25 April 2013
EMA/419554/2013
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report for Omontys

International Nonproprietary Name: peginesatide

Procedure No.: EMEA/H/C/002600

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Questions and Answers" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	**Omontys (previously Peginesatide Takeda)**
INN (or common name) of the active substance(s):	peginesatide
Applicant:	Takeda Global Research and Development Centre (Europe) Ltd
Applied Indication(s):	Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients undergoing dialysis.
Pharmaco-therapeutic group (ATC Code):	not yet assigned
Pharmaceutical form(s) and strength(s):	Solution for injection in pre-filled syringe 1, 2, 3, 4, 5, 6 and 8 mg

LIST OF ABBREVIATIONS

CHF	Congestive Heart failure
CKD	Chronic Kidney Disease
CSE	Composite Safety Endpoint
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HR	Hazard ratio
Hgb	Haemoglobin
MI	Myocardial infarction
NKF-KDOQI	National Kidney Foundation Kidney Dialysis Outcome Quality Initiative
PRCA	Pure red cell aplasia
PT	Preferred Term
Q4W	Once every 4 weeks
SA	Scientific advice
SMQ	Standard MedDRA Queries
SOC	System organ class
TEAE	Treatment emergent adverse event
TIW	Three times per week

1. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for AF37702 (peginesatide), in the "Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients undergoing dialysis",

is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (see section 6).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of outstanding issues.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

1. The benefit-risk of peginesatide in the correction of anaemia in ESA-naïve dialysis patients is currently considered negative. A concern remains on a potential increased risk in deaths and cardiovascular events as observed in the ESA-naïve non-dialysis patients compared to current ESA treatment. The increased risk vs current ESA treatment was highest in ESA-naive patients who showed a poor Hgb response upon initiation of ESA treatment. The correction study in ESA-naïve dialysis patients is too small to provide reassurance on this safety issue. Furthermore, although current target Hgb levels may be achievable upon peginesatide treatment within acceptable time-frames and there appears to be no clear unfavourable profile with regards to Hgb excursions vs Epoetin, data were obtained in a limited and this needs to be substantiated within a larger population. Currently, the benefits of peginesatide in the correction of anaemia in ESA-naïve dialysis patients are not considered to outweigh the potential risks in the presence of currently available safe and effective ESA treatment.

   The applicant should further justify the benefit/risk of peginesatide in the correction of anaemia in ESA naïve dialysis patients in relation to currently available ESA treatment.

2. Efficacy of peginesatide in the maintenance studies has not been demonstrated sufficiently.

   GCP inspection findings from two investigational sites and the sponsor have indicated findings with regards to insufficient oversight and monitoring, irregularities in data handling, out of protocol dosing (adjustment) for the Epoetin groups and concerns with regards to the definition of the PP Population. The GCP findings will require further follow-up and will have an impact on the overall evaluation of the application.

   The applicant should provide satisfactory responses to the final GCP findings and discuss whether these findings affected the results of the studies, taking into account the open-label non-inferiority design of the studies.

3. The Applicant has initiated several lines of investigation in order to identify the root cause of the serious hypersensitivity reactions, including fatal reactions, that have led to the withdrawal of the medicinal product in the USA. The Applicant should elaborate on such root cause analysis including quality, non-clinical, clinical and epidemiological approaches.

4. The Applicant should also elaborate on the measures being put in place to mitigate the risk of serious hypersensitivity reactions, including fatal reactions, in patients treated with peginesatide, with special attention to patients with multiple cardiovascular comorbidities.

5. The Benefit/Risk of the product is currently considered negative subject to the Applicant being able to remedy or mitigate the incidence of serious hypersensitivity reactions, including fatal reactions as currently reported to the CHMP. The Applicant is invited to discuss the Benefit/Risk balance of peginesatide (Omontys).

Questions to be posed to additional experts

Not applicable

Inspection issues

GMP inspection(s)

All relevant manufacturing sites underwent GMP inspections by EEA/MRA authorities with a satisfactory outcome within the last 3 years. Hence, no GMP inspections deem necessary within the scope of this MAA evaluation procedure.

GCP inspection(s)

A request for GCP inspection has been adopted for the following clinical studies: AFX01-12 and AFX01-14. The satisfactory responses to its findings in the GCP inspections report are part of the responses to the LoOI and will be needed by Day 181.

New active substance status

Based on the review of the data the CHMP considers that the active substance peginesatide contained in the medicinal product Omontys / Peginesatide Takeda Injection, 1-8 mg/0.5 ml pre-filled syringes is to be qualified as a new active substance in itself. It is not authorized in the European Union, and furthermore it is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorized substance in accordance with Directive 2001/83/EC.

Peginesatide is a synthetic dimeric peptide linked to polyethylene glycol; the molecule binds specifically to and activates the erythropoietin receptor and stimulates erythropoiesis in red blood cell precursors in a manner similar to recombinant erythropoeisis-stimulating agents (ESAs). Peginesatide is produced synthetically and the peptide portion of the molecule has no amino acid sequence homology to human erythropoietin; therefore peginesatide is not a derivative, active metabolite or pro-drug of other ESA authorized active substances.

An INN name has been requested from the WHO, which was granted and published in the WHO Drug Information, Vol. 25, No. 1, 2011 List 65. INNs are selected in principle only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula). It is the policy of the INN program not to select names for mixtures of substances, while substances that are not fully characterized are included in the INN system in exceptional cases only.

2. EXECUTIVE SUMMARY

2.1. Problem statement

Renal anaemia is a condition defined by low levels of red blood cells (RBC) and haemoglobin (Hgb) in patients with chronic kidney disease (CKD), caused by insufficient production of the endogenously secreted glycoprotein hormone erythropoietin (EPO) in the diseased and/or shrunken kidneys. EPO stimulates the progenitor cells of the RBCs in the bone marrow. The mass of functional kidney parenchyma is decisive for the production of EPO and the level of anaemia.

Renal anaemia will become apparent when the GFR becomes lower than 70 ml/min in men and 50 ml/min in women and is present in >90% of the patients undergoing dialysis (CKD stage 5). However, the diagnosis can only be established after exclusion of all other causes that may contribute to the anaemia.

All over the world there is an increase in patients with CKD reflected in the number of patients with stage 5 CKD that need any kind of renal replacement therapy (dialysis or transplantation). The data of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA) registry (2009), in which roughly 80% of patients were on haemodialysis and 20% on peritoneal dialysis, show an incidence of renal replacement therapy for end stage renal disease of 100 to 200 patients per million (ppm) population in different countries with an average around 140/ppm.

The prevalence of haemodialysis and peritoneal dialysis patients per million population differs from 300 to 700 ppm in different countries.

The main impact of anaemia on organ function is reduced oxygen delivery to tissues and the heart's compensatory changes, leading to fatigue and effort intolerance. The heart responds with increased cardiac output and left ventricular hypertrophy; impaired cardiac function may be the outcome. Other consequences are impaired cognitive function, sleep disorders, altered haemostasis and depressed immune function.

Treatment with exogenous replacement of EPO by recombinant hormone epoetin can relieve symptoms, reduce complications of anaemia and improve the quality of life while at the same time it offers the opportunity to avoid blood transfusions with risks of infection, iron overload and immunogenicity in kidney transplantation candidates.

Treatment of renal anaemia is indicated if the anaemia is symptomatic. The CHMP recommends a Hgb target range of 10 g/dL to 12 g/dL (EMEA/496188/2007).

Until now treatment with exogenous EPO is possible with several erythropoiesis stimulating agents (ESA), all produced by DNA recombinant techniques. Basically these ESAs are human-EPOs with different glycosylation. Many require frequent administration to maintain adequate Hgb levels. However, later on also a pegylated ESA (methoxy polyethylene glycol-epoetin, Mircera) was introduced and registered in Europe, offering the possibility to limit the administration of EPO (IV or SC) to once monthly.

Treatment with currently available exogenous human EPO-like ESAs can be complicated by pure red cell aplasia (PRCA). This can occur in a small minority of treated patients, leading to severe anaemia that can not be treated adequately. Anti-erythropoietin antibodies develop that block not only exogenous EPO, but also endogenous EPO. As a result the bone marrow is not stimulated.

2.2. About the product

AF37702 (peginesatide) is a synthetic dimeric peptide linked to polyethylene glycol (PEG). It is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients undergoing dialysis. The proposed dosing frequency is once monthly.

AF37702 binds specifically to and activates the EPO receptor and stimulates erythropoiesis in RBC precursors in a mode similar to currently available recombinant ESAs. Unlike currently available recombinant ESAs, AF37702 has no amino acid sequence homology to human EPO and hence is expected not to be immunologically cross-reactive to human EPO. On the basis of this feature,

AF37702 can be expected to have a reduced or absent risk for the complication of PRCA, and also to be a treatment option in patients with PRCA. The latter indication has not been included in the current MAA.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical program for AF37702 was initially designed to support the indication of treatment of anaemia in dialysis as well as non-dialysis CKD adult patients. Due to safety reasons, the non-dialysis population has been excluded from the MAA and the indication now being sought is focused on CKD dialysis patients only.

The dialysis development program included 3 main randomized, open-label, multicentre, comparative active-controlled, parallel group studies. Correction of anaemia was investigated in a phase 2 study and maintenance treatment was investigated in 2 pivotal phase 3 studies.

Within recent years, the EMA has reviewed the safety of ESAs. The review was initiated because of a possible increased risk in mortality and cardiovascular morbidity associated with the use of ESAs to achieve high target haemoglobin (Hgb) levels. Based upon this review, the CHMP recommended a uniform target Hgb range for all epoetins of 10 g/dL to 12 g/dL (EMEA/496188/2007). Hence, this target range is considered also applicable for AF37702.

During the development program, Scientific Advice (SA) from the CHMP was sought three times. In June 2006 SA was sought on toxico-pharmacological development. The SA in February 2008 covered several aspects of clinical development and the SA in February 2010 mainly covered quality development aspects.

In two procedures questions were provided involving the non-clinical development program. The subject of these questions were carcinogenicity studies (see also Non-clinical AR section 4.4) and QTc valuation (EMEA/H/SA/720/1/206/III/SME), and peptide-related impurities and degradants (EMEA/H/SA/1493/1/2010/II).

During the SA of February 2008 on the clinical development, the following comments and recommendations were made by the CHMP:

- Hgb target ranges: The CHMP recommended target ranges are applicable. The inclusion criteria of Hgb <11 g/dL and target range of 11-12 g/dL in the correction studies are not in line with the CHMP recommendations.
- Efficacy endpoints: The proposed primary endpoint of mean change in Hgb was acceptable. Hgb (sustained) responder rates and time to response were considered important secondary endpoints in correction studies.
- Non-inferiority margin: The non-inferiority margin of -1.0 g/dL was deemed too generous. A non-inferiority margin of -0.5 g/dL was recommended.
- Open-label design: Blinding is preferred. If blinding is deemed impossible, adequate justification for the open-label has to be provided and evidence should be provided that bias is at least highly unlikely.
- Safety of specific events: Incidence of elevated Hgb levels >12 g/dL and >14 g/dL should be provided. Events thought to be manifestations of exaggerated pharmacodynamics effects should be assessed, including information on most recent Hgb values, short-term change in Hb and ESA dose prior to the event. Immunogenicity should be assessed in all patients.

The Applicant has complied with the second and (partly) complied with the fifth recommendation. Other recommendations have not been taken into account sufficiently, most likely because studies were already on-going at the time SA was requested.

In accordance with Regulation (EC) No 1901/2006 ("Paediatric Regulation"), the Applicant has obtained from the EMA, prior to submission of MAA for this medicinal product:

- agreement of a Paediatric Investigational Plan (PIP) in accordance with Article 18 of the said Regulation.

- grant of a deferral in accordance with Article 21 of the said Regulation.
- grant of a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation on the grounds that AF37702 does not represent a significant benefit over existing treatments for paediatric patients.

(PIP Decision Number: P/130/2010).

The waiver applies to the paediatric population from birth to less than 1 year of age; for solution for injection, intravenous route, subcutaneous route; on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. The PIP completion, for studies with paediatric population from 1 to less than 18 years of age, is deferred until October 2024 with no dates stipulated for initiation of the studies. No compliance check is considered required for the MAA, as was confirmed by the European Medicines Agency at the MAA pre-submission meeting (on 23rd September 2011).

2.4. General comments on compliance with GMP, GLP, GCP

GMP:

Recent GMP certificates have been provided for the drug product manufacturing sites. No GMP inspection action prior to authorisation is considered necessary for the sites involved in manufacturing and testing of the drug product.

GLP:

According to the applicant, with the exception of the preliminary Ames assay, the dose range-finding reproductive toxicity studies, and antigenicity and antibody analysis studies, the toxicology studies and safety pharmacology studies were conducted in compliance with Good Laboratory Practices (GLP). The primary pharmacodynamic and the PK studies were non-GLP.

GCP:

According to the Applicant, the clinical studies were conducted with respect to Good Clinical Practice (GCP) guidelines. GCP issues were identified by the Applicant at some sites within the phase 2 dose-finding study AFX01-07 and at some sites included in the pivotal phase 3 studies AFX01-12 and AFX01-14. GCP issues were identified pre- and post-database lock. The Applicant performed post-hoc sensitivity analyses excluding data from 5 dialysis centers. These sensitivity analyses were conducted for the primary efficacy endpoint as well as key secondary efficacy endpoints, and showed no changes in the results when the data from these sites were excluded.

GCP inspections were requested to assess GCP compliance and the validity of the data within the MAA.

The reliability of the data should be assessed on the following points at the investigators sites:
- Completeness of source documentation
- Dosing information; adherence to study medication and dosing regimen
- Use of non-study ESAs
- Compliance with selection criteria
- Safety reporting

In addition, it should be assessed whether the sponsor/CRO performed adequate monitoring of the study sites.

Findings of the GCP inspection identified issues with regards to insufficient oversight and monitoring, irregularities in data handling, out of protocol dosing (adjustment) for the Epoetin groups and concerns with regards to the definition of the PP Population.

The integrated inspection report was issued on 07 December 2012. The applicant was requested to provide complete response to the findings of the GCP inspection. The applicant requested a metting during which were discussed the proposals, including new analyses, that could demonstrate if the acknowledged findings did or not impact the integrity and reliability of the data.

2.5. Type of application and other comments on the submitted dossier

- **Legal basis**

The application has been submitted in accordance with Article 8 (3) (full application) of Directive 2001/83/EC, as amended (New active substance). This full application contains results of quality, pre-clinical and clinical studies.

- **Accelerated procedure**

Not applicable

- **Conditional approval**

Not applicable

- **Exceptional circumstances**

Not applicable

- **Biosimilar application**

Not applicable

- **1 year data exclusivity**

Not applicable

- **Significance of paediatric studies**

A Paediatric Investigation Plan with deferral and a waiver have been agreed with the Paediatric Committee (PIP Decision Number(s): P/130/2010). See also section 2.3.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Quality aspects

Introduction

Peginesatide is considered as a new active substance, and it is not authorized in the European Union, and furthermore it is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorized substance in accordance with Directive 2001/83/EC. Peginesatide is a synthetic dimeric peptide linked to polyethylene glycol; the molecule binds specifically to and activates the erythropoietin receptor and stimulates erythropoiesis in red blood cell precursors in a manner similar to recombinant erythropoeisis-stimulating agents (ESAs). Peginesatide is designed for once monthly dosing and has no amino acid sequence similarity to human EPO. The proposed initial starting dose for the correction of anaemia is 0.04 mg/kg and the conversion from other ESAs is possible via a conversion scheme. Peginesatide Injection will be available in 7 strengths of solution for injection in prefilled syringes (PFS): 1 mg/0.5 ml, 2 mg/0.5 ml, 3 mg/0.5 ml, 4 mg/0.5 ml, 5 mg/0.5 l, 6 mg/0.5 ml, and 8 mg/0.5 ml.

Drug substance

General Information

Concise general information has been provided on the complex drug substance.

Manufacture

Details on the manufacturing process and synthetic scheme to produce the drug substance are provided. Standard techniques and procedures for synthesis and purification are used.

In general adequate specifications are applied for in-process parameters.

Based on the results obtained the manufacturing process can be considered successfully validated.

Through the phases of clinical development the manufacturing process has been subject to various changes none of which did have a significant impact on the quality attributes of drug substance. The most notable changes were implemented before the start of the pivotal clinical studies and were mainly addressing technical issues and process efficiency. All changes implemen-ted have been extensively discussed and are supported by a detailed process evaluation summary for each step of the manufacturing process where the changes were discussed in the context of the related process evaluation studies performed.

Characterization

The drug substance is extensively characterized. Elucidation of structure and characterization of Peginesatide have been conducted using techniques commonly employed for peptides as well as those used for higher molecular weight molecules. These include structural studies, physicochemical tests, purity and impurity tests, and biophysical and biological testing.

Impurities

Among the impurities occurring in Peginesatide the peptide-related impurities were characterised most extensively. The potential or observed occurrence of each particular impurity candidate was supported by synthesis of each impurity along with its structural and functional characterisation and analytical detection within the Peginesatide drug substance lot.

Heavy metals and residual solvents are effectively controlled by respective limits in the drug substance specification(s).

Specification

In general a broad set of drug substance specifications is applied to control the drug substance. These include identification tests (HPLC, SEC [molecular weight], acetate ion [IC]), 3 HPLC methods for impurities, Heavy metals by ICP-MS, residual solvents by GC, assay methods (HPLC peginesatide content, acetate content by IC, biopotency by ELISA), physical-chemical methods (Water content, MALDI-TOF molecular weight), and microbial methods (TAMC, TYMC, and bacterial endotoxins). . Questions on (validation) aspects of various methods have been asked for. Batch analysis results have been provided on commercially representative batches.

The applicant is asked to discuss some aspects for a characterisation method.

Reference standards or materials

All standards follow a predefined acceptable mode of qualification and recertification.

The applicant is asked to confirm and provide additional data on the origin and full characterisation of some reference standards.

Container closure system

The drug substance is stored in amber glass bottles with polytetrafluoroethylene (PTFE)-lined polypropylene closures.

Stability

Stability testing of Peginesatide has been performed with primary stability batches and process validation batches at the recommended storage condition of below 0ºC (protected from light), and at an accelerated condition of 2–8ºC (protected from light). The drug substance has been shown to be stable according to the results obtained when tested according to stability-indicating test parameters. Peginesatide is sensitive to light as detected by a photostability study. Apart from the light protecting properties of the container, storage at long term conditions (below 0°C) will ensure further protection from light. All on-going stability studies will be completed up to the intended duration of studies.The proposed retest period and retesting can be supported based on sufficient available stability data covering the proposed retest period.

Drug product

Description and composition of the drug product

Peginesatide Injection, PFS (5 mg/0.5 mL) is manufactured aseptically and contains peginesatide in an aqueous, phosphate-buffered, isotonic, solution (pH approximately 6.0) for parenteral administration. The formulation also contains Polysorbate 20 as a surfactant and sorbitol for tonicity. The drug product is packaged in USP / Ph. Eur. Silicone-coated Type I clear glass syringes with rubber stoppers, staked needles, needle shields and plungers. Each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

The quantitative description of the drug product presentations is satisfactory. Comprehensive development studies have been performed to evaluate the nature and concentration of excipients for the liquid drug product formulation. The finally selected formulation contains excipients frequently used for parenteral protein solutions. No new excipients are employed.

Pharmaceutical development

The target formulation during development was a liquid formulation for single-use. The pH was optimised with respect to solubility and stability of the drug substance. At the target pH of 6.0, the solution is sufficiently stable while avoiding local injection pain due to low pH. The information on the formulations used throughout clinical development is sufficiently detailed. The main difference between the clinical trial material and the commercial product is the drug substance con-centration and the primary packaging (SDV versus PFS). The two single dose formulation presentations developed, single dose vials (SDV) and pre-filled syringes (PFS) are based on the same formulation. Only the PFS presentation is proposed for commercial distribution in the EU.

The drug product manufacturing process has undergone a number of minor adjustments throughout development that are described in detail in the dossier. Comparability has been demonstrated between the proposed commercial drug product and the drug product used for the clinical studies.

Adequate manufacturing process development data have been provided.

Manufacture of the product

The manufacturing process consists of a formulation step that includes dissolution of the excipients and drug substance (DS) followed by aseptic filtration and filling into syringes.

Critical and in-process controls have been designated for the drug product manufacturing process.

Commercial scale process validation batches have been manufactured at the proposed commercial manufacturing site. The process validation strategy as agreed in CHMP Scientific Advice was followed. No differences in manufac-turability were observed across the strengths. The manufacturing process performed consistently and the results for all batches were acceptable.

Control of excipients

All excipients used are described in Ph. Eur. Sufficient information has been provided.

Product specification

Drug product specifications are applied for appearance, identification (RP-HPLC, SEC), peginesatide HPLC content, ELISA biopotency, HPLC impurities HPLC Total Sulfoxidation, total degradation products (calcul.), physical-chemical methods (pH, osmolarity, volume in container, particulate matter) and microbial methods (bacterial endotoxins, sterility). All analytical methods have been adequately described. All quantitative methods have been validated.

Some additional data is asked with regards to one specification.All other drug product specifications are either pharmacopoeial or usual, and in accordance with the Ph. Eur. Monograph on *Parenteral Preparations*. Batch analysis results have been provided for Peginesatide PFS batches used for primary stability studies.

Reference standard

Identical reference standards as for control of the drug substance are employed for control of the drug product.

Container Closure System

The container closure system for AF37702 Injection, PFS drug products consists of a USP/Ph. Eur. Type I clear glass syringe with staked needle and needle shield, and a rubber stopper. The extractables identified have been evaluated and found to be safe and acceptable. Overall, the container closure system is considered suitable to support stability of the Peginesatide drug product, if the syringes are packed into the outer cartons to ensure protection from light.

Stability

PFS batches, covering the whole range of strengths, have been put on stability (2-8°C, up to 24 months data, and 25°C/60% RH for 6 months, and tested according to a matrix design. In addition some stress scenarios like freeze-thaw cycles and light exposure have been investigated. The photostability studies demonstrate that the product is sensitive to light but is sufficiently protected from light by the outer paperboard carton.

In summary, the analytical methods applied are considered adequate to assess the stability profile of the DP.

The shelf-life specifications suffice for storage for 2 years at 2-8°C for and max. 30 days at 25°C/ 60% RH. Based on these data the additional storage label of allowing one single period of ≤ 30 days at room temperature ≤ 25ºC, without possi-bility to return to refrigerator, can be accepted. Based on the presented data the claimed shelf-life if stored in the proposed pre-filled syringe at 2-8°C can be accepted. Keep the pre-filled syringes in the outer carton in order to protect from light. Additional storage instruction: The end-user may store the medicinal product, if necessary, at a room temperature not above 25°C for one single period of no more than 30 days. Once removed from the refrigerator the medicinal product must be used within this period.

TSE Risk Materials

No TSE risk materials either from human or animal source have been used in the manufacture of either the drug substance or the drug product.

Discussion and conclusions on chemical, pharmaceutical and biological aspects

Most outstanding quality issues have been resolved by the applicant. However, regarding one issue additional data is asked for conserning quality attribute of the active substance.

3.2. The issue above and some other concerns should be resolved during this procedure.Non clinical aspects

Pharmacology

Peginesatide (AF37702) is a synthetic, covalent conjugate of a dimeric peptide comprised of two identical, 21 amino acid chains coupled to two polyethylene glycol moieties via a linker. The amino acid sequence was identified through screening of the human EPO receptor with recombinant peptide display libraries. The peptide sequence has no similarities with erythropoietin. The recommended human starting dose is 0.04 mg/kg, which then needs subsequent titration towards the desired pharmacological effect (Hb target range of 10-12 g/dl).

Primary pharmacology

In vitro

In vitro pharmacology studies demonstrate that peginesatide binds to and activates the human erythropoietin (EPO) receptor (HuEPOr) and stimulates human red blood cell (RBC) precursors to undergo proliferation and differentiation similar to other erythropoiesis stimulating agents (ESAs). It was shown that the presence of the PEG moiety does not decrease the magnitude of *in vitro* HuEPOr activation or signal transduction. No in vitro data were provided regarding the affinity of peginesatide against the EPO receptor in the non-clinical species. However, in vivo data indicate a similar level of affinity of AF37702 for the erythropoietin receptor (EPOr) and AF37702 pharmacologic activity expected all species tested except the dog. Cynomolgus monkey receptor binding affinity has not been experimentally evaluated; however the homology between the monkey and human receptor sequence, particularly in respect to key residues for AF37702 binding, suggest that the affinity would be similar to that of the human receptor.

In vivo

In vivo pharmacodynamics studies indicate that AF37702 administered by either the intravenous (IV) or subcutaneous (SC) route induces a transient, dose-dependent increase in reticulocytes (percentage and numbers), resulting in a dose- and time-dependent increase in hematological parameters (hemoglobin [Hgb], hematocrit [Hct], RBC counts) in mice, rats, rabbits and monkeys, but not in dogs. The earliest change indicative of an erythropoietic response was a transient, roughly dose-dependent increase in the percentage of reticulocytes. The increase in reticulocytes usually peaked by Days 4 to 6 after dosing, and followed by a decrease in values to generally less than the concurrent or to baseline values before reticulocyte numbers return to or towards control values. The increase in reticulocytes was subsequently followed by an increase in hematological parameters such as red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct). Dose- and time-dependent increases in RBC, Hct and Hgb levels were seen in all the various species at doses ≥ 0.1 mg/kg. Also the duration of the hematology alterations and the time to maximal response appeared exhibit a dose-dependent relationship similar to the reticulocyte response. Repeat dosing resulted in a sustained increase in the hematological parameters, which translates into a pronounced polycythemia regardless of the length of the study.The hematological response is reversible upon cessation of dosing.

Effects on secondary parameters (including mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH)) were found in several of the PD studies (and all of the repeated dose toxicity studies). Smaller RBCs in mice and the decreases in MCV, MCHC and MCH in rats were observed concurrently with intense production of RBCs. These effects were attributed to insufficient iron stores needed to adequately generate normal (normocytic) RBCs. During the recovery phase a significant increase in serum Fe was note which was attributed to release of Fe following the degradation of the (high levels) of RBCs. Not only the size but also dose dependent change in RBC morphology (incidence and severity) was noted in some of the PD studies and all of the toxicity studies. In addition, increases in WBC were noted.

The pharmacodynamic effect after SC administration in normocytic rats appears to be similar to that of the IV route.

Disease models

Three studies were conducted to determine if a single IV or SC dose of peginesatide would correct anaemia in 5/6 nephrectomized rats as a model for chronic kidney disease (CKD). Significant erythropoiesis with characteristic changes in reticulocyte levels (as seen in normocytic animals), and dose- and time- dependent increases in RBCs, Hgb and Hct levels were noted in all three studies. The effect of peginesatide on creatinine levels was studied in one study. Treatment with peginesatide resulted in a decrease of creatinine levels of anaemic/renal impaired rats at all dose levels which was statistically significant in the 10 mg/kg group.

One study was performed to evaluate the potential for peginesatide to reverse anaemia in an EPO specific antibody mediated pure red cell aplasia (PRCA) rat model. In this model EPO-specific antibodies were induced in rats which subsequently suffer from severe anaemia that is associated with the presence of anti-EPO antibodies. Administration weekly of peginesatide (0.15 mg/kg, by IV or SC) resulted in an increase in Hgb and a correction of the anaemia for the duration of the study. Cessation of peginesatide treatment was followed by a re-emergence of persistent anaemia secondary to the on-going presence of the anti-EPO antibodies.

Secondary pharmacology

Absence of cross-reactivity in cell proliferation assays with related human hematopoietic cytokine receptors, including the thrombopoietin receptor (TPOr) and granulocyte colony stimulating factor receptor (G-CSFr) was demonstrated at concentrations up to 100 nmol/L. Binding specificity of peginesatide was evaluated in an *in vitro* binding assay encompassing a wide variety of receptor types. Of the 66 receptors tested, 65 showed no significant binding, 1 showed weak binding at doses far above clinical relevant levels.

No proliferative or anti-proliferative activity of peginesatide was seen of a panel of 7 human epithelial adherent tumour cell lines treated with peginesatide at concentrations far above clinical relevant levels (up to 1 µmol/L). This study indicates that peginesatide will probably not have a direct effect on the growth of epithelial tumors.

Safety pharmacology:

In dedicated safety pharmacology studies, no effects or no clinically relevant effects of peginesatide treatment were noted on neurological (CNS) parameters in mice (doses up to 100 mg/kg), on respiratory system in guinea pigs (doses up to 50 mg/kg) and on renal system in rats (doses up to 50 mg/kg). No clinically relevant effects were noted in hERg assay *in vitro*, or on ECG parameters evaluated in *in vivo* monkeys repeated dose toxicity studies. The dog was used in the CV safety pharmacology evaluations as it was the nonrodent species used to support the development program for other ESAs. However, as noted above subsequent pharmacology studies indicate that AF37702 is not active in the dog.

Pharmacodynamic drug interactions.

No studies were performed. This is agreed.

Pharmacokinetics

The kinetics of peginesatide after single and repeated dose administration by either IV or SC administration were studied in mice, rats (pregnant and non-pregnant), rabbits, dogs, and/or monkeys. Furthermore, the kinetics of peginesatide were evaluated in a rat model of chronic kidney disease. Pharmacokinetic studies were under non-GLP and toxicokinetic studies were under GLP. ELISA methods were used to analyse peginesatide in plasma from the (toxico)kinetic studies. Not all analytical methods were sufficiently validated and can lead to unreliable measurements of the peginesatide plasma concentrations and thus to unreliable kinetics.

After single dose IV or SC administration, the pharmacokinetics were similar between the different non-clinical species, except that bioavailability after SC administration was much higher in monkeys compared to rats and humans (~85% versus ~35%). After SC administration of AF37702 to rats, absorption was slow and bioavailability was ≈26%. In general, the Cmax increased dose-proportional and the AUC increased more than dose-proportional. Plasma clearance was slow and decreased with increasing dose (increased half-life). Vss was dose-independent and less than the blood volume

indicating confinement to the vascular compartment, but slow distribution was observed to organs. Similar kinetic profiles were observed at a clinically relevant dosing regimen in the non-clinical species after repeated dosing compared to Day 1. Peginesatide plasma levels were below the limit of quantification prior to the new dose, but plasma accumulation was observed after repeated dosing. This is most likely due to the pharmacologically-related hemoconcentration. Antibody formation against peginesatide was observed, but the formation did not influence the kinetics of peginesatide in the non-clinical kinetic and toxicokinetic studies. In addition, impurities in the clinical formulation did not appear to have an effect on the pharmacokinetics of peginesatide in rats after IV administration.

Evaluation of the PK profile in an experimental model of CKD in rats demonstrated that AF37702 following a single IV administration is cleared more slowly in the 5/6 nephrectomized rats compared to normal rats, which is consistent with a predominantly urinary excretion of the drug.

The PK profile of AF37702 was not altered by variations in molecular weight (MW) as a result of a 6 kDa difference in the MW of the PEG component of AF37702.

Organ distribution was slow and tended to be greatest to organs associated with extramedullary hematopoiesis (e.g. bone marrow and spleen), excretion, and/or are highly perfused. Once distributed to an organ, elimination was slow (detected up to 60 days after dosing). It is therefore likely that at a clinically relevant dosing regimen accumulation will occur in these organs. This will lead to a sustained pharmacologic effect after ending the peginesatide administration. Following SC administration, distribution to tissues is slower versus IV dosing with a depot effect at the site of injection. No distribution to blood cells or binding to plasma proteins or melanine was observed for peginesatide.

Peginesatide is directly excreted via the urine as parent compound (minor via faeces). Peginesatide is not metabolised or only to a slight extent in the non-clinical species and humans. The potential of for drug-drug interaction between peginesatide and drugs metabolised by CYP isozymes or drug transporters is negligible.

Peginesatide is a large molecule and the placental transfer of peginesatide is most likely very limited in humans. This was supported by the pre-clinical finding that the placental transfer is very low at dosages much higher than the clinically used dose. Drug-derived radioactivity was excreted via milk in lactating rats. (the concentration of peginesatide in milk was ~12% to ~13% of that in plasma ~ at 24 and 48 hours after dosing).

Toxicology

A comprehensive evaluation of the safety and toxicity of AF37702 was performed in Good Laboratory Practice (GLP) toxicology studies that were consistent with CHMP and ICH-Guidelines. The toxicology studies were conducted to support chronic use of AF37702 for the treatment of anemia associated with chronic kidney disease (CKD). The dosing regimen in the nonclinical studies approximated the intended clinical dosing interval of every 4 weeks (Q4W) at an anticipated maximum human dose (MHD) of 0.35 mg/kg and utilized routes of administration (ie, intravenous [IV] and subcutaneous [SC]) that will be used clinically. The initial nonclinical toxicology studies were conducted with a dosing regimen of once a week based on a potential once a week dosing regimen initially planned for oncology patients.

In all toxicity studies peginesatide-treatment induced changes in hematology parameters that are consistent with the pharmacology of peginesatide (see pharmacology section). These changes included increases in RBC parameters (RBC, Hgb, Hct,), increase and subsequent decrease in the number of reticulocytes, and altered RBC morphology. Also changes in the secondary parameters (MCV, MCHC and MHC) were observed. Splenic and liver enlargement was seen in rodents but not monkeys, and this was accompanied by morphologic changes indicative of increased red cell production (extramedullary hematopoiesis). Furthermore, increased bone marrow cellularity was seen in the femoral bone marrow smears of all treated rats and monkeys. Partial but mostly full reversibility of these effects was noted during the recovery phase.

In addition to these pharmacological effects also other, adverse, effects were seen including mortality in both the rat and monkey repeated dose studies. All these effects considered due to exaggerated pharmacology. Effects attributed to the pronounced hemoconcentration and increased blood viscosity included heart and vascular lesions, renal pathology, ocular changes, congestion and/or darkened tissue, inflammation of the choroid plexus (monkeys), and darkening of extremities (rodents). Effects on coagulation parameters, AST, glucose, bilirubin, creatinine were generally considered due to *in vitro*

artifacts cause by polycythemia (eg *in vitro* RBC lysis). The increase in WBC was attributed to general peginesatide-induced bone marrow activation.

Peginesatide was not genotoxic based on the core battery of genotoxicity studies. No treatment-related neoplastic findings were seen in the 2-year rat carcinogenicity studies. In the 26-week transgenic (Tg.Ras.H2) mice carcinogenicity study a treatment related increase was seen in hemangiosarcomas in particular in the spleen.

In the 26 week Tg.RasH2 carcinogenicity study a treatment-related increase in the frequency of uterine angiectasis was observed. It was stated that this is a spontaneous lesion in this strain of mice.

In all reproductive and development toxicity studies treatment-related effects on embryo, perinatal and postnatal development were seen with no or limited safety margin. Adverse effects on fertility and F1 sexual maturation, reproductive performance and learning and memory were also noted but at higher doses. However also the observed reproductive toxic effects were considered due to hemoconcentration and thus caused by exaggerated pharmacology.

Local tolerance data indicate that SC administration of peginesatide is well tolerated at the injection site.

Evaluation of the potential immunogenicity conducted as part of the repeat dose toxicity studies in rats and monkeys, and in a separate monkey study. It was found that peginesatide was not immunogenic in rats and had a low potential for immunogenicity in the monkey.

Not all of the proposed specification limits for impurities have been qualified in the non-clinical toxicity studies.

Ecotoxicity / environmental risk assessment

The PECsurfacewater is lower than the trigger value of 0.01 µg/L. Therefore, tThere is no need for a Phase II Tier A environmental risk assessment. Peginesatide is not expected to cause adverse effects to the aquatic environment.

Substance (INN / Invented Name): peginesatide					
CAS-number (if available): 118570-58-9					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} ranged from -0.6761 to -1.2848 at pH 4 to pH 9			Not PBT
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	log K_{ow} ranged from -0.6761 to -1.2848 at pH 4 to pH 9			not B
	BCF				not B
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	4.4 x 10^{-3}	µg/L			< 0.01 threshold
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Result**			**Remarks**
Adsorption-desorption	Only summary	K_{oc} = 6.820 L/kg			
Ready Biodegrability test	OECD 301B	3.6% (28 days)			Not readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Conclusion**
Algae, Growth inhibition test	OECD 201	NOEC	> 100000	µg/L	
Daphnia sp. Acute toxicity test	OECD 202	NOEC	> 100000	µg/L	
Fish, Acute embryo test	OECD 212	NOEC	> 100000	µg/L	
Activated sludge, Respiration inhibition test	OECD 209	EC50	1000000	µg/L	

Discussion on non-clinical aspects

The Applicant has performed an extensive in vitro and in vivo programme to demonstrate that AF37702 fully mimics all actions of epoetin, e.g. that it is a full agonist on the human epoetin receptor. It turned out that AF37702 has a lower potency than human epoetin, meaning that higher concentrations are required to elicit the same magnitude of the effect. However, the magnitude of the maximal response was the same as with human epoetin so that AF37702 is indeed a full agonist, and its lower potency can be overcome by increasing the dose. No in vitro data were provided regarding the affinity of peginesatide against the EPO receptor in the non-clinical species was provided. The choice of the animal models was solely based on in vivo responsiveness to peginesatide which appear to be similar across the species except the dog.

In the in vivo studies no direct comparison of AF37702 and epoetin was performed. The main endpoints in the in vivo studies were increase in reticulocyte count and increase in hemoglobin what is appropriate for an epoetin agonist. All other standard red blood parameters were also determined and were in line with increased hematopoiesis. Also the effects of peginesatide on WBC and platelets appear to be a class effect of epoetin receptor agonist and are not related to a new toxicity of peginesatide.

In one study using the CKD model (AF04-001) the number of animals/sampling point varied between time points, and generally reduced in time. This time-dependent decrease in the number of animals, including vehicle-controls, can be attributed to premature death. The explanation that this was due to surgical procedure and not to the test drug is considered plausible as the rate of mortality was comparable across all groups. Furthemore no test article-related effect on survival was seen in the other studies using a CKD.

The Applicant has discussed various issues with regard to the PK/PD analysis. The serum half-life time of the PD effect (in particular the Hgb and Hct increase) does not correspond to the plasma half-life of peginesatide, but corresponds to the life-time of the RBC. Even a short exposure to EPO can result in a sustained increase in RBC numbers, without apparently impacting the actual duration of the maturation process or the RBC lifespan. With an increase in EPO receptor occupancy, the rate of RBC formation will increase because there will be an increase in the recruitment and subsequent maturation of erythroid precursor cells. Once a certain threshold is reached, an increase in dose will not result in an increase in the rate but in the overall response. Thereofe increased dosing does not speed up the RBC production, but rather prolong the duration of increased RBC production, resulting in higher levels of RBC, Hgb and Hct.

At repeated dosing at clinically relevant dosages and dosing regimen, peginesatide is cleared from plasma prior to the subsequent dose, but will most likely accumulate in organs involved in the erythropoiesis (see kinetics section). RBC count data collected from the 9-month monkey reversal group indicate that there was no apparent tissue accumulation of AF37702 which could elicit continued stimulation to maintain the high level of RBC counts even after cessation of treatment.

Since no good comparison can be made of the effects of QW, Q2W or Q3W dosing on PD it is not possible to determine if monthly dosing as is proposed in the clinic is the best treatment regimen. It is not clear if more frequent administration of lower dose levels could provide similar PD effects, but may reduce adverse effects or provide opportunities to prevent the induction of too high levels of RBC production (see clinical section).

Secondary pharmacodynamics was investigated by a standard screen for binding to 66 different potential off-target receptors. The battery included G-protein coupled receptors, ion channels, cytokine/growth factor receptors, nuclear receptors, and transporters. Relevant interaction (61% inhibition of tracer binding at 10 µM AF37702) was observed with the estrogen receptor alpha (ERα). The Applicant considered it unlikely that this interaction plays a role in vivo because AF37702 would have to cross the plasma membrane before binding to the intracellularly located ERα is possible. Since crossing the plasma membrane is unlikely for a peptide, this argument is endorsed.

Furthermore, the Applicant studied the effect of AF37702 on tumour cell proliferation in vitro since it is known that tumour cells may express epoetin receptors and that activation of these receptors may contribute to proliferation. This study was performed because it cannot be excluded that epoetin receptors on tumour cells differ in some aspects from normal epoetin receptors on hematopoietic cells. No relevantly increased proliferation was observed in the tumour cell lines tested at concentrations that yielded a clearly positive response in the positive control TF-1 cells. Several comments on the study design can be made which prohibit a definite conclusion based on this study. However current

clinical data, including a clinical; trial in tumour patients reveal no hints for accelerated tumour proliferation with peginesatide. Although the number of study participants and the study duration appear rather limited, suitable follow-up measures may yield more reliable information than additional non-clinical studies which are never fully predictive for humans. Thus, no new non-clinical data are requested.

Safety pharmacology was also studied in respect to CNS, CV function, respiration and kidney. There were no relevant findings; however, full CV parameters were only determined in dogs, according to standard procedures, but AF37702 was found to have no pharmacodynamic effects in dogs. Hence, the value of safety pharmacology studies in dogs is limited to the absence of CV effects via an off-target receptor.. ECG data from the monkey repeated-dose toxicology study did not reveal relevant alterations in response to peginesatide. Thus, heart rate, rhythm and other ECG parameters are obviously not influenced by peginesatide, but other cardiovascular (CV) effects, e.g. blood pressure, cannot be detected in the ECG. In conclusion, data from dogs and monkeys make it unlikely that peginesatide has undesired acute effects on CV parameters. Further CV safety assessment has to be done in the clinical setting.

Most of the dosages investigated in the single and repeated non-clinical studies were (much) higher than the clinical dosage used to treat patients with chronic kidney disease (0.04-0.1 mg/kg). The AUC of peginesatide is more than dose-proportional, resulting in an overprediction of the exposure when extrapolating the data from the non-clinical species and humans. Furthermore, in humans with chronic kidney disease higher AUC values and slower clearance were observed compared to healthy humans. This was also observed in the rat model for chronic kidney disease compared to healthy rats, indicating that in healthy animals an underestimation of the exposure and overestimation of the clearance might be made.

An extensive package of non-clinical toxicity studies were provided. Based on the nature of the substance (PEGylated peptide) which can be expected to be relatively specific, and the absence of placental transfer, omission of certain studies (eg genotoxicity, long term repeated dose toxicity studies in two species, full set of reproductive toxicity studies, antigenicity studies) or an altered approach addressing a safety concern reducing then number of test animals (carcinogenicity) might have been justifiable.

It is agreed that the peginesatide-induced toxicity seen in general toxicity as well as reproductive toxicity studies are most likely caused by the sustained and pronounced hemoconcentration caused by an erythropoietin stimulating agent administered to healthy, normocytic animals. The doses used in the general toxicity studies were very high and (by far) exceeded the clinical dose/exposure. In addition, the clear toxic effects were noted at least one dose level above which pharmacological activity was detected. A no-observable-effect level was generally not identified in the toxicology studies because the pharmacological effects of AF37702 were noted across all test article groups.

In addition to pharmacodynamics effects, minimal macrophage cytoplasmic vacuolation in the choroid plexus of the brain were noted. The Applicant argues that this finding is consistent with secondary effects of exaggerated pharmacology. However literature data on the toxicityu of PEG indicates thate these effects are more likely related to the PEG moiety of AF37702. The possible impact of this finding on brain function especially after long-term treatment with PEGylated drugs, remains unclear.

Carcinogenic potential of AF37702 was tested in a 2 year rat bioassays and a 26 week transgenic bioassay in Tg.rasH2 mice.

In the 26-week transgenic (Tg.Ras.H2) mice carcinogenicity study a treatment related increase was seen in hemangiosarcomas in particular in the spleen at doses similar to the human maximal exposure. This was attributed to exaggerated pharmacology causing splenic hypoxia which has been associated with induction of hemangiosarcomas. This reasoning is agreed. A dose-dependent increase in the frequency of uterine angiectasis was noted in the 26 week Tg.RasH2 carcinogenicity study. This phenomenon was not association with cell proliferation and hyperplasia. The apparent dose-response relationship might be caused by an interaction with the vascular development, however it appears to be rather a chance finding, as the frequency is in the range of the historical controls in the testing facility.

In all reproductive and developmental toxicity studies exaggerated pharmacology was observed which resulted in embryo-fetal toxicity in both, the rat and rabbit, by perturbing placental blood flow. In the embryo-fetal development studies in the rat, malformations like cleft palate, sternoschisis or/ sternum anomaly and thymic remnant in the neck were observed at doses of ≥0.05 mg/kg Q3D. Thymic

remnant in the neck is considered a variation and not a malformation, and the high dose group the incidende was only marginally above historical control values from the conducting CRO..

While not all of the proposed specification limits for impurities have been qualified in the non-clinical toxicity studies, most of these limits can be deemed acceptable. Further discussion on one impurity was deemd necessary Metabolism of this substance is not expected, and clearance cannot occur. However new data indicate that it is not stable under simulated physiological conditions. It is agreed that it is likely that in a plasma environment the breakdown will be faster. No accumulation of this impurity is to be expected. In addition, new studies indicate a lack of genotoxic potential. In addition a 4-week IV studyhas been performed with increased levels of this impurity but the study report is not yet available.

Conclusion on non-clinical aspects

Non-clinical studies indicate that peginesatide is an effective erythropoiesis stimulating agent with an acceptable safety profile. From a non-clinical point of view no major objections have been raised, and there are no objections to the grant of a marketing authorisation. However some amendments to the SPC are needed.

3.3. Clinical aspects

Tabular overview of clinical studies

Table 1 provides a tabular overview of the most relevant clinical studies for AF37702.

Table 1: Summary of AF37702 Clinical Development Program

Study ID	No. of study centres / locations	Design	Study Posology	Route	Study Objective	Subjects by arm entered/ compl.	Duration	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
Phase 1/2 studies										
AFX01-0401	1 Europe	Double blind placebo controlled randomized sequential cohort, single dose excalation	AF37702: single dose 0.025, 0.05 or 0.1 mg/kg	IV	First in human evaluation of safety, PD and PK	28/25	Single dose	M	Healthy subjects	PK
AFX01_101	2 United States	Phase 1, randomized, double-blind, placebo and positive controlled three-way crossover study QTc study	AF37702: Single 0.1 mg/kg IV Moxafloxacin 400 mg tablet Placebo	IV	QT/QTc study	65/61	Single dose	M/F = 19/46 35.6 (19-50 yrs)	Healthy subjects with normal ECG and QTcF interval of ≤450 msec and a heart rate of 45-90 bpm	QTc interval
AFX01_102	1 United States	Open label, randomized, single dose, crossover	AF37702: Single 0.1 mg/kg	IV	Bioavailability/bio-equivalence	20/20	Single dose	M/F = 9/11	Healthy male and female subjects	PK
AFX01_103	1 United States	Open label, randomized, single dose, crossover	AF37702: single 0.05 mg/kg	SC	Bioavailability/bio-equivalence	36/33	Single dose	M/F= 18/18	Healthy male and female subjects	PK
AFX01_104	2 United States	Open label, randomized, single dose, crossover	AF37702: single 0.05 mg/kg	SC	Bioavailability/bio-equivalence	80/74	Single dose	M/F= 58/22	Healthy male and female subjects	PK
AFX01_105	2 United States	Open label, randomized, single dose, crossover	AF37702: single 0.05 mg/kg	SC	Bioavailability/bio-equivalence	80/70	Single dose	M/F= 52/28	Healthy male and female subjects	PK
CPH-001	1 Japan	Single dose, sequential cohort, dose escalation	AF37702: single, 0.0125, 0.025, 0.05 or 0.1 mg/kg	IV, SC	safety, PD and PK	80/79	Single dose	M	Healthy male subjects	PK
Phase 2 dose-finding, PD and PK dialysis studies										
AFX01-03	15 United States	Phase 2, open-label, sequential, dose-finding, PD and PK trial	11 cohorts received AF37702 in different Epoetin alfa-to-AF37702 conversion factor-, tiered weight-based or tiered fixed dose dosing strategies with or without a 1wk transition period	IV	Conversion from Epoetin alfa and maintenance: Dose finding	164/127	13 or 27 wks	M/F = 94/70 59.1 (23-94 yrs)	Subject with CRF on dialysis and previously treated with Epoetin alfa	PD, PK, Safety
AFX01-07	15 Bulgaria, Romania,	Phase 2, open-label, sequential,	6 cohorts received AF37702 in different Epoetin alfa-to-AF37702	IV or SC	Conversion from Epoetin alfa and	91/83	29 wks	M/F = 57/34	Subject with CRF on dialysis and	PD, PK, Safety

Study ID	No. of study centres / locations	Design	Study Posology	Route	Study Objective	Subjects by arm entered / compl.	Duration	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
	United Kingdom	dose-finding, PD and PK trial	conversion tier as weight-based dose, with or without a 1wk transition period		maintenance: Dose finding			59.1 (19-77 yrs)	previously treated with Epoetin alfa	
Main studies: Phase 2 and 3 active-controlled dialysis studies										
AFX01-15	17 Russia	Phase 2, randomized, active-controlled, open-label, multicentre study	AF37702: 0.04 mg/kg or 0.08 mg/kg Q4W Epoetin: 50 U/kg three times a week	IV	Correction phase: Dose response and safety	AF37702 0.04 mg/kg: 39/37 AF37702 0.08 mg/kg: 37/36 Epoetin alfa: 38/34	28 wks	M/F = 69/45 49.7 (18-78 yrs)	Subjects with CRF on dialysis and not on ESA treatment	Mean change in Hgb between baseline and Evaluation Period
AFX01-12	92 United States	Phase 3, randomized, active-controlled, open-label, multicentre study	AF37702: 0.04, 0.08, 0.12 or 0.16 mg/kg Q4W, with 1-wk ESA-free transition period Epoetin alfa: 1-3 times per wk	IV	Conversion from Epoetin alfa and maintenance: Efficacy and Safety	AF37702: 524/366 Epoetin alfa: 269/202	52–104+ wks	M/F = 437/356 57.4 (20-91 yrs)	Subject with CRF on dialysis and previously treated with Epoetin alfa	Mean change in Hgb between baseline and Evaluation Period
AFX01-14	86 United States, Spain, United Kingdom, Germany, Italy, France, Bulgaria, Poland, Romania	Phase 3, randomized, active-controlled, open-label, multicentre study	AF37702: 0.04, 0.08, 0.12 or 0.16 mg/kg Q4W, with 1-wk ESA-free transition period Epoetin alfa: 1-3 times per wk	IV (80%) or SC (20%)	Conversion from Epoetin alfa/beta and maintenance: Efficacy and Safety	AF37702: 542/421 Epoetin: 273/211	52-104+ wks	M/F = 484/331 58.8 (20-91 yrs)	Subject with CRF on dialysis and previously treated with Epoetin	Mean change in Hgb between baseline and Evaluation Period
Supportive studies: uncontrolled dialysis studies										
AFX01_201	26 United States, United Kingdom, Italy, Australia, New Zealand	Phase 2, open-label, single arm, multicentre study	AF37702: 0.04, 0.08, 0.12 or 0.16 mg/kg Q4W	SC	Conversion from Epoetin: Efficacy and Safety	59/43	25 wks	M/F = 27/32 54.0 (21-81 yrs	Subjects with CRF on *peritoneal* dialysis and previously treated with Epoetin	Mean change in Hgb between baseline and Evaluation Period
AFX01-06 (Ongoing)	5 United Kingdom, Germany, France	Phase 2, long-term, open-label, multicentre study	AF37702 Q4W x 60 doses starting dose 0.05, 0.075, and 0.1 mg/kg	SC	Rescue treatment: Efficacy and Safety	As of 30 April 2010: 18 Enrolled 18 Dosed	Up to 60 months	M/F = 13/5 72.7 (37-91 yrs)	Transfusion dependent subjects with CRF and anti-EPO antibody mediated PRCA, on dialysis and not on dialysis	Proportion of subjects with 2 consecutive Hgb values of >11.0 g/dL
Supportive studies: Non-dialysis studies										
AFX01-11	71 United States	Phase 3, randomized, active-controlled, open-label, multicentre study	AF37702: starting dose 0.025 or 0.04 mg/kg Q4W Darbepoetin alfa: 0.75 mcg/kg Q2W	SC	Correction phase: Efficacy and Safety	AF37702 0.025 mg/kg: 161/120 AF37702 0.04 mg/kg: 165/127 Darbepoetin alfa: 164/125	52-104+ wks	M/F = 211/279 66.9 (20-96 yrs)	Subjects with CRF not on dialysis and not on ESA treatment	Mean change in Hgb between baseline and Evaluation Period
AFX01	62	Phase 3,	AF37702: starting dose 0.025 or	SC	Correction phase:	AF37702 0.025	52-104+	M/F =	Subjects with	Mean change in

Study ID	No. of study centres / locations	Design	Study Posology	Route	Study Objective	Subjects by arm entered/ compl.	Duration	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
-13	United States, Bulgaria, Hungary, Romania, Poland, Czech Rep, Germany, United Kingdom, Italy	randomized, active-controlled, open-label, multicentre study	0.04 mg/kg Q4W Darbepoetin alfa: 0.75 mcg/kg Q2W		Efficacy and Safety	mg/kg: 167/124 AF37702 0.04 mg/kg: 163/124 Darbepoetin alfa: 163/139	wks	205/288 67.9 (19-92 yrs)	CRF not on dialysis and not on ESA treatment	Hgb between baseline and Evaluation Period

Pharmacokinetics

Seven Phase I studies in healthy volunteers and 9 Phase II and III studies were submitted, next to 9 in vitro studies, to support the pharmacokinetics of peginesatide. The Phase II and III studies included 6 studies not in the intended population, i.e. subjects with chronic kidney disease not on dialysis and subjects with cancer chemotherapy-induced anaemia. In addition, a population pharmacokinetic/pharmacodynamics analysis has been submitted including four Phase 2 studies (in non dialysis population and in haemodialysis patients) and a single Phase 3 study (in haemodialysis patients previously treated with Epoetin).

These studies provided a basic understanding of the clinical pharmacokinetic characteristics of peginesatide as well as information on its drug-drug interaction potential.

Peginesatide is a synthetic, dimeric peptide that is covalently linked to PEG. The PEG moiety has been added to enhance peptide solubility and stability while still having affinity for the human erythropoietin receptor.

Analytical methods:

In principle one ELISA method has been used for the analysis of peginesatide in plasma. The method proved to be sensitive and robust for analysis of peginesatide. Validation results showed acceptable performance within the normal standard criteria.

Also for analysis of antibodies validated methods have been applied. Interference of peginesatide was observed and therefore for future clinical studies of peginesatide antibody analysis, sampling time points at which peginesatide concentrations have declined to well below a certain level should be taken into account.

Absorption:

The absolute bioavailability of peginesatide after subcutaneous administration ranges from 27 – 46%. The lower bioavailability after subcutaneous administration may be due to the fact that PEGs polymers (depending on mass, number of linking chains, the molecular site of PEG attachment) absorption from the site of injection may be hampered and or delayed which may affect bioavailability. In addition, proteolyse at the site of injection and during distribution to the plasma compartment may also lower bioavailability.

After i.v. administration, tmax values are observed of 15 – 30 min, while after subcutaneous administration tmax values are much longer (about 48h) reflecting the slow release/distribution from the site of injection.

No unexpected accumulation is observed at the intended dosing scheme of Q4W. Following single i.v. and s.c. injection at doses ranging from 0.03 to 0.14mg/kg to healthy subjects and dialysis patients, Cmax and AUC show some evidence of non-linearity and a slight over-proportional increase with higher doses.

Inter-individual variability in peginesatide pharmacokinetics (AUC and Cmax) after subcutaneous injection is about 30 - 50% and after i.v. injection about 20%. An intra-individual variability of 25 – 40% after subcutaneous and 3.5 – 5% after i.v. injection was estimated based upon the results of the bioequivalence studies, however it should be taken into account that no replicate design study is submitted to substantiate these values.

Although bioavailability after i.v. and subcutaneous administrations differs, the same doses are recommended for i.v. and subcutaneous administrations. The population pharmacokinetic-pharmacodynamic analysis substantiated that the same intravenous and subcutaneous dose can be used, based upon the fact that after i.v. administration and subcutaneous administration peginesatide plasma concentrations are above the estimated SC50 (concentration required to obtain 50% of the maximum effect for Hgb value) for the same time period, i.e. about 5 -6 days.

Bioequivalence:

Peginesatide injection will be available in prefilled syringes in strengths ranging from 1 mg/0.5 ml to 8 mg/0.5 ml. Only the concentration of the drug substance differs in these formulations; the amount of excipients is the same. Diferent formulations were used during the in the overall clinical program. Bioequivalence studies showed that the data obtained for the different formulations can be bridged to the commercial formulation. Bioequivalence assessment data on clearance and elimination half-life

should be provided.

Distribution:

Peginesatide does not bind to plasma proteins. As such, interactions due to drug-protein displacement are not expected. After i.v. injection, the volume of distribution in the intended patient group was about 35 mg/kg, i.e. 2450 ml for a 70 kg subject, which is in the range of the vascular plasma volume. Peginesatide is not extensively distributed which may be expected for a large hydrophilic molecule.

Based upon animal data, peginesatide may accumulate in tissues and thus in organs involved in the erythropoiesis. In addition, peginesatide crosses the placenta and is excreted into mother milk.

Metabolism:

Peginesatide is not subject to metabolism by CYP enzymes. In animal studies mono-PEGs were identified as the major component next to parent. In addition, only a small fraction of radioactivity could not be identified. It can be expected that peginesatide may undergo catabolic processes, i.e. proteolysis resulting in amino acids that can be eliminated via dialysis or incorporate into the amino acid pool.

Elimination:

In patients with chronic kidney disease on dialysis the elimination half-life is about 48 h and the clearance 0.5 ml/h/kg. After subcutaneous administration, clearance/F is about 1.5 ml/h/kg.

The Applicant has not discussed the possible impact of haemodialysis on elimination of Peginesatide. Peginesatide is a novel pegylated peptide. It is known that the type of dialysis membrane (pore size) may have a significant effect on clearance of medicinal products, like pegylated interferon alfa. According to the protocols of both studies AFX01-12 and AFX01-14, Peginesatide was instructed to be administered Q4W as rapid IV bolus injections at anytime during dialysis. The Applicant is requested to discuss whether the timing of Peginesatide injection during haemodialysis and the type of dialysis membranes used could have any impact on efficacy and safety of the product.

No mass balance study has been conducted. Considering the molecular weight of peginesatide, peginesatide may be partly excreted intact in urine in humans, as observed in animals.

Special patient groups:

No studies in patients with hepatic impairment are submitted. Considering the fact that peginesatide is not subject to metabolism by CYP enzymes and is metabolised by proteolysis resulting in amino acids, an effect of an impaired liver function on the pharmacokinetics of peginesatide is considered limited. In addition, the population pharmacokinetic analysis did not identify aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin as clinical relevant covariates. The SPC indicates that no dose adjustment is considered necessary which is agreed based upon the pharmacokinetics.

Peginesatide is indicated for patients with chronic kidney disease on haemodialysis. As such, Phase II and III studies were carried out in this study population. Overall pooled pharmacokinetic data after i.v. administration from studies in healthy volunteers and patients with chronic kidney disease on dialysis, indicated an increase in the elimination half-life (from 25 h to 48h) and a decrease in clearance (from 0.7 ml/h/kg to 0.5 ml/h/kg). As peginesatide can be partly eliminated by the kidneys, these findings are not unexpected.

Based upon the metabolic and elimination profile and the results of the population pharmacokinetic/pharmacodynamics analysis, the effect of gender, weight, age and race is considered not clinically relevant.

No data is available for children/adolescents. The SmPC states that safety and efficacy of peginesatide in children < 18 years have not yet been established.

Interactions:

Peginesatide is not a substrate for CYP enzymes or does inhibit or induce CYP enzymes. In vitro studies evaluating the effect of peginesatide on transporters are not submitted, however considering the fact that peginesatide is a pegylated large molecule, an interaction at this level is not expected. Such interactions are also not indicated in interaction data bases.

Considering the fact that peginesatide is not a substrate of CYP enzymes, is metabolised by proteolysis resulting in amino acids, and does not inhibit and induce CYP enzymes, it is expected that the interaction potential is low. In addition, pharmacokinetic and pharmacodynamics of peginesatide were not affected by any of the co-medications taken by more than 10% of the patient population during 80% of the study period. Based upon the covariate analysis for co-medications, none of the co-medications evaluated appear to have statistically or clinically significant effect.

Overall conclusion regarding pharmacokinetics: No major objections and ~~3~~ 4 concerns remain.

Pharmacodynamics

In vitro data suggest that the mechanism of action for AF37702 is similar to rHuEPO and darbepoetin alfa at the biochemical level. AF37702 binds to and activates the human erythropoietin receptor (HuEPOr) and stimulates RBC precursors to undergo proliferation and differentiation similar to other ESAs. It seems that AF37702 acts as a functional agonist of the HuEPOr. The binding of AF37702 and subsequent agonistic activity appears to be highly specific as demonstrated by an absence of detectable cross-reactivity in cell proliferation assays with related human hematopoietic cytokine receptors.

In healthy subjects, single AF37702 IV injections of 0.025 mg/kg and 0.1 mg/kg induced a reticulocyte and Hgb response in a dose-dependent manner. The pharmacologically active dose of AF37702 was 0.1 mg/kg in healthy subjects, as it was associated with a maximum change in baseline Hgb of at least 1 g/dL.

The multiple-dose pharmacodynamics of AF37702 was examined in dialysis CKD patients, previously treated with Epoetin, in studies AFX01-03 (n=165) and AFX01-07 (n=91). These studies are also discussed below under clinical efficacy and dose-response studies. Several cohorts were investigated with different Epoetin-to-AF37702 conversion strategies. Multiple IV or SC AF37702 doses in a Q4W schedule (once every 4 weeks) resulted in a reticulocyte response, which followed a cyclical pattern with mean values above baseline 1 to 2 weeks after dosing and values returning to Baseline 3 to 4 weeks after dosing. In general, mean Hgb levels remain within ±1 g/dL of Baseline values, indicating that AF37702 was able to maintain Hgb levels after conversion from Epoetin. Although the initial Hgb increase over the first 4 weeks appeared to be a slower with SC versus IV using the same dose of AF37702, thereafter the change in Hgb from baseline appears similar using either routes of administration.

The applicant has performed population PK-PD analyses investigating several subpopulations, factors and drug-drug interactions. No clinically significant effect of any factor was found (see also under pharmacokinetics). As AF37702 undergoes proteolytic degradation and hepatic metabolism seems to be irrelevant, genetic polymorphisms of classical metabolic enzymes are of minor relevance. In the D121 response, it was shown that genetic polymorphisms in the HuEPO receptor are unlikely to be of clinical relevance with regards to AF37702 treatment.

Overall, the pharmacodynamics data was limited, but showed a clear cyclical reticulocyte response following AF37702 dosing in a Q4W schedule.

Discussion on clinical pharmacology

The main issue is the fact that although bioavailability after i.v. and subcutaneous administrations differs, the same doses are recommended for i.v. and subcutaneous administrations. However, this is supported by the population pharmacokinetic-pharmacodynamic analysis, i.e. after i.v. administration and subcutaneous administration peginesatide plasma concentrations are above the estimated SC50 (concentration required to obtain 50% of the maximum effect for Hgb value) for the same time period, i.e. about 5 -6 days. In addition, dosing in subjects will be monitored on Hgb level and doses will be adapted, if necessary.

Conclusions on clinical pharmacology

Overall, the pharmacokinetic data supports the efficacy and safety of the product sufficiently. Pharmacodynamic data was limited, but the results are in line with what can be expected of an erythropoietin stimulating product.

Clinical efficacy

Dose-response studies and main clinical studies

The dose-finding and main studies are shown in Table 1.

Dose-response studies

Correction of anaemia

The justification for the starting doses was mainly based upon extrapolation from data of the non-dialysis population. Non-dialysis dose-finding correction study AFX01-04 suggested a starting dose of 0.04 mg/kg for the correction of anaemia in non-dialysis patients. With the assumption that the dose in dialysis patients would be 2-3 times higher than in non-dialysis patients, two doses were proposed for dialysis patients: 0.04 mg/kg and 0.08 mg/kg. Overall, the starting dose of 0.04 mg/kg appears to be low.

Maintenance treatment

Two dose-finding studies in the dialysis population were conducted (AFX01-03 and AFX01-07). Both studies investigated conversion strategies and dose ranges of AF37702 that could maintain Hgb in stable patients after switching from Epoetin to AF37702. Within the first study (AFX01-03), 11 cohorts (total of 165 patients) were investigated with several different Epoetin-to-AF37702 conversion strategies (fixed conversion factors, tiered-fixed conversions and tiered weight-based conversions), with or without a 1-wk ESA-free transition period between the last dose of Epoetin and first dose of AF37702. The weight-based doses ranged from 0.033 mg/kg to 0.15 mg/kg and fixed doses ranged from 4-16 mg. The results suggested that AF37702 was able to maintain Hgb levels in patients converting from their previous Epoetin treatment. The tiered weight-based conversion strategy with a 1-wk ESA-free transition period seemed to yield the best results and was further explored in the second study AFX01-07. In this study, six cohorts (total of 91 patients) were investigated with two different tiered weight-based conversion schemes, with and without a 1-wk ESA-free transition period, given SC or IV. The weight-based doses ranged from 0.04 mg/kg to 0.10 mg/kg. The results of this study were in line with AFX01-03. Hgb levels were maintained and cohorts with a 1-wk ESA free transition period gave the best results. In general, mean Hgb values were comparable between IV and SC cohorts.

The dose-finding studies resulted in the selection of the following conversion scheme for the pivotal phase 3 studies, with a 1-wk ESA free transition period between the last dose of Epoetin and the first dose of AF37702:

Epoetin dose (U/kg/week)	AF37702 Injection (mg/kg/Q4W)
< 100	0.04
100 to < 200	0.08
200 to < 300	0.12
≥ 300	0.16

Long-term extension studies AFX01-09 and AFX01-10, including subjects previously enrolled at selected sites of studies AFX01-03 (n=81) and AFX01-07 (n=51), showed that Hgb levels could be maintained within the target range over a longer period of time.

Main studies

Three main studies were performed: One small phase 2 study on the correction of anaemia in patients not on ESA treatment (AFX01-15) and two larger pivotal phase 3 studies on maintenance treatment

following conversion from another ESA (AFX01-12 and AFX01-14). All three studies were randomized, open-label, multicenter, comparative active-controlled, parallel group studies.

In studies AFX01-15 and AFX01-12, the active comparator was Epoetin alfa. In study AFX01-14, the active comparators were Epoetin alfa or beta in the same reference arm. The primary endpoint for the studies was the mean change in Hgb between Baseline and the Evaluation Period. The secondary endpoints were the proportion of patients with transfusions and the proportion of patients achieving Hgb levels fulfilling certain criteria or within certain target ranges ("Hgb responders").

Correction of anaemia

A single study (AFX01-15) was conducted investigating 2 starting doses of AF37702 compared to the active comparator Epoetin alfa for the correction of anaemia in patients not on ESA treatment. The study was conducted in one country (Russia) and included a total of 114 CKD patients. The study was not powered for any formal comparison between AF37702 doses and Epoetin. Included patients were haemodialysis CKD patients not on ESA treatment with a Hgb of 8.0-11.0 g/dL.

Patients were randomized to a starting dose of AF37702 0.04 mg/kg Q4W (n=39), AF37702 0.08 mg/kg QW4 (n=37), or Epoetin 50 U/kg TIW (three times per week, n=38). After the initial starting dose, subsequent individual patient's dose adjustments were in line with current practice with other ESAs and were according to pre-defined protocol guidelines based on Hgb values and Hgb increases or decreases. The target Hgb range was 11-12 g/dL. Patients were treated for a total duration of 28 wks.

A summary of the main results of the correction study is shown in Table 2.

Table 2: Main results for correction study AFX01-15, Full Analysis Population

		AFX01-15		
		AF37702 0.04 mg/kg N=39	**AF37702 0.08 mg/kg N=37**	**Epoetin N=38**
Primary Endpoint: Change in Hgb from Baseline to Evaluation Period (wks 21-28)				
	Hgb at baseline – Mean (SE)	9.34 (0.118)	9.20 (0.115)	9.07 (0.120)
	Change from baseline – Mean (SE)	2.15 (0.171)	2.39 (0.160)	2.41 (0.165)
	Difference in LS Means (SE) vs Epoetin	**-0.25 (0.238)**	-0.02 (0.238)	NA
	2-sided 97.5% CI	**(-0.79, 0.29)**	(-0.56, 0.52)	NA
Secondary Endpoint: Proportion of patients receiving transfusions				
	Transfusions during the Correction and Evaluation Period	1 (2.6%)	0 (0.0%)	0 (0.0%)
Secondary Endpoint: Proportion of subjects achieving a Hgb response				
	Hgb responders during Correction and Evaluation Period (within wks 0-28)	**92.3%**	97.3%	100%
Other Endpoints				
	Hgb responders during Correction Period (within wks 0-20)	**87.2%**	97.3%	100%
	Sustained Hgb responders during Correction and Evaluation Period (wk 0-28)	**82.1%**	89.2%	94.7%
	Median time to initial Hgb response (wks)	7.0	5.1	6.3
	Median time to initial sustained Hgb response (wks)	9.1	9.1	7.9

In the D121 response, posthoc analyses were performed for the subgroup of patients with baseline Hgb of <10 g/dL (n=29 for 0.04 mg/kg AF37702; n=31 for 0.08 mg/kg AF37702; n=33 for Epoetin). The results for the primary and secondary endpoints were in line with those of the Full Analysis Population.

The primary endpoint demonstrated that AF37702 was able to increase Hgb levels in anaemic dialysis patients. However, AF37702 appears to be less effective as compared to Epoetin, in particular the lower starting dose of 0.04 mg/kg QW4, which is the Applicant's proposed dose for the SPC. This is supported by the proportion of responders; the proposed AF37702 dose of 0.04 mg/kg showed a 8%-13% lower proportion of responders as compared to Epoetin. In the D121 response, it was shown that non-responders at wk 28 in the 0.04 mg/kg AF37702 group (n=3) included 2 subjects that withdrew

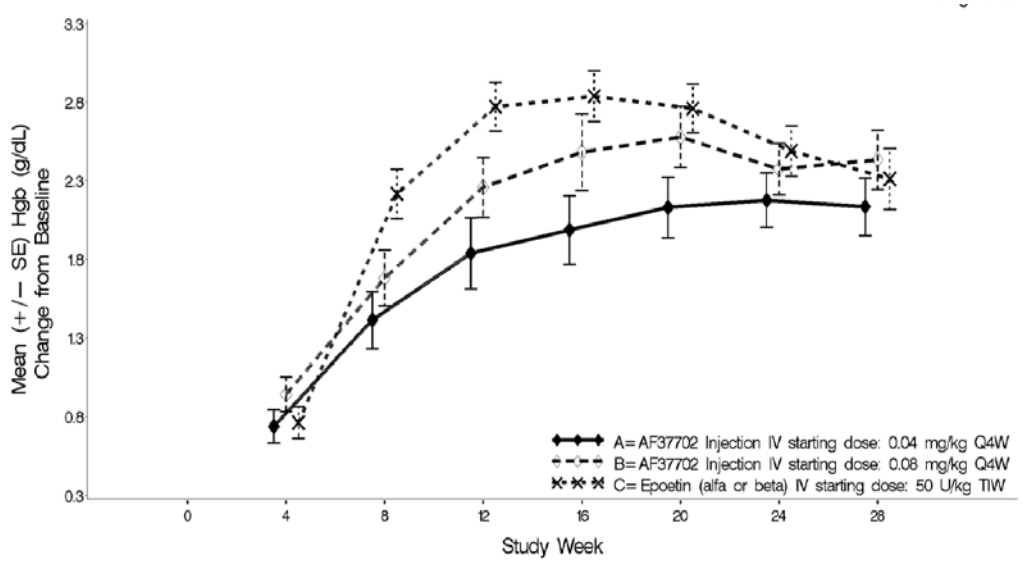
from the study after 1 and 2 doses, and 1 subject experienced multiple SAEs and hepatitis C. Two out of 3 patients had post-treatment Hgb of ≥10 g/dL

In addition to a lower response, the AF37702 0.04 mg/kg starting dose also appeared to take longer to increase Hgb to target levels, hence the correction of anaemia appeared slower. However, in the D121 response, it was shown that in all treatment groups mean Hgb levels of ≥10 g/dL were achieved within 2-3 weeks of treatment initiation.

Results of the higher dose of 0.08mg/kg appear comparable to that of Epoetin.

The lower and slower response of AF37702, in particular of the proposed starting dose of 0.04 mg/kg, was supported by the profiles over 4-wk intervals in mean change from Baseline in Hgb. As shown in **Error! Not a valid bookmark self-reference.**, from wks 6 to 20, the order of mean Hgb change from Baseline was consistently Epoetin giving the highest Hgb change, followed by the AF37702 0.08 mg/kg dose and the AF37702 0.04 mg/kg dose giving the lowest Hgb change. Maximum mean change in Hgb was reached at wk 12 for Epoetin, while for AF37702 this was reached at wk 20.

Figure 1: Mean (±SE) Hgb change from baseline in Hgb over time by 4-week intervals (Full Analysis Population)



For the AF37702 0.04 mg/kg group, the median (min-max) last dose during wks 20-28 was 0.05 (0.01-0.13) mg/kg. For the AF37702 0.08 mg/kg, this was also 0.05 (0.02-0.16) mg/kg. Thus, over the course of the study, dose adjustments to increase and maintain Hgb levels in the target range resulted in converging median doses in the two AF37702 groups. In the 0.04 mg/kg group, in general doses tended to increase, while in the 0.08 mg/kg group, doses tended to decrease over time.

Rates for confirmed (2 consecutive) Hgb excursions are summarized below.

Confirmed Hgb Excursions (2 Consecutive Values) by Treatment Group in AFX01-15

Hemoglobin Excursion Variable	AF37702 Injection Starting Dose 0.04 mg/kg N=39	AF37702 Injection Starting Dose 0.08 mg/kg N=37	Epoetin Starting Dose 50 U/kg N=38
Correction Period (Week 1 to 20)	N=38	N=37	N=38
>12.0 g/dL (a), N (%)	14 (36.8)	27 (73.0)	28 (73.7)
>13.0 g/dL (a), N (%)	3 (7.9)	7 (18.9)	4 (10.5)
>14.0 g/dL (a), N (%)	1 (2.6)	0	0

<10.0 g/ dL (a), N (%)	22 (57.9)	20 (54.1)	22 (57.9)
Evaluation Period (Week 21 to 28)	N=37	N=37	N=36
>12.0 g/dL (a), N (%)	14 (37.8)	20 (54.1)	15 (41.7)
>13.0 g/dL (a), N (%)	2 (5.4)	6 (16.2)	0
>14.0 g/dL (a), N (%)	1 (2.7)	1 (2.7)	0
<10.0 g/ dL (a), N (%)	4 (10.8)	6 (16.2)	4 (11.1)
Duration of excursions >13.0 g/ dL (a), days, mean (SD)	12.5 (3.1)	21.1 (7.7)	25.5 (12.1)
Rapid rate of hemoglobin increase, (b) N (%)	20 (52.6)	27 (73.0)	29 (76.3)

(a) Confirmed (2 consecutive values) excursion(s).
(b) Hemoglobin increase of >2.0 g/dL during any 4-week interval.

The 0.08 mg/kg AF37702 dose showed higher rates of confirmed excursions of >12, >13 and >14 g/dL as compared to the 0.04 mg/kg AF37702 dose and Epoetin. For the 0.04 mg/kg AF37702 dose, during the first 20 weeks rates of excursions were lower or comparable to Epoetin, after 20 weeks rates of excursions of >13 and >14 g/dL were slightly higher as compared to Epoetin. One patient in the 0.04 mg/kg AF37702 group had confirmed excursions of >14 g/dL. This patient only received 1 dose and had dose withheld throughout the remainder of the study. The Hgb excursions of >13 g/dL in the 0.04 mg/kg AF37702 group responded to dose decreases and do not appear to be of longer duration than the excursions on Epoetin. However, numbers were small and results should be interpreted cautiously.

Maintenance treatment

Both pivotal phase 3 studies (AFX01-12 and AFX01-14) were of similar design and had the objective to show non-inferiority to Epoetin in maintenance of Hgb levels. The studies were of at least 52 weeks duration.

Study AFX01-12 included US patients and IV administration. Study AFX01-14 included US (60%) and EU (40%) patients, as well as IV (80%) and SC (20%) administration.

Included patients were haemodialysis CKD patients on stable Epoetin maintenance treatment with stable Hgb levels of 10.0-12.0 g/dL.

The studies included 803 and 823 patients. Patients were randomized in a 1:2 ratio to continue their Epoetin at the same dose, or to switch to AF37702 after a 1-week ESA-free transition period at an AF37702 starting dose based upon their total weekly Epoetin dose according to a 4-tier weight-based conversion scheme. Subsequent individual patient's dose adjustments were according to pre-defined protocol guidelines based on Hgb values and Hgb increases or decreases. The Hgb threshold that triggered a dose increase was the same for AF37702 and Epoetin, but differed for a dose decrease (>12.5 g/dL for AF37702 and >12.0 g/dL for Epoetin) and for a dose delay (≥13.0 g/dL for AF37702 and ≥12.5 g/dL for Epoetin). The Hgb target was 10.0-12.0 g/dL.

The non-inferiority margin was set at -1.0 g/dL. The Full Analysis Population was taken as primary population. A total of 30%-50% of patients were excluded from the Per Protocol (PP) Population.

GCP issues were identified in both studies as outlined in Section 2.4.

Major protocol deviations were observed in 22%-32% of subjects. These included the use of non-study ESAs, which was prohibited but occurred in 10%-17% of patients.

Table 3 summarizes baseline demographic and disease characteristics for the Full Analysis Population.

Table 3: Baseline demographic and disease characteristics of maintenance studies AFX01-12 and AFX01-14, Full Analysis Population

	AFX01-12	AFX01-14

		AF37702 N=524	Epoetin N=269	AF37702 N=542	Epoetin N=273
Age (years) mean (SD) N (%) <65 years N (%) ≥65 years		57.3 (13.96) 370 (70.6) 154 (29.4)	57.5 (13.68) 190 (70.6) 79 (29.4)	58.8 (14.47) 350 (64.6) 192 (35.4)	58.6 (13.73) 173 (63.4) 100 (36.6)
Sex	N (%) male N (%) female	293 (55.9) 231 (44.1)	144 (53.5) 125 (46.5)	331 (61.1) 211 (38.9)	153 (56.0) 120 (44.0)
Race	N (%) White N (%) Black N (%) Other	263 (50.2) 234 (44.7) 26 (5.0)	116 (43.1) 136 (50.6) 17 (6.3)	354 (65.3) 165 (30.4) 23 (4.2)	183 (67.0) 75 (27.5) 15 (5.5)
Ethnicity	N (%) Hispanic N (%) non-Hispanic	135 (25.8) 388 (74.0)	69 (25.7) 200 (74.3)	95 (17.5) 447 (82.5)	52 (19.0) 221 (81.0)
BMI (kg/m^2) mean (SD)		30.12 (7.661)	29.56 (7.571)	27.93 (7.129)	27.93 (6.777)
Baseline Hgb (g/dL) mean (SD)		11.30 (0.523)	11.32 (0.493)	11.20 (0.553)	11.21 (0.546)
Screening Epoetin dose (U/kg/week) Median (25th-75th percentile)		127 (69-213)	141 (74-255)	105 (57-169)	96 (62-174) 220
N (%) on dialysis >1 year		475 (90.6)	237 (88.1)	460 (84.9)	233 (85.3)
Primary cause for chronic renal failure	Diabetes Hypertension Autoimmune disease Polycystic Kidney disease Pyelonephritis Interstitial nephritis Urologic Unknown Other	222 (42.4%) 184 (35.1%) 13 (2.5%) 11 (2.1%) 1 (0.2%) 5 (1.0%) 4 (0.8%) 21 (4.0%) 63 (12.0%)	118 (43.9%) 97 (36.1%) 10 (3.7%) 6 (2.2%) 1 (0.4%) 1 (0.4%) 1 (0.4%) 6 (2.2%) 29 (10.8%)	174 (32.1%) 155 (28.6%) 17 (3.1%) 29 (5.4%) 34 (6.3%) 15 (2.8%) 11 (2.0%) 31 (5.7%) 76 (14.0%)	96 (35.2%) 57 (20.9) 14 (5.1%) 15 (5.5%) 26 (9.5%) 7 (2.6%) 7 (2.6%) 11 (4.0%) 40 (14.7%)
Cardiovascular risk	Cardiovascular risk history Hypertension Diabetes Coronary artery disease Arrhythmia Cerebrovascular dissease Peripheral vascular disease Hyperlipidemia Cigarette use	519 (99.0%) 517 (98.7%) 298 (56.9%) 238 (45.4%) 102 (19.5%) 99 (18.9%) 145 (27.7%) 353 (67.4%) 210 (40.1%)	268 (99.6%) 266 (98.9%) 151 (56.1%) 100 (37.2%) 65 (24.2%) 54 (20.1%) 70 (26.0) 190 (70.6%) 96 (35.7%)	534 (98.8%) 522 (96.3%) 238 (43.9%) 209 (38.6%) 122 (22.5%) 88 (16.2%) 112 (20.7%) 276 (50.9%) 147 (27.1%)	270 (98.9%) 266 (97.4%) 124 (45.4%) 91 (33.3%) 40 (14.7%) 45 (16.5%) 49 (17.9%) 126 (46.2%) 75 (27.5%)
NYHA CHF Class	Class 0-I Class II-IV	414 (79.0%) 110 (21.0)%)	209 (77.7%) 60 (22.3%)	432 (79.7%) 110 (20.3%)	224 (82.1%) 49 (17.9%)

Baseline characteristics were generally balanced between treatment groups.

Results of the primary endpoint are shown in Table 4. In both studies, the change in mean Hgb between Baseline and the Evaluation Period was comparable between AF37702 and Epoetin. Most changes were close to zero (no change). The difference between AF37702 and Epoetin in mean Hgb change from Baseline for the Full Analysis Population were -0.15 g/dL (95% CI: -0.30, -0.01) and 0.10 g/dL (95% CI: -0.05, 0.26) for AFX01-12 and AFX01-14, respectively. Similar results were obtained for the PP Population and sensitivity analyses using different strategies for missing data, all showing lower limits of the 95% CIs that were within the non-inferiority limit of -1.0 g/dL.

Table 4: Results of primary endpoint for maintenance studies AFX01-12 and AFX01-14 , Full Analysis and Per Protocol Population

		AFX01-12		AFX01-14	
		AF37702 N=524	Epoetin N=269	AF37702 N=542	Epoetin N=273
Primary Endpoint: Change in Hgb from Baseline to Evaluation Period					
Full Analysis Population					
	Hgb at baseline – Mean (SD)	11.30 (0.523)	11.32 (0.493)	11.20 (0.553)	11.21 (0.546)
	Change from baseline – Mean (SD)	-0.24 (0.956)	-0.09 (0.922)	-0.07 (1.009)	-0.17 (1.000)
	Difference in LS Means vs Epoetin	-0.15	NA	0.10	NA
	2-sided 95% CI	(-0.30, -0.01)	NA	(-0.05, 0.26)	NA
Per Protocol Population					
	Hgb at baseline – Mean (SD)	11.28 (0.521)	11.32 (0.457)	11.22 (0.547)	11.24 (0.547)

Change from baseline – Mean (SD)		-0.14 (0.908)	-0.02 (0.790)	-0.03 (0.964)	-0.13 (0.842)
Difference in LS Means vs Epoetin		-0.12	NA	0.13	NA
	2-sided 95% CI	(-0.27, 0.04)	NA	(-0.06, 0.31)	NA

For study AFX01-14, results by geographic region showed changes in Hgb from Baseline to the Evaluation Period that were close to zero for both AF37702 and Epoetin for the US as well as the EU population. Post-hoc analyses in the D121 response showed that the difference between AF37702 and Epoetin in mean Hgb change from Baseline for the US and EU population were 0.00 g/dL (95% CI: -0.20, 0.19) and 0.26 g/dL (95% CI: 0.01, 0.51), respectively, based upon the Full Analysis Population. Results for the PP Population were similar, also fulfilling the non-inferiority criteria for both populations.

For study AFX01-14, results appeared comparable for the IV and SC routes of administration.

Results of the secondary endpoints are shown in Table 5. The proportion of patients with transfusions appear similar between treatment groups. In the D121 response, it was shown that this was also the case when analyzing transfusions due to lack of effect only.

Differences were noted in the proportion of patients with Hgb within target range of 10.0 – 12.0 g/dL, which appears to be lower for AF37702 as compared to Epoetin. This was observed for both studies and for the Full Analysis and PP Population, although the magnitude of the difference was variable and small in some instances (2.4%-8.7%). This effect was also consistently shown when looking at individual 4-week intervals: in nearly each 4-week interval in study AFX01-12 and in all 4-week intervals in study AFX01-14, the proportion of patients with Hgb in the target range was lower for the AF37702 as compared to Epoetin.

Table 5: Results of secondary endpoints for maintenance studies AFX01-12 and AFX01-14, Full Analysis and Per Protocol Population

		AFX01-12		AFX01-14	
		AF37702 N=524	**Epoetin N=269**	**AF37702 N=542**	**Epoetin N=273**
Secondary Endpoint: Proportion of patients receiving transfusions during Titration and Evaluation Periods					
	Full Analysis Population				
	N (%)	54 (10.3)	23 (8.6)	42 (7.7)	27 (9.9)
	Per Protocol Population				
	N (%)	25 (7.3)	7 (4.2)	13 (3.5)	5 (3.5)
Secondary Endpoint: Proportion of subjects with mean Hgb within target range (10-12 g/dL) during the Evaluation Period					
	Full Analysis Population				
	N (%)	330 (63.0)	193 (71.7)	344 (63.5)	180 (65.9)
	Per Protocol Population				
	N (%)	259 (76.0)	132 (80.0)	261 (70.2)	110 (78.0)

For study AFX01-14, differences were noted in the results of the secondary endpoints when comparing the US and the EU population. Transfusion rates were lower in the EU. The proportion of patients with Hgb within the target range was lower in the EU, with a larger difference between AF37702 and Epoetin (difference of 5.4% and 21.3% for the Full Analysis and PP Populations).

Other efficacy endpoints investigated the mean Hgb and mean Hgb change from Baseline during 4-wks intervals. Hgb levels similar to Baseline were maintained up to wk52 without an increase in dosing, supporting persistence of the effect.

The median AF37702 dose during the Evaluation period was 5.7 mg (0.08 mg/kg) and 4.8 mg (0.06 mg/kg) for, respectively, studies AFX01-12 and AFX01-14. In study AFX01-14, doses were similar for the IV and SC routes and higher for US patients as compared to EU patients. For study AFX01-14, the median IV AF37702 dose during the Evaluation Period was 5.5 mg (0.07 mg/kg) for US patients and 3.5 mg (0.05 mg/kg) for EU patients.

Concerning Hgb excursions, a slightly higher proportion of AF37702 patients had below target Hgb excursions, but the above target Hgb excursions were similar between AF37702 and Epoetin.

Summary of main efficacy results

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

Table 6. Summary of efficacy for trial AFX01-12

Title: A phase 3, Randomized, Active-controlled, Open-label, Multi-centre study of the safety and efficacy of AF37702 Injection for the Maintenance Treatment of Anemia in Hemodialysis Patients Previously Treated with Epoetin Alfa.			
Study identifier	AFX01-12		
Design	Phase 3, randomized, active-controlled, open-label, multi-centre.		
	Duration of study: Duration of screening period: Duration of titration period:		Minimum 52 weeks Maximum 6 weeks 28 weeks
	Duration of evaluation period (main phase)		8 weeks
	Duration of long-term safety and efficacy period:		Minimum of 16 weeks
Hypothesis	To demonstrate non-inferiority of AF37702 Injection to Epoetin Alfa in the maintenance treatment of anemia		
Treatments groups	Treatment group		AF37702 Injection administered i.v. Q4W at starting dose of 0.04mg/kg to 0.16mg/kg based on the patient's prior epoetin alfa dose, 532 patients randomized
	Active control group		Epoetin alfa administered i.v. 1-3 times per week, 271 patients randomized
Endpoints and definitions	Primary endpoint		Mean change in Hgb between baseline and the evaluation period
	Secondary endpoint		Proportion of patients who received red blood cell transfusions during the titration and evaluation periods.
	Secondary endpoint		Proportion of patients whose mean Hgb level during the evaluation period was within the target range of 10.0-12.0 g/dL.
Database lock	29 January 2010		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Population: all randomized patients who received at least one dose of study medication.		

Descriptive statistics and estimate variability	Treatment group	Treatment Group	Active control group	
	Number of subject	524	269	
	Mean Hgb Baseline	11.30 g/dL	11.32g/dL	
	Standard deviation	0.523	0.493	
	Mean Hgb During evaluation period (SD)	11.06 g/dL	11.25 g/dL	
	Standard deviation	0.956	0.922	
	Proportion of patients receiving RBC transfusions during Titration and evaluation periods %	54 10.3%	23 8.6%	
	Proportion of patients whose mean HgB level remained within the target range during the evaluation period	330	193	
	%	63%	71.7%	

Effect estimate per comparison	Primary endpoint	Treatment group	Mean change in Hgb between baseline and the evaluation period
		Mean	-0.24
		Standard Deviation	0.956
	Primary endpoint	Active Control group	Mean change in Hgb between baseline and the evaluation period
		Mean	-0.09
		Standard Deviation	0.922
	Primary endpoint	Treatment vs active control groups	Mean change in Hgb between baseline and the evaluation period
		Difference of LS Means	-0.15
		95% CI	(-0.30, -0.01)
	Secondary endpoint	Treatment vs active control groups	Proportion of patients receiving RBC transfusions during Titration and evaluation periods

		Relative risk	1.21
		95% CI	(0.76, 1.92)
	Secondary endpoint	Treatment vs. active control groups	Proportion of patients whose mean HgB level remained within the target range during the evaluation period
		Relative response rate	0.88
		95% CI	(0.79, 0.97)
Notes			
Analysis description	Primary and Secondary Analysis		
	Results for the primary efficacy endpoint in Per Protocol and Supplemental Per Protocol Populations showed treatment differences of –0.12 g/dL (95% CI: –0.27, 0.04) and –0.12 g/dL (95% CI: –0.27, 0.03), respectively. In addition, results of a non-parametric analysis, a sensitivity analysis excluding Hgb values obtained within 28 days of a transfusion, and of three sensitivity analyses which imputed missing Hgb data during the Evaluation Period using Full Analysis Population were similar to the primary efficacy analysis results. Results for subgroup analyses appeared to be consistent with those observed for the Full Analysis Population. The proportion of patients with RBC transfusions was similar in each treatment group. The proportion of patients with mean Hgb within the target range was slightly lower for AF37702 (63.0%) as compared to Epoetin (71.7%), but the differences were less pronounced in the Per Protocol (76.0% vs 80.0%) and the Supplemental Per Protocol (77.2% vs 80.4%) Populations, which included only patients who had Hgb values during the Evaluation Period and adequate iron stores.		

Table 7. Summary of efficacy for trial AFX01-14

Title: A phase 3, Randomized, Active-controlled, Open-label, Multi-centre study of the safety and efficacy of AF37702 Injection for the Maintenance Treatment of Anemia in Hemodialysis Patients Previously Treated with Epoetin Alfa.			
Study identifier	AFX01-14		
Design	Phase 3, randomized, active-controlled, open-label, multi-centre.		
	Duration of study: Duration of screening period: Duration of titration period:		Minimum 52 weeks Maximum 6 weeks 28 weeks
	Duration of evaluation period (main phase)		8 weeks
	Duration of long-term safety and efficacy period:		Minimum of 16 weeks
Hypothesis	To demonstrate non-inferiority of AF37702 Injection to Epoetin Alfa in the maintenance treatment of anemia		
Treatments groups	Treatment group		AF37702 Injection administered i.v. or s.c. Q4W at starting dose of 0.04mg/kg to 0.16mg/kg based on the patient's prior epoetin alfa dose, 549 patients randomized
	Active control group		Epoetin alfa administered i.v. or s.c. 1-3 times per week, 274 patients randomized
Endpoints and definitions	Primary endpoint		Mean change in Hgb between baseline and the evaluation period

	Secondary endpoint		Proportion of patients who received red blood cell transfusions during the titration and evaluation periods.
	Secondary endpoint		Proportion of patients whose mean Hgb level during the evaluation period was within the target range of 10.0-12.0 g/dL.
Database lock	22 January 2010		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Population: all randomized patients who received at least one dose of study medication.			
Descriptive statistics and estimate variability	Treatment group	Treatment Group	Active control group	
	Number of subject	542	273	
	Mean Hgb Baseline	11.20 g/dL	11.21g/dL	
	Standard deviation	0.553	0.546	
	Mean Hgb During evaluation period (SD)	11.13 g/dL	11.05 g/dL	
	Standard deviation	1.018	0.958	
	Proportion of patients receiving RBC transfusions during Titration and evaluation periods %	42 7.7%	27 9.9%	
	Proportion of patients whose mean HgB level remained within the target range during the evaluation period	344	180	
	%	63.5%	65.9%	
Effect estimate per comparison	Primary endpoint	Treatment group	Mean change in Hgb between baseline and the evaluation period	
		Mean	-0.07	

		Standard Deviation	1.009
	Primary endpoint	Active Control group	Mean change in Hgb between baseline and the evaluation period
		Mean	-0.17
		Standard Deviation	1.00
	Primary endpoint	Treatment vs active control groups	Mean change in Hgb between baseline and the evaluation period
		Difference of LS Means	0.10
		95% CI	(-0.05, 0.26)
	Secondary endpoint	Treatment vs active control groups	Proportion of patients receiving RBC transfusions during Titration and evaluation periods
		Relative risk	0.79
		95% CI	(0.50, 1.24)
	Secondary endpoint	Treatment vs. active control groups	Proportion of patients whose mean HgB level remained within the target range during the evaluation period
		Relative response rate	0.96
		95% CI	(0.87, 1.07)
Notes			
Analysis description	Primary and Secondary Analysis		
	Results of subgroup analyses of the primary endpoint by geographic region and route of administration were consistent with those observed for the Full Analysis Population. Results for the primary efficacy endpoint in Per Protocol and Supplemental Per Protocol Populations showed treatment differences of 0.13 g/dL (95% CI: −0.06, 0.31) and 0.13 g/dL (95% CI: : −0.03, 0.30), respectively. In addition, results of a non-parametric analysis, a sensitivity analysis excluding Hgb values obtained within 28 days of a transfusion, and of three sensitivity analyses which imputed missing Hgb data during the Evaluation Period using Full Analysis Population were similar to the primary efficacy analysis results. Results for subgroup analyses appeared to be consistent with those observed for the Full Analysis Population. The proportion of patients with RBC transfusions was similar in each treatment group. The proportion of patients with mean Hgb within the target range was slightly lower for AF37702 (63.5%) as compared to Epoetin (65.9%), but the differences were more pronounced in the Per Protocol (70.2% vs 78.0%) and the Supplemental Per Protocol (71.0% vs 77.5%) Populations, which included only patients who had Hgb values during the Evaluation Period and adequate iron stores.		

Clinical studies in special populations

No studies were performed in special populations.

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

Pooled analyses of the maintenance studies were performed to explore the effects of selected demographic and baseline disease characteristics as measured by the primary efficacy endpoint. These factors concern age, gender, race, BMI, ethnicity, presence of diabetes, baseline hsCRP and NYHA CHF Class. Small differences were noted between NYHA CHF classes 0-I and II-IV. Otherwise, there were

no apparent effects of any of the selected factors. For all subgroups the mean change in Hgb from Baseline to the Evaluation Period was close to zero. Lower boundaries of 95% CIs for the difference between AF37702 and Epoetin for all subgroups was within the non-inferiority margin of -1.0 g/dL.

Supportive study(ies)

Maintenance therapy in *peritoneal* dialysis patients was investigated in a small (n=59) uncontrolled study (AFX01_201). The results were supportive of the fact that AF37702 could maintain Hgb levels in peritoneal dialysis patients following conversion from Epoetin.

A small (n=18) on-going study in PRCA patients (AFX01-06) showed that Hgb could be corrected into the target range, while the need for transfusions was decreased to a large extent following AF37702 treatment. Prior to the study, 17/18 patients received a cumulative total of 98 transfusions to achieve clinically acceptable Hgb levels. After treatment with AF37702, 8/18 patients had a total of 18 transfusions.

Two supportive phase 3 correction studies in *non-dialysis* patients were conducted (AFX01-11 and AFX01-13). The objective of both studies was to demonstrate non-inferiority to darbepoetin alfa in the primary endpoint with a non-inferiority margin of -1.0 g/dL. Non-dialysis patients included were anaemic CKD patients (Hgb 8.0-11.0 g/dL) not on ESA treatment. Mean baseline Hgb was 10.1 g/dL. Patients were randomized to starting doses of AF37702 SC 0.025 mg/kg Q4W (n=161 and n=167 for AFX01-11 and AFX01-13), AF37702 SC 0.04 mg/kg Q4W (n=165 and n=163) or darbepoetin alfa SC 0.75 µg/kg Q2W (n=164 and n=163). The primary endpoint was the mean change in Hgb between Baseline and the Evaluation Period (wks 25-36). Secondary endpoints were the proportion of patients receiving transfusions and the proportion of patients achieving a Hgb response during wks 0-36. Following treatment with study medication, Hgb change between Baseline and the Evaluation Period was 1.3-1.7 g/dL. The lower limit of the 95% CIs of the difference between both AF37702 doses and darbepoetin was within the non-inferiority margin of -1.0 g/dL. The proportion of patients with transfusions was higher for AF37702 groups as compared to Epoetin, in particular in study AFX01-13. The proportion of Hgb responders was similar between treatment groups.

Discussion on clinical efficacy

Design and conduct of clinical studies

Data from the dose-finding studies was rather limited, investigating few different doses and focussing mainly on different conversion strategies. Furthermore, GCP issues leading to closure of sites including about half of the patient population were identified within study AFX01-07.

Three main studies were performed to demonstrate efficacy. The studies were conducted in an open-label fashion due to practical problems and complex requirements needed to blind the studies. Considering the GCP findings, potential bias cannot be excluded. The extent and impact of potential bias is currently unclear.

Only short-term ESA treatment was used as active comparator which is acceptable. However, a comparison with a longer acting ESA (e.g. Mircera) for (one of) the maintenance studies would have been preferred, but Mircera was not available globally at the start of the studies as indicated in the D121 response.

Study AFX01-15 had several methodological limitations, including the lack of a formal comparison vs Epoetin, the inclusion of patients already on target range (10-11 g/dL), the conduct of the study in a single country and the small sample size. In the D121 response, the applicant has justified that the target ranges were consistent with the ESA labeling at the time. Additional post-hoc analyses were performed for the subgroup of patients with baseline Hgb of <10 g/dL. Furthermore, the study population was shown to be globally similar to the EU CKD population as derived from epidemiological databases. Overall, the target ranges used and the included patient population derived from a single country could be acceptable, but the limited size of the study –hampering adequate interpretation of the data- remains of major concern.

The Full Analysis Population was set as the primary analysis population. However, in a non-inferiority trial this population may not be conservative enough (ICH E9) and the results of the PP Population are

of interest as well, especially within the maintenance studies AFX01-12 and AFX01-14 where discontinuation rates were high (about 25-30%).

The primary endpoint based on change in Hgb from baseline is acceptable and clinically relevant as are the major secondary endpoints being the proportion of patients with Hgb on target and the proportion of patients receiving transfusions. The non-inferiority margin of -1.0 g/dL within the maintenance studies AFX01-12 and AFX01-14 is considered too generous and a non-inferiority margin of -0.5 g/dL was recommended within the SA.

Evaluation of the primary endpoint at week 21-28 within the correction setting is rather late, as with current licensed ESAs correction of anaemia is usually achieved within 12-16 weeks. Also for the maintenance treatment, evaluation at week 29-36 is rather late, but can be acceptable within the maintenance setting. Follow-up until 52 weeks enables to study the durability of effect.

The in- and exclusion criteria for the maintenance studies seem appropriate. However, the studied population did not comprise high-risk anaemic CKD patients, as eligible subjects needed to be on stable Epoetin doses and Hgb values within the screening period. It is unclear whether the proposed conversion scheme is also appropriate for high-risk patients on high instable Epoetin doses without adequate response **(LoOI)**.

GCP issues were noted for both maintenance studies and a GCP inspection was requested. Findings of the GCP inspection identified issues with regards to insufficient oversight and monitoring, irregularities in data handling, out of protocol dosing (adjustment) for the Epoetin groups and concerns with regards to the definition of the PP Population. It is currently unclear how these findings would impact the overall results. The applicant's responses to its findings are awaited. In view of the open-label non-inferiority nature of the studies, it should be shown that the GCP findings did not impact the sensitivity of the studies to detect differences between treatments and that any bias introduced would not be in favour of AF37702 treatment. This is of importance, given the already less sensitive setting of the maintenance studies to detect differences, as all patients were already on target Hgb levels at baseline with subsequent multiple titration steps before evaluation of the primary endpoint.

The high degree of major protocol deviations in both maintenance studies (22%-32%) gives an impression of poor conduct of the studies. Of particular concern is the use of non-study ESAs, which was prohibited, but occurred in 10%-17% of patients. This not only questions compliance, but also hampers adequate assessment of the effect of the study ESAs. In the D121 response, post-hoc analyses were performed excluding all patients with non-study ESA use, which showed similar results to the primary analyses.

The degree of patients excluded from the PP Population was very high (30%-50%). Given the latter, the representativeness of the PP Population for the target population is of concern**.** However, in response to the D120 LOQ, it was demonstrated that the PP Population and the population excluded from the PP were generally comparable**.** Furthermore, there are several unclarities with regards to exclusion of patients from the PP Population. It appears that the PP Population excluded patients that did not comply to certain criteria, but only limited to wks 25-35/36. Patients that did not comply to certain criteria (including use of non-study ESA) prior to wk 25 appear to have been included in the PP Population. In the D121 response, it was explained that the time period of wks 25-35 was chosen based upon the time-frame of the pharmacological response to ESAs, where the delay between dose and Hgb effect is up to 4 weeks. Therefore, it was considered that non-compliance prior to wk 25 would not have influenced Hgb values during the Evaluation Period. Additional analyses excluding also patients that did not comply to certain criteria prior to wk 25 were performed to show that this did not impact the results. Nevertheless, considering the GCP findings, the value to such sensitivity analyses is unclear if the overall reliability of the data has not been confirmed. Furthermore, it is still not clear why some major protocol violators (e.g. patients who did not meet inclusion criteria) were not excluded from the PP population. The definition of the PP Population and reasons for exclusions should be further clarified **(LoOI).**

Disposition of patients in the maintenance studies was not clear. Based upon revised disposition figures in the D121 response, slightly higher proportions of patients discontinued study and/or study drug in the AF37702 group vs the Epoetin group in AFX01-12, while the rates in AFX01-14 were similar. There was no clear difference in the reasons for discontinuation between treatment groups, with the exemption of a higher proportion of discontinuations due to AEs for AF37702 in study AFX01-12.

<u>Efficacy data and additional analyses</u>

Correction of anaemia was investigated in study AFX01-15, which showed that AF37702 was able to increase Hgb levels in anaemic CKD dialysis patients at both doses investigated. However, the Hgb response to the 0.04 mg/kg dose appears both lower and slower as compared to Epoetin. In the D121 response, some additional post-hoc analyses were performed based upon the current Hgb target of ≥10 g/dL. Albeit slower than Epoetin, it appears that the current Hgb target level of ≥10 g/dL may be achievable within acceptable time frames. The results for the subgroup of patients with baseline Hgb <10 g/dL were similar to those of the Full Analysis Population, hence the inclusion of patients already on target Hgb did not appear to impact the overall study results. Compared to Epoetin, the 0.04 mg/kg dose showed slightly more confirmed excursions of >13 and >14 g/dL after 20 wks, which responded to dose decreases and do not appear to be of longer duration than excursions on Epoetin. Furthermore, there appears to be no correlation between Hgb excursions and an increased risk of cardiovascular events (see safety section). Overall, the data of AFX01-15 appears to show that current target Hgb levels may be achievable within acceptable time-frames and there appears to be no clear unfavourable profile with regards to Hgb excursions vs Epoetin. However, this was based upon very small numbers. Adequate interpretation of the data is therefore hampered and firm conclusions cannot be drawn **(MO, see LoOI)**. Additional data from the larger non-dialysis correction studies might support efficacy in the dialysis correction setting. As the non-dialysis correction studies were limited by a population with mean baseline Hgb of 10.1 g/dL and a long and late Evaluation Period of wks 25-36, additional data is required based upon patients with baseline Hgb of <10 g/dL and based upon an Evaluation Period of wks 21-28. It should be demonstrated that the slower Hgb rise for AF37702 as compared to the comparator does not result in an increased risk of blood transfusions **(LoOI)**.

Maintenance treatment after switching from another ESA was investigated in two larger pivotal phase 3 studies with a non-inferiority design. The in- and exclusion criteria adequately reflected the susceptible population of treatment.

In both studies it was shown that AF37702 was able to maintain Hgb levels after switching from Epoetin. In both studies, numerically the criterion for non-inferiority was consistently met for different populations, as well as sensitivity analyses and subgroup analyses. Based upon the results, non-inferiority would also be met for the more stringent non-inferiority criterion of -0.5 g/dL. However, in the presence of issues with regards to GCP compliance and the PP Population, a conclusion currently cannot be drawn without further assurance on the quality of the data. The final results of the inspection and responses to its findings should be awaited before efficacy of AF37702 can be confirmed **(MO, see LoOI).**

The proportion of patients with transfusions appear similar between treatment groups. This was also the case when analyzing transfusions due to lack of effect only. The proportion of patients with Hgb within target range of 10.0 – 12.0 g/dL appeared to be somewhat lower for AF37702 as compared to Epoetin, throughout the study. This difference vs Epoetin is most prominent in the EU population in study AFX01-14, where AF37702 showed a 21.3% lower proportion of patients in target range as compared to Epoetin in the PP analysis. However, it should be noted there were only 44 Epoetin-treated subjects in the EU PP Population. In the D121 response, the applicant indicated that in clinical practice dose adjustment is used to achieve the Hgb target range and that the Hgb change in response to dose adjustment is similar for AF37702 as compared to Epoetin. However, it remains unclear why this subsequently did not translate into similar proportions of patients with Hgb within target range. This requires further discussion as well as the differences between the EU and US population in this respect **(LoOI).**

The studies primary included US patients (80% US, 20% EU). Differences were noted between the US population and the target EU population with regards to baseline characteristics, results of secondary endpoints and dosing. The D121 response showed comparable results for the US and EU patients in AFX01-14 with regards to the primary endpoint. Despite a much smaller number of included patients, the EU population met the protocol specified non-inferiority criteria (≥-1.0 g/dL), as well as the more stringent non-inferiority criteria recommended by the Scientific Advice (≥-0.5 g/dL). The dosing differences are not considered a clinical issue, because of the individualized dosing requirement for ESA treatment. The differences in the secondary endpoint of proportion of patients with Hgb within target range requires further discussion (see above).

About 10% of patients received SC treatment. Although numbers were limited, there were no indications that efficacy or dosing was different between SC and IV administration.

Both studies used a 4-tier weight-based Epoetin-to-AF37702 conversion scheme. For the SmPC, the Applicant is proposing a conversion table based upon *total dose* instead of *weight/based doses*. Using a

method analogous to the currently prescribed Epoetin-to-darbepoetin dose conversion, the Applicant has derived a 9-tier Epoetin-to-AF37702 and darbepoetin-to-AF37702 total dose-based conversion scheme. Furthermore, the Applicant is proposing a 1-wk ESA-free transition period between the last dose of Epoetin and the first dose of AF37702. The Applicant is proposing the same doses for the IV and SC routes of administration. Although data for SC administration was small, it is agreed that the data showed no indication that efficacy or maintenance dosing was different from IV administration. The proposed dose adjustment recommendation in the SmPC was derived from standard ESA recommendations and was not identical to the adjustment recommendations for AF37702 used in the maintenance studies. However, in the D121 response the SmPC dose adjustment recommendations were sufficiently justified.

Maintenance treatment in peritoneal dialysis was shown in a small uncontrolled study. Based upon past clinical experience with ESAs, there is no indication of a different efficacy in haemodialysis and peritoneal dialysis patients. Peritoneal dialysis has been included in the RMP, which is acceptable.

A study in PCRA patients is on-going. Interim data up to 31 Dec 2011 indicate that AF37702 could reduce the need for transfusions, supporting efficacy of AF37702. The Applicant is encouraged to submit the final study report upon completion of the study.

Conclusions on clinical efficacy

Within an exploratory study, AF37702 was effective in increasing Hgb levels in anaemic CKD patients which is clinically relevant. Although the initial Hgb rise was slower as compared to Epoetin, it appears that current target Hgb levels may be achievable within acceptable time-frames and there appears to be no clear unfavourable profile with regards to Hgb excursions vs Epoetin. However, the data was obtained within a very limited population and needs to be substantiated within a larger population. AF37702 was able to maintain Hgb levels after switching from Epoetin. In both studies, numerically the criterion for non-inferiority was consistently met for different populations, as well as sensitivity analyses and subgroup analyses. However, issues with regards to GCP compliance and the PP Population were identified, which were also shown in the GCP inspection report. The applicant's responses to its findings are awaited. Until data validity is assessed and ascertained, it is considered that efficacy of AF37702 has not been confirmed.

Clinical safety

Patient exposure

An overview of the number of exposed patients, duration of exposure, and median doses for the dialysis and non-dialysis studies is presented in **Table 8**.

Overall, the total exposure is considered sufficient in number and duration for adequate safety assessment and in line with ICH E1.

Table 8: Summary of patient exposure in main dialysis studies and non-dialysis studies

	Patient exposure in main dialysis and non-dialysis studies						
	Treatment groups	**Nr of exposed patients**	**Treatment Duration (wks): Mean (min-max)**	**Absolute doses**		**Weight adjusted doses**	
				First dose: Median (min-max) AF37702: mg Epoetin: U/wk Darbepoetin: mcg	**Last dose during Evaluation Period: Median (min-max)** AF37702: mg Epoetin: U/wk Darbepoetin: mcg	**First dose: Median (min-max)** AF37702: mg/kg Epoetin: U/kg/wk Darbepoetin: mcg	**Last dose during Evaluation Period: Median (min-max)** AF37702: mg/kg Epoetin: U/kg/wk Darbepoetin: mcg
Phase 2 Dialysis Correction Study							
AFX01-15	AF37702 0.04 mg/kg	39	26.6 (4-31)	3.0 (2.0-4.3)	2.9 (1.0-11.8)	0.04 (0.03-0.05)	0.05 (0.01-0.13)
	AF37702 0.08 mg/kg	37	28.9 (26-32)	5.8 (3.6-8.6)	3.4 (1.4-16.9)	0.08 (0.08-0.09)	0.05 (0.02 – 0.16)

	Patient exposure in main dialysis and non-dialysis studies						
	Treatment groups	**Nr of exposed patients**	**Treatment Duration (wks): Mean (min-max)**	**Absolute doses**		**Weight adjusted doses**	
				First dose: Median (min-max) AF37702: mg Epoetin: U/wk Darbepoetin: mcg	**Last dose during Evaluation Period: Median (min-max)** AF37702: mg Epoetin: U/wk Darbepoetin: mcg	**First dose: Median (min-max)** AF37702: mg/kg Epoetin: U/kg/wk Darbepoetin: mcg	**Last dose during Evaluation Period: Median (min-max)** AF37702: mg/kg Epoetin: U/kg/wk Darbepoetin: mcg
	Epoetin	38	27.3 (3-29)	3500 (2500-5500)	2000 (500-10000)	50 (45-57)	27 (7-109)
Phase 3 Dialysis Population							
AFX01-12	AF37702	524	59.7 (2.0-116.0)	5.9 (1.8-22.4)	5.9 (0.4-101.0)	0.08 (0.03-0.20)	0.08 (0.007 – 1.06)
	Epoetin	269	65.1 (0.7-116.4)	10500 (600-84000)	9900 (300-90000)	136 (8-1151)	126 (3-1183)
AFX01-14	AF37702	542	61.3 (1.9-109.0)	4.6 (1.7-20.8)	4.8 (0.4-108.0)	0.08 (0.03-0.20)	0.06 (0.005-1.10)
	Epoetin	273	60.5 (0.4-107.1)	6600 (600-88000)	6600 (100-89100)	94 (5-1209)	93 (1-1478)
Phase 3 Non-Dialysis Population							
AFX01-11	AF37702 0.025 mg/kg	161	71.3 (4.0-107.1)	2.1 (1.0-3.9)	1.6 (0.3-17.8)	0.025 (0.012-0.055)	0.02 (0.004-0.212)
	AF37702 0.04 mg/kg	165	72.3 (7.6-108.9)	3.3 (1.6-7.3)	2.3 (0.3-14.7)	0.04 (0.037-0.041)	0.03 (0.005-0.165)
	Darbepoetin	164	72.9 (4.0-107.0)	59 (25-130)	31 (6-585)	0.75 (0.37-0.81)	0.39 (0.06-4.69)
AFX01-13	AF37702 0.025 mg/kg	167	63.5 (4.0-97.9)	2.0 (1.0-4.0)	1.6 (0.3-13.3)	0.025 (0.014-0.041)	0.02 (0.004-0.182)
	AF37702 0.4 mg/kg	163	61.7 (4.0-97.9)	3.1 (1.8-9.9)	1.8 (0.2-31.4)	0.04 (0.015-0.042)	0.02 (0.003-0.515)
	Darbepoetin	163	65.6 (2.0-98.6)	59 (32-109)	30 (6-273)	0.75 (0.38-0.78)	0.33 (0.07-3.19)

The MAA pertains to dialysis patients only. Non-dialysis patients were excluded from the MAA due to the results found for this population in the Composite Safety Endpoint (CSE) analysis on cardiovascular safety (see below). The non-dialysis population differs from the dialysis patients with regard to demographic and baseline disease characteristics. Patients in the non-dialysis population were older (mean age 67.6 yrs vs 58.1 yrs for AF37702) with a higher proportion of patients above 75 years of age (35.8% vs. 13.0% for AF37702). The non-dialysis population included more females (55.8% vs. 41.5% for AF37702). Furthermore, the non-dialysis population consisted of more diabetics (67.7% vs. 50.3% for AF37702) and more patients with hyperlipidaemia (78.2% vs. 59.0% for AF37702). The phase 3 dialysis population had higher rates of arrhythmia (21.0% vs. 15.9%) and smokers (33.5% vs. 11.0% for AF37702). There were also differences with regards to dosing; the doses given in the non-dialysis correction studies were 1.5-3 times lower as compared to doses given in the dialysis studies (see Table 8). Therefore, safety data of the non-dialysis population is only discussed in this Overview where it raises serious and/or unexpected safety signals or safety signals related to the pharmacodynamics of AF37702. For general AE data of the non-dialysis population, reference is made to the Clinical AR.

Adverse events

Correction of anaemia

In dialysis correction study AFX01-15, treatment-emergent adverse events (TEAE) were reported at similar rates for AF37702 (84.2%) and Epoetin (81.6%), with also similar rates for treatment-related TEAEs (11.8% for AF37702 and 13.2% for Epoetin). The most commonly reported TEAEs for AF37702 were hypertension (21.1%), procedural hypotension (17.1%), muscle spasms (13.2%), procedural hypertension (11.8%) and headache (7.9%). When comparing AF37702 to Epoetin, some TEAEs were reported at higher frequencies for AF37702 (hypertension), while other events were reported at higher incidences for Epoetin (angina pectoris, hypotension, nasopharyngitis, arteriovenous fistula operation,

headache, hyperparathyroidism). Due to the small size of the study, the clinical relevance of these differences cannot be assessed. The most commonly reported treatment related TEAE was hypertension (AF37702 6.6%; Epoetin 7.9%). Other treatment related TEAEs were reported once.

Overall, review of AEs in this study did not reveal clear or unexpected safety signal. However, the study was small and further data on the AE profile has to be derived from the larger maintenance studies (see below).

Maintenance treatment

In the dialysis maintenance studies, TEAEs were reported at similar rates for AF37702 (94.6%) and Epoetin (93.0%). The most commonly reported TEAEs for AF37702 were dyspnoea (18.4%), diarrhoea (18.4%), nausea (17.4%), arteriovenous fistula site complication (16.1%), and cough (15.9%). Similar rates were also observed for these events in Epoetin patients. Overall, review of individual events did not reveal unexpected safety findings.

Treatment-related TEAEs were reported at low rates, but at higher rates for AF37702 (7.8%, n=83) as compared to Epoetin (4.2%, n=23). These pertain to a diversity of events, without any events predominating, as shown in Table 9. The most commonly reported treatment-related TEAEs for AF37702 were hypertension (AF37702 0.8%, Epoetin 0.0%), hypotension (0.7% and 0.0%), anaemia (0.6% and 0.2%) and nausea (0.4% and 0.0%). Higher frequencies of treatment-related myocardial infarction, acute myocardial infarction and cerebrovascular accident for AF37702 (0.3%, 0.2% and 0.2%) were found as compared to Epoetin (0.0%). Other treatment-related TEAEs were reported at frequencies of ≤0.3%, mainly included non-serious events and are not considered to be of concern.

Table 9: Treatment-related TEAEs with incidences of ≥0.2%, maintenance studies

System Organ Class Preferred Term		Treatment-related TEAEs Phase 3 Dialysis Population	
		AF37702 N=1066	Epoetin N=542
Blood and lymphatic system disorders			
	Anaemia	6 (0.6%)	1 (0.2%)
Cardiac disorders			
	Myocardial infarction	3 (0.3%)	0 (0.0%)
	Acute myocardial infarction	2 (0.2%)	0 (0.0%)
	Cardiac failure congestive	0 (0.0%)	1 (0.2%)
Gastrointestinal disorders			
	Nausea	4 (0.4%)	0 (0.0%)
	Diarrhoea	1 (0.1%)	1 (0.2%)
	Haemorrhoids	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions			
	Fatigue	3 (0.3%)	0 (0.0%)
	Asthenia	2 (0.2%)	0 (0.0%)
	Chest pain	2 (0.2%)	0 (0.0%)
	Pain	2 (0.2%)	0 (0.0%)
	Pyrexia	2 (0.2%)	0 (0.0%)
Immune system disorders			
	Drug hypersensitivity	3 (0.3%)	1 (0.2%)
Infections and infestations			
	Folliculitis	0 (0.0%)	1 (0.2%)
	Lower respiratory tract infections	0 (0.0%)	1 (0.2%)
	Skin candida	0 (0.0%)	1 (0.2%)
Injury, poisoning and procedural complications			
	Thrombosis in device	2 (0.2%)	0 (0.0%)
	Arteriovenous fistula site complication	1 (0.1%)	1 (0.2%)
	Arteriovenous graft thrombosis	1 (0.1%)	1 (0.2%)
	Procedural hypertension	1 (0.1%)	2 (0.4%)
	Procedural hypotension	1 (0.1%)	1 (0.2%)
	Arteriovenous fistula site haemorrhage	0 (0.0%)	1 (0.2%)
Metabolism and nutrition disorders			

	Fluid overload	0 (0.0%)	1 (0.2%)
	Iron deficiency	0 (0.0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders			
	Muscle spasms	0 (0.0%)	1 (0.2%)
Nervous system disorders			
	Headache	3 (0.3%)	0 (0.0%)
	Cerebrovascular accidents	2 (0.2%)	0 (0.0%)
	Ischaemic stroke	1 (0.1%)	1 (0.2%)
	Convulsion	0 (0.0%)	1 (0.2%)
Psychiatric disorders			
	Restlessness	0 (0.0%)	1 (0.2%)
Reproductive system and breast disorders			
	Menorrhagia	0 (0.0%)	1 (0.2%)
	Vaginal disorder	0 (0.0%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders			
	Dyspnoea	3 (0.3%)	0 (0.0%)
	Productive cough	1 (0.1%)	1 (0.2%)
	Cough	0 (0.0%)	4 (0.7%)
Vascular disorders			
	Hypertension	8 (0.8%)	0 (0.0%)
	Hypotension	7 (0.7%)	0 (0.0%)

Serious adverse events and deaths

Correction of anaemia

In dialysis correction study AFX01-15, no deaths were reported. A higher percentage of TESAEs were reported for AF37702 (18.4%, n=14) as compared to Epoetin (10.5%, n=4). The TESAEs mainly pertain to expected events (hypertension and arteriovenous fistula thrombosis) or non-related events reported one or twice.

Maintenance treatment

In the dialysis maintenance studies, the frequencies of on-study deaths were similar for AF37702 (10.8%) and Epoetin (11.8%).

The frequencies of TESAEs were similar for AF37702 (53.7%) and Epoetin (57.0%), with similar distributions over the different system organ classes (SOC). Most commonly reported TESAEs were infections (pneumonia, 6.3% vs. 5.7% for AF37702 and Epoetin, respectively) and congestive heart failure (5.7% vs. 6.8% for AF37702 and Epoetin, respectively). The rates of treatment-related TESAEs were very low, but higher for AF37702 (1.4%, n=15) as compared to Epoetin (0.4%, n=2). With the exception of the aforementioned events of treatment-related myocardial infarction (n=3), acute myocardial infarction (n=2) and cerebrovascular accident (n=2) (see below for further analysis of these events), these pertain to TESAEs that were reported only once.

Events of special interest

The Applicant presented an analysis of events of special interest for the phase 3 studies, based upon groupings of Preferred Terms (PT) (Standard MedDRA Queries (SMQ) or Applicant-defined groups of PTs). These concern cerebro- and cardiovascular events (cerebrovascular disorders, cardiac failure, cardiac arrhythmia, torsade de pointes/QT prolongation, ischaemic heart disease including myocardial infarction, and arterial thromboembolic events) and potential class effects of approved ESAs (hypertension, venous and other thromboembolic events, convulsions, infusion/injection related reactions, gastrointestinal disorders and malignancy).

For all events of special interest, including cerebro- and cardiovascular events, similar or slightly lower rates were observed for AF37702 as compared to Epoetin for the dialysis maintenance studies. For the non-dialysis studies, slightly higher rates were observed for the events of special interest as compared

to the comparator ESA. The cerebro- and cardiovascular events are discussed in detail in the Composite Safety Endpoint analysis presented below.

An analysis of the Hgb rate of change in relation to the events of interests showed that the Hgb rate of change within 6 weeks prior to the onset of the event was considered small for both AF37702 and Epoetin (Table 10). The occurrences of the events of interest do no appear to be related to the Hgb rate of change.

Table 10: Summary of the Rate of Change in Hgb (g/dL/week) for Subjects With TEAEs of Special Interest by Category (Phase 3 Dialysis Population)

	Phase 3 Dialysis Population	
MedDRA SMQ (a)	**AF37702 Injection (N=1066)**	**Epoetin (N=542)**
Cardiac Failure, N (b)	218	113
Mean Rate of Change in Hgb (g/dL/week)	-0.012	-0.019
(SD)	(0.2871)	(0.2292)
Median	-0.0096	-0.0131
Ischemic Heart Disease, N (b)	107	65
Mean Rate of Change in Hgb (g/dL/week)	-0.049	-0.128
(SD)	(0.3837)	(0.3190)
Median	-0.0104	-0.1000
Myocardial Infarction, N (b)	49	35
Mean Rate of Change in Hgb (g/dL/week)	-0.179	-0.099
(SD)	(0.5088)	(0.3378)
Median	-0.0800	-0.0449
Cerebrovascular Disorders, N (b)	44	37
Mean Rate of Change in Hgb (g/dL/week)	-0.012	0.028
(SD)	(0.2891)	(0.3353)
Median	-0.0539	-0.0392
Embolic and Thrombotic Events, N (b)	284	162
Mean Rate of Change in Hgb (g/dL/week)	-0.024	-0.014
(SD)	(0.3183)	(0.2998)
Median	-0.0229	-0.0130
Hypertension, N (b)	202	98
Mean Rate of Change in Hgb (g/dL/week)	-0.050	-0.064
(SD)	(0.2903)	(0.3881)
Median	-0.0500	-0.0375
Convulsions, N (b)	22	11
Mean Rate of Change in Hgb (g/dL/week)	0.088	-0.025
(SD)	(0.2612)	(0.3185)
Median	0.0967	-0.0801

Source: ad hoc Tables 4.1 to 4.7.
(a) Categories of TEAEs of Special Interest were derived from MedDRA SMQs; the hypertension SMQ was defined by the Applicant
(b) Number of subjects with TEAE of Special Interest and a value for rate of change in Hgb.
(c) Rate of change is defined as the slope of the linear relationship between Hgb values and time (g/dL/week) within 6 weeks on or prior to the AE onset. For subjects with more than 1 AE of special interest, the AE with nonmissing slope and the earliest onset was used.

Hgb Excursions

For dialysis correction study AFX01-15, for the 0.04 mg/kg AF37702 dose, during the first 20 weeks rates of excursions were lower or comparable to Epoetin, after 20 weeks rates of excursions of >13 and >14 g/dL were slightly higher as compared to Epoetin. The 0.08 mg/kg AF37702 dose appears to show more confirmed excursions of >13 and >14 g/dL as compared to Epoetin, in particular after 20

wks of treatment (see efficacy section). Adequate assessment of this risk, and the possible clinical consequences, was hampered by the small size of the study.

The non-dialysis correction studies AFX01-11 and AFX01-13 were of larger size and appear to show a similar trend. From first dose through End of Treatment, AF37702 showed higher rates of confirmed excursions >13 g/dL (AF37702 16.7%; darbepoetin 10.8%) and >14 g/dL (AF37702 1.2%; darbepoetin 0.6%).

In dialysis maintenance studies AFX01-12 and AFX01-14, a slightly higher proportion of AF37702 patients had below target Hgb excursions, but the above target Hgb excursions were similar between AF37702 and Epoetin. During the Evaluation Period 33.9% (AF37702) and 33.0% (Epoetin) of patients showed confirmed excursions of >12 g/dL, 8.4% (AF37702) and 8.3% (Epoetin) of patients showed confirmed excursions of >13 g/dL, and 1.4% (both AF37702 and Epoetin) showed confirmed Hgb excursions of >14 g/dL

In the D121 response, analyses with relevant adverse events of interests showed no evidence of any difference between treatment groups with regards to the temporal association of these events with Hgb rate of rise, Hgb excursions or dosing. No clinically relevant differences were identified between AF37702 and the comparator treatments in both the dialysis (maintenance) and non-dialysis (correction) populations.

Composite Safety Endpoint Analysis

To evaluate the cardiovascular safety of AF37702, a CSE analysis was prospectively planned for the pooled data from the 4 phase 3 studies AFX01-12 and AFX01-14 (Phase 3 Dialysis Population) and AFX01-11 and AFX01-13 (Phase 3 Non-Dialysis Population), with pre-specified analyses by subpopulation (dialysis and non-dialysis). Non-dialysis studies AFX01-11 and AFX01-13 were correction studies in patients not on ESA treatment.

The aim of the CSE analysis was to exclude a hazard ratio (HR) greater than 1.3 as compared to the comparator ESA (Epoetin in the dialysis studies and darbepoetin in the non-dialysis studies). For the primary endpoint, the CSE consisted of the following component events: death from any cause, stroke, myocardial infarction (MI), SAEs of congestive heart failure (CHF), unstable angina, and arrhythmia. As secondary endpoint, the CHOIR-like CSE[1] was specified that consisted of 4 of the 6 CSE events (death, stroke, MI, and CHF). Furthermore, a post-hoc analysis of MACE CSE events was performed, which consisted of the CSE events of death, stroke, and MI. Potential CSE events were identified using pre-specified MedDRA PTs and adjudicated by an independent, blinded Event Review Committee.
The results of the CSE analysis by population is shown in Table 11. Incidences of individual CSE events and HRs relative to the comparator ESA is shown in Table 12.

Table 11: CSE by Population

	Dialysis		Non-Dialysis		Pooled Dialysis and Non-Dialysis	
	AF37702 Inj. (n=1066)	**Epoetin (n=542)**	**AF37702 Inj. (n=656)**	**Darbepoetin (n=327)**	**AF37702 Inj. (n=1722)**	**Comparator (n=869)**
Subjects with CSE Events	243 (22.8%)	132 (24.4%)	141 (21.5%)	56 (17.1%)	384 (22.3%)	188 (21.6%)
HR	0.95		1.32		1.06	
90% CI	(0.79, 1.13)		(1.02, 1.72)		(0.91, 1.22)	
95% CI	(0.77, 1.17)		(0.97, 1.81)		(0.89, 1.26)	

Table 12: Incidences and hazard ratios of individual CSE component events

CSE event	**Phase 3 Dialysis Population**	**Phase 3 Non-Dialysis Population**

[1] Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anaemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355 (20):2085-98.

	AF37702 N=1066	Epoetin N=542	Hazard ratio (90% CI)	AF37702 N=656	Darbepoetin N=327	Hazard ratio (90% CI)
Death	115 (10.8)	64 (11.8)	0.90 (0.70, 1.17)	58 (8.8)	22 (6.7)	1.42 (0.93, 2.17)
Stroke	26 (2.4)	20 (3.7)	0.67 (0.41, 1.09)	7 (1.1)	3 (0.9)	1.14 (0.37, 3.55)
Myocardial Infarction	49 (4.6)	29 (5.4)	0.86 (0.58, 1.26)	24 (3.7)	11 (3.4)	1.12 (0.61, 2.04)
Unstable Angina	24 (2.3)	12 (2.2)	1.04 (0.58, 1.86)	16 (2.4)	3 (0.9)	2.91 (1.03, 8.25)
Congestive heart failure	103 (9.7)	49 (9.0)	1.08 (0.81, 1.44)	56 (8.5)	28 (8.6)	1.06 (0.72, 1.55)
Arrhythmia	63 (5.9)	35 (6.5)	0.91 (0.64, 1.29)	37 (5.6)	13 (4.0)	1.53 (0.90, 2.60)

The results of the Phase 3 Dialysis Population showed no increased risk in CSE events between AF37702 and the comparator ESA. The HR for the Phase 3 Dialysis Population of AF37702 vs the comparator ESA was 0.95 (95% CI: 0.77, 1.17). The results of studies AFX01-12 and AFX01-14 individually were consistent with the pooled data showing HRs of 1.01 (90% CI: 0.79, 1.30) and 0.89 (90% CI: 0.69, 1.14) for studies AFX01-12 and AFX01-14, respectively. Also, no increased risk as compared to Epoetin was observed for any of the individual CSE events. The results were confirmed by secondary analyses using different CSE definitions (CHOIR-like and MACE CSE), also showing no increased risk for AF37702 as compared to the comparator ESA.

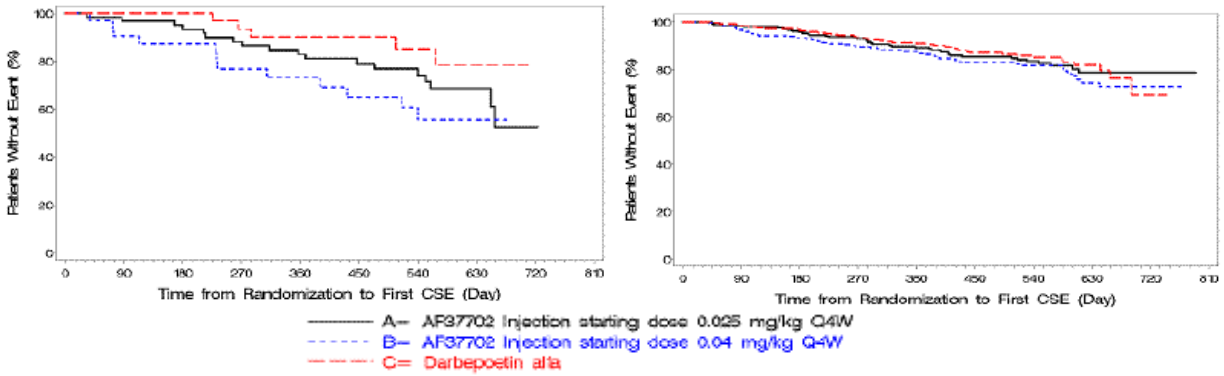
In contrast to the Phase 3 Dialysis Population, the Phase 3 Non-Dialysis Population showed an increased risk for AF37702 as compared to the comparator ESA with an overall HR of 1.32 (95% CI: 0.97, 1.81). This increased risk was primarily derived from study AFX01-13, which showed a HR of 1.53 (90% CI: 1.06, 2.20). Study AFX01-11 did not show a clear increased risk with a HR of 1.14 (90% CI: 0.78, 1.65). Considering the individual CSE events, the incidences of death (AF37702 8.8%, comparator ESA 6.7%), unstable angina (2.4% and 0.9%) and arrhythmia (5.6% and 4.0%) were numerically higher for AF37702 as compared to the comparator ESA. This was observed in both studies, although the difference for death and arrhythmia was more pronounced in study AFX01-13. The difference in arrhythmias appeared to be predominantly in the rates of atrial fibrillation. Rates of ventricular arrhythmias were low. The difference in deaths appeared to be mainly attributable to deaths due to sudden deaths, which was also one of the most common causes of deaths in the AF37702 group (AF37702 n=14 (2.1%), Epoetin n=1 (0.3%)). In the D121 response, it was indicated that the rates of sudden death were not clustered during the initial treatment period. There was no temporal relationship between the occurrence of sudden death and dosing of AF37702.

Additional analyses were performed to investigate the possible mechanism for the increased CSE risk found in the Phase 3 Non-Dialysis Population. For the Phase 3 Non-Dialysis Population, after adjustment for baseline imbalances in cardiovascular risk factors between treatment groups, the CSE HR was lower than in the primary analysis (1.20 (95% CI: 0.87,1.64)), but baseline imbalances could not fully account for the difference in risk between AF37702 and the comparator ESA.

In the D121 response, it was indicated that CSE events in the Phase 3 Non-Dialysis Population were well distributed over time and not clustered during the initial treatment period. The CSE risk for both dialysis and non-dialysis populations and in all treatment groups was found to be inversely related to Hgb levels with low Hgb being associated with a greater risk of CSE events. Risk of CSE events was also associated with rapidly increasing or decreasing Hgb levels. The CSE rates in patients with Hgb excursions >12 g/dL or rapid increasing Hgb values were comparable between treatment groups. There was no correlation between Hgb excursions and rates of increased blood pressure or thromboembolic events.

An analysis was performed for the Phase 3 Non-Dialysis Population investigating the CSE rates in initial poor and initial better Hgb responders (Figure 2). It was shown that the increased risk in CSE events of AF37702 vs darbepoetin was highest in ESA-naïve patients who showed an initial poor Hgb response upon initiation of study treatment. Figure 2 shows survival curves that are very much more diverging in the group of initial poor responders, with higher CSE events for AF37702 as compared to darbepoetin.

Figure 2: Time to first CSE event by initial Hgb poor (left) and better (right) responders, Phase 3 Non-Dialysis Population



Laboratory findings

No unexpected safety findings have been identified. The laboratory findings and vital signs are acceptable.

QT study

The thorough QT/QTc study AFX01_101 was a phase 1, single-dose, multi-center, randomized, double-blind, double-dummy, placebo and positive controlled (moxifloxacin), three-period crossover study with 65 healthy subjects. The results showed that IV injection of AF37702 in a dose of 0.1 mg/kg in healthy subjects lacked effect on the QTc interval. Assay sensitivity was confirmed by the results of the positive control moxafloxacin.

Safety in special populations

There were no clinically relevant differences in AE profile between AF37702 and Epoetin within subgroups based on age, sex, race as well as presence or history of comorbidities and baseline disease factors.

In general, AE rates after IV and SC administration were similar for AF37702 (IV 92.6% ; SC 88.0%). However, there was a difference in favor of the IV route for AF37702 concerning TEAE rates in 2 SOCs: blood and lymphatic system disorders (7.1% vs 15.7% [particularly anemia: 4.1% vs. 12.0%]) and immune system disorders (3.9% vs. 10.2%).The proportion of subjects with TESAEs was higher in the IV route for AF37702 (IV 50.7% vs SC 44.4%). Only 1 TESAE (pneumonia: IV 6.5%, SC 2.8%) was reported more frequently by subjects receiving IV administration than SC, and no TESAEs occurred more frequently in the SC group. Events related to local injection and infusion site reactions were reported with similar frequency in either subgroup.

In peritoneal dialysis, the mean (SD) duration of exposure to AF37702 administered SC was 21.9 weeks (5.68) and the median exposure was 24.1 weeks. The incidence of TEAEs was 91.5%. Most commonly reported AEs (>10%) were peritonitis (20.3%), diarrhoea (15.3%), hypertension (13.6%), dyspnoea (11.9%), cough (10.2%), and hypotension (10.2%). Four (6.8%) treatment-emergent deaths were reported. The causes of death were ischemic heart disease, peritonitis/respiratory failure/sepsis, sepsis, and myasthenia gravis. The incidence of TESAEs was 45.8%. The most common TESAE was peritonitis (15.3%). TEAEs that led to treatment discontinuation were experienced by 11.9% of patients. There were no trends noted in abnormal laboratory values, changes in vital signs, or physical examination findings.

Immunological events

A total of 1.2% and 0.9% of patients had, respectively, AF37702-specific binding and neutralizing antibodies. As expected, SC injection was associated with higher rates of antibodies as compared to the IV injection. The highest rates were observed in the SC dialysis population with 2.8% and 2.4% for AF37702 binding and neutralizing antibodies, respectively. The presence of antibodies was associated with reduced efficacy in a large proportion of antibody-positive patients (17 out of 29 subjects), but appears not to induce clinical manifestations of immunogenicity.

Of the subjects who developed AF37702-specific antibodies, none developed de novo anti-EPO antibodies following exposure to AF37702. Albeit based on limited follow-up data, AF37702-antibody positive subjects with AF37702 treatment failure appear to respond to EPO-based ESAs.

Safety related to drug-drug interactions and other interactions

Not applicable. Formal drug-drug interaction studies in humans have not been conducted for AF37702.

Discontinuation due to AES

In the correction study AFX01-15, there were no TEAEs leading to treatment discontinuation. In the maintenance studies, the percentage of patients who discontinued treatment due to TEAEs were similar for AF37702 (12.8%) and Epoetin (12.0%). The percentage of patients who discontinued or had their dose modified due to TEAEs was also similar between treatment groups (AF37702 20.1%; Epoetin 21.0%). The most common of these TEAEs in either treatment group were anemia (2.1%;2.2%), cardiac arrest (1.6%;1.8%), and sepsis (1.2%;0.9%).

Newly emerging safety issue

On 23 February 2013, the applicant notified the CHMP of a voluntary recall of all lots of Omontys in the US due to serious hypersensitivity reactions, including fatal reactions.

In follow-up to this and as requested by the Rapporteurs, the Applicant submitted a document with background information, case summaries and CIOMS forms of these serious hypersensitivity cases that led to a recall of the product in the US. The currently available data from clinical trial experience and post-marketing use is summarized below.

Clinical trial experience

The formulation of Omontys used in the clinical trials was a sterile, aqueous, phosphate-buffered, isotonic solution at pH 6.0 in a single dose vial at a concentration of 10 mg/ml.

During clinical trials, of the 4,305 patients (CKD on dialysis, CKD not on dialysis and healthy volunteers) who received at least one dose of Omontys, six patients experienced a hypersensitivity reaction with systemic symptoms following the first dose of Omontys. These clinical trial reports of hypersensitivity reactions were mild and symptoms included hypotension, flushing, dyspnea, urticaria, and pruritus, and occurred in five patients with intravenous administration (IV) and in one patient with subcutaneous administration (SC) of Omontys. Serious features such as laryngeal edema, bronchoconstriction, angioedema were not observed. Three cases were considered medical significant and hence reported as SAEs. In two of these cases, symptoms occurred within 15 minutes after receiving IV Omontys and resolved with treatment in the dialysis unit. The third case concerns a Japanese woman who had presented with intermittent generalized wheals and itching, which started hours after SC injection of Omontys. She was treated in the Emergency Room (ER) and by a dermatologist. Her symptoms resolved after 16 days.

Post-marketing experience

The formulation of Omontys used in the US market is a Multi Use Vial (MUV) formulation which is a sterile, aqueous, acetate buffered, isotonic, preserved sorbitol solution at pH 5.4.

Through 12 February 2013, it is estimated that more than 25,000 patients have received at least one dose of Omontys in the post-marketing setting based on distribution data. The uptake of Omontys in the US dialysis setting has occurred in a step-wise fashion with increasing numbers of dialysis centers converting to Omontys for the management of anemia in end stage renal patients. According to the applicant, the volume of adverse event reports received by Affymax has reflected this step-wise pattern of uptake.

Through 12 February 2013, there have been a total of 59 (reporting rate 0.2%) patients who have experienced hypersensitivity reactions. Of these 59 cases, 23 cases (reporting rate 0.1%) were considered serious. In 5 cases (reporting rate 0.02%) the outcome was fatal.

MedWatch (CIOMS) forms of the 23 serious cases have been reviewed by the assessor and these cases can be summarized as follows:

The cases were reported by different dialysis centres. One centre reported 3 SAEs, another reported 2 SAEs, and the remaining 18 SAEs were reported each by a different dialysis centre. The 5 fatal cases were reported by 5 different dialysis centres.

Reviewing the patient characteristics no trends could be identified. All patients had multiple (cardiovascular) co-morbidities and co-medication, which is in line with the general dialysis population.
Based upon the reported symptoms and treatments, in the majority of the cases the clinical picture appears in line with an acute hypersensitivity, anaphylaxis-like reaction, although in some cases the clinical picture was less clear. Reported symptoms included hypotension, difficulties breathing, swelling of face/lip/eye/throat, itching, syncope and loss of consciousness. The reactions occurred very shortly after Omontys administration, in most cases within 5-10 minutes. In almost all cases, Omontys was administered IV (22 cases IV and 1 case unknown). The IV doses of Omontys given ranged from 2 mg-15 mg. Patients were initially treated in the dialysis clinics with IV antihistamines, oxygen, fluids, adrenaline and/or IV steroid. Many patients were then transferred to the Emergency Room (ER)/hospital. Of the 23 serious cases, in 5 cases the outcome was fatal. In another 6 cases, the case was considered to be life-threatening.
Of note in the fatal cases is the very fast clinical course of the events. After Omontys administration reported events included feeling unwell, “burning all over”, shortness of breath, nausea, distress and seizure-like activity. In all 5 cases, within 5-10 minutes after Omontys administration patients were unresponsive and had a cardiopulmonary arrest. The IV Omontys doses given in the fatal cases were 3.5 mg in 1 patient, 10 mg in 1 patient and 15 mg in 3 patients.

Actions taken by the applicant

Based upon the above reports of serious hypersensitivity reactions, the applicant - in discussion with the FDA- has initiated a voluntary product recall of all lots of Omontys in the US. In addition, Dear Health Care Professional letters were issued. The applicant is initiating several lines of investigation in order to identify the root case of these reactions. These include manufacturing/quality, epidemiological, non-clinical and clinical approaches. The investigation is ongoing. The applicant has withdrawn the Marketing authorisation Application, having determined that it will not be able to complete the investigation and propose appropriate risk mitigation measures within the procedure timeframe.

Discussion on clinical safety

The total exposure to AF37702 in the dialysis population was considered sufficient in number and duration and is in line with ICH E1. Data in peritoneal dialysis patients was limited, but based on current knowledge with ESA treatment it is unlikely that this will show a different safety profile to

haemodialysis patients, except for the events known to occur in peritoneal dialysis (e.g. peritonitis). Peritoneal dialysis is included in the RMP and further information should be obtained post-marketing.

In the maintenance studies, the AE profiles of AF37702 and Epoetin appear similar in the dialysis population. Type and rates of AEs were in line with those to be expected in the CKD patient population. The most commonly reported TEAEs for AF37702 were dyspnoea (18.4%), diarrhoea (18.4%), nausea (17.4%), arteriovenous fistula site complication (16.1%), and cough (15.9%). Most commonly reported TESAEs were infections (pneumonia, 6.3%) and congestive heart failure (5.7%), which can be expected and is consistent with the co-morbidities of this population.

Treatment-related TEAEs were reported at low rates, but at higher rates for AF37702 (7.8%, n=83) as compared to Epoetin (4.2%, n=23). These pertain to a diversity of events, without any events predominating. For the dialysis population, no apparent increased risks or safety signals were identified for AF37702 with regards to (treatment-related) TEAEs, deaths, (treatment-related) TESAEs and TEAEs leading to discontinuations.

Events of special interest are cerebro- and cardiovascular events and potential class effects of approved ESAs (hypertension, venous and other thromboembolic events, convulsions, infusion/injection related reactions, gastrointestinal disorders and malignancy). These appeared similar for both treatment groups in the dialysis population. The occurrences of the events of interest do not appear to be related to the Hgb rate of change.

With regards to Hgb excursions, in the dialysis correction study for the 0.04 mg/kg AF37702 dose, during the first 20 weeks rates of excursions were lower or comparable to Epoetin, after 20 weeks rates of excursions of >13 and >14 g/dL were slightly higher as compared to Epoetin. The 0.08 mg/kg AF37702 dose appears to show more confirmed excursions of >13 and >14 g/dL as compared to Epoetin, in particular after 20 wks of treatment, but the Hgb excursions responded to dose decreases and did not appear to be of longer duration than excursions on Epoetin. Adequate assessment of this risk, and the possible clinical consequences, was hampered by the small size of the study. The non-dialysis correction studies, which were of larger size, appear to show a similar trend with increased rates of confirmed excursions of >13 and >14 g/dL as compared to darbepoetin. In the maintenance treatment, the above target Hgb excursions were similar between AF37702 and Epoetin. In the D121 response, post-hoc analyses with selected relevant adverse events of interests showed no evidence of any difference between treatment groups with regards to the temporal association of these events with Hgb rate of rise or Hgb excursions, for both the phase 3 dialysis (maintenance) and non-dialysis (correction) studies. It therefore appears that fluctuations in Hgb did not translate into an increased risk of events such as hypertension and thrombosis, also not during the correction phase.

In the past years, ESA use has been associated with an increased risk of cardiovascular events and the CSE cardiovascular analysis is therefore of importance. The CSE analysis, including death from any cause, stroke, myocardial infarction, SAEs of congestive heart failure, unstable angina, and arrhythmia as composite endpoint, did not reveal an increased risk for AF37702 over current ESA treatment within the dialysis population. This was consistently shown when using different events included in the composite endpoint, also taking into account composite endpoints used before in literature. However, the CSE analysis in the non-dialysis population (in the setting of correction of a anaemia in patients not on ESA treatment) showed an increased risk in deaths and cardiovascular events as compared to the comparator ESA (darbepoetin), with an overall unadjusted HR of 1.32 (95% CI: 0.97, 1.81). The point estimate slightly decreased to 1.20 (95% CI: 0.87, 1.64) when adjusting for baseline characteristics, but still points towards a higher risk compared to current ESA treatment. An increased risk of 20-30% is of concern given the seriousness of the events.

The D121 response elaborated on the possible mechanism for the increased CSE risk found in the Phase 3 Non-Dialysis Population. As CSE events were well distributed over time without clustering during the initial phase and there was no correlation between Hgb excursions and events such as increased blood pressure or thrombosis, neither differences between treatment groups, it appears that the increased CSE risk is unlikely related to the possible fluctuations or increases in Hgb levels that may occur during the correction phase in the non-dialysis phase 3 studies. Furthermore, based upon the D121 response, a significant arrhythmogenic effect of AF37702 (that may subsequently result in an increased risk of sudden deaths) appears unlikely. There seems to be no pattern between the timing or dosing of AF37702 and the occurrence of sudden deaths. The rates of ventricular arrhythmia in the non-dialysis studies were much lower than the rates of sudden deaths, hence ventricular arrhythmia

does not seem to be the underlying cause of the sudden deaths. Furthermore, there were no cases of torsade the point and the QTc study did not show QT prolongation.

It has been suggested that a poor initial hematopoietic response to ESA treatment in subjects not previously receiving ESAs is associated with an increased cardiovascular risk (TREAT study, Solomon et al 2010). The mechanism of action is not clear, but appears to be different from that of aggravated pharmacodynamics resulting in too high Hgb levels. Analysis of CSE events in the ESA-naïve non-dialysis population showed that the increased risk of AF37702 versus darbepoetin was highest in patients who showed an initial poor Hgb response upon initiation of study treatment. This observation is of particular concern as it cannot be excluded that this would also be applicable to the ESA naïve dialysis population, which will also include patients with a poor initial response to ESA treatment **(MO, see LoOI)**. The correction study in ESA naïve dialysis patients was too small to provide reassurance on this safety issue.

The large dialysis maintenance studies, including patients previously exposed to and previously known to respond to ESA therapy, consistently showed no increased safety risk versus Epoetin. Based on the consistent results, and based on the lack of evidence for any clear drug effects, including an arrhythmogenic effect, the safety of AF37702 in this ESA-experienced population seems acceptable.

The incidences of antibody formation, in particular in the SC dialysis population, is considered relatively high as for Mircera and Aranesp (darbepoetin) no antibodies were found during clinical development. In a large proportion of antibody-positive patients the presence of antibodies was associated with reduced efficacy. However, this issue appears manageable. The D121 response showed that AF37702-antibody positive subjects with AF37702 treatment failure appear to respond to EPO-based ESAs, albeit this was based upon limited follow-up data. Long-term immunogenicity remains an uncertainty and needs to be addressed in the RMP **(LoOI).** This should be addressed both in terms of loss of efficacy and adverse events. Up to now, no subjects developed anti-EPO antibodies, supporting the proposed lack of immunological cross-reactivity between AF37702 and human EPO or marketed rHuEPO-derived ESAs. This also needs to be followed up post-marketing, as events might be rare and/or occur after a longer period of time.

From the post-marketing experience, a new emerging safety issue was identified which concerns serious hypersensitivity reactions. Based upon the strong temporal relationship, where events occur within minutes of Omontys administration, the causality with Omontys is probable.

The post-marketing cases appear to differ from the clinical trial cases in severity and nature. The clinical trial cases were less severe, mainly resolved in the dialysis unit and did not include serious features of laryngeal edema, bronchoconstriction or angioedema. In contrast, the post-marketing cases are of major concern and included serious anaphylaxis-like reactions which required hospitalization, and have led to life-threatening situations or fatal outcomes. Of note is that different vials were used in the clinical trials and post-marketing setting (single dose vials vs multi use vials). Whether this is of relevance is unclear and needs to be investigated.

Although it is difficult to assess AE frequency based upon post-marketing data, the reporting rates of approximately 1/1000 for serious and 1/5000 for fatal hypersensitivity reactions appear high, also considering the fact that these are “best-case” figures as there is undoubtedly some degree of underreporting.

Reviewing the post-marketing cases, no trends could be identified. It is agreed with the applicant that with the current data it is not possible to identify potential predictors for patients at risk of developing these hypersensitivity reactions. However, the vulnerability of the population with multiple (cardiovascular) co-morbidities will increase the risk of poor outcomes if such events occur.

Of major concern is the question whether these serious hypersensitivity reactions can be adequately managed. It should be noted that patients have all received Omontys within a well-controlled clinical environment, where adequate treatment was available (e.g. IV antihistamines, steroids and adrenaline) and presumably timely given, which however did not prevent life-threatening situations or fatal outcomes. Of note is also the very fast course of the events (for the fatal cases, patients had a cardiopulmonary arrest within 5-10 minutes of Omontys administration), which could also explain the poor outcomes despite availability of timely medical treatment.

The applicant provided an update on the ongoing root cause investigation and noted that it will not be able to complete the investigation and propose appropriate risk mitigation measures within the procedure timeframe. Hence, the applicant has decided to withdraw the MAA at this stage.

Based upon the available information, no root cause has been identified for these serious hypersensitivity reactions. It is unclear whether this safety issue is related to the compound itself, to the product or batch, or to a population at increased risk. Hence, it is currently unclear whether this issue could be remedied or mitigated. Further investigation is required.

Conclusions on clinical safety

For the ESA-naïve non-dialysis population, an increased risk in deaths and cardiovascular events was found as compared to the comparator ESA. This increased risk versus darbepoetin was highest in patients who showed an initial poor Hgb response upon initiation of ESA treatment. It cannot be excluded that this safety issue is also applicable to the ESA naïve dialysis population. Study AFX01-15 was too small to provide reassurance on this matter and the safety in the ESA naïve dialysis population remains a major concern.

For the dialysis population, previously exposed to and previously known to respond to ESA therapy, the maintance studies showed an AE profile of AF37702 that appears similar to that of Epoetin and that appears in line with what can be expected of ESA treatment in the CKD population. The incidence of antibody formation, in particular for the SC route, is considered high. However, this appears manageable as AF37702-antibody positive subjects with AF37702 treatment failure appear to respond to EPO-based ESAs. Based upon the consistent results in the maintenance studies showing no increased safety risk vs Epoetin, and based on the lack of evidence for any clear drug effects, including an arrhythmogenic effect, the safety of AF37702 in this ESA-experienced population as derived from the maintenance studies appears acceptable.

However, from the post-marketing experience, a new emerging safety issue was identified. The post-marketing serious (fatal and life-threatening) hypersensitivity reactions within minutes of peginesatide injection are of major concern. No root causes have currently been identified and it is unclear whether this risk can be remedied or mitigated. Root cause investigation by the applicant is ongoing and the applicant decided to withdraw the MAA at this stage, having determined that it will not be able to complete the investigation and propose appropriate risk mitigation measures within the procedure timeframe.

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk management plan (version 02, dated 06 September 2012)

Safety concern	**Proposed Pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Important identified risks: Hypertension	Routine PV Activities Drug Utilization study AFX01-19: A Prospective, Observational Cohort Study of Peginesatide Injection Compared to Epoetin Alfa Evaluating Cardiovascular Outcomes in Hemodialysis Patients with Anemia due to Chronic Kidney Disease,	SmPC section 4.3, 4.4 and 4.8

	AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU) of the Safety and Efficacy of Peginesatide Injection for the Treatment of Anemia in Incident Hemodialysis Patients.	
Cerebrovascular accident	Routine PV Activities Drug utilization study AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.2 and 4.4
Myocardial infarction	Routine PV Activities Drug utilization study AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.2 and 4.4
Venous thromboembolic events	Routine PV Activities Drug utilization study AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.2 and 4.4
Thrombosis of hemodialysis vascular access	Routine PV Activities Drug utilization study AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.4 and 4.8
Convulsions	Routine PV Activities Drug utilization study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.4 and 4.8
Important potential risks Effect on tumour growth	Routine PV Activities AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.4
Intrauterine developmental toxicity	Routine PV Activities Monitoring of EUROCAT site for	SmPC section 4.2 and 4.6

	possible toxicity reports Follow-up of pregnancies in EU Drug Utilization Study	
Off-label use	Routine PV Activities	SmPC section 4.1, 4.2 and 4.4
Important missing information: Effects of long-term use (beyond 2 years)	Routine PV Activities AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.8
Safety in pregnancy or during breast-feeding	Routine PV Activities EU Drug Utilization Study	SmPC section 4.2 and 4.6
Safety in paediatric population	Routine PV Activities EU Drug Utilization Study	SmPC section 4.2
Safety in patients >75 years	Routine PV Activities EU Drug Utilization Study AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.2
Safety in peritoneal dialysis	Routine PV Activities	SmPC section 4.2 and 4.8
Safety in patients with bleeding or coagulation disorders	Routine PV Activities EU Drug Utilization Study AFX01-19: A Prospective, Observational Cohort Study AFX01-20: A Randomized, Active-Controlled, Open-Label, Multicenter Study (US and EU)	SmPC section 4.2
Drug-drug interactions	Routine PV Activities	SmPC section 4.5
Hypo-responders to peginesatide	Routine PV with targeted questionnaire	SmPC section 4.2 and 4.4

Limitations of the Human Safety Database

Clinical trial patient exposure to peginesatide was in the overall safety population 2,733 patient exposure years (PEY) with an average of 1.15 PEY/patient. In the Dialysis Population, patient exposure to peginesatide was 1,236 PEY with an average of 1.16 PEY/patient. The size of the clinical safety database precludes drawing conclusions about AEs with an incidence of less than rare (≥1:10,000 to <1:1,000).

Based on the limited exposure in some populations, the following topics have been included as important missing information in the updated RMP version 2:

- Safety in patients with bleeding or coagulation disorders
- Safety in the pediatric population
- Safety in pregnant and lactating women
- Safety in hyporesponders to peginesatide
- Effects of long-term treatment (>1 year)
- Peritoneal dialysis
- Drug interactions.

Venous thromboembolic events (VTE) represent identified risks in other erythropoiesis-stimulating agents (ESAs) and are labelled in the respective product information. VTE can be considered to be a class-effect of ESAs due to their capability to increase cellularity. VTE incidence rates in the clinical studies presented in the RMP suggest no differences in the occurrence between peginesatide and the reference group (epoetin group), therefore the applicant should add VTE to the list of important identified risks. In the updated RMP, thrombosis of vascular access has been included in the RMP as an identified risk. In the clinical trials with peginesatide the incidence rates of convulsions are similar between the peginesatide and the reference (epoetin) group. In the updated RMP convulsions has been included to the section of important identified risks.

In general the important risks listed above are comparable with other ESAs. In response to D120 LoQ the Applicant provided more discussion regarding the following topics:

Routine risk minimisation of important identified and potential risks

In order to minimize adverse outcomes due to increased blood viscosity (i.e. Hypertension, Cerebral infarction, Myocardial infarction, Venous thromboembolic events) the Applicant recommends maintaining haemoglobin within a specified target range of 10-12 g/dL as routine risk minimisation (SmPC labelling). In order for this risk minimisation to be effective, it is of the utmost importance that the prescriber will be able to timely monitor and adjust the dose in case the Hb reaches values >12 g/dL. It is of concern that in study AF37702 the higher dose of 0.08 mg/kg appears more effective, but also gave more excursions of >13 and >14 g/dL, which may suggest that the Hb levels cannot be sufficiently controlled, in comparison with other ESAs. It should be noted that the frequency of monitoring and dose adjustment from Peginesatide (monthly) is much less frequent than Epoetin or Darbepoetin (weekly). The Applicant has provided a discussion and justification for the conservative starting dose. It is acknowledged that at the starting dose of 0.04 mg/kg the number of Hgb excursions >12 g/dl was not higher compared with epoetin. This issue could be considered resolved provided the Applicant will routinely evaluate Hb levels during the correction phase and closely monitor cases reporting Hgb excursions. **See also unresolved Clinical MOs.**

Anti-peginesatide antibody formation

At D120 the CHMP requested that the lack or loss of efficacy due to the occurrence of peginesatide-specific antibodies should be included and thoroughly discussed in the RMP as important identified risk. Appropriate Pharmacovigilance and Risk minimisation activities should be proposed. The section of Adverse events should be updated accordingly. Although the development of blocking anti-peginesatide antibodies was observed in only a small (0.6%) portion of patient population, this warrants a more thorough discussion, since their occurrence was higher than other recently approved ESAs (e.g. MIRCERA, methoxy polyethylene glycol-epoetin beta). Moreover, the antibodies were correlated with reduced efficacy.

The Applicant does not believe that lack or loss of efficacy due to the occurrence of AF37702-specific antibodies should be included in the RMP as an important identified risk.

The Applicant committed to perform assays for binding and neutralizing antibodies in case of lack or loss of haemoglobin response to peginesatide on request of the clinicians. The information will be clearly described in the warning section of the SmPC. An instruction how to act if neutralizing antibodies were detected will also be mentioned in the warning section of the SmPC. The Applicant is prepared a questionnaire that will be sent to the clinicians in case of requests for conducting an assay

for binding and neutralising antibodies in order to collect meaningful patient information of cases with lack or loss of efficacy. Follow-up and outcome should be documented.

The Applicant provided a comprehensive overview of all cases reporting development of antibodies (both anti-peginesatide and anti-EPO) including more information about the treatment duration, dose and time-to-onset. At the moment no trends were detectable (due to low numbers), but the Applicant should commit to closely monitor any new cases reporting anti-AF33702 antibodies and where possible evaluate the conditions (dose, treatment duration, mode-of-administration) under which these antibodies occur. Any unexpected findings should be thoroughly discussed in the PSURs. ***See section 7, RMP/PSUR commitment.***

Additional Pharmacovigilance activities

Important **Identified and potential risks** will be further evaluated by:

- Drug utilization study to compare the use of peginesatide in the European Union with that in the United States and to ensure that the results of the above US study are relevant to the European Union. The proposed Drug utilisation Study should be amended to include evaluation of off-label use.
- Drug utilization study to compare the use of peginesatide in the European Union with that in the United States and to ensure that the results of the two US studies (below) are relevant to the European Union.
- Affymax, the former US NDA holder committed to conduct 2 studies, which will provide data that will also contribute to further the knowledge and continue the evaluation of both safety and efficacy of AF37702 Injection. While these data will be useful and communicated as appropriate, Takeda, not being the study sponsor, cannot independently modify the design of these studies and therefore, cannot offer them to be part of RMP commitments. These studies are:
    - (AFX01-19) A real-world, observational study utilizing the US Medicare Claims database to study a large cohort of dialysis patients, including both incident patients not receiving an ESA previously and prevalent patients being switched to AF37702 Injection from another ESA. This study will evaluate ESA use in dialysis patients in a very large cohort of patients in the real world setting and has the potential to inform any potential early CV signals in the post-marketing setting. Projected cohort sample size of 71,678 patients overall, comprising 61,575 prevalent hemodialysis (HD) peginesatide patients, 8,478 incident HD peginesatide patients without prior ESA use, and 1,625 incident HD peginesatide patients with prior ESA use
    - (AFX01-20) A prospective randomized controlled study of AF37702 Injection vs Epoetin in anemic patients with CKD who are in the early months of dialysis (incident dialysis patients) is planned. This study will involve a large number of incident dialysis patients globally, including US and EU countries. Approximately 1,510 patients (755 subjects per treatment group) will be enrolled to accumulate 596 CSE events in approximately 5 years. The study will not only assess the comparative risk of cardiovascular events, but also will generate data to further assess efficacy in the setting of correction of anemia in CKD dialysis patients.

Additional Risk minimisation:

None proposed.

Conclusion

In the updated RMP the Applicant highlighted the important issues,and provided adequate response to the CHMP's questions regarding the RMP. It is however noted that there are still outstanding Major objections regarding Efficacy and Safety.

The RMP could be acceptable provided the Applicant adequately addresses the points detailed in the List of outstanding Questions.

Upon the CHMP's requests the RMP has been amended considerably. All consequential changes to the relevant sections (e.g. pharmacovigilance plan, discussion on need of risk minimisation) have been made accordingly. A clean and change-tracked-version of the updated RMP has been provided.

4. ORPHAN MEDICINAL PRODUCTS

Not applicable

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

AF37702 is submitted for the indication of anaemia in CKD dialysis patients. It is a pegylated EPO-receptor agonist, with no amino acid sequence homology to human EPO, thereby potentially offering ESA treatment with a monthly dosing interval and with a reduced or absent risk for pure red cell aplasia (PRCA). The proposed initial starting dose for the correction of anaemia is 0.04 mg/kg and the conversion from other ESAs is possible via a conversion scheme.

Currently, the CHMP recommended Hgb target for all ESAs is 10-12 g/dL (EMEA/496188/2007).

Correction of anaemia

Correction of anaemia was studied in one exploratory, open-label, randomized, active-controlled phase 2 study (AFX01-15). CKD dialysis patients not on ESA treatment with Baseline Hgb of 8-11 g/dL were treated with AF37702 doses of 0.04 mg/kg (n=39) and 0.08 mg/kg (n=37) or with Epoetin (n=38). The target range in this study was 11-12 g/dL, based upon standards at the time.

The results showed that AF37702 was able to increase Hgb levels in anaemic patients in a dose-dependent manner. Mean change in Hgb from Baseline to wk 28 was 2.15 g/dL (SE: 0.171), 2.39 g/dL (SE: 0.160), and 2.41 g/dL (SE: 0.165) for 0.04 mg/kg AF37702, 0.08 mg/kg AF37702, and Epoetin, respectively. The proportion of patients achieving a Hgb response (defined as Hgb increase of ≥1.0 g/dL above baseline and ≥11.0 g/dL) within 20 and 28 wks was 87.2% and 92.3% for the 0.04 mg/kg dose, and 97.3% for the 0.08 mg/kg dose at both time points. Epoetin showed 100% responders at both time points.

Median time to initial Hgb response was 7.0, 5.1, and 6.3 wks for the 0.04 mg/kg dose, the 0.08 mg/kg dose and Epoetin, respectively.

Primary and secondary endpoints consistently showed a numerically lower and slower response for AF37702 at the proposed dose of 0.04 mg/kg as compared to Epoetin.

Maintenance treatment

Dose-finding studies showed that patients on Epoetin with stable Hgb levels (10-12 g/dL) could maintain Hgb levels after switching to AF37702. The best results were obtained with a 1-wk ESA free transition period and a tiered weight-based conversion schedule.

Two phase 3 pivotal, open-label, randomized, active-controlled studies (AFX01-12 and AFX01-14) were performed to demonstrate non-inferiority of AF37702 to Epoetin in maintenance of Hgb levels after switching from Epoetin to AF37702. Patients included were CKD dialysis patients on Epoetin treatment with stable Hgb levels (10-12 g/dL), which were representative for the target dialysis population.

The Full Analysis Population (primary analysis population) included a total of 1066 patients switched to AF37702 and 542 patients continuing Epoetin treatment. Both studies showed that AF37702 was able to maintain Baseline Hgb levels after switching from Epoetin, with changes from Baseline to wks 29-36 of close to zero. The mean difference in mean Hgb change from Baseline to wks 29-36 (primary endpoint) between AF37702 and Epoetin was -0.15 g/dL (95% CI: -0.30, -0.01) and 0.10 g/dL (95% CI: -0.05, 0.26), respectively, and non-inferiority was met (predefined non-inferiority margin of -1.0 g/dL).

The proportions of patients with Hgb within target range (10-12 g/dL) was numerically lower for AF37702 (about 63.0%) versus Epoetin (65.9% to 71.7%). The proportions of patients receiving transfusions were 10.3% and 7.7% for AF37702 versus 8.6% and 9.9% for Epoetin for the individual studies, respectively.

Similar results were obtained for the PP analyses for the primary endpoint.

Hgb levels similar to Baseline were maintained up to wk52 without an increase in dosing, supporting persistence of the effect.

Efficacy or maintenance dosing appears similar for the IV and SC routes. In study AFX01-14, subjects given AF37702 by IV or SC routes received similar doses, however, the SC dose started at a lower level (as derived from the prior lower SC Epoetin dose) and approached the level of the IV dose during the study duration; both achieved similar Hgb levels.

Subgroup analyses with regards to age, gender, race, BMI, ethnicity, presence of diabetes, baseline hsCRP and NYHA CHF Class showed no apparent effects of any of these factors. Results stratified for these subgroups met the non-inferiority criterion.

Uncertainty in the knowledge about the beneficial effects

The correction and maintenance studies were conducted in an open-label fashion. Considering the GCP findings in the maintenance studies, potential bias cannot be excluded. The extent and impact of potential bias is currently unclear.

Correction of anaemia

Study AFX01-15 had methodological issues including the small size and lack of a formal comparison vs Epoeting, the inclusion of patients already on current target Hgb and the conduct of the study in a single country in a population that may not match the EU CKD population. In the D121 response, the applicant has justified that the target range (11-12 g/dL) was consistent with the ESA labeling at the time. Post-hoc analysis showed that the results for the subgroup of subjects with baseline Hgb <10 g/dL were in line with those of the Full Analysis Population. Furthermore, the study population appears globally consistent with the EU CKD population as derived from epidemiological databases. The limited size of the study remains a concern.

The response to AF37702 was lower and slower as compared to Epoetin. In response to the D120 LOQ, post-hoc analyses were performed based upon the current target level of ≥10 g/dL. It appears that, albeit lower and slower than Epoetin, upon AF37702 treatment the current target level of ≥10 g/dL was achievable within acceptable time-frames. However, study AFX01-15 was small, hampering adequate assessment and firm conclusions. Efficacy in the correction of anaemia remains to be confirmed in a larger population. In particular, it remains to be confirmed in a larger population that the slower initial response of AF37702 does not pose patients at a higher risk for blood transfusions.

Maintenance treatment

Findings of the GCP inspection (see the cumulative outcome report) have indicated issues with regards to insufficient oversight and monitoring, irregularities in data handling, out of protocol dosing

(adjustment) for the Epoetin groups and concerns with regards to the definition of the PP Population. It is currently unclear how these findings would impact the overall results. Considering the open-label non-inferiority nature of the studies, sensitivity to detect differences between treatments and introduction of bias is of particular concern. The applicant's responses to its findings are awaited.

After the D121 response, concerns remain on the definition of and the reasons for exclusion from the PP Population. This is not clear and should be further justified.

The study population did not include high-risk anaemic CKD patients, as eligible subjects were on stable Epoetin doses with stable Hgb values. It remains unclear whether the proposed dose conversion scheme is also appropriate for high-risk patients on high instable Epoetin doses without adequate response.

The maintenance studies included primarily US patients (80% US, 20% EU). Analyses in the D121 response stratified by geographic region have shown comparable results for the US and EU population in the primary endpoint, with both populations fulfilling the non-inferiority criteria.

Differences were noted in the secondary endpoint of proportion of patients with Hgb within target range. The results of AF37702 were numerically lower than those of Epoetin. This difference was in particularly large in the EU population of study AFX01-14 and is considered of concern.

The results of the proportion of patients with transfusions included transfusions for reasons other than lack of effect. This was resolved in the D121 response, which showed similar rates between AF37702 and Epoetin for transfusions due to lack of effect only.

Data on peritoneal dialysis patients was limited (n=59), as was the number of patients receiving SC injection (n=110).

The proposed dose and dose adjustment recommendations were different to those tested in clinical studies, but were sufficiently justified in the D121 response.

AF37702 was shown to reduce the number of transfusions in patients with PCRA, but study AFX01-06 is not finalised. Up to now, no subjects developed anti-EPO antibodies within all studies submitted, supporting the proposed lack of immunological cross-reactivity between AF37702 and human EPO or marketed rHuEPO-derived ESAs. However, this may need a longer follow-up in a much larger population as events might be rare and/or occur after a longer period of time.

Risks

Unfavourable effects

The MAA pertains to dialysis patients only. Safety concerns were identified in the non-dialysis correction studies in ESA-naive patients, which has led the Applicant to exclude the non-dialysis population from the MAA.

Adverse events

In the dialysis correction study, 78 and 38 patients were exposed to AF37702 and Epoetin. The mean duration of treatment was 27-29 wks. TEAEs were reported at similar rates for AF37702 (84.2%) and Epoetin (81.6%), with also similar rates for treatment-related TEAEs (11.8% for AF37702 and 13.2% for Epoetin). The most commonly reported treatment-related TEAE was hypertension (AF37702 6.6%; Epoetin 7.9%). Other treatment-related TEAEs were reported once. No new safety signals were identified.

In the dialysis maintenance studies, 1066 and 542 CKD patients on dialysis were exposed to AF37702 and Epoetin, with mean duration of exposure of 60-65 wks. Respectively 938 and 825 patients received AF37702 for >26 and >52 wks. TEAEs were reported at high rates for AF37702 (94.6%) and Epoetin (93.0%). The most commonly reported TEAEs for AF37702 were dyspnoea (18.4%), diarrhoea (18.4%), nausea (17.4%), arteriovenous fistula site complication (16.1%), and cough (15.9%). Most commonly reported serious adverse events were infections (pneumonia, 6.3%) and congestive heart failure (5.7%). The adverse events were reported at comparable rates as for the control group and expected within the CKD population. Treatment-related TEAEs were reported at low rates, but at higher rates for AF37702 (7.8%) as compared to Epoetin (4.2%). These pertain to a diversity of events, without any events predominating. The most commonly reported treatment-related TEAEs for

AF37702 were hypertension (AF37702 0.8%, Epoetin 0.0%), hypotension (0.7% and 0.0%), anaemia (0.6% and 0.2%) and nausea (0.4% and 0.0%).

Grouping of potential class effects described for approved ESAs were reported at comparable rates for AF37702 and Epoetin. The most commonly reported class effects for AF37702 were other thromboembolic events (21.7%), hypertension (19.5%), and vascular access complications (18.1%).

The percentage of patients who discontinued treatment due to TEAEs was similar for AF37702 (12.8%) and Epoetin (12.0%).

Hgb excursions

In the dialysis correction studies, for the 0.04 mg/kg AF37702 dose during the first 20 weeks rates of excursions were lower or comparable to Epoetin, after 20 weeks rates of excursions of >13 and >14 g/dL were slightly higher as compared to Epoetin.

The non-dialysis correction studies, which were of larger size, appear to show a similar trend. From first dose through End of Treatment, AF37702 showed higher rates of confirmed excursions of >13 g/dL (AF37702 16.7%; darbepoetin 10.8%) and of >14 g/dL (AF37702 1.2%; darbepoetin 0.6%).

In the dialysis maintenance treatment, above target excursions were similar between AF37702 and Epoetin. During the Evaluation Period 34%, 8.4% and 1.4% of patients on AF37702 had confirmed excursions of respectively >12 g/dL, 13 g/dL and >14 g/dL.

Cardiovascular events

In the dialysis correction study, 7.9% (6 out of 76) of AF37702 patients and 15.8% (6 out of 38) of Epoetin patients reported events in the SOC Cardiac disorders. All events in this SOC were considered non-serious. No events of MI, stroke or serious events of heart failure, unstable angina or arrhythmia were reported in this study.

For the dialysis maintenance studies, cerebro- and cardiovascular events were also reported at comparable rates for AF37702 and Epoetin. An additional cardiovascular safety analysis using a Composite Safety Endpoint (consisting of the component events death, stroke, myocardial infarction, unstable angina, congestive heart failure and arrhythmia) showed a similar risk for AF37702 and Epoetin. CSE events were reported at 22.8% for AF37702 and 24.4% for Epoetin. The HR vs Epoetin was 0.95 (95% CI: 0.77, 1.17). AF37702 did not show an increased risk vs Epoetin for any of the individual CSE events death (AF37702 10.8%; Epoetin 11.8%), stroke (2.4%; 3.7%), myocardial infarction (4.6%; 5.4%), unstable angina (2.3%; 2.2%), congestive heart failure (9.7%; 9.0%), and arrhythmia (5.9%; 6.5%).

In the non-dialysis population, in the setting of correction of anaemia in ESA-naïve patients, the cardiovascular safety showed an increased risk of AF37702 versus darbepoetin. The increase in cardiovascular risk of AF37702 versus darbepoetin was highest in the ESA-naive patients who showed a poor Hgb response upon initiation of study treatment. Cardiovascular events and deaths were reported at 21.5% for AF37702 and 17.1% for darbepoetin in the Composite Safety Endpoint analysis. The HR was 1.32 (95% CI: 0.97, 1.81). This increased risk mainly pertained to the events death (AF37702 8.8%; darbepoetin 6.7%), unstable angina (2.4%; 0.9%) and arrhythmia (5.6%; 4.0%). The difference in arrhythmias appeared to be predominantly in the rates of atrial fibrillation. Rates of ventricular fibrillation were low. The increased risk in death was mostly related to the higher incidence of sudden deaths for AF37702 (2.1%) as compared to darbepoetin (0.3%). Sudden deaths were not clustered during the initial treatment period. There was no temporal relationship between the occurrence of sudden death and dosing of AF37702.

The QTc study, using a dose that covers the majority of patients in the maintenance studies, showed no evidence of QT prolongation.

Immunogenicity

AF37702-specific binding and neutralizing antibodies were found in 1.2% and 0.9% of patients. SC injection gave higher rates as compared to IV injection. The highest rates were observed in the SC dialysis population with 2.8% and 2.4% for AF37702 binding and neutralizing antibodies, respectively.

In a large proportion of antibody-positive patients, the presence of antibodies was associated with reduced efficacy. Follow-up of a limited number of AF37702-antibody positive subjects with AF37702 treatment failure showed that these patients responded to EPO-based ESAs.

Postmarketing experience

Cases have been reported in the US post-marketing setting of serious hypersensivity reactions within minutes of Omontys injection, which have included life-threatening and fatal reactions. These hypersensitivity reactions have led to a voluntary recall of the product in the US. The applicant has initiated a root cause investigation and acknowledged that it will not be able to complete it and propose appropriate risk mitigation measures within the procedure timeframe.Uncertainty in the knowledge about the unfavourable effects

Accurate assessment of the risk of confirmed Hgb excursions, and the possible clinical consequences thereof, during the dialysis correction phase was hampered by the small size of study AFX01-15. The non-dialysis correction studies, which were of larger size, showed a similar trend of increased risk of Hgb excursions of >13 and >14 g/dL. In the D121 response, post-hoc analyses with selected relevant adverse events of interests showed no evidence of any difference between treatment groups with regards to the temporal association of these events (including cardiovascular events) with Hgb rate of rise or Hgb excursions, for both the phase 3 dialysis (maintenance) and non-dialysis (correction) studies. Furthermore, in the D121 response the applicant argued that the AF37702 excursions in AFX01-15 responded to dose decreases and did not appear to be of longer duration than excursions on Epoetin. However, the latter claim was based upon very small numbers and need to be confirmed with data from a larger population.

It is uncertain whether the increased risk of AF37702 versus the comparator ESA in deaths and cardiovascular events observed in the ESA-naive non-dialysis population could also emerge in the dialysis population. The exact mechanism of action is unclear, but it appears different from that of aggravated pharmacodynamics resulting in too high Hgb levels. In the D121 response, post-hoc analyses were performed, showing no temporal correlation between Hgb excursions or Hgb rates of rise and cardiovascular events. Considering this, and the fact that events were not clustered during the initial phase of treatment, it appears unlikely that the mechanism is related to fluctuations or increases in Hgb levels that are more likely to occur during the correction phase. An arrhythmogenic effect of AF37702 also appears unlikely, considering the lack of any relationship with regards to timing or dose of AF37702, the low rates of ventricular arrhythmias and the lack of evidence for QT prolongation.

Of particular concern is the uncertainty how this increased cardiovascular risk relates to the *ESA-naïve dialysis* population in the correction of anaemia. Literature has suggested that a poor initial hematopoetic response to ESA treatment in subjects not previously receiving ESAs may be associated with an increased cardiovascular risk (TREAT study, Solomon et al 2010). Data in the ESA-naïve non-dialysis population showed that the increase in cardiovascular risk of AF37702 as compared to darbepoetin was highest in this group of patients who showed a poor Hgb response upon initiation of study treatment. This observation is of concern as it cannot be excluded that this increased risk would also emerge in the ESA-naïve dialysis population, a population that will also include patients with a poor response when treatment is started. Study AFX01-15 is too small to provide reassurance on the safety in this population and the D121 response did not sufficiently address this major concern.

Uncertainties remain regarding the immunogenicity of AF37702. Highest rates are seen for SC administration (2.4% neutralizing antibodies), but long-term data on antibody formation is lacking and the impact on efficacy remains uncertain. Up to now no subjects developed anti-EPO antibodies. Albeit this is not expected given the lack of amino acid sequence homology to human EPO, lack of anti-EPO antibodies needs to be confirmed by long-term data in a larger population.

Postmarketing experience

Currently, no root cause of the serious hypersensivity reactions has been established, and it is unclear whether this issue could be remedied or mitigated. The applicant is currently performing several root cause investigations and the final results and conclusions are awaited.

Balance

Importance of favourable and unfavourable effects

In the correction of anaemia, AF37702 induced a dose-dependent increase in mean Hgb levels, which is considered clinically relevant. The majority of the patients (>90%) achieved a Hgb response at week 28. The Hgb response for the 0.04 mg/kg dose (SPC proposed dose) was lower and slower as compared to Epoetin, but it appears that current Hgb target levels of ≥10 g/dL were achievable within acceptable time-frames. Although Hgb excursions of >13 and >14 g/dL were slightly higher after 20 weeks as compared to Epoetin, the Hgb excursions responded to dose decreases and were not longer in duration than those of Epoetin. In addition, fluctuations in Hgb during the correction phase did not translate into an increased risk of cardiovascular events, based upon analyses of the non-dialysis correction studies. These results may suggest that acceptable efficacy based upon current Hgb target levels could be achieved without a clear unfavourable profile with regards to Hgb excursions, but the data was derived from a limited population and needs to be substantiated in a larger population.

In the maintenance treatment, monthly AF37702 was shown to maintain Hgb levels close to Baseline after switch from conventional short-term ESA treatment. Mean change in Hgb from Baseline was similar to Epoetin. Although the clinical relevance of the predefined non-inferiority margin of -1.0 g/dL is questioned, non-inferiority was also met based upon the more stringent and recommended non-inferiority margin of -0.5 g/dL. Within the maintenance setting, a monthly dosing may be of advantage for the patients. However, GCP findings and uncertainties with regards to the PP Population are of major concern and question the overall data validity. This is of particular importance in non-inferiority trials, where a clean study conduct is required to minimize the risk that true differences between treatments would not become apparent. The applicant's responses to its findings are awaited. Until data validity is ascertained and a systematic problem has been excluded, it is considered that the efficacy results are questionable. Furthermore, the proportion of patients with Hgb levels within target range was slightly, but consistently lower for AF37702 as compared to Epoetin. This difference was most pronounced for the EU population in AFX01-14. The clinical relevance of this finding is unclear.

The safety profile of AF37702 was comparable to that of Epoetin within the dialysis maintenance studies and in line with what can be expected of ESA treatment in the CKD population. In the non-dialysis correction studies in the ESA-naïve population, an increased risk in (sudden) deaths and cardiovascular events was observed for AF37702. The mechanism for this increased risk is unknown, but it appears unlikely to be related to fluctuations in Hgb levels that may occur during the correction phase or to an arrhythmogenic effect of AF37702.

In the absence of a clear explanation, the relevance of the safety findings in the non-dialysis population for the dialysis population is difficult to judge. The results of the dialysis maintenance studies, consistently showing no increased safety risk vs Epoetin, together with the lack of evidence for any drug effect, is considered sufficient evidence for acceptable safety in this population of ESA-experienced subjects, who are known to respond to and known to be stable on previous ESA treatment. The safety in the ESA-naïve dialysis population for the correction of anaemia remains of major concern, given the limited data available in this population and the findings in the ESA-naïve non-dialysis population showing an increased cardiovascular risk, in particular in the group of ESA-naïve non-diaysis patients with a poor Hgb response upon initiation of ESA treatment. These findings may be relevant for the ESA-naïve dialysis population, a population which will also include patients with a poor response when treatment is started. The larger dialysis maintenance studies showed no increased risk versus the comparator ESA, but these studies only included patients who have responded well to ESA treatment and may therefore be less predictive for the safety in the ESA-naïve dialysis population in the correction of anaemia.

The incidence of AF37702-specific binding and neutralizing antibodies is high compared to current ESA treatment, in particular after SC injection (2.8% and 2.4%). This appears manageable, as patients with AF37702 treatment failure seem to respond to EPO-based ESAs. SC use of AF37702 seems therefore acceptable. The data, however, was based upon a small number of patients. Long-term data on immunogenicity and the impact on efficacy remains uncertain.

The serious hypersensitivity reactions within minutes of peginesatide injection, as seen in the post-marketing setting, are of major concern considering their nature, severity and frequency.This issue needs to be fully clarified before conclusions can be drawn with regards to this MAA.

The expected (albeit no yet proven) reduced or absent risk of PRCA is considered significant, as this is the only ESA that is not human EPO-like and that offers this advantage over existing ESAs. Although a very serious complication of current ESA treatment, PRCA is rare. Hence, this advantage of AF37702 is very important, but would benefit small numbers of patients only. The interim results of the ongoing AFX01-06 study in PRCA patients are favourable and if confirmed, AF37702 may offer treatment of an unmet medical need for a small population, who are currently dependent on blood transfusions.

Benefit-risk balance

In the correction of anaemia, AF37702 at the proposed starting dose of 0.04 mg/kg increased Hgb in an anaemic ESA-naïve dialysis population. Although the correction study suggested that upon AF37702 treatment current target Hgb levels may be achievable within acceptable time-frames and there appears to be no clear unfavourable profile with regards to Hgb excursions, the data was obtained in a limited population and efficacy remains uncertain without substantiation of the data within a larger population. With regards to safety, concerns remain on the potential increased risk of deaths and cardiovascular events, as was observed in the ESA-naïve non-dialysis population. It cannot be excluded that this risk is also applicable to the ESA-naïve dialysis population, given the limited data available in this population and the findings in the ESA-naïve non-dialysis population.

In the maintenance treatment, AF37702 appears to maintain Hgb levels after switching from Epoetin and Hgb changes from Baseline were comparable to current short-term ESA treatment. The efficacy of AF37702 appears non-inferior to current ESA treatment, but the results need further justification due to uncertainties with regards to GCP compliance and data validity. The findings of the GCP inspection have indicated several issues that question reliability of the data. This is of special importance considering the open-label non-inferiority nature of the studies, where increased variability may mask differences between treatments.

The safety profile as seen in the maintenance studies in ESA-experienced dialysis patients was comparable to Epoetin and appears acceptable. The SC route of administration gave a much higher risk to develop binding and/or neutralizing antibodies, compared to IV administration and compared to other ESAs. This appears manageable as patients with AF37702 treatment failure seem to respond to EPO-based ESAs, although long-term data and data in a larger population is lacking.

However, the post-marketing serious (fatal and life-threatening) hypersensitivity reactions within minutes of peginesatide injection are of major concern. No root causes have currently been identified and it is unclear whether this risk can be remedied or mitigated.

In considering the benefit/risk, the advantages of a monthly dosing interval and the potential reduced or absent risk of the rare complication of PRCA do not outweigh

(1) the uncertainties in the correction of anaemia in ESA-naïve patients with regards to efficacy and potential less favourable cardiovascular profile,

(2) the uncertainties with regards to the reliability of the data in the maintenance studies,

(3) the risk of serious hypersensitivity reactions,

in the presence of effective and safety established ESA treatments.

Discussion on the benefit-risk assessment

Although from the dialysis correction study it appears that current target Hgb levels may be achievable upon AF37702 treatment and there appears to be no unfavourable profile with regards to Hgb excursions vs Epoetin, the data was obtained in a limited population only. This should be substantiated with data from a larger population. With regards to safety, it cannot be excluded that the increased risk as seen in the ESA-naïve non-dialysis population would also be applicable to the ESA-naïve dialysis population. The safety in the ESA-naïve dialysis population remains to be demonstrated in a larger population. The proposed post-marketing studies AFX01-19 and AFX01-20 in the RMP could provide relevant safety information in this regard.

AF37702 at the proposed conversion scheme appears effective in maintaining Hgb levels after switching from Epoetin treatment and appeared non-inferior to current ESA treatment. However, concerns are raised with regards to the validity of the data, given the GCP findings. A discussion is required on whether the GCP findings affected the results of the studies. In particular, in view of the open-label non-inferiority nature of the studies, it should be shown that any bias introduced was not in favour of AF37702 treatment and subsequent demonstration of non-inferiority. Furthermore, a discussion is required on the sensitivity of the studies to detect differences between treatments as a result of any bias, taking also into account the already less sensitive setting of the maintenance studies where all patients were already on target Hgb levels at baseline with subsequent multiple titration steps before evaluation of the primary endpoint.

The issue with regards to the serious hypersensitivity reactions within minutes of peginesatide injection needs full clarification with regards to root causes and risk mitigation.

Data on peritoneal dialysis patients is limited. Based on previous experience, no differences in efficacy are expected and (if approved) data on haemodialysis could be extrapolated to peritoneal dialysis. Additional information on peritoneal dialysis should be obtained post-marketing.

5.1. Conclusions

The overall B/R of AF37702 is considered negative for the proposed indication including both treatment of anaemia in ESA naïve patients and patients on ESA treatment.

- Currently, a reduced benefit and an increase in risk cannot be excluded compared to currently available ESA treatment in the correction of anaemia.
- Efficacy in the maintenance treatment is not considered confirmed in the presence of GCP findings and uncertainties with regards to reliability of the data.
- Serious hypersensivity reactions have been reported within minutes of Omontys injection, which have included life-threatening and fatal reactions. No root causes have currently been identified and it is unclear whether this risk can be remedied or mitigated. This issue needs to be fully clarified before conclusions can be drawn with regards to this MAA.