumatic diseases, systemic corticosteroids in Crohn's disease) or infectious condition (e.g. use of antibiotics in bronchiectasis). In AA amyloidosis associated with familial Mediterranean fever, treatment with colchicine for the periodic fevers has shown some beneficial effects**.**
However, these approaches are non-specific and not sufficiently effective in many cases. Most AA amyloidosis patients still progress from renal insufficiency to ESRD/dialysis to death, despite the use of adjunctive medications (e.g. angiotensin converting enzyme inhibitor (ACEi) and angiotensin II

receptor blocker (ARBs) given to control blood pressure, anti-inflammatory or immunosuppressive agents).

Amyloid deposits are complex structures consisting of the amyloid fibrils and several associated proteins that are always present in the deposits regardless of the type of amyloid fibril. Highly sulfated proteoglycans (e.g. heparan sulfate proteoglycan, HSPG), which are structural components of basement membranes, have been identified as common constituents of amyloid deposits in all known types of amyloidosis. Sulfated glycosaminoglycans (GAGs), as found in the basement membrane-derived HSPG, have been shown to play a role in the pathogenesis of amyloidosis. They bind to amyloidogenic proteins and mediate their deposition by enhancing the polymerization of the amyloidogenic protein into extracellular macrofibrillar aggregates. GAGs also appear to protect amyloid proteins from proteolysis while they form insoluble complexes. Sulfate ions and heparin sulfate glycosaminoglycan have been shown to enhance the polymerization of an amyloidogenic protein (e.g. Aβ) into macrofibrillar aggregates. Compounds that could compete with sulfated GAGs for the binding to the amyloidogenic protein may represent effective therapeutic agents. Large sulfated molecules such as heparan and dextran sulfate have been shown to inhibit the binding of heparan sulfate GAG to an amyloidogenic protein (e.g. Aβ) in vitro**.**

There is, at present, no approved drug for the treatment of AA amyloidosis.

About the product

NC-503 (1,3-propanedisulfonic acid disodium salt) is a low molecular weight, negatively charged sulfonated molecule that shares certain structural similarities with heparan sulfate, a sulphated glycosaminoglycan that is known to bind to amyloid protein.
It has been developed as the first therapeutic agent that can compete with sulfated glycosaminoglycans for binding to amyloidogenic proteins, and thus interfere with amyloid fibril formation and deposition.

The proposed indication of Kiacta is: *"treatment of patients with amyloid A (AA) amyloidosis"*.

3.2 Quality aspects

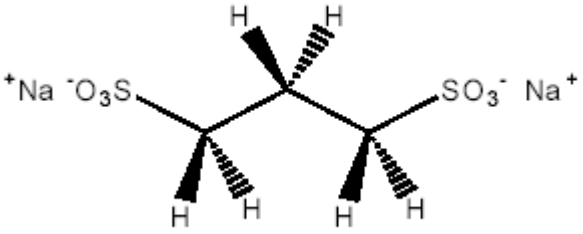
Introduction

Kiacta is presented as opaque, white hard gelatin capsules, containing 400 mg of eprodisate disodium (active substance). The excipients used in the preparation of Kiacta are well known excipients used in hard capsules preparations such as lactose monohydrate and magnesium stearate (present in the capsule content), gelatin and titanium dioxide (present in the capsule shells) and yellow iron oxide and blue dye FD&C Blue No. 1 (the green printing ink).

Kiacta 400 mg hard capsules are marked F / 400 with green ink. The capsules are packaged in HDPE bottles with HDPE/PP child resistant safety cap.

Drug Substance (to be changed in the EPAR to "Active Substance")

Eprodisate disodium is chemically designated as 1,3-propanedisulfonic acid disodium salt or disodium propane-1,3-disulfonate and has the following structure:



It is a white powder, which melts at temperatures above 350 °C. It is freely soluble in water, hydrochloric acid 0.1 N (pH 1.5), phosphate buffer (pH 6.8), and is insoluble in ethanol. Its pKa are 1.21 and 2.05. The pH of 10 mg/ml solution in water is 5.5 – 8.0.

Eprodisate disodium can exist in two pseudo-polymorphic forms (hemi-hydrate and monohydrate) which are present at relative humidity levels above 55 %. Hydrated forms revert to the anhydrous form upon drying. The moisture uptake after the exposure to relative humidity of less than 55 % is negligible. The anhydrous form will be used for the commercial formulation

- Manufacture

The manufacturing process of eprodisate disodium is a one-step chemical synthesis process followed by purification and milling. The proposed manufacturing process has been well described, and critical steps with accompanying in-process controls have been identified. Appropriate specifications for the starting materials and reagents have been established.

The manufacturing process has been optimised during the development however the general pathway, including starting materials, remained unchanged. As a result of up-scaling and optimisation of the manufacturing conditions a routine milling process was introduced in order to ensure consistency of the drug substance with respect to particle size.

The chemical structure of the drug substance has been confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. The elemental analysis data of Na, S, C, H correspond with the theoretical values. The IR, ^{1}H NMR and ^{13}C NMR spectra are in complete accord with the structure of 1,3-propanedisulfonic acid disodium salt.

The assessment of possible polymorphism has been performed using X-Ray Powder Diffraction (XRPD). The XRPD pattern exhibits resolution of reflections, indicating that the drug substance is crystalline

Moisture sorption/desorption studies demonstrated that the drug substance may contain various amounts of water when relative humidity levels exceed 55 %.

- Specification

The drug substance specification is includes tests for appearance, identification (IR, ion-exchange HPLC and XRPD), identification of sodium salt, pH, assay (ion-exchange HPLC), sodium assay (ion-exchange HPLC), impurities (ion-exchange HPLC), water content (Karl Fisher), heavy metals, residual solvents (GC), barium limit test (ICP), particle size (Laser light scattering) and bioburden.

All analytical methods have been suitably validated. It has been proven that the proposed methods are suitable to control the quality of the drug substance.

Batch analysis data have been provided 45 batches of the drug substance used in the non-clinical and clinical studies as well as for three commercial scale batches manufactured at the proposed manufacturing site. All batches complied with the requirements from the drug substance specification.

- Stability

Stability studies have been performed on 10 commercial scale batches of the drug substance. Data was provided for batches stored up to 18 months at 25 °C/60 % RH (long term stability studies) and 6 months at 40 °C/75 % RH (accelerated conditions). Additionally, data from photostability study and from the stressed degradation studies (thermal degradation, alkaline degradation and UV irradiation). Since eprodisate disodium was found to be sensitive to moisture, a study was conducted to assess the effect of packaging on the stability of the drug substance.

The stability data provided for the drug substance confirmed the proposed re-test period.

Drug Product (To be changed in the EPAR to "Medicinal Product")

- Pharmaceutical Development

No major changes have been introduced to the manufacturing process and to process parameters during the development. Optimisation of the manufacturing process mainly included changes to the batch size and process equipment capacity (up-scaling).

In early development two critical parameters that could compromise the drug product performance have been identified and investigated. In order to eliminate the impact of particle size variability on dissolution profile a milling step has been introduced to the manufacturing process. Also it has been demonstrated that content of magnesium stearate plays an important role in the finished product performance, especially when combined with large particles of drug substance. Therefore the composition of the drug formulation has been modified in order to avoid over lubrication of the capsule blend. The quantity of magnesium stearate was reduced and the amount of lactose monohydrate was increased to compensate reduction. Furthermore the drug product manufacturing process has been adjusted to assure the appropriate environmental conditions during manufacture, and eliminate the impact of humidity.

The proposed *in vitro* dissolution method is a single-point measurement which is considered suitable for immediate release dosage forms

- Adventitious Agents

Among excipients used in the drug product only lactose (ingredient of the formulation) and gelatin (component of the capsule shell) are of animal origin. Declarations from the lactose suppliers were provided, stating that the lactose was sourced from healthy animals under the same conditions as milk collected for human consumption.
For gelatin used for manufacture of capsule shells a PhEur TSE Certificates of Suitability were provided.
Magnesium stearate used in the formulation is of vegetable origin.

- Manufacture of the Product

The commercial manufacturing process of the drug product, which utilizes conventional solid dosage form manufacturing procedures and equipment, can be summarized as milling of the active substance followed by dry ingredient blending and encapsulation. The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

Process validation was carried out on three batches of commercial scale, manufactured with different drug substance batches, and showed that the capsules can be manufactured reproducibly according to the finished product specifications.

- Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identity (ion-exchange HPLC and IR), assay (ion-exchange HPLC), uniformity of dosage units, impurities (ion-exchange HPLC), dissolution, disintegration, loss on drying and bioburden.

All non pharmacopoeial methods have been satisfactorily validated.

Batch analyses data on 32 batches, including at least three of commercial scale, of the drug product have been provided and confirmed consistency of the manufacturing process. All results comply with specifications.

- Stability of the Product

Stability data for six commercial scale batches stored at 25 °C/60 % RH (long term storage conditions) up to 18 months and for three batches stored at 40 °C/75 % RH (accelerated conditions) have been provided for the drug product. In addition supportive stability data from long-term stability studies up to 48 months under normal conditions (25°C /60%RH) have been provided. All results remain within the specifications.

Based on the stability data the proposed shelf-life and storage conditions are acceptable.

The applicant has committed to place at least one commercial batch of drug product in the stability program each year, according to the approved stability protocol.

In summary the stability data provided support the proposed shelf-life and storage conditions.

Discussion on chemical, pharmaceutical and biological aspects

The drug substance and the drug product have been appropriately described and generally satisfactory documentation has been provided. The excipients used in the preparation of the drug product and manufacturing process selected are standard for capsules preparation. The results indicate that the drug substance and the drug product can be reproducibly manufactured.

3.3 Non-clinical aspects

Pharmacology

- Primary pharmacodynamics

NC-503 (Kiacta) competes with sulphated GAGs for binding to amyloidogenic proteins, thereby interfering with amyloid fibril formation and deposition. However, the mechanism of action is not yet well elucidated as it is speculative to conclude that the complex is stable enough to exist indefinitely *in vivo*.
Seven non-clinical studies have been conducted to evaluate the primary pharmacological action of NC-503 in two murine models of splenic AA amyloidosis. In these models, AA amyloidosis was induced by concomitant injections of amyloid enhancing factor (AEF) and either an irritant (AgNO3) or an antigenic inflammatory (casein) stimulus. An anti-amyloid activity was demonstrated for NC-503 but it cannot be definitively concluded that NC-503 is more potent in one model versus the other.

- Secondary pharmacodynamics and Safety pharmacology programme

The safety pharmacology battery of tests did not show any adverse effect of NC-503 on major organ systems (CNS, renal, gastrointestinal, cardiovascular and respiratory). In particular, there is no potential for prolongation of the QT interval (no detectable block of hERG channel current was observed (up to 1000 µM) and no anomalies of the cardiac action potential in isolated rabbit Purkinje fibers study.)

- Pharmacodynamic drug interactions

No animal studies have been performed.

Pharmacokinetics

Pharmacokinetic studies of Kiacta have been performed in mice, rats and dogs following both intravenous and oral dosing.

Absorption
Oral absorption of Kiacta is slow and variable within and between species. The absolute bioavailability after oral administration is 15% in the mouse, 27% to 37% in the rat and 44% to 77% in the dog. Kiacta is not taken up by red blood cells in the rat or dog, nor does it bind *in vitro* to plasma protein in humans, mice, rats, and dogs or *in vivo* to plasma protein in the rat and dog. This is in accordance with the physico-chemical properties of Kiacta and the results of the Caco-2 study which showed that Kiacta was poorly transported through the Caco-2 cell monolayers and was not considered as a substrate or an inhibitor of the P-gp efflux system.

Distribution
Volume of distribution of Kiacta is small and almost the same between rat and dog.
Protein binding and blood cells binding is negligible in any species including human and cannot have any impact on the pharmacokinetics of Kiacta.

Tissue distribution in rat showed that Cmax of radioactivity was reached faster in tissues perfused by an high blood flow; for the others, Cmax is reach only at 8 h. Radioactivity was high in prostate, but this organ seems not to be a target organ in toxicology studies. Placental transfer and excretion into milk were not studied. This is reflected in the SPC.

Metabolism
It has been shown that Kiacta is not metabolised by the rat, but there are no specific metabolic studies neither in mouse, rabbit and dog nor in human *in vivo*. The assumption that there were no metabolites in dog and human consists on the comparison between the total radioactivity and unchanged Kiacta concentration in plasma or urine, and the *in vitro* metabolic stability in human. Results *in vitro* and in urine (when samples are complete) are the most convincing. Little, if any, metabolism of Kiacta should occur.
An *in vitro* study using cloned CYP450 isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) demonstrated no inhibition by Kiacta. Another study performed with pooled human liver microsomes to evaluate the potential of Kiacta to inhibit human

cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4/5 demonstrated no biologically significant inhibition. An *in vitro* study in primary cultured human hepatocytes demonstrated no induction of CYP1A2, CYP3A4 and CYP2C9.

Elimination and excretion
Radioactivity balance in rat and dog is almost complete (94-97 % of the dose). Elimination is rapid and occurs mainly or even solely in urine through glomerular filtration and tubular excretion in rats (similarly to humans).

Toxicology

- Single dose toxicity

Kiacta presents a low level of acute toxicity in rats and dogs. The principal signs associated were diarrhea in both species at a single dose of 1250 mg/kg or above in single-dose toxicity studies.

- Repeat dose toxicity (with toxicokinetics)

The toxicity of Kiacta has been addressed in rodents (rats) and non-rodents (dogs) in studies up to 26 weeks and 39 weeks duration respectively. The maximal doses used in both species amounted to 2000 mg/kg/day.
Diarrhea was noted in both species after repeated administrations (from 1000 mg/kg/day in rats, 500 mg/kg/day in dogs).
The kidney was identified as a target organ identified in rats but not in dogs. Indeed, tubular vacuolation was observed from 500 mg/kg/day in rats. This finding was reversible in animals allowed a 4-week recovery period. Blood in urine was reported at high doses in both species. Clinical laboratory parameters of the kidney remained unchanged. Slight transitional urinary bladder hyperplasia was observed in some rats given doses from 1000 mg/kg/day in the 26-week toxicity study. In addition to kidney (tubular) vacuolation, cortical vacuolation in the adrenals of treated male rats was observed at histopathological examination. The relevance of these findings for long-term safety will be further evaluated with the results of the ongoing 2-year carcinogenicity study. The SPC should be updated accordingly (section 5.3)

- Genotoxicity

Kiacta was shown to be devoid of genotoxic potential in a standard battery of *in vitro* (Ames test, chromosomal aberration test on CHO cells) and *in vivo* (micronucleus tests in rat and mouse bone marrow) tests.

- Carcinogenicity

No increase in the incidence of tumours in a 26-week carcinogenicity study in Tg.rasH2 transgenic mouse model was reported.
A 2-year carcinogenicity study in rats was ongoing at the time of submission. The final report has been submitted towards the end of the procedure (D180) and will be subject to an evaluation for the next steps of the procedure.

- Reproduction Toxicity

In the rat fertility study, the fertility index and the conception rate of rats administered Kiacta were not significantly affected. The oral administration of Kiacta did not result in any teratogenicity or embryolethality at doses up to 1000 mg/kg/day in rats. In rabbits, reduced body weight gain, reduced feed consumption and diarrhea were observed in the high dose group administered 1000 mg/kg/day. At this maternotoxic dose level, fetal weight was decreased. These findings were not reported at the two lower dose levels (100 and 300 mg/kg/day). In the prenatal and postnatal development study, behavioural and reproductive performance (F1 adult generation) and the viability and growth of the F2 generation pups were unaffected by treatment with Kiacta up to 1000 mg/kg/day.

- Toxicokinetic data

Together, results from pharmacokinetic and toxicokinetic studies in rat and dog show that the kinetics seems to be linear (with a large variability in dog). There is no difference between male and female. Cmax and AUC are almost the same compared to those following the Day 1 toxicokinetic. There is

neither accumulation, (as expected as half-life is short) nor diminution (there is no auto-induction) of the plasma concentrations of Kiacta during repeated administration in rat and dog.
In terms of safety ratio, at the NOAEL defined in the dog, the exposure is 2.3 to 4.3-fold higher than in patients at the therapeutic dose but widely depending on the patient's creatinine clearance. Without defined NOAEL in the rat (kidney findings), no safety margin may be identified in this species.

- Other toxicity studies

Ecotoxicity/environmental risk assessment
In the phase I environmental risk assessment, the $PEC_{Surfacewater}$ calculated for Kiacta based on default Fpen was 0.2µg/L which exceeded the action limit of 0.01 µg/L. However, taking into consideration the published data on the prevalence of this orphan disease (less than 2/10000), the refined PEC value is below the action limit. Furthermore as the product is unlikely to accumulate ($logK_{ow} = -3.5$), the CHMP considered that Kiacta does not represent a risk for the environment.

Discussion on the non-clinical aspects

Kiacta competes with sulphated GAGs for binding to amyloidogenic proteins, thereby interfering with amyloid fibril formation and deposition. In animal models of inflammation (irritant or antigenic stimulus), an anti-amyloid activity was demonstrated for Kiacta but it cannot be definitively concluded if Kiacta is more potent in one model versus the other.

Oral absorption of Kiacta is slow and variable within and between species. In rats and dogs the elimination is rapid and almost complete (94-97 % of the dose), occurring mainly or even solely in urine. There seems to be little, if any, metabolism of Kiacta. *In vitro* studies did not show any inhibition or induction of CYP450 major isoforms.

The kidney was identified as a target organ of toxicity in rats but not in dogs. Transitional urinary bladder hyperplasia was also observed in rats at high dose after 26 weeks treatment.
Kiacta is devoid of genotoxic potential in vitro and in vivo models. Cortical vacuolation in the adrenals of treated male rats was observed at histopathological examination in 28-day and 26-week studies. The relevance of these findings for long-term safety will be further evaluated with the results of the ongoing 2-year carcinogenicity study. The SPC would have to be updated accordingly (section 5.3)

No increase in the incidence of tumours in a 26-week carcinogenicity study in Tg.rasH2 transgenic mouse model was reported. A 2-year carcinogenicity study in rats was ongoing at the time of submission will be subject to an evaluation for the next steps of the procedure.
No significant effects were observed in reproduction toxicology.
In toxicokinetics, the safety ratio (exposure) at the NOAEL defined in the dog, is approximately 2 to 4-fold higher than in patients at the therapeutic dose, but widely depending on the patient's creatinine clearance.
Kiacta is not considered to represent a risk for the environment.

3.4 Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. However following a GCP inspection request adopted by the CHMP, there are inspection findings in relation to an unscheduled interim analysis and the lack of documentation of when the decision to perform Cox proportional hazards test was made. These issues remain unresolved.

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

Pharmacokinetics
Four clinical pharmacology studies in 80 healthy volunteers and 16 AA amyloidosis patients, and one Population Pharmacokinetic Analysis have been conducted to characterize the clinical pharmacokinetics of eprodisate:

- **Study CL- 503001**: single centre, phase I, double blind, randomized, placebo controlled study to investigate the safety, tolerability, pharmacokinetic profile and the effect of food on single rising oral doses of NC-503 when given to healthy male adult volunteers.
- **Study CL-503003 :** single Centre, Phase I, Double-Blind, Randomized, Placebo-Controlled Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Multiple Rising Oral Doses of NC-503 when Given to Healthy Male Adult Volunteers.
- **Study CL-503007:** A Phase I Study to Investigate the Absorption, Metabolism and Excretion of 14C-NC-503 following a Single Oral Administration (800 mg) to Healthy Male Volunteers.
- **Study CL-503006:** A Single Centre, Phase I, Open-Label Study to Compare the Safety and Pharmacokinetic Profile of A Single Oral Dose of NC-503 (800 mg) in Patients with Impaired Renal Function and Healthy Volunteers.
- **Pivotal study CL-5003004 :** population pharmacokinetic analysis

Methods

Plasma and urine concentrations of eprodisate and 2-hydroxyeprodisate were determined by HPLC methods. The lower limits of detection were 50 ng/ml for plasma and 1 or 2.94 µg/ml for urine. All the bio-analytical methods were properly validated and met the usual acceptance criteria.

Conventional non-compartmental and population pharmacokinetic analyses of NC-503 in AA amyloidosis patients and identification/quantification of covariate effects on the population pharmacokinetic parameters were used in all studies.
The population pharmacokinetic analysis used a non linear mixed effect modelling approach (NONMEM® version V level 1.1). During the initial model development, the first order (FO) method was used until the model stability was sufficiently good to allow the first order conditional estimation (FOCE) to converge. Eprodisate concentration data were modelled using a two-compartment open model with first absorption and first elimination from the central compartment. Most of the results were expressed as arithmetic means ± standard deviations (sd) or as geometric means with coefficient of variations.

Results

- Absorption

Because no intravenous formulation was developed, the absolute oral bioavailability of the oral formulation was not determined. Eprodisate did not appear to be a substrate of Pgp. In fed conditions, the mean T_{max} values was delayed from 0.5 to 2.25 h and the mean AUC and C_{max} values were approximately 2.8 fold and 11 fold lower. The results are summarised in the table below:

Table: Pharmacokinetic parameters of eprodisate under fasted and fed conditions after oral administration of single dose of 1600 mg to healthy male volunteers (CL503001)

Dose	Cmax (ng/mL)	Tmax (h)	AUCo-tlast (ng.h/mL)	AUC∞* (ng.h/mL)	T½* (h)
1600 mg (fasted) (n = 8)	6455 (2764)	0.5 (0.25-0.5)	11546 (3119)	12807 (-)	12.2 (-)
1600 mg (fed) (n = 8)	563 (349)	2.25 (0.5-4)	4014 (624)	6320 (2474)	17.7 (116)

Values are mean with the SD in parentheses except for Tmax for which the median is presented with the range in parentheses.
*Parameters derived only for subjects for whom the eliminetaion rate could be estimated
(-) : No standard deviation could be calculated since n=1

- Distribution

Owing to the lack of intravenous formulation, the apparent volume of distribution was not determined. Eprodisate was not found to be bound to plasma protein nor distributed into red blood cells.

- Elimination

A mass balance study showed that 89% and 7% of 14C labelled eprodisate oral dose was recovered in feces and urine respectively (total 96%). 6.5% of the dose were excreted unchanged in urine. The renal clearance ranged between 238 and 330 ml/min across studies. These values all together with the absence of protein binding suggested that eprodisate was actively secreted. Eprodisate was not found to be metabolised by CYP nor subjected to sulfation or glucuronidation. Eprodisate plasma concentrations declined in a multiexponential manner with a mean terminal half-life ranging between 15.7 and 25.7 h.

- Dose and time dependency

Although the dose proportionality could not be clearly demonstrated due to a large between subject variability, there was evidence of non linear pharmacokinetics. Steady state was achieved by 3 to 4 days. The pharmacokinetics of eprodisate was not shown to be time dependent.

- Variability

The interindividual variability was high for Cmax (CV up to 90%) and AUC (CV up to 70%). The intraindividual variability is unknown.

- Target population

A population pharmacokinetic analysis of eprodisate dosed to treat patients suffering from secondary amyloidosis during the conduct of phase 2/3 studies was conducted. The effect of two covariates were identified i.e the effect of creatinine clearance on eprodisate clearance and the effect of dose on bioavailability (30% decrease from 400mg bid to 1200mg bid) .

- Special populations

In subjects with renal impairment, the AUC values showed a 3 fold increase in the mild and moderate renal impairment groups and a 9 fold increase in the severe renal impairment group. In all groups there was a 2 to 3 fold increase in Cmax values. The effect of end stage renal disease managed by dialysis is not documented.

Since eprodisate is primarily excreted unchanged by renal route, the effect of impaired hepatic function was not investigated.

The effects of gender, race, weight were not studied. No pharmacokinetic studies were conducted in elderly subjects and in pediatric population.

An important issue remains: the dose reductions in renal impairment recommended in the SPC do not ensure similar patient exposures across all grades of renal function. Indeed, the proposal of a dose reduction in renal impairment subjects should not be based on population PK analysis since the applicant seems to be unable to separate out the effect of dose and the effects on the renal function. A conventional PK study should be more appropriate to determine the posology to be administered in subjects with renal impairment.

- Pharmacokinetic interaction studies

In vitro studies have shown that NC-503 is not bound to plasma protein nor does it interact with P-glycoprotein. There was no metabolism of NC-503 when incubated with pooled human hepatocytes and NC-503 did not inhibit nine human CYP450 isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). This was further examined using pooled human liver microsomes and results demonstrated that there was no biologically significant inhibition of NC-503. However, the treatment of human hepatocytes with NC-503 resulted in a suppression of CYP3A4 activity by approximately 30-50%. The CYP3A4 activity inhibition may be associated with a repression of CYP3A4 gene expression or an inactivation/mechanism-based inhibition of the CYP3A4 enzyme. No formal drug-drug interaction studies between NC-503 and other drugs known to be metabolized by the P450 3A4 (CYP3A4) isoenzyme have yet been conducted.

The induction of CYP2C by eprodisate has not been studied.

Kiacta is eliminated by the kidneys unchanged. Active secretion is involved in the renal elimination of Kiacta suggesting that Kiacta and other drugs that are renally secreted may interact.
In the clinical Phase II/III study in patients with AA amyloidosis, there was no apparent effect of methotrexate or furosemide (two renally secreted drugs) on the clearance of Kiacta in the population PK analysis. However, since no specific pharmacokinetic drug interaction studies have been conducted, care should be exercised when Kiacta and other renally secreted drugs are administered

As a commitment, the applicant would undertake to conduct drug-drug interaction studies in healthy volunteers to assess the potential for eprodisate to interfere with the excretion of drugs known to be actively secreted in the renal tubules as well as the potential for these drugs to interfere with the excretion of eprodisate.

There was no clinical evidence of any drug-drug interactions occurring between Kiacta and the common concomitant medications/drug classes in this population (corticosteroids, immunosuppressive agents, colchicine, methotrexate, anti-inflammatory and antirheumatic products, diuretics and ACEi.

Pharmacodynamics

The pharmacodynamic effects of Kiacta have not been assessed, nor in the clinical pharmacology studies nor in efficacy studies.

- Mechanism of action

Kiacta is a low molecular weight, highly charged sulfonated molecule that was specifically designed to compete with the naturally occurring sulfated glycosaminoglycans (GAG) for the binding to amyloidogenic precursor proteins, and inhibits amyloid deposition into tissues. Sulfated GAG, as found in heparan sulfate proteoglycans (HSPG), have been shown to play a crucial role in the pathophysiology of amyloidosis. By blocking the GAG binding site on the amyloid precursor protein, Kiacta would prevent the sulfated GAG/amyloidogenic protein interaction, resulting in an inhibition of amyloid deposition into the tissues

- Primary and Secondary pharmacology

There is no pharmacology studies have been performed in humans. PD data have been extrapolated from animal data

- Relationship between plasma concentration and effect

The anti-amyloid activity of eprodisate has been demonstrated in two different animal models of murine splenic AA amyloidosis. Both models differ from the human AA disease in that they are acute models generating much higher SAA levels (over 1000-fold) and inducing much more rapid amyloid deposition (days versus years).Therefore, a much lower effective dose of Kiacta could be anticipated for the treatment of AA amyloidosis in patients.

When correlating eprodisate anti-amyloid activity with the drug plasma levels in the amyloidotic mice, it was found that significant effects were obtained when eprodisate plasma levels were maintained above a threshold level of 8.8 µg/mL. Considering that SAA levels in amyloidotic mice is 1000 times higher than that seen in AA patients, the company hypothesized that a plasma concentration of 0.0088 µg/mL would be required to show equivalent efficacy in AA patients.

Clinical efficacy

- Dose response studies

No dose response study was performed. The rationale for dose selection was explained by the applicant during the first protocol assistance in 2004 (EMEA/CHMP/SAWG/18/04/Final).

The proposed dose was selected based on the following criteria:

- To obtain an average steady state plasma concentration (Css) in AA patients that is 50-100 times higher than the anticipated effective plasma concentration derived from animal studies
- To obtain an animal/man safety margin that is between 5 to 10
- Results from phase I study 5003006, which was performed in only 24 patients (6 healthy volunteers and 16 with renal impairment). In this phase I study, it was shown that the systemic exposure to Kiacta (characterized by AUC) was approximately 3-fold greater in subjects with mild to moderate renal impairment and approximately 9-fold greater in those with severe renal impairment as compared to healthy subjects.
  As a result, the daily doses of Kiacta chosen in the Phase II/III study (CL-503004) were based upon patient's creatinine clearance to maintain a comparable drug systemic exposure in patients with varying degrees of renal impairment:
  - Patients with CrCl >80 mL/min received 1200 mg BID;
  - if CrCl was ≥ 30 to 80 mL/min, the patient received 800 mg BID;
  - if CrCl was ≥ 20 to < 30 mL/min, the patient received 400 mg BID.

The animal to man safety margin of Kiacta was established using the relative exposure in the toxicology species at the no-observed adverse effect level (NOAEL) to that in man (i.e. animal/man AUC ratio) obtained from Phase I (study 5003006). The proposed doses for Phase II/III study (400 mg to 1200 mg BID) showed animal/man AUC ratios of 5 to 9.

The difficulties of a comprehensive development programme in this population are accepted, and the use of the mouse minimal effective dose to estimate an approximate human minimal effective dose is a useful starting point. It is however uncertain how precisely any extrapolation can be made from a murine model to man. Reductions in splenic amyloid burden (versus placebo) of up to 80% were reported with Kiacta in murine models.
Comparable human quantitative data regarding amyloid deposition, which may have provided greater reassurance as to where on the hypothetical dose response curve clinical doses lie, could not be obtained during the clinical programme.

The proposed doses resulted in a difference of 13.4% of worse events in Kiacta group as compared with placebo in the pivotal study CL-503004 (i.e less than the expected difference of 20%). Therefore, it can not be excluded that higher Kiacta doses might have been more efficacious.

The Applicant did not provide evidence that a near optimal dose has been established in humans but proposes to explore a higher dose as a post-marketing study.

This would be accepted if the product was considered as approvable. However, requested sensitivity analysis do not confirm the original findings of the primary efficacy endpoint and the CHMP considers that the benefit risk of this product is negative at present. (See below)

- Main study

One pivotal study (CL-5003004) has been performed:
"A Phase II/III Study of the Safety and Efficacy of NC-503 in Patients Suffering from Secondary (AA) Amyloidosis."
This was a multicenter, multinational, randomized, double-blind, placebo-controlled, and parallel-design study. The primary objective of this clinical phase II/III study was to assess the efficacy and safety of Kiacta in patients suffering from AA amyloidosis. At the end of this study, Kiacta was offered to all participating patients through an open label extension study to assess long term safety (Study CL-503009). This is summarised below:

Study ID	**Number of Study Centers Locations**	**Study Design Diagnosis (Randomized/ Completed)**	**Study Objective Status**	**Duration**	**Age (yrs) Mean (S.D.) (range) Gender M/F**	**Primary Endpoint**
CL-503004	27 centers 13 countries North America (US), Middle East, Europe and Eastern Europe	double-blind, placebo-controlled, parallel group AA amyloidosis NC-503: 89/63 Placebo: 94/61 dose based upon creatinine clearance*	Efficacy and safety Complete	24 months	**NC-503** 49.9 (13.5) (21 – 75) 40 M: 49 F **Placebo** 51.8 (13.4) 42.0 – 105.0 37 M: 57 F	Composite assessment of clinical improvement/worsening of renal function and death. At the end of the study, patients were classified into 3 categories: **"worse"** (doubling of SCr, or ≥ 50% decrease in CrCl, or progression to dialysis/ESRD or death); **"improved**" (≥ 50% increase in CrCl AND no clinical milestones of worsening); or **"stable"** (none of the criteria above). CrCl was normalized for body surface area.
CL-503009	20 centers 13 countries North America (US), Middle East, Europe and Eastern Europe	non-randomized, uncontrolled, open-label AA amyloidosis NC-503: 110 dose based upon creatinine clearance*	Efficacy and safety Ongoing	36 months	**NC-503** 53.2 (12.1) (24-77) 53 M: 57 F	Composite assessment of clinical improvement/worsening of renal function and death. After 12 months patients were classified into 3 categories: "worse" (doubling of SCr, ≥ 50% decrease in CrCl, progression to dialysis/ESRD or death); "improved" (≥ 50% increase in CrCl AND no clinical milestones of worsening); or "stable" (none of the criteria above). CrCl was normalized for body surface area.

* > 80 mL/min – 1200 mg BID; 30 – 80 mL – 800 mg BID; ≥ 20 and < 30 mL 400 mg BID
NOTE: dose could be adjusted in study based on changes in CrCl

METHODS

Study Participants
183 AA amyloidosis patients were enrolled: 89 patients receiving Kiacta and 94 receiving placebo. The duration of the study was 2 years.
The following criteria applied to the patients enrolled in the study:
• Patients had to be 18 years of age or older
• Males and females. If a woman was of childbearing potential (i.e. not surgically sterilized or post-menopausal greater than one year), the patient had to be using effective birth control.
• Diagnosis of AA amyloidosis demonstrated by positive staining of biopsied tissue (Congo red staining and immunohistochemistry or immunoelectron microscopy) at the screening visit. Tissue from a previous biopsy could be used for confirmation of diagnosis, if available.

• Persistent proteinuria defined as urinary protein excretion ≥ 1 g/24 h in two distinct 24-h urine collections at least 1 week apart within 3 months prior to study entry (Baseline, Month 0 visit) without evidence of urinary tract infection or overt heart failure (NYHA class III or more); **OR** creatinine clearance ≤ 60 mL/min in two distinct measures at least 1 week apart within 3 months prior to study entry (Baseline, Month 0 visit)
• Creatinine clearance ≥ 20 mL/min AND serum creatinine ≤ 3 mg/dL within 3 months prior to study entry (Baseline, Month 0 visit).

Patients receiving concomitant therapy such as angiotensin converting enzyme (ACE) inhibitors or cytotoxic agents/colchicine/anti-TNFα antibodies for their underlying inflammatory disease were to be on stable therapy for at least 3 months prior to the screening visit.

Evidence or suspicion of renal or renovascular diseases other than renal AA amyloidosis, presence of diabetes mellitus (Type I or II), existence of a liver disease were a cause for exclusion.

Treatments
Kiacta 400 mg capsule was administered orally as 1 to 3 capsules twice a day. Dose regimen depended on a patient's CrCl:
• CrCl > 80 mL/min (1200 mg BID or three 400 mg capsules BID);
• 30 ≤ CrCl ≤ 80 mL/min (800 mg BID or two 400 mg capsules BID);
• 20 ≤ CrCl < 30 mL/min (400 mg BID or one 400 mg capsule BID).
Patients were instructed to take study medication a minimum of 1 hour before or 2 hours after meals in the morning and in the evening.
The duration of the study was 2 years.

Outcomes/endpoints

Efficacy:

• ***Primary Endpoint***: Composite assessment of clinical improvement/worsening of renal function and death.
At the end of the study, patients were classified into 3 categories:
-"worse" (doubling of SCr, or ≥ 50% decrease in CrCl, or progression to dialysis/ESRD or death) or;
- "improved" (≥ 50% increase in CrCl AND no clinical milestones of worsening); or
- "stable" (none of the criteria above).
CrCl was normalized for body surface area.

This composite primary outcome (improvement/worsening of renal function and death), which focuses on renal function and agreed with CHMP, is considered as a robust and clinically relevant endpoint since renal involvement is the dominating and most life-threatening feature of AA amyloïdosis. This primary efficacy outcome is similar to that previously used in clinical trials with ACEi and ARBs (e.g losartan in patients with type 2 diabetes and nephropathy) in chronic kidney disease, except for the second component "50% decrease in the CrCl" which is not included in the primary endpoint of those trials.
Of note, the primary composite endpoint was changed three months before the end of the study and added as a secondary endpoint (further to FDA request). The originally primary endpoint, which included assessment of changes in nephrotic syndrome and gastrointestinal symptoms showed no difference between eprodisate and placebo (p= 0.79).

• ***Secondary Endpoints:***
There were many secondary and other clinical endpoints:
- Slope of CrCl, slope of the reciprocal of SCr over time,
- time to doubling of SCr, ≥ 50% decrease in CrCl, dialysis/ESRD, ≥50% increase in CrCl, death,
- changes from Baseline to End of Study in proteinuria and CrCl,
- composite assessment of clinical improvement/worsening of renal and gastrointestinal functions
- changes from Baseline in amyloid content in aspirated abdominal fat tissue, changes from Baseline in visceral amyloid content using ^{123}I-SAP scintigraphy, changes from Baseline to

month 4, 8, 12, 16, and 20 in proteinuria and CrCl, changes from Baseline in SCr, serum albumin, and serum alkaline phosphatise, clinical gastrointestinal signs (changes in lean body weight and new onset or worsening of diarrhea), progression/remission of nephrotic syndrome, Presence/absence of orthostatic hypotension, splenomegaly, and hepatomegaly, use of rescue medications.

Not all the secondary criteria are considered useful, the most important are those related to the deterioration of renal function.

Safety: Adverse events, clinical laboratory parameters (including inflammatory markers), renal function parameters (including urinary microproteins, CrCl, SCr), vital signs/physical examinations, and concomitant medications.

Statistical methods

Primary Analysis Population: Intent-To-Treat (ITT) (for primary and all secondary endpoints)
The full analysis set (FAS) or intent to treat (ITT) population include all randomised patients who took at least one dose of study drug. Safety population consist of the ITT population: all randomised patients who have taken any amount of the of study drug.

Secondary Analysis Population: Per protocol (PP) (for primary endpoint, composite assessment of both renal and gastrointestinal symptoms, slope of CrCl, slope of the reciprocal of SCr).

The primary efficacy analysis of the ITT population was analysed according to 2 methodologies: the Cochran- Mantel-Haenszel (CMH) row mean scores test using a last observation carried forward (LOCF) approach for missing data and the Cox regression analyses (both tests were adjusted for nephrotic syndrome at baseline).
Of note, the sample size estimate was generated in order to detect a difference between Kiacta and placebo groups with a significance level of 0.01. This level was set at 0.01 since there is only one pivotal planned trial for Kiacta.

RESULTS

Participant flow

Table 2 Summary of Patient Disposition

PATIENTS	NC-503	PLACEBO	OVERALL
Screened	-	-	261
Randomized	89	94	183
Completed 24 months	63	61	124
Discontinued	26	33	59
Reasons for discontinuation:			
• Progressed to dialysis/ESRD	7	13	20
• Died during the study	5	5	10
• Voluntary withdrawal, lost to follow-up	4	8	12
• AE or SAE	5	5	10
• Pregnancy	2	0	2
• Miscellaneous	3	2	5

Baseline data

There were no statistically significant differences between Kiacta and placebo groups with respect to Baseline demographic characteristics.

The baseline characteristics of this study population are summarized in Table 6:

Table 6 Summary of Baseline Conditions in the Phase II/III Study – AA Amyloidosis Patients

TREATMENT PARAMETER	**NC-503 (N=89)**		**Placebo (N=94)**	
Underlying Condition	Rheumatic inflammatory disease Infectious disease Hereditary fever Inflammatory bowel disease Miscellaneous or not identified	69.7% 21.3% 16.9% 3.4% 6.7%	Rheumatic inflammatory disease Hereditary fever Infectious disease Inflammatory bowel disease Miscellaneous or not identified	63.8% 22.3% 8.5% 7.4% 6.4%
Time Since First Diagnosis (Median – months)	32.4		37.3	
Nephrotic/Non-Nephrotic (n, %)	34 (38.2%)/55 (61.8%)		39 (41.5%)/55 (58.5%)	
Most Commonly Reported Clinical Manifestations of Amyloidosis (% of patients)	Proteinuria Hypoalbuminemia Edema Renal insufficiency Hypertension Hypercholesterolemia	92.1% 64.0% 52.8% 36.0% 34.8% 30.3%	Proteinuria Hypoalbuminemia Edema Renal insufficiency Hypertension Hypercholesterolemia	91.5% 56.4% 52.1% 50.0% 37.2% 37.2%
Creatinine Clearance (mL/min/1.73 m2) **Mean (S.D.)** **Median [range]**	80.63 (56.38) 65.91 [11.55 – 265.73]		71.64 (53.05) 51.92 [9.43 – 257.42]	
Proteinuria (g/24 h) Mean (S.D.) Median [range]	4.08 (3.87) 3.09 [0.05 – 18.94]		4.19 (3.73) 3.16 [0.03 – 16.42]	
Serum Creatinine (mg/dL) **Mean (S.D.)** **Median [range]**	1.22 (0.63) 1.05 [0.29 – 2.94]		1.42 (0.73) 1.32 [0.27 – 4.10]	
C-Reactive Protein (mg/dL) Mean (S.D.) Median [range]	15.99 (19.75) 9.16 [0.23 – 110.00]		20.20 (20.99) 15.30 [0.61 – 105.00]	
ESR (mm/h) Mean (S.D.) Median [range]	66.44 (36.22) 58.50 [1.5 – 145.0]		73.48 (36.21) 77.0 [5.0 -140.0]	
SAA (mg/L) Mean (S.D.) Median [range]	33.13 (48.17) 16.00 [0.8 – 348.0]		49.14 (69.27) 24.00 [0.8 – 424.0]	

Although non-statistically significant, some imbalances in baseline characteristics were considered by the CHMP of clinical relevance:

- Renal Function at Baseline
  Median CrCl was higher and SCr slightly lower in the Kiacta group than in the placebo group (CrCl: 65.91 vs 51.92 mL/min/1.73 m2 and SCr: 1.05 vs 1.32 mg/dl), indicating that Kiacta patients are less severe than placebo treated patients with regards to renal function at baseline.
- Inflammatory Markers at Screening
  The median SAA concentrations in the placebo group are superior to those in the Kiacta group (respectively 24 mg/L vs16 mg/L, p=0.14). Similarly, the median CRP concentrations were

higher in the placebo group than in the Kiacta group (9.16 mg/L vs 15.30 mg/L). Again, concentrations in inflammatory markers reveal that the placebo group is more severe than the Kiacta group.

- Underlying Condition
  The most noteworthy differences are related to hereditary fever (Kiacta: 16.9% vs. placebo: 22.3%), infectious diseases (21.3% vs. 8.5%) and inflammatory bowel diseases (3.4% vs 7.4%)

These imbalances reveal the heterogeneity of the study groups and, although not statistically significant are considered as clinically relevant since they may induce a methodological bias in favour of Kiacta in efficacy results.

Imbalance was also noted with regards to concomitant medications specific of the underlying diseases, for metothrexate (MTX) use (21.3 % of patients in the NC-503 group, vs 14.9% in the placebo group) and for colchicine use (25.8 % of patients in the NC-503 group, vs 38.3% in the placebo group).

Outcomes and estimation

The Cochran-Mantel-Haenszel (CMH) row mean scores test showed that 13.4% fewer patients treated with Kiacta were classified as "worse" at the end of the study when compared to placebo treated patients (respectively 27 % vs, 40.4%).Therefore, there was a risk reduction of 32% for experiencing renal decline/death for a patient in the NC-503 group, as compared to placebo (p=0.063).

Table 11.9: Primary Endpoint – Composite Assessment of Clinical Improvement/Worsening at End of Study, Pooled "Stable/Improved" vs "Worse" (Results of Analyses on the ITT population using LOCF according to the CMH Row Mean Scores Test)

FINAL CATEGORY	STAT	NC-503 (N=89)	PLACEBO (N=94)	RELATIVE RISK OF BEING "WORSE"	95% C.I.	99% C.I.	P-VALUE
Stable/Improved	n (%)	65 (73.0)	56 (59.6)	-	-	-	
Worse	n (%)	24 (27.0)	38 (40.4)	0.68	(0.45, 1.02)	(0.35, 1.35)	0.063[1]

[1] p-value is from a Cochran-Mantel-Haenszel (CMH) row mean scores test adjusted for nephrotic status at baseline

In a Kaplan-Meier plot, the time it took patients to experience a first "worse" event was significantly prolonged in Kiacta treated patients as compared to placebo treated patients (p=0.016). In those patients who experienced a worsening event, it was estimated that the median time to the first "worse" event was 6.4 months longer in patients treated with Kiacta (median time to first "worse" event for NC-503 group : 14.5 months ; for placebo group : 8.1 months)

The Cox proportional hazards regression model showed a relative risk of 42% for renal decline or all-cause mortality in NC-503 treated patients (p=0.025).
However, the definition of the first worse event used in this original Cox analysis was not appropriate since it included patients who worsened only transiently during the 24 months of the pivotal study (e.g. patients with a creatinine that doubled, then became less than doubled on later measurements).
With a relevant Cox analysis using an appropriate definition of the worse event (i.e a persistent worse event at 24 months), the primary endpoint lead to a 39% reduction in the risk of first persistent worse event (p=0.062). This p-value is close to that observed with the CMH test (p= 0.063).

Therefore, the primary endpoint of the pivotal study is not significant at the alpha level of 0.05 and even less at the level of 0.01 prespecified in the statistical analysis plan (SAP), whatever the methodology used.

The following secondary endpoints were statistically significant: slope of CrCl, reciprocal of SCr, mean change of ClCr, time to worse event. However, it is noted that there was no statistical difference between treatments groups in changes of proteinuria (only a trend in favour of Kiacta was observed). Based on its mechanism of action, Kiacta should prevent new amyloid formation but have no effect on the concentration of SAA and may not reduce SAA oligomers/protofibrils. Since proteinuria in AA

amyloidosis probably results from damage caused by the amyloid deposits as well as from glomerular toxicity of SAA oligomers/protofibrils this may explain Kiacta's lack of effect on proteinuria during the 2 year follow-up. Since the amyloid fibril precursors are putatively removed through endogenous activities (most likely macrophages), it is possible that longer follow-up might reveal a reduction of precursors and a subsequent decrease in proteinuria.

Ancillary analyses

According to the Cox model, analysis of the individual components of the composite primary endpoint revealed a consistent effect of Kiacta on renal function:

- a relative risk of 59% for a doubling SCr (p=0.019),
- a relative risk of 52% for a 50% decrease in CrCl (p=0.008)
- a relative risk of 46% for progression to dialysis/ESRD (p=0.20).
- There was no difference between the two groups in terms of all-cause mortality (5 cases each).

The third component "progression to dialysis/ESDR" is considered as the less reliable since it was not defined by the MAH. It would have been more appropriate to use the current definition of stage 5 of CKD, which defined renal failure with a GFR <15 mL/min/1.73 m^2.

Multivariate analyses

In order to address baseline imbalance on several variables, the applicant has performed multivariate analyses to assess whether these above variables have an impact on the primary outcome. The results showed that age, renal function, underlying disease, drugs acting on the renine –angiotensin system blood pressure and average SAA concentrations did not significantly impact on efficacy results.

Sensitivity analyses

In order to confirm the robustness of the primary endpoint, sensitivity analyses were requested by the CHMP.

The main concerns were:

- the definition of the first worse event used in the original Cox analysis was not appropriate since it included patients who worsened only transitory during the 24 months of the pivotal study.

A more relevant Cox analysis with a worse event defined as a persistent event during the study was performed. This lead to a non significant result (p=0.062, with a hazards ratio of 0.061). This relevant p-value is close to that observed with the CMH test (p=0.063), which means that the counting of time to events, has no influence on efficacy results in this study.

A sensitivity analysis of the primary outcome imputing all discontinuations to the "worse" category demonstrated the lack of robustness of the primary outcome (p=0.340).

Subgroup analysis

Of particular note among exploratory subgroup analyses, was the assessment of treatment effects by nephrotic versus non-nephrotic status. Although conclusions based upon such an analysis must be cautious, the available data suggested potentially important treatment benefits in patients with nephrotic syndrome, but much less evidence of conclusive benefit or sustained effect in non-nephrotic patients.

Inspection findings

The CHMP adopted a GCP inspection request during the procedure since:

- the sponsor had changed the primary endpoint during the study and the CHMP wanted to be reassured that the study was not prematurely unblinded, all the more that DSMB has partially unblinding the data for safety evaluations (EMEA/CHMP/SAWP/32866/05).
- The CHMP wanted to know if the (unplanned) decision of the sponsor to change the statistical analysis, (i.e. the use of the Cox proportional hazards (CPH) regression instead of the planned proportional odds regression model test) could be data driven or not.

Results of the inspection

After a clarification meeting and examination of supplemental documentation, the inspectors confirmed the inspection findings in relation to the way in which the pivotal study CL-503004 was analysed.
The explanations and the documentation provided by the applicant were insufficient to guarantee complete reassurance that the randomization list was not used for the purpose of an interim analysis.

Furthermore, as an interim analysis was not reported in the study documentation. Despite additional information and due to a deviation related to the blinding process and lack of documentation, the EMEA cannot be certain that the decision to change the primary efficacy endpoint was not data-driven. The sponsor's explanation that this interim analysis was not revealed as it was not considered to fulfil the exact definition of an interim analysis per ICH E9 is not considered to be acceptable.

A Cox analysis was performed which was not described in the statistical analysis plan, with this analysis subsequently presented as the principal evidence of product efficacy. Additional documentation provided by the sponsor regarding the date on which the Cox analysis was planned was not convincing.

- Supportive study

The supportive **Study 5003-009** is an open label extension of the Phase II/III Study CL-503004. It is still ongoing but all patients completed the Month 12 visit for this analysis.

METHODS
This is the Month 12 analysis for a multicenter, multinational, uncontrolled, open-label, 3-year extension study.
A total of 110 AA patients who completed the double-blind study CL-503004 elected to participate in the open-label extension study CL-503009. Fifty seven of them were from the NC-503 group (named as NC-503/NC-503 continuous treatment) and 53 from the Placebo group (named as Placebo/NC-503 delayed treatment).
All patients that were enrolled in the open-label extension study were to receive NC-503 for 3 years.

The primary efficacy endpoint of the composite assessment of renal function or death was assessed over two periods:
1) over the 3-year follow-up (2 years of study CL-503004 and 1 year of open-label study CL-503009) using all patients enrolled in study CL-503004 (N=183), and Baseline of study CL-503004; and
2) during the first 12 months of the open-label study CL-503009 using all patients enrolled in the open-label study (N=110), and the Baseline of study CL-503009. The analyses compared patients treated for 3 years with NC-503 (NC-503/NC-503 group) to patients receiving Placebo for 2 years and then switched to NC-503 for one year (Placebo/NC-503 group).

Furthermore, each dataset was analyzed according to the two statistical methodologies: the Cox proportional hazards regression model and the Cochran-Mantel-Haenszel (CMH) row mean scores test. Both were adjusted for nephrotic status at Baseline (nephrotic vs non-nephrotic status at the Baseline of study CL-503004).

The secondary efficacy endpoints of time to individual renal events (doubling of SCr, $\geq$ 50% decrease in CrCl, progression to dialysis/ESRD) were assessed using all patients followed for 3 years (N=183), respecting the original randomization scheme. The secondary efficacy endpoints of slope of CrCl and changes in proteinuria, were assessed using all patients entered into the open-label extension study (CL-503009) (N=110) and compared data obtained from these patients before and after entry into CL-503009.
For the primary endpoint, the last observation carried forward (LOCF) methodology was used during the CMH test analysis. For the secondary endpoints, missing data was not replaced and the last available measurement was used, resulting in observed-case analyses.
For the primary and secondary efficacy analyses, all statistical tests were two-sided and conducted with an α=0.05.

RESULTS

Over the 3 years of follow-up (2 years of study CL-503004 and 1 year of study CL-503009): The Cox proportional hazards regression model showed that in patients continuously treated with NC-503 for 3 years (NC-503/NC-503 group, N=89), there was a reduction in the risk of any "worse" event of renal decline/death to 41%, relative to patients who received NC-503 for one year after a delay while on Placebo for 2 years (Placebo/NC-503 group, N=94) (p=0.011).

When patients were categorized at the end of the 3 year follow-up and the distribution was evaluated by the CMH test, there were 15.0% fewer "worse" patients in the NC-503/NC-503 group in comparison to the Placebo/NC-503 group (p=0.047).

In a Kaplan-Meier plot, the time it took for patients to experience a first "worse" event was significantly prolonged in the NC-503/NC-503 group (N=89) as compared to the Placebo/NC-503 group (N=94) during the 3- year follow-up (p=0.010).

During the first 12 months of the open-label study CL-503009: The primary composite endpoint as evaluated by the Cox proportional hazards model showed that in patients continuously treated for 3 years with NC-503 (NC-503/NC-503 group, N=57), there was a reduction in the risk of any "worse" event of renal decline/death to 45% of the risk for patients treated with NC-503 for one year after a delay while on Placebo for 2 years (Placebo/NC-503 group, N=53, p=0.14).
When patients were categorized at the end of Month 12 and the distribution was evaluated by the CMH test, the data show that there were 11.2% fewer "worse" patients in the NC-503/NC-503 group in comparison to the Placebo/NC-503 group (p=0.16).

In conclusion, continuous treatment with NC-503 during a 3 year follow-up resulted in a statistically significant delay in the progression of renal disease in AA amyloidosis patients, as shown by the relative risk of 41% (p=0.011) for renal decline or all-cause mortality. This finding is supported by the slower rate of loss in renal function as measured by the slope of CrCl in patients switched from Placebo to NC-503 treatment for 1 year. These treatment effects seem consistent with the findings from the double-blind, Placebo-controlled study (CL-503004). However, no firm conclusion can be drawn since it is an open label study

- Discussion on clinical efficacy

The pivotal study was a multicenter, multinational, randomized, double-blind, placebo-controlled, and parallel-design study. The duration of the study was 2 years.
Kiacta 400 mg capsule was administered orally as 1 to 3 capsules twice a day. Dose regimen depended on a patient's CrCl:

A composite assessment of clinical improvement/worsening of renal function and death was chosen as the primary efficacy endpoint in the pivotal study and in its open label extension.

This primary efficacy outcome is similar to that previously used in clinical trials with ACEi and ARBs (e.g losartan in patients with type 2 diabetes and nephropathy) in chronic kidney disease, except for the second component "50% decrease in the CrCl" which is not included in the primary endpoint of those trials.
Of note, the primary composite endpoint was changed three months before the end of the study. The originally primary endpoint, which included assessment of changes in nephrotic syndrome and gastrointestinal symptoms showed no difference between eprodisate and Kiacta (p= 0.79). A doubt remains that the change was data driven (see inspection concerns).

Both CMH test and Cox analyses were adjusted from nephrotic status at baseline, whereas dosing regimen depends on creatinine clearance. This stratification is highly questionable, all the more that the definition of the nephrotic syndrome used in this study is not the one used by European nephrologists. Therefore, the CHMP was of the opinion that it would have been more relevant to stratify patients into ClCr at baseline.

There are also some notable imbalances at baseline in pivotal study (mainly with regards to renal function, underlying conditions, inflammation markers, concomitant medications). However, the sponsor has performed a multivariate Cox regression analysis which confirms that the observed effect in favour of Kiacta is not biased or explained by CrCl, SCr, average SAA concentrations, underlying disease, or drugs acting on the renine angiotensin system (ARBs or IECs).

The Cochran-Mantel-Haenszel (CMH) row mean scores test showed that 13.4% fewer patients treated with Kiacta were classified as "worse" at the end of the study when compared to placebo treated patients (respectively 27 % vs, 40.4%).Therefore, there was a risk reduction of 32% for experiencing renal decline/death for a patient in the Kiacta group, as compared to placebo (p=0.063). A sensitivity analysis of the primary outcome imputing all discontinuations to the "worse" category demonstrated the lack of robustness of the primary outcome (p=0.340).

The Cox proportional hazards regression model showed a relative risk of 42% for renal decline or all-cause mortality in Kiacta treated patients (p=0.025).
However, the definition of the first worse event used in this original Cox analysis was not appropriate since it included patients who worsened only transiently during the 24 months of the pivotal study. With a relevant Cox analysis using an appropriate definition of the worse event (i.e. a persistent worse event at 24 months), the primary endpoint lead to a 39% reduction in the risk of first persistent worse event (p=0.062). This p-value is close to that observed with the CMH test (p= 0.063).

Another concern is the inspection findings showing that the use of a Cox analysis was not adequately documented in the statistical analysis plan (see below).

In conclusion, the primary endpoint of the pivotal study is not significant at the alpha level of 0.05 and even less at the level of 0.01 prespecified in the statistical analysis plan (SAP), whatever the methodology used. Appropriate statistical evaluation of these data yield p-values ranging from 0.06 to 0.340.
Thus, the pivotal study failed to demonstrate the effectiveness of Kiacta in the treatment of renal manifestations of amyloïdosis.

Finally, the CHMP adopted a request for a GCP inspection of the clinical trial CL-503004 regarding the way in which this study was analysed. The main concerns which are not solved are the following:

- The sponsor could not ascertain that the blind was properly maintained throughout the trial. The explanations and the documentation provided by the applicant were insufficient to guarantee complete reassurance that the randomization list was not used for the purpose of an interim analysis.

- An interim analysis was not reported in the study documentation. Despite additional information and due to a deviation related to the blinding process and lack of documentation, the EMEA cannot be certain that the decision to change the primary efficacy endpoint was not data-driven. The sponsor's explanation that this interim analysis was not revealed as it was not considered to fulfil the exact definition of an interim analysis per ICH E9 is not considered to be acceptable.

- A Cox analysis was performed which was not described in the statistical analysis plan, with this analysis subsequently presented as the principal evidence of product efficacy. Additional documentation provided by the sponsor regarding the date on which the Cox analysis was planned was not convincing.

Overall, the CHMP considers that the efficacy of Kiacta has not been sufficiently established in AA amyloïdosis patients and in addition, inspection findings cast a doubt on the results

Clinical safety

Safety data were based on the four phase I PK studies and on the pivotal efficacy study with its open label extension. The phase I PK studies are not considered as relevant for safety evaluation since most of patients (80/96) are healthy volunteers patients, who are not representative of the target population.

- Patient exposure

A total of 238 patients have been exposed to Kiacta (as of December 2005).
142 patients have been exposed to Kiacta(89 in the double-blind phase, 53 in the open-label phase) for at least one year, 95 patients have been exposed for at least 2 years and 85 patients for at least 3 years.
Daily dose of Kiacta administered to each patient was depending on creatinine clearance level, between 800 and 2400mg.
The mean duration of CL-503004 study within the intent-to-treat population was 1.60+/-0.57 years for the Kiacta group and 1.42+/- 0.70 years for the placebo group.

In the phase I PK studies, 96 patients have been exposed to Kiacta, single or multiple dose.

Table: Overall Extent of NC-503 Exposure in the Phase II/III Study - Patients with AA Amyloidosis (Study CL-503004)

Treatment Duration (years)	Statistics	NC-503 (N=89)	Placebo (N=94)
Overall	N	89	94
	Mean	1.60	1.42
	S.D.	0.57	0.70
	Median	1.86	1.84
	Range	0.011 - 2.11	0.003 - 2.20
Among Completers Only	N	63	61
	Mean	1.91	1.89
	S.D.	0.082	0.076
	Median	1.88	1.86
	Range	1.80 - 2.11	1.78 - 2.20

- Adverse events

In the pivotal study, the following SOCs (all causalities) were more frequent in the Kiacta group than in the placebo group: Gastrointestinal disorders (68.5% vs 62.8%), Infection and infestations 62.9% vs 50%, Nervous system disorder 46.1% vs 39.4%, Musculoskeletal and connective tissue 41.6% vs 34%, General disorders and administration site 36.0% vs 31.9%, Skin and subcutaneous disorders 27% vs 25.5% and Renal and Urinary Disorders 22.5% vs 21.3%.

The following adverse events occurred more frequently in the Kiacta group than in the placebo group: diarrhoea 32.6% vs 26.6%, nasopharyngitis 16.9% vs 14.9%, dizziness 11.2% vs 5.3%, cough 13.5% vs 9.6%.

Most of the treatment emergent adverse events (TEAEs) were considered by the investigator as being mild or moderate in severity in the Kiacta group (93%) as well as in the placebo group (91.7%).

Fifty-one out of 89 patients (57.3%) in the Kiacta arm experienced at least one TEAE considered possibly related to treatment compared to 36 of 94 patients (38.3%) in the placebo arm (p=0.012)
Of those events considered possibly related to treatment, there were slightly higher incidences of diarrhea, dyspepsia and headache in the Kiacta treatment group, albeit these differences were not statistically significant. The majority of the all causality TEAEs were mild or moderate in severity (93.0% and 91.7% in the Kiacta and placebo groups, respectively, and there were no differences between treatments in the reported severity of TEAEs.

TEAE and related TEAE data from the ongoing open-label extension study was generally similar to that from the preceding study, although a lower incidence of related events was reported in the

extension study. No important differences were noted between patients originally randomised to Kiacta (NC-503/NC-503 group) and those originally randomised to placebo (PBO/NC-503)

Table: Summary of the Most Common (≥ 5%)* Treatment Emergent Adverse Events in the Phase II/III Study, Study CL-503004

		All Causalities		Related**	
		NC-503 N=89	Placebo N=94	NC-503 N=89	Placebo N=94
SYSTEM ORGAN CLASS	Preferred Term (MedDRA)	n patients (%)			
Cardiac	Tachycardia	5 (5.6)	1 (1.1)	1 (1.1)	0
Gastrointestinal	Diarrhea	29 (32.6)	25 (26.6)	15 (16.9)	3 (3.2)
	Nausea	12 (13.5)	19 (20.2)	4 (4.5)	8 (8.5)
	Vomiting	12 (13.5)	16 (17.0)	6 (6.7)	6 (6.4)
	Abdominal pain	9 (10.1)	7 (7.4)	4 (4.5)	3 (3.2)
	Dyspepsia	9 (10.1)	6 (6.4)	2 (2.2)	0
	Toothache	8 (9.0)	5 (5.3)	0	0
	Abdominal pain upper	5 (5.6)	8 (8.5)	1 (1.1)	3 (3.2)
	Loose stools	5 (5.6)	1 (1.1)	5 (5.6)	1 (1.1)
General and Administration Site	Edema	8 (9.0)	7 (7.4)	1 (1.1)	0
	Edema peripheral	7 (7.9)	10 (10.6)	0	0
	Fatigue	6 (6.7)	7 (7.4)	1 (1.1)	1 (1.1)
	Chest pain	5 (5.6)	3 (3.2)	0	1 (1.1)
Infections and Infestations	Nasopharyngitis	15 (16.9)	14 (14.9)	1 (1.1)	1 (1.1)
	Influenza	7 (7.9)	2 (2.1)	0	0
	Upper respiratory tract infection	6 (6.7)	7 (7.4)	0	0
	Bronchitis	6 (6.7)	6 (6.4)	0	0
	Urinary tract infection	5 (5.6)	5 (5.3)	0	0
	Pneumonia	5 (5.6)	2 (2.1)	0	0
Investigations	Blood creatinine increased	5 (5.6)	4 (4.3)	5 (5.6)	3 (3.2)
Musculoskeletal and Connective Tissue	Arthralgia	11 (12.4)	10 (10.6)	2 (2.2)	0
	Back pain	11 (12.4)	8 (8.5)	0	2 (2.1)
	Pain in extremity	5 (5.6)	5 (5.3)	0	1 (1.1)
Nervous System	Headache	25 (28.1)	27 (28.7)	12 (13.5)	9 (9.6)
	Dizziness	10 (11.2)	5 (5.3)	1 (1.1)	1 (1.1)
Psychiatric	Insomnia	5 (5.6)	3 (3.2)	1 (1.1)	3 (3.2)
Renal and Urinary	Renal insufficiency	6 (6.7)	6 (6.4)	0	0
Respiratory, Thoracic, and Mediastinal	Cough	12 (13.5)	9 (9.6)	1 (1.1)	0
Skin and Subcutaneous Tissue	Pruritus	9 (10.1)	7 (7.4)	4 (4.5)	5 (5.3)
Vascular	Hypertension	9 (10.1)	10 (10.6)	2 (2.2)	2 (2.1)

** an incidence of ≥ 5% for a given preferred term in the NC-503 group

TEAEs appear very similar in both treatment groups. A combined assessment of TEAEs, related TEAEs and severity (severity data not separately presented above) suggests that diarrhoea has a highly probable relationship to treatment, although the excess incidence versus placebo is low. The non-clinical findings and large amount of drug excreted unchanged in the faeces support a causal relationship for this event.

Dizziness and headache are also considered likely to be associated with Kiacta. This would have to be mentioned in the SPC (sections 4.7 and 4.8) and in the risk management plan (RMP).

- Serious adverse events/deaths/other significant events

Serious adverse events

No SAEs occurred in the Phase I studies.
Among the 183 patients, 71(38.8%) patients reported at least one serious adverse event (SAE), the number of patients with at least one SAE was lower in the group Kiacta than in the group placebo (32/89 (36%) in the group Kiacta and 39/94 (41.5%) in the group placebo, p=0.45).
A tabulation of the most common SAEs is provided in the following table.

Table: Summary of the Most Common (> 2.0%)* Serious Adverse Events (All Causalities, Preferred Term) in the Phase II/III Study, Study CL-503004

		NC-503 N=89	Placebo N=94
SYSTEM ORGAN CLASS	**Preferred Term (MedDRA)**	**n patients (%)**	
Cardiac	Myocardial infarction	2 (2.2)	0
Gastrointestinal	Diarrhea	3 (3.4)	2 (2.1)
	Vomiting	2 (2.2)	1 (1.1)
	Gastrointestinal hemorrhage	0	2 (2.1)
General Disorders and Administration Site	Asthenia	0	2 (2.1)
Infections and Infestations	Pneumonia	3 (3.4)	2 (2.1)
	Gastroenteritis	0	2 (2.1)
	Infection	2 (2.2)	0
Metabolism and Nutrition	Hyperkalemia	0	2 (2.1)
Renal and Urinary	Renal insufficiency	3 (3.4)	6 (6.4)
	Renal impairment	3 (3.4)	2 (2.1)
	Renal failure chronic	1 (1.1)	3 (3.2)
	Nephrotic syndrome	2 (2.2)	0
Respiratory, Thoracic, and Mediastinal	Dyspnoea	2 (2.2)	2 (2.1)
Source: Study Report CL-503004, Table 12.10			

*more than 1 patient was reported as experiencing a given SAE in either treatment group

Among the most common SAEs were renal insufficiency, renal impairment, pneumonia, chronic renal failure and diarrhea. There were no marked differences in the occurrence of SAEs between the two treatment groups. The cases of myocardial infarction reported for the Kiacta group and other relevant cardiovascular safety events are discussed below.
In the open-label study (CL-503009), 30/110 (27.3%) patients experienced at least one serious adverse event. There were no SAE findings of particular note.

Deaths
No deaths occurred in the Phase I studies.

In the Phase II/III study (CL-503004), a total of 10 patients died during the study period (i.e. during treatment period or within 15 days of study treatment discontinuation). These events were equally distributed between the treatment groups, with 5 deaths in each group. Beyond the 15-day window after treatment discontinuation, 6 deaths were known to have occurred in Kiacta-treated patients, and another 4 patients died who had been treated with placebo. A listing of deaths is included below:

Table: Listing of All Deaths, Study CL-503004

Patient ID	Age* Gender (yrs M/F)	Treatment	Duration of Exposure (months)	Treatment Causality	Diagnosis
Deaths During Study Period (End of Study + ≤ 15 Days)					
5-8	34 F	placebo	11.0	not related	cardiac failure
6-21	46 M	placebo	11.7	not related	septic shock
8-9	68 F	placebo	19.0	not related	severe myelodepression
13-4	55 F	placebo	0.4	unlikely	gastroenteritis
26-11	56 M	placebo	16.1	unlikely	ischemic stroke
18-22	63 F	NC-503	23.0	not related	pneumonia
20-19	68 F	NC-503	20.8	unlikely	cerebrovascular accident
26-06	70 F	NC-503	12.2	unlikely	ischemic stroke
26-10	63 F	NC-503	15.7	unlikely	gastrointestinal hemorrhage
26-18	35 F	NC-503	0.1	not related	nephrotic syndrome
Deaths During Retrieved Follow-up Period (End of Study + > 15 days)					
6-28	63 M	placebo	1.7	n/av	n/av
10-1	69 F	placebo	3.4	n/av	n/av
20-16	63 F	placebo	4.2	n/av	n/av
20-21	59 F	placebo	5.6	n/av	n/av
3-5	38 M	NC-503	10.2	n/av	n/av
4-13	63 F	NC-503	1.3	not related	multiple organ failure
5-2	56 M	NC-503	15.4	not related	progressive ESRD
11-2	68 F	NC-503	5.8	not related	renal failure
18-23	56 M	NC-503	3.7	not related	sepsis
20-28	64 F	NC-503	16.4	n/av	n/av
Source: Study Report CL-503004, Table 12.8					

*age at screening
n/av – not available

None of these deaths were reported as possibly related to study medication. Of the ten reported deaths occurring 16 days or more after discontinuation of study medication, information on the events leading up to the death is therefore not available in 6 cases (Kiacta: 2 patients vs placebo: 4 patients).

In the open-label study (CL-503009), 5 patients died (NC-503/NC-503: n=2, placebo/NC-503: n=3) prior to the Month 12 visit analysis. None of the deaths were reported as drug related.

Cardiovascular events

The number of cardiovascular events in Study CL-503004 is shown in the table below:

Table: Study CL-503004 Cardiac Disorder Treatment Emergent Adverse Events (all causality)*

	NC-503 (N=89) n (%)	PLACEBO (N=94) n (%)
CARDIAC DISORDERS	**14 (15.7)**	**12 (12.8)**
TACHYCARDIA	5 (5.6)	1 (1.1)
PALPITATIONS	2 (2.2)	3 (3.2)
ANGINA PECTORIS	2 (2.2)	1 (1.1)
MYOCARDIAL INFARCTION	2 (2.2)	0
ATRIAL FIBRILLATION	1 (1.1)	3 (3.2)
BRADYCARDIA	1 (1.1)	0
MYOCARDIAL ISCHAEMIA	1 (1.1)	0
RIGHT VENTRICULAR FAILURE	1 (1.1)	0

* Occurring in at least 1 NC-503 patient
Source: Study CL-503004

In addition to, the following events have been discussed by the applicant:

- 2 fatal cases of myocadial infarction previously mentioned
- 3 cases of myocardial ischemia (1 in CL-503004 and 2 in CL-503009). In these three cases, all the patients presented history of hypertension, no discontinuation was carried out, the event occurred more than 6 months after having started Kiacta treatment. The cases have been considered as non serious by the sponsor, and not related to study drug. Kiacta was not discontinued and the event did not reoccur.
- Non serious cases of angina pectoris. They appeared in three Kiacta patients and 1 placebo patient. 2 Kiacta had recurrence of the event during the open-label study.
- Cases of tachycardia. Seven non serious cases were reported, among them 1 in the placebo group. Co-suspect medication as well as medical history have to be considered for all cases. No discontinuation as observed.
- Cases of chest pain. 16 events were reported in 8 patients, among them 8 were treated with Kiacta. No discontinuation was reported, one case has been considered as serious. It concerned a 55-year-old-male patient with history of atrial fibrillation, who developed chest pain, palpitations and dizziness. The patient was treated with nasal drops (xylometazolin) for a congestive nose, which was seriously co suspected.
- Cases of ischemic stroke, CVA. 3 cases of ischemic stroke were observed, 2 in the Kiacta group and 1 in the placebo group, all with a fatal outcome. The patients treated with Kiacta were female respectively of 70 and 71 years of age. They presented medical history such as atherosclerosis and chronic thrombosis for the first case and hypertension for the second. Time to onset were between 5 days and 2 years.
  An additional case of stroke is mentioned during the open-label phase, in a patient previously treated with placebo.

In summary, by adding all cardiovascular events reported and mentioned in the above table, a total of 15 (16.8%) in the eprodisate group and a total of 8 (8.5%) in the placebo group can be found.
In study in CL-503009, 9 patients had cardiac disorders corresponding to 11 adverse events: 7 (6.4%) events among patients previously treated with Kiacta in the double-blind study and 4 (3.6%) in patients previously treated with placebo.

According to the sponsor, the causal role of Kiacta in the CV events observed in the clinical study was not established and the underlying diseases and concomitant medications may have been associated with these events. However, the CHMP considers that these findings are in favour of a possible signal

for an increased arteriopathic/cardiac risk. Furthermore, due to the fact that the population studied and the number of events to date is too small, no definitive conclusions can be drawn on the long-term safety of Kiacta.
Consequently, the applicant agreed at the request of the CHMP to monitor the cardiovascular risk as part of the RMP. The cardiac events myocardial infarction, myocardial ischaemia and angina pectoris will be included in section 4.8 of the SPC.

- Laboratory findings

In the pivotal study, there was a statistically significant lower increase from baseline in alkaline phosphatase in the Kiacta group, which has been considered as non clinically significant.
A lower decrease of platelets level is observed in the Kiacta group as compared with the placebo group. However, the CHMP agrees that this observation do not seem to be associated with eprodisate treatment.

With regards to urinalysis parameters, the presence of blood in the urine (>10 RBC/µL) at baseline was observed in 29.5% of Kiacta patients and 27.2% of placebo patients. The incidence of haematuria was similar between the treatment groups over time.

- Safety in special populations

Kiacta does not seem to affect renal function. The dosing regimen employed in the phase II/III clinical trial which adjusts dose according to ClCr ensures all treated patients have approximately equivalent exposures. Although patients with lowest ClCr values were shown n the population PK analysis to have somewhat greater exposures, no safety concerns are apparent from the overall safety data to suggest that this is of concern, or to suggest a safety analysis by ClCr would be of value.
In study CL-503004, the median of SAA level changes from baseline to month 24 indicates an increase of 8.5mg/L in the Kiacta group vs a decrease of 22.1mg/L in the placebo group. However, SAA levels are highly variable and can fluctuate widely within patients. The normal value of SAA is usually considered to be around1-3mg/L in the absence of inflammatory co-morbidities, which can lead to important SAA levels. The observed differences between both groups for the 2 years period is minimal regarding the SAA values. Furthermore, according to its mechanism of action, eprodisate is not expected to cause a change in SAA level.

The effect of age on the adverse event profile was assessed in 2 different age groups: < 65 years old (n=156) and ≥ 65 years old (n=27). Overall, it does not appear that there was an influence of age on the adverse event profile of Kiacta.

- Safety related to drug-drug interactions and other interactions

There is very limited clinical evaluation of drug interactions, but in view of the *in vitro* findings the potential for pharmacokinetic drug interactions appears low, with the exception of drugs known to be metabolized by the P450 3A4 isoenzyme. (See “Pharmacokinetic interaction studies” section)

- Discontinuation due to adverse events

No subjects withdrew from a Phase I study due to an adverse event.

In the Phase II/III study (CL-503004), 20 out of 89 patients (22.5%) in the Kiacta study arm experienced AEs leading to study discontinuation as compared to 23 out of 94 (24.5%) in the placebo group. There were no statistically significant differences in the occurrence of AEs leading to study discontinuation between the two treatment groups. A tabulation of most common adverse events leading to study discontinuation (> 2.0%), reported by preferred term, is shown in the table below. Among the most frequent AEs leading to study discontinuation were renal insufficiency, renal impairment, and chronic renal failure.

Table: Summary of Most Common (> 2.0%) Adverse Events Leading to Study Discontinuation (All Causalities, Preferred Term) in the Phase II/III Study, Study CL-503004,

		NC-503 N=89	Placebo N=94
SYSTEM ORGAN CLASS	Preferred Term (MedDRA)	n patients (%)	
Blood and Lymphatic System	Anemia	1 (1.1)	2 (2.1)
Cardiac	Myocardial infarction	2 (2.2)	0
Gastrointestinal	Diarrhea	1 (1.1)	2 (2.1)
	Nausea	0	2 (2.1)
General Disorders and Administration Site	Asthenia	0	2 (2.1)
Pregnancy, Puerperium and Perinatal	Pregnancy	2 (2.2)	0
Renal and Urinary	Renal insufficiency	4 (4.5)	4 (4.3)
	Renal impairment	3 (3.4)	3 (3.2)
	Renal failure chronic	1 (1.1)	3 (3.2)
	Nephrotic syndrome	2 (2.2)	0
Respiratory, Thoracic and Mediastinal	Dyspnoea	0	3 (3.2)

In the open-label study (CL-503009), there were 2 (1.8 %) patients who experienced an adverse event that led to study discontinuation.

Overall, adverse events leading to drug discontinuation seem to be predominantly disease rather than treatment related. There were no trends to warrant concern except for cardiovascular events (see above discussion)

- Post marketing experience

Not applicable

- Discussion on clinical safety

It should be kept in mind that the number of patients, as for all orphan drug, was very low and that the number of events was still lower. Thus, the power of the safety conclusions is limited and the results should be considered carefully.
The adverse events occurring more frequently in the Kiacta group than in the placebo group were: diarrhoea 32.6% vs 26.6%, nasopharyngitis 16.9% vs 14.9%, dizziness 11.2% vs 5.3%, cough 13.5% vs 9.6%.
Most of the treatment emergent adverse events (TEAEs) were considered by the investigator as being mild or moderate in severity in the Kiacta group (93%) as well as in the placebo group (91.7%).
They are listed in the proposed SPC.

The most common SAEs were renal insufficiency, renal impairment, pneumonia, chronic renal failure and diarrhea. There were no marked differences in the occurrence of these SAEs between the two treatment groups.
However, cardiovascular events (myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular ischaemia/infarction and transient ischaemic attack are considered by the CHMP as a

possible signal for an increased arteriopathic/cardiac risk. Consequently these events have been added as potential risks of the revised RMP. These will also be listed in the SPC.
Furthermore, a detailed cardiac risk assessment should be included in any further patient studies.

3.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The MAH has provided a description of the pharmacovigilance system. Through this description, the applicant shows that he has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of adverse reactions.

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

Risk Management Plan

Not applicable

3.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable. The drug substance and the drug product have been appropriately described and generally satisfactory documentation has been provided. The excipients used in the preparation of the drug product and manufacturing process selected are standard for capsules preparation. The results indicate that the drug substance and the drug product can be reproducibly manufactured.

Non-clinical pharmacology and toxicology

Kiacta competes with sulphated GAGs for binding to amyloidogenic proteins, thereby interfering with amyloid fibril formation and deposition. In animal models of inflammation (irritant or antigenic stimulus), an anti-amyloid activity was demonstrated for Kiacta but it cannot be definitively concluded if Kiacta is more potent in one model versus the other.

Oral absorption of Kiacta is slow and variable within and between species. In rats and dogs the elimination is rapid and almost complete (94-97 % of the dose), occurring mainly or even solely in urine. There seems to be little, if any, metabolism of Kiacta. *In vitro* studies did not show any inhibition or induction of CYP450 major isoforms.

The kidney was identified as a target organ of toxicity in rats but not in dogs. Transitional urinary bladder hyperplasia was also observed in rats at high dose after 26 weeks treatment.
Kiacta is devoid of genotoxic potential in vitro and in vivo models. Cortical vacuolation in the adrenals of treated male rats was observed at histopathological examination in 28-day and 26-week studies. The relevance of these findings for long-term safety will be further evaluated with the results of the ongoing 2-year carcinogenicity study. The SPC would have to be updated accordingly (section 5.3)

No increase in the incidence of tumours in a 26-week carcinogenicity study in Tg.rasH2 transgenic mouse model was reported. A 2-year carcinogenicity study in rats was ongoing at the time of submission will be subject to an evaluation for the next steps of the procedure.
No significant effects were observed in reproduction toxicology.
In toxicokinetics, the safety ratio (exposure) at the NOAEL defined in the dog, is approximately 2 to 4-fold higher than in patients at the therapeutic dose, but widely depending on the patient's creatinine clearance.
Kiacta is not considered to represent a risk for the environment.

Efficacy

The definition of the first worse event used in the original Cox analysis (p= 0.025) was not appropriate since transient events were classified as "worse" by the Applicant (e.g. patients with a creatinine that doubled, then became less than doubled on later measurements, were counted as worse in the Cox analysis).
With a relevant Cox analysis using an appropriate definition of the worse event (i.e a persistent worse event at 24 months), the primary endpoint lead to a 39% reduction in the risk of first persistent worse event (p=0.063). This p-value is close to that observed with the CMH test (p= 0.063).
In addition, a sensitivity analysis of the primary outcome imputing all discontinuations to the "worse" category demonstrated the lack of robustness of the primary outcome (p=0.340).
Therefore, the two tests are not significant at the alpha level of 0.05 and even less at the level of 0.01 prespecified in the statistical analysis plan, whatever the methodology used.

Therefore, appropriate statistical evaluation of these data yield p-values ranging from 0.06 to 0.340 even before concerns related to inspection are taken into account.

Thus, the pivotal study failed to demonstrate the effectiveness of Kiacta in the treatment of renal manifestations of amyloïdosis.

Lastly, inspection findings discredit the efficacy results.

Finally, the Applicant requested the CHMP, at the time of the responses to List of Outstanding issues, to consider a conditional marketing authorisation. The CHMP considered that, although the scope would apply to Kiacta according to Art. 2, (1st and 3^{d} paragraphs) of the Commission Regulation (EC) 507/2006, the conditions of Art. 4 (1) (a) of the same Regulation were not fulfilled as the risk-benefit balance of Kiacta is negative.

Safety

The adverse events occurring more frequently in the Kiacta group than in the placebo group were: diarrhoea, nasopharyngitis, dizziness, and cough. They are listed in the proposed SPC.

The most common SAEs were renal insufficiency, renal impairment, pneumonia, chronic renal failure and diarrhea. Additionally, the cardiovascular events occurrence in the Kiacta group remains an issue of concern: there were 15 patients (16.8%) in the eprodisate group, vs 8 patients (8.5%) in the placebo group who experienced cardiac events. Therefore, the CHMP is of the opinion that this is a signal for an increased arteriopathic/cardiac risk. Consequently this risk would have to be added in the revised RMP. These events would also have to be listed in the SPC.
Furthermore, a detailed cardiac risk assessment would have to be included in any further patient studies.

Inspection

After a clarification meeting and examination of supplemental documentation, the inspectors confirmed the inspection findings in relation to the way in which the pivotal study CL-503004 was analysed.
The explanations and the documentation provided by the applicant were insufficient to guarantee complete reassurance that the randomization list was not used for the purpose of interim analysis.

An interim analysis was not reported in the study documentation. Despite additional information and due to a deviation related to the blinding process and lack of documentation, the EMEA cannot be certain that the decision to change the primary efficacy endpoint was not data-driven. The sponsor's explanation that this interim analysis was not revealed as it was not considered to fulfil the exact definition of an interim analysis per ICH E9 is not considered to be acceptable.

A Cox analysis was performed which was not described in the statistical analysis plan, with this analysis subsequently presented as the principal evidence of product efficacy. Additional

documentation provided by the sponsor regarding the date on which the Cox analysis was planned was not convincing.

- User consultation

The evaluation will be performed for the next steps of the procedure.

Risk-benefit assessment

The definition of the first worse event used in the original Cox analysis (p= 0.025) was not appropriate since transient events were classified as "worse" by the Applicant (e.g. patients with a creatinine that doubled, then became less than doubled on later measurements, were counted as worse in the Cox analysis).

With a relevant Cox analysis using an appropriate definition of the worse event (i.e a persistent worse event at 24 months), the primary endpoint lead to a 39% reduction in the risk of first persistent worse event (p=0.063). This p-value is close to that observed with the CMH test (p= 0.063).
In addition, a sensitivity analysis of the primary outcome imputing all discontinuations to the "worse" category demonstrated the lack of robustness of the primary outcome (p=0.340).
Therefore, the two tests are not significant at the alpha level of 0.05 (even in the absence of correction for multiplicity) and even less at the level of 0.01 pre-specified in the statistical analysis plan, whatever the methodology used.

Overall, appropriate statistical evaluation of these data yield p-values ranging from 0.06 to 0.340 even before concerns related to inspection are taken into account.
Thus, the pivotal study failed to demonstrate the effectiveness of Kiacta in the treatment of renal manifestations of amyloïdosis.

Even if the very low number of AE preclude robust safety conclusions, the cardiovascular events occurrence in the Kiacta group remains an issue of concern: there were 15 patients (16.8%) in the eprodisate group, vs 8 patients (8.5%) in the placebo group who experienced cardiac events.
Therefore, there does appear to be a signal here for an increased arteriopathic/cardiac risk.

In addition, all of the above results are undermined by the inspection findings which question the validity of efficacy data submitted. (see above)

In summary,

- Efficacy has not been demonstrated to a statistically robust level: the primary efficacy endpoint is not significant at the alpha level of 0.05 and even less at the alpha level of 0.01 (pre-specified in the statistical analysis plan).

- The cardiovascular events occurrence in the Kiacta group remains an issue of concern: there were 15 patients (16.8%) in the eprodisate group, vs 8 patients (8.5%) in the placebo group who experienced cardiac events.

- Inspection results cast a doubt on the statistical analysis and its results.

Finally, the Applicant requested the CHMP, at the time of the responses to List of Outstanding issues, to consider a conditional marketing authorisation. The CHMP considered that, although the scope would apply to Kiacta according to Art. 2, (1st and 3d paragraphs) of the Commission Regulation (EC) 507/2006, the conditions of Art. 4 (1) (a) of the same Regulation were not fulfilled as the risk-benefit balance of Kiacta is negative.

In conclusion, although there is a suggestion of an activity of the product, the pivotal study failed to demonstrate the efficacy of Kiacta in AA amyloïdosis. Another controlled and randomized study would be necessary to demonstrate the efficacy.

Grounds for refusal

The efficacy of Kiacta has not been sufficiently demonstrated.

- The only pivotal study failed to sufficiently demonstrate the efficacy of Kiacta in the treatment of AA amyloidosis. Another controlled and randomized study is deemed necessary.
- The GCP inspection results cast a doubt on the statistical analysis and its results (pivotal study):
    - It could not be ensured that blindness was properly maintained.
    - An interim analysis was performed but not reported in the documentation of the study and therefore, it could not be ascertained that the decision to change the primary efficacy endpoint was not data-driven.
    - A Cox analysis was performed, but had not been planned in the statistical analysis plan.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Kiacta in the treatment of patients with amyloid A (AA) amyloidosis was unfavourable and therefore did not recommend the granting of the marketing authorisation.