Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Luveniq

voclosporin

Procedure No.: EMEA/H/C/002069//0000

Note

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

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List of Abbreviations

AC Anterior chamber

ANOVA Analysis of variance

API Active pharmaceutical ingredient

BID Twice a day

BMI Body mass index

BOCF Baseline observation carried forward

BP Blood pressure

CMH Cochran-Mantel-Haenszel

CNI Calcineurin inhibitor

CRF Case report form

CRO Contract Research Organization

CsA Ciclosporin A

CYP Cytochrome

DMC Data Monitoring Committee

ECG Electrocardiogram

eGFR Estimated glomerular filtration rate

EMEA European Medicines Agency

EOT End of Treatment

EQ-5D Euro Quality of Life-5 domains

EQ-VAS Euro Quality of Life –visual analog scale

ETDRS Early Treatment Diabetic Retinopathy Study

FA Fluorescein angiography

GCP Good Clinical Practices

GFR Glomerular filtration rate

ICH International Conference on Harmonisation

IMT Immunomodulatory therapy

INN International Nonproprietary Name

ITT Intent-to-treat (analysis population)

ISA247 Synonym for LX211 used by Isotechnika, Inc.

IWRS Interactive Web-Response System

LS Least Square

LOCF Last observation carried forward

MCT Medium-chain triglyceride

MDRD Modification of Diet in Renal Disease Study

MM Mixed Model

NEI VFQ-25 National Eye Institute Visual Functioning Questionnaire (25 questions)

OCT Optical coherence tomography

PD Pharmacodynamic

PK Pharmacokinetic

P.O. Per os (orally)

PP Per-Protocol

Q1h, Q2h Every hour, every 2 hours

QD Every day

QID 4 times a day

QoL Quality of Life

SAE Serious adverse experience or event

SAP Statistical analysis plan

SD Standard deviation

SF-36 36-Item Short Form Health Survey

TID Three times a day

VAS Visual analog scale

VH Vitreous haze

WOCF Worst observation carried forward

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lux Biosciences GmbH submitted on 10 February 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Luveniq, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 June 2009.

Luveniq was designated as an orphan medicinal product EU/3/07/472 on 14 September 2007. Luveniq was designated as an orphan medicinal product in the following indication: Treatment of chronic non-infectious uveitis. The calculated prevalence of this condition was 4 per 10,000 EEA population.

The applicant applied for the following indication: treatment of patients with chronic non-infectious uveitis involving the posterior or intermediate segments of the eye.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/7/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market exclusivity

Not applicable.

New active substance status

The applicant requested the active substance voclosporin contained in the above medicinal product to be considered as a new active substance in itself.

Scientific advice

The applicant received Scientific Advice from the CHMP on 24 January 2008. The Scientific Advice pertained to quality and non-clinical aspects of the dossier. The clinical aspects discussed concerned another indication, psoriasis.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann

Co-Rapporteur: Prieto Yerro

The application was received by the EMA on 10 February 2010.

- The procedure started on 24 February 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2010.
- During the meeting on 24 June 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 June 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 November 2011.
- The summary report of the inspection carried out at the following sites: site no. 204 / Dr. Murthy; (India); site no. 212 / Dr. Gupta (India); PRA International, Lenexa (US) between 28 Sep 2010 and 12 Nov 2010 was issued on 11 Feb 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 February 2011.
- During the CHMP meeting on 17 February 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 18 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding issues to all CHMP members on 13 May 2011.
- During the CHMP meeting on 17 May 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 June 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion refusing the granting of a Marketing Authorisation to Luveniq on 23 June 2011.

2. Scientific discussion

2.1. Introduction

Problem statement

Uveitis represents a group of serious inflammatory eye conditions and is associated with either vision loss or adverse effects due to steroid use. Non-infectious uveitis involving the posterior segment of the eye is one of the main causes of vision loss, long-term disability and the blindness in the industrialised world. The majority of uveitis patients are first diagnosed when they are less than 40 years old. Non-infectious uveitis involving the intermediate or posterior segment of the eye affects approximately 100,000 patients in the United States. The prevalence of any form of uveitis in the European Union has been estimated at around 230,000.

The gold standard in the treatment of uveitis in most European countries and United States are corticosteroids. Steroids are available to uveitis patients in the form of eye drops, oral formulations, implants, and injection. Treatment depends on several factors, such as location of the inflammation. If inflammation occurs in the front of the eye (anterior uveitis) steroid eye drops are sufficient to treat the disease in most patients; if inflammation occurs in the back of the eye (posterior uveitis), patients will likely require steroid injections or oral formulations for therapeutic levels of medication to reach the disease location. The therapy is typically individualised and requires regular monitoring.

Though steroids are effective in quickly controlling inflammation, they cannot be used long-term without incurring serious side effects, which is required in some severe cases of posterior or intermediate uveitis. New treatment alternatives are needed in such cases that allow corticosteroids to be tapered off to levels not associated with long-term adverse events, or eliminated altogether, while providing effective control of the chronic eye inflammation.

While currently several of these agents, called corticosteroid-sparing agents, are used experimentally, none of these is yet approved in uveitis in first-line therapy.

About the product

Voclosporin is the oral form of a next-generation calcineurin inhibitor (CNi). Like other molecules of this class, the compound reversibly inhibits immunocompetent lymphocytes, particularly T-lymphocytes, in the G0 or G1 phase of the cell cycle and it also inhibits lymphokine production and release. Voclosporin mediates its immunosuppressive effects by binding to the intracellular protein, cyclophilin. This complex, in turn, inhibits the calcium- and calmodulin-dependent serine-threonine phosphatase activity of the enzyme calcineurin. Calcineurin inhibition then prevents the activation of various transcription factors necessary for the induction of cytokine genes (IL-2, IFN-γ, IL-4 and GM-CSF) during T-cell activation.

Voclosporin is structurally identical to cyclosporine A (CsA), except for a modification of a functional group on the amino acid-1 residue of the molecule. This alteration has changed the binding of voclosporin to CN leading to a molecule with a presumed higher potency when compared to CsA. This modification has also shifted metabolism away from amino acid-1, the major site of metabolism for CsA, thus altering the metabolic profile.

The original compound, designated as ISATX247 or mix-ISA247, consists of two geometric isomers; a trans- isomer and a cis- isomer, depending on the orientation of the modified functional group at amino acid one. This drug substance, used in early nonclinical and clinical studies, was a mixture of both isomers (45-50% trans, 50-55% cis). A new drug substance, enriched with the trans-isomer (≥ 90% trans-isomer, ≤ 10% cis-isomer), was manufactured, and is referred to as voclosporin (also trans-ISA247, ISA247 and LX211). ISA247 is sometimes used to denote the compound irrespective of the isomer. The trans-enriched form, voclosporin, is the intended commercial form of LX211.

The indication applied for was: the treatment of chronic non-infectious uveitis involving the intermediate or posterior segments of the eye.

2.2. Quality aspects

2.2.1. Introduction

Luveniq is presented in the form of soft gelatin capsules for oral administration containing 10 mg of Voclosporin per finished product unit, filled into a size 5 oval soft gelatin capsule. Solubility of voclosporin in water is very low and therefore, it is formulated as a non-aqueous solution for encapsulation.

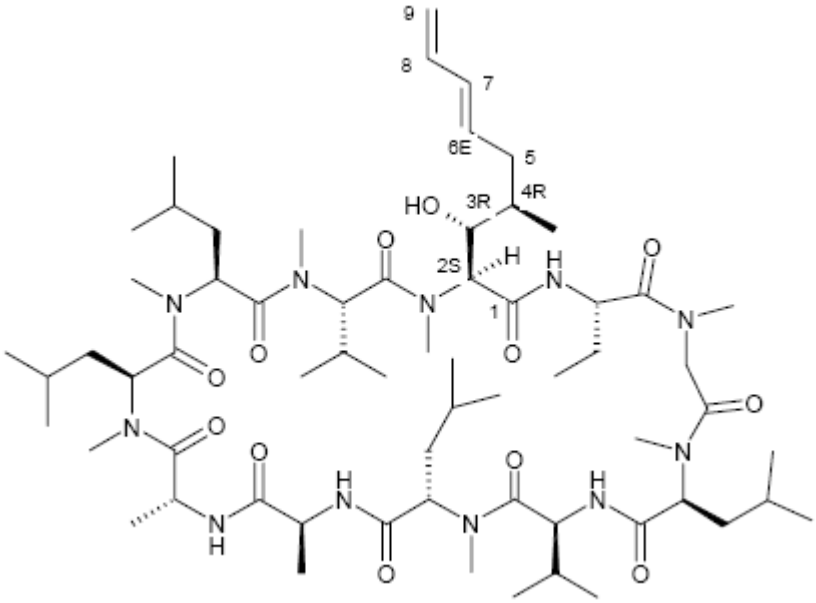
The new active substance voclosporin is a next generation calcineurin (CN) inhibitor and is intended for the use in prevention of autoimmune diseases such as uveitis and psoriasis.

The capsules are packed in a peel-push blister composed of backing (PVC / Al / polyamide laminate) and lidding (PVC-copolymer / Al / polyethylene terephthalate).

2.2.2. Active Substance

Voclosporin is the common name of the chemical substance Cyclo{[(6E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6,8-nonadienoyl]-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-Lvalyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}. The molecular formula is $C_{63}H_{111}N_{11}O_{12}$ with relative molecular mass of 1214.6

and the following formula:



Voclosporin is a white to off-white solid powder, slightly hygroscopic, practically insoluble in water and heptane and freely soluble in acetone, acetonitrile, ethanol and methanol.

Voclosporin is a cyclic undecapeptide API containing a D-alanyl moiety, a L-2-aminobutyryl moiety and an unnatural unsaturated chiral amino acid moiety with a diene side-chain with *trans* configuration (E configuration at carbon 6). The active substance voclosporin consists in a mixture of two *cis*-*trans* isomers: NLT 90% of *trans* (E configuration at carbon 6) isomer and NMT 10% of *cis* isomer (Z configuration at carbon 6). The structure contains 12 centers of chirality and is levorotatory. Chiral centers are fixed based on the stereochemistry of the incoming intermediate, cyclosporine A. Polymorphism is not considered critical because voclosporin is formulated in solution. A polymorph with thermodynamic stability is produced.

Information on the active substance voclosporin is presented in form of an Active Substance Master File.

Manufacture

Voclosporin is manufactured from the starting material Cyclosporin A, which is produced via fermentation and is available from two suppliers which both hold a valid CEP.

The chemical modification of cyclosporin A (ciclosporin A PhEur) to voclosporin is carried out in 4 chemical reaction steps, each leading to an isolated intermediate, and one final purification/re-crystallization step.

An adequate description of the manufacturing process including enumeration of reaction conditions, amounts of starting material, solvents and reagents is provided. Appropriate in-process controls are performed on each step of the manufacturing process. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and considered satisfactory. Six batches of commercial scale are manufactured with staring materials from both suppliers and comply with proposed specifications. The batch analysis data shows that the

manufacturing process produces batches of active substance which consistently meet the same quality standards.

Specification

A suitable specification for the active substance is proposed taking into account the PhEur standards and ICH guidelines. The active substance specification includes tests for appearance, colour, identification (IR, HPLC), assay (HPLC), impurities (HPLC), *trans*- isomer content (HPLC), water content (Karl-Fischer), residual solvents (GC), specific rotation (Ph. Eur./USP), residue on ignition/sulphated ash (Ph. Eur.), heavy metals (PhEur) and microbial quality (harmonised PhEur).

The analytical methods used in routine controls are suitable to check the quality of the active substance. They are either compendial or in-house methods and have been appropriately described. Adequate validation data was presented for the in-house analytical methods following the ICH Q2 (R1) Guideline.

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

Stability

Stability study results of three pilot scale batches at ICH Q1A conditions covering 36 months at long term conditions and 9 months at accelerated conditions, stored in the proposed packaging material, justify the proposed retest period of 36 months at warehouse conditions (up to 25°C).

The parameters investigated were the same as those per batch release: appearance (visual), assay (HPLC), structurally related impurities (HPLC), E/Z isomer ratio (HPLC), water (KF), and polymorphic form (by XRD).

Stability tests on production scale batches are in progress. In that respect, the applicant agreed to place three production scale batches into ICH stability studies at long term and accelerated conditions.

In addition, the CHMP recommended re-evaluation of the specified acceptance criteria following completion of the ongoing stability program, including scale-up batches to Applicant and Active Substance Manufacturer.

Voclosporin was also exposed to various stress conditions, i.e. exposure in the solid state to elevated temperature under both uncontrolled humidity and high humidity, and to light irradiation; exposure in aqueous solution to elevated temperature and different pH values, and to strongly oxidising conditions. The parameters tested were impurities (HPLC) and assay (HPLC).

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The product is presented as a non-aqueous solution of voclosporin drug substance, nominally containing 10 mg of active substance per finished medicinal product unit, filled into a size 5 oval soft gelatin capsule. The capsule shell is imprinted with a "10" in black ink.

The chosen excipients are well known and their functions are well explained. All excipients met the requirements of their respective compendial monographs. There are no novel excipients used in the finished product.

The formulation development has been adequately described. Due to the low solubility of voclosporin in aqueous solutions a non-aqueous formulation for oral administration was developed.

The dissolution has been optimised to meet Ph Eur. requirements using a Design of Experiment approach. Trends in dissolution behaviour and in other quality characteristics were evaluated by statistical methods.

The gelatine used for the manufacture of the soft-gelatin capsule shell is derived from a porcine (non ruminant) source. A BSE/TSE statement for gelatine from the current supplier was provided.

All excipients other than gelatin are derived from non-human and non-ruminant sources.

Manufacture of the product

The manufacturing process is performed in four steps: manufacture of the gel mass, compounding of liquid fill, encapsulation and packaging.

A description of the manufacturing process and a flow chart is included. The in-process control performed at nearly all relevant stages of the process are considered suitable. A validation scheme for the first three commercial batches is included.

Product specification

The product specification is appropriate for a liquid filled soft gelatine capsule. The proposed test procedures and acceptance criteria follow the principles of the ICH Q6A.

The product specification includes tests for description, identification (HPLC, UV), assay (HPLC), impurities (HPLC), mass variation, dissolution (PhEur), rupture time of capsule, ethanol content (GC/FID-detector), moisture content (KF) and microbial quality (harmonised PhEur).

Analytical methods are described and validated according to the guideline ICH Q2 (R).

Analysis results of drug product batches (pilot to full production scale) indicate compliance with the proposed specification.

Stability of the product

The stability studies are carried out in the proposed container/closure system in accordance with current ICH/CHMP guidelines. On the basis of results from three pilot scale batches covering 24 months at long term conditions and 6 months at accelerated conditions a shelf life of 36 months is assigned by the applicant, when stored in the original container to protect from moisture and to prevent from evaporation of ethanol.

The proposed shelf life of 36 months is considered justified by the results.

However, the CHMP recommended re-evaluation of the specified acceptance criteria (including ethanol content) for luveniq soft gelatine capsules following the completion of stability programme from registration and industrial scale batches.

Stability data on hardness showed a decrease by aging of the capsules. Therefore, hardness was considered to be a stability indicating parameter. Based on this, the Committee recommended further evaluation of batch data and inclusion of this parameter in the finished product specification.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The new active substance voclosporin was demonstrated to be quite stable and suitable for the manufacture of the applied dosage form Luveniq soft-gelatin capsule, 10 mg. The results of tests carried out indicate satisfactory consistency of all relevant product quality characteristics. The application dossier from Lux Bioscience including the Active Substance Master File from the Active Substance Master Lonza is of sufficient quality. All relevant guidelines and regulatory recommendations were considered in an appropriate way.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The pharmaceutical quality of the finished medicinal product under investigation was demonstrated to be acceptable. From the submitted data it is concluded that the drug product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

The Non-clinical part of the dossier includes studies performed by the applicant and literature data.

All main toxicology studies, half of the pharmacokinetics studies and the *in vivo* safety pharmacology studies were GLP compliant. The CHMP noted however that some single-dose toxicity studies and most of the repeat dose toxicity studies were conducted in a facility with an unknown GLP status. These studies were not considered as pivotal for the overall benefit/risk assessment of the product. Therefore the CHMP considered data as acceptable, as they were supportive only, and did not recommend a GLP inspection.

The majority of the nonclinical program was completed with mix-ISA247, with the exception of studies conducted late in development including carcinogenicity, pharmacology and pharmacokinetic (PK) studies. Additionally, toxicology studies were conducted with voclosporin to bridge mix-ISA247 data with voclosporin data.

Scientific Advice given by EMA/CHMP (EMEA/H/SA/986/1/2007/SME/III) was provided in the context of other intended therapeutic use, i.e. psoriasis. The EMA/CHMP considered the non-clinical bridging programme to support the use of the trans-enriched drug substance in clinical practice to be adequate. Some discussion remained open regarding observed increased incidence of lymphosarcomas in long term studies in monkeys, their potential relationship with viral infections and time of exposure. The EMA/CHMP also considered conventional carcinogenicity studies in rodents sufficient to address any potential carcinogenic risk. The EMA/CHMP encouraged further review of hepatotoxic findings in rats despite the lack of statistical significance.

2.3.2. Pharmacology

Voclosporin is a potent immunosuppressive agent that is structurally similar to cyclosporine A (CsA) and can be classified as a calcineurin inhibitor (CNi). CN inhibitors have been shown to mediate suppressive effects on T-lymphocytes via binding to the cytosolic protein cyclophilin. This complex, in turn, inhibits the calcium- and calmodulin-dependent serine-threonine phosphatase activity of the enzyme calcineurin. Inhibition of this enzyme prevents the activation of various transcription factors necessary for the induction of cytokine genes (IL-2, IFN-γ, IL-4, and GM-CSF) during T-cell activation.

Primary pharmacodynamic studies

The immunosuppressive activities of voclosporin, mix-ISA247, cis-ISA247 and CsA were assessed *in vitro* using a human whole blood CN inhibition assay (ISA02-06 and ISA00-05). Mix-ISA247, cis-ISA247 or voclosporin demonstrated greater potency, when directly compared to CsA, and the trans-isomer of ISA247 was a more potent inhibitor of CN activity *in vitro* than the cis-isomer.

Similar results were obtained *in vivo* in a 39-week oral gavage toxicity study (ISA02-01) in cynomolgus monkeys where mix-ISA247 induced dose-dependent calcineurin inhibition. In another study in monkeys (ISA01-08), mix-ISA247, as well as CsA inhibited lymphocyte proliferation, T-cell activation and cytokine production following oral administration twice daily for 7 days. Despite much lower blood concentrations and total exposure, mix-ISA247 produced the same or greater pharmacodynamic effect than CsA. Voclosporin metabolites were significantly less potent than the parent drug in the lymphocyte proliferation assay, a surrogate of CN inhibition: from <1% (IM1-Diol-1) to 12.9% (IM9) of voclosporin (study ISA08-40).

In experimental autoimmune uveitis (EAU) in rats (Cunningham et al., 2009), incidence and severity of uveitis as well as histopathological changes were reduced in a dose-dependent manner for voclosporin; high dose voclosporin (40 mg/kg) was as effective as CsA (40 mg/kg). However, the route of application (subcutaneous injection) differed from the proposed therapeutic oral administration, and the administered dose range (2.5, 10 and 40 mg/kg) significantly exceeded the intended clinical dose (0.4 mg/kg). Consequently the CHMP considered that without generated voclosporin PK data, it was not possible to bridge data from the EAU rat model to clinical use in patients. Therefore, efficacy of Luveniq in uveitis patients, especially the chosen dose and modalities of treatment (frequency, add on treatment to corticosteroids) could not be justified by the EAU rat model.

Secondary pharmacodynamic studies

Mix-ISA247 has demonstrated a dose-dependent effect on study endpoints in an arthritis model in mice and rabbits (study ISA00-21). In organ transplant models, mix-ISA247 showed greater potency than CsA in graft survival of mouse islet cell allotransplants (ISA01-20). In renal allograft study in cynomolgus monkeys, mix-ISA247 was more potent than CsA at similar exposures (ISA01-14). However, it was not significantly better than CsA in heterotopic heart transplantation survival in rats (studies ISA00-07, ISA03-05).

In order to better define secondary pharmacodynamics and pharmacodynamic drug interactions of voclosporin, the CHMP recommended a receptor screening assay assessing potential binding affinity and agonistic/antagonistic properties of voclosporin on conventional drug targets (receptors, enzymes and ion channels).

Safety pharmacology programme

The core battery of safety pharmacology studies as defined in EMA Guideline (CPMP/ICH/539/00) was performed. Additional safety studies on renal system following a single voclosporin administration were also conducted.

No behavioural effects were noted in the Irwin test conducted in rats at mix-ISA247 doses of 2.5, 10 and 25 mg/kg/day (ISA05-28). However, neurological clinical signs and effects in histopathology were noted in repeat-dose toxicity studies in rats (see repeat-dose toxicity studies for more detail). A transient and slight decrease in body temperature was observed in the CNS safety pharmacology study in rats (25 mg/kg) as well as the cardiovascular safety pharmacology studies in cynomolgus monkeys (200 mg/kg).

In vitro results of a hERG assay in CHO cells (study ISA03-14) indicated that mix-ISA247, cis-ISA247 and voclosporin inhibited repolarising currents through hERG K+ channels at IC20 values of ~6-18 µM (7,000 – 22,000 ng/ml), i.e. concentrations in excess of the estimated clinical Cmax of 0.1 µM (~120 ng/ml). In a rabbit Purkinje fiber assay (study ISA03-15), mix-ISA247 did not induce arrhythmias up to 10 µM. However, *in vivo* voclosporin and mix-ISA247 prolonged the QT/QTc interval in cynomolgus monkeys at a dose of 200 mg/kg, which resulted in Cmax level about 5-times higher compared to the estimated clinical Cmax of 0.1µM (~120 ng/ml) [studies ISA02-07, ISA03-02].

In the respiratory safety pharmacology study in rats (ISA05-29), voclosporin exhibited a transient decrease in respiration rate at the highest dose (25 mg/kg), but no effect on tidal volume was observed.

There was a statistically not significant effect on renal function (i.e. 25% decrease in urine volume at 25 mg/kg voclosporin) in the single-dose safety pharmacology study in rats (ISA07-11).

Pharmacodynamic drug interactions

Pharmacodynamic interaction studies were not performed.

2.3.3. Pharmacokinetics

Method of analysis

Mix-ISA and voclosporin were determined by liquid chromatography combined with mass or tandem mass spectrometry (LC/MS and LC/MS/MS); following the switch to a trans-enriched drug substance, an isomer specific method for the separation and quantification of the cis- and trans-isomers of voclosporin was developed. Validation of all analytical methods used to support nonclinical studies was conducted in compliance with GLP Principles.

Absorption

The bioavailability of voclosporin in SD rats following a single oral administration of 10 mg/kg was determined to be 7.6% in both sexes (study ISA99-03). Pharmacokinetic parameters were also calculated following a single oral dose of voclosporin, mix-ISA247 and cis-ISA247 to cynomolgus monkeys in cardiovascular safety pharmacology studies (ISA02-07, ISA03-02) and in the tissue distribution study (ISA08-01). The maximum concentration in whole blood was attained between 2 and 4 hours post-dose, and t1/2 was between 3.8 and 9.0 hours.

There was no evidence of accumulation following repeat dosing for 10 days in rats. In general, Cmax and AUC values were higher in males than in females. Following repeated administration for 10 days in monkeys the absorption of voclosporin was dose-related up to approximately 150 mg/kg; higher doses did not result in an increased drug exposure. Female monkeys generally exhibited greater voclosporin exposure than males. Exposure to the trans- isomer was greater than that of the cis-isomer (~ 2-fold) in rats, rabbits, and monkeys.

Distribution

Tissue distribution and retention studies were performed in rats (ISA00-25, ISA05-18) and monkeys (ISA08-01) following oral administration of either [3H]mix-ISA247 or [14C]voclosporin. Radioactivity was rapidly distributed into all of the major organs/tissues, the highest concentrations in both species were in all tissues associated with the gastrointestinal tract. In rats, mean whole-blood concentrations of total radioactivity were still measurable at 72 hours post-dose, where concentrations were 1.5% (males) and 1.2% (females) of the observed Cmax values. Maximal concentrations occurred in all tissues within 12 hours post-dose in males and 8 hours post-dose in females. In monkeys radioactivity was still measurable at the final sampling time (168 hours post-dose) where measured concentrations represented 5.0% (males) and 4.4% (females) of the mean Cmax values. The highest concentrations of radioactivity were detected in essentially all tissues at 2 hours. In monkeys, radioactivity concentrations and whole blood:tissue ratios were generally low in the tissues of the central nervous system, indicating that voclosporin and/or its metabolites do not readily cross the blood/brain barrier following a single oral dose. Tissue distribution in albino and pigmented rats was similar revealing low binding to melanin.

In vitro plasma protein binding of voclosporin was high in both human and animal plasma samples (CD-1 mouse, SD rat, NZW rabbit, Beagle dog, cynomolgus monkey), ranging from 97-98% (ISA08-29). In vitro blood cell distribution studies demonstrated that voclosporin partitioned extensively into red blood cells (ISA00-29, ISA09-26).

Metabolism

Voclosporin and mix-ISA247 are extensively metabolised by CYP450 mediated Phase I hydroxylation and oxidative N-demethylation reactions. Metabolism of voclosporin is similar across species, with no unique human metabolites. The metabolic profile of primates was the most comparable to the human metabolic profile: IM1-diols monkey 21.3% versus human 38.7%, IM9 48.8% vs. 33.1, IM4n 14.1% vs. 12.3%, and IM4n9 14.3% vs. 2.4% (metabolite given as % of parent compound in sample)

(ISA01-19). In monkeys, at 1 hr post-dose, about 38% of radioactivity was associated with parent drug and about two-thirds with metabolites, respectively (ISA 08-01).

Voclosporin, mix-ISA247 and cis-ISA247 inhibited the metabolism via CYP3A4 whereas they did not inhibit the metabolism via CYP2D6 or CYP2C9. Isoenzymes responsible for the metabolism of mix-ISA247 in human liver microsomes were CYP3A4/5 and CYP2B6. Voclosporin was a direct competitive inhibitor of CYP3A4/5 (as measured by midazolam 1'-hydroxylation) with IC50 value of 1.2 µM. and Ki value of 1.1 µM. It did not induce CYP1A2 or CYP3A4/5 enzyme activities in cultured human hepatocytes.

Conversion of cis-ISA247 to trans-ISA247 (or visa versa) did not occur in vitro in human whole blood or denatured human whole blood incubated at 37°C for up to 6 hours neither did it occur in cynomolgus monkeys *in vivo*. No evidence of conversion to the cis- isomer was noted in rats and humans after repeated administration of voclosporin.

Excretion

Faecal excretion was the primary route of elimination accounting for 89-97% in rats and 77-79% in monkeys. Excretion was rapid, the majority of drug being eliminated within 24 hours (rats) or 48 hours (monkeys). Urine was a minor route of elimination of [14C]voclosporin, [3H]mixISA247 and drug-related material, accounting for 1.3-6.3% in rats and 0.8-1.9% in monkeys.

A placental and milk transfer study with [14C]voclosporin in SD rats indicated that transfer of radioactivity across the placental barrier was slow and limited (study CRL420696). Transfer of dose-related material into the milk was relatively rapid, but systemic absorption by the pups was slow and limited.

Pharmacokinetic interaction

Voclosporin was tested in co-administration with prednisone in a 13-week repeat-dose toxicity study in rats (study 70881). No new toxic effects were noted when compared to the known effect of each of the test items assayed separately. Mortality noted in the mid and high voclosporin dose groups (10 and 25 mg/kg/day with prednisone 0.5 mg/kg/day) was attributed to a secondary infection process due to the immunosuppressive action of both agents. Accumulation of prednisone/prednisolone in males following dosing of voclosporin (25 mg/kg) + prednisone (0.5 mg/kg) for 10 weeks and slightly higher voclosporin exposure when dosed alone were attributed to the pharmacokinetic variability of the active substance and were considered of no clinical relevance.

In vitro study with Caco-2 cells as well as a phase I drug interaction study with digoxin confirmed that voclosporin was a P-gp substrate/inhibitor.

In a pharmacokinetic drug interaction study in SD rats voclosporin, in contrast to CsA, did not interact with mycophenolate mofetil (MMF).

2.3.4. Toxicology

Most of the studies included in the nonclinical toxicity program were conducted with mix-ISA247. The toxicology profile of ISA247 has been studied *in vivo* in mice, rats, rabbits, dogs and cynomolgus

monkeys. For most of the studies, the oral route of administration was used, which is the proposed route for administration in humans. Bridging studies including a 13-week oral voclosporin toxicity study in rats, some genotoxicity studies and a foetal development reproductive toxicity study in rabbits were performed with voclosporin as test item in order to allow data extrapolation. In addition, the Environmental Risk Assessment was also performed with voclosporin. All main toxicology studies were GLP compliant.

Single dose toxicity

In rats, the single intravenenous doses of voclosporin up to 2.5 mg/kg, the highest dose tested, were well tolerated. In dogs, emesis was the only effect noted with single oral doses of mix-ISA247 up to 75 mg/kg.

Study ID	**Species/ Sex/Number/ Group**	**Dose/Route [Test article]**	**Observed max non-lethal dose (mg/kg)**	**Major findings**
ISA07-04	SD rats/ 6/sex/group	0 (vehicle), 1 or 2.5 mg/kg / intraveneous [voclosporin]	2.5	No deaths, decreased activity level at both doses
ISA00-18	Dogs 1M/1F	8, 10, 20 mg/kg (by gavage) 20, 30, 50 and 75 mg/kg (by capsule) [mix-ISA247]	75	Gavage: vomiting and/or regurgitation at 8 and 10 mg/kg Capsule: regurgitated pieces of capsule at doses ≥30 mg/kg

Repeat dose toxicity

Pivotal oral repeat-dose toxicity studies conducted with mix-ISA247 or voclosporin are presented in the table below.

Study ID	**Species (Number/Sex/ dose)**	**Dose mg/kg/day [Test article]**	**Duration**	**NOAEL (mg/kg/day)**
ISA00-08	Rat (10/sex/dose), plus (5/sex for control and high dose recovery)	0, 4.6, 24.2, 80 [Mix-ISA247] Vehicle/Formulation: Vitamin ETPGS/medium chain triglyceride (MCT)oil/Tween 40/95% ethanol (4/2/2/1)	28 days + 14-day recovery	24.2
ISA00-17	Rat (10/sex/dose), plus (8/sex for control and high dose recovery)	0 (saline, vehicle), 2.5, 10, 25 [Mix-ISA247]	13 weeks + 28-day recovery	not determined
ISA01-18	Rat (20/sex/dose), + (10/sex for interim sacrifies at week 4,8,13 and 17, 6/sex/group for recovery)	0 (vehicle), 1.25, 10 [Mix-ISA247, CsA]	26 weeks + 28-day recovery	1.25

ISA03-03	Rat (10/sex/dose) + (5/sex for interim sacrifies at week 4, 5/sex/group for recovery)	0 (vehicle), 2.5, 10, 25 [Mix-ISA247, cis-ISA247, trans-ISA247], 10, 25 [CsA]	13 weeks + 28-day recovery	2.5
ISA05-11	Rat (10/sex/dose) + (5/sex/group for recovery)	0, 2.5, 10, 25 [Mix-ISA247] in nVE* or 10, 25 [Mix-ISA247]VE*	13 weeks + 28-day recovery	2.5
ISA00-09	Dog (3/sex/dose) and (2/sex for control and high dose recovery)	0, (vehicle), 2.5, 10, 51.5 [Mix-ISA247]	14 days + 14-day recovery	2.5
ISA01-01	Dog (3/sex/dose) and (3/sex for control and high dose recovery)	0 (saline, vehicle), 2.5, 10, 35 [Mix-ISA247]	13 weeks + 28-day recovery	2.5
ISA01-05	Monkey (3/sex/dose) and (3/sex for recovery)	0 (saline, vehicle), 25, 75, 150/300 [Mix-ISA247]	13 weeks + 28-day recovery	nd
ISA02-01	Monkey (5/sex/dose) and (3/sex for recovery)	0 (saline, vehicle) , 25, 75, 150 [Mix-ISA247]	39 weeks + 28-day recovery	25

*nVE=vehicle without vitamin E-TPGS [MCT oil/Tween 40/95% ethanol (5:3:1, w/w/w)]

*VE= standard vehicle [vitamin E-TPGS/medium chain triglyceride (MCT) oil/Tween 40/95% ethanol (4:2:2:1, w/w/w/w)]

In the rat, cataract formation, renal effects and neurohistological findings were the primary adverse effects following administration of mix-ISA247 or voclosporin. Cataracts and associated microscopic findings of lenticular degeneration were observed mainly in males at high doses (80 mg/kg/day for 28 days) and did not resolve during recovery. Renal effects included increases in BUN and creatinine, tubular basophilia and degeneration/regeneration, and corticomedullary mineralisation. They occurred at dose levels of ≥ 2.5 mg/kg/day and were not reverted following recovery periods up to 4 weeks. A narrow margin of exposure (1.61, rat/human) was calculated for renal toxicity. The observed neurohistopathological changes in rats occurred at dose levels of ≥ 2.5 mg/kg/day, but, whereas comparable findings with CsA were identified in the 13-week study in rats (ISA01-18), no such findings were observed in other species (dog, monkey). Given that similar effects were observed following CsA administration a class effect may be the cause of neurological changes.

Decreased Mg levels were noted in biochemistry analyses in rats in the 26-week repeat dose toxicity study and in the 13-week repeat dose toxicity bridging study at 10 and/or 25 mg/kg/day. The exact cause of voclosporin-induced hypomagnesaemia is uncertain. In the case of Cyclosporin A the proposed mechanism is intracellular redistribution of Mg within renal tubular epithelium and the urinary loss. Similar effects on serum Mg were found between Cyclosporin A and Voclosporin in animals and in patients.

In a 13-week repeat-dose oral bridging study in rats (ISA03-03), administration of voclosporin produced slightly higher incidences and/or severity of adverse effects than administration of either mix-ISA247 or cis-ISA247 at the same dose level. These differences may possibly be due to the difference in bioavailability, as voclosporin demonstrated greater systemic exposure than cis-ISA247.

Another 13-week study in rats (ISA05-11) did not indicate any significant differences in toxicity between the standard formulation used in the pivotal toxicity studies with mix-ISA247 and voclosporin, and the formulation without vitamin E. Therefore, the applicant concludes, that vitamin E component of the vehicle was unlikely to mask any hepatic effect of mix-ISA247 or voclosporin in the toxicology studies.

Other reported findings in repeat-dose toxicity studies in rats included effects related to exaggerated primary pharmacodynamics (e.g. decreased WBC counts, atrophy of the thymic medulla, lymphocytolysis, absence of germinal centres in the spleen and lymph nodes).

In the dog (ISA00-09, ISA01-01), an emetic effect in all dose groups as well as gingival hyperplasia at higher doses were observed, but no ocular, renal, or neurological effects were noted. Exaggerated primary pharmacodynamic effects were also seen. The results of other oral toxicity studies with mix-ISA247 in rats and monkeys suggest that the emetic effect is species-specific and Beagle dogs exhibit a higher susceptibility compared to mongrel dogs. Gingival hyperplasia is a known effect with this class of compounds.

In the monkey (ISA02-01), pathologic findings following 39-week chronic treatment with mix-ISA247 did not induce any adverse effects on body weight, food intake, electrocardiography, blood parameters or organ weights. Clinical signs for the most part were associated with faecal changes. Occurrence of gingival hyperplasia was dose-dependent (75 and 150 mg/kg) and generally there was no recovery during the treatment-free period. Microscopically, lymphosarcomas were identified in 1 male and 4 females of the high-dose group (150 mg/kg/day). The safety margin at 75 mg/kg/day (NOAEL for lymphosarcoma) was lower than 11.5-fold the exposure at clinical therapeutic dose.

Genotoxicity

Genotoxicity studies are presented in the table below.

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
In vitro			
Bacterial Reverse Mutation Assay / AC33TS.503.BTL / Yes	AMES; *Sal. typh*. TA98, 100, 1535, 1537, *E. coli* WP2 uvrA	voclosporin 50, 150, 500, 1500, 5000 µg/plate / rat S9	Negative for reverse mutations; precipitation at and above 5000 µg/plate
Bacterial Reverse Mutation Assay / ISA99-05 / Yes	AMES; *Sal. typh*. TA98, 100, 1535, 1537, *E. coli* WP2 uvrA	mix ISA247 0, 15, 50, 150, 400, 1200 µg/plate / rat S9	Negative for reverse mutations; precipitation at and above 400 µg/plate
Cytogenetic assay in mammalian cells / ISA09-29 / yes	Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells	voclosporin without S9: 4 h and 20h treatment: 0.5-5000 µg/ml With S9 4h treatment: 0.5-5000 µg/ml	Negative for cytogenicity; precipitation ≥ 150 µg/ml without S9 and ≥ 150 µg/ml with S9
Cytogenetic assay in mammalian cells	Chromosomal Aberrations in	mix ISA247 without S9: 4 h	Negative for cytogenicity; precipitation ≥ 150 µg/ml

/ ISA99-04 / yes	Chinese Hamster Ovary (CHO) Cells	treatment: 12.5-200 µg/ml; 20h treatment 2.5-10 µg/ml With S9 4h treatment: 31.3-1000 µg/ml	without S9 and ≥ 125 µg/ml with S9
In vivo			
Cytogenetics test *in vivo* Rat bone marrow Micronucleus Test / ISA00-22 / yes	Rat (SD) 5/sex/group	mix ISA247 500, 1000, or 2000 mg/kg single dose (oral gavage) harvest time 24 and 48 h after treatment	Negative for genotoxicity; no clinical signs or significant reduction in PCE/NCE ratio

Mix-ISA247 did not show any genotoxic potential in the standard test battery for genotoxicity. Additionally, the final formulation of voclosporin was studied in bacterial reverse mutation assay and mammalian (CHO) cell cytogenetic assay. Results of both of these assays were negative. CHMP noted that in the in vitro cytogenetic assay in CHO cells mix-ISA247 concentrations evaluated were comparatively low, especially in the 20h continuous treatment, and with inconsistent levels of cytotoxicity. The applicant was requested to explain these findings. The applicant performed a second CHO assay (ISA09-29) with voclosporin and the final report was submitted during the assessment period. These data confirmed that voclosporin did not induce chromosome aberrations in CHO cells.

Carcinogenicity

Long term studies with ISA247 were performed in mice and rats according to ICH S1 guidelines. Both studies (ISA06-01, ISA04-08) were performed with the trans-isomer enriched formulation of ISA247 (voclosporin).

2-year mouse study (study no ISA06-01)

The chosen doses for the study were determined in a 14-day (ISA05-16) and a 13-week dose-range finding study (ISA05-17). Based on NOAEL the dose of 30 mg/kg/day was chosen as a high dose for this study. During the long-term study significantly decreased survival was seen in the high dose groups with discontinuation of treatment at week 60. High mortality also was the reason for scarification of all low and high dose group males at week 82 and 80. The complete study was terminated because of the high mortality in the vehicle groups at week 88-89. In females mortality was significantly increased in the vehicle group compared to saline. Due to the also high mortality rate in the vehicle control groups mortality effects were attributed more to the vehicle than to voclosporin. However, in males there was a significant reduction of survival rates in the low and high dose compared to vehicle group also. No treatment-related statistically significant effects for clinical signs, body weight, food consumption, macroscopic ophthalmologic, macroscopic or non-neoplastic microscopic evaluations were observed. Treatment-related effects were a statistically significant trend in dose-related increases in malignant lymphomas in all dose groups (3, 10, 30 mg/kg/day) in males and females compared to vehicle and saline groups. Incidences for malignant lymphomas in the high dose groups were statistically significant and exceeded the historical control values of the test facility for CD1.mice (6.56% for males and 17.76% for females). Historical values in other test facilities and

published information (Maita, 1988) suggest that these incidences are borderline. A statistically significant increase of tumours from vehicle controls was also seen for bronchiolo-alveolar adenoma and for bronchiolo-alveolar carcinomas and adenomas combined in the mid-dose females compared to vehicle but not to saline control group. As this effect was also not dose related it was considered incidential.

In conclusion the NOAEL for neoplastic effects in this study was considered to be 10 mg/kg/d.

2-year rat study (study no ISA04-08)

The chosen doses for the study were determined in a 26-week dose-finding study (ISA01-18). Based on the NOAELs doses of 1.25 mg/kg/day for males and 2.5 mg/kg/day for females were chosen as the top doses for the life-time study. Other tested doses were 0.05 and 0.25 for males, and 0.1 and 0.5 mg/kg/day for females. Due to low survival in the vehicle control group in males the study was terminated for males at weeks 95 and 96 and for females at weeks 95 to 97. Survival in all treated male groups was significantly reduced compared to saline control but not compared to vehicle control group. Treatment related effects were therefore considered most likely related to the vehicle and not to voclosporin. Survival rates in females treatment groups were not reduced compared to any control group but instead were lowest in control groups. No test article related clinical findings or effects on body weight, food consumption, haematology or clinical chemistry were observed, except for a statistically significant decrease in sodium and chloride in the high dose females. There was a dose-related trend for lower sodium levels in male urine also but it did not reach statistical significance. Decreased sodium and chloride levels were associated with slightly higher urine volumes. Chronic progressive nephropathy (CPN) was similar in all groups with a slightly increased incidence for severe CPN in high-dose males compared to control groups. Effects on urine sodium and chloride concentration were however considered unrelated to CPN as there was only statistical significance in female for urine chemistry but no difference in CPN compared to controls.

Significant differences were only found for combined pancreatic islet cell adenoma and carcinoma in males compared to the vehicle control group, however there was no difference when compared to the saline control group. No such effect was found in females. Pancreatic islet neoplasias were not considered treatment-related as significant differences to the saline control group were missing. In females there was a significant effect for benign cervix granular cell tumors in the mid-dose group compared to saline control group but not to vehicle control group and for combined benign cervix and vaginal granular cell tumors in vehicle, mid- and high-dose animals compared to saline control group. These effects were considered more likely to be related to the vehicle than related to voclosporin treatment as there was no difference to the vehicle control group.

Voclosporin is considered to have immunosuppressive activity and therefore increased incidences in neoplastic effects like lymphomas in long-term treatments could be expected.

When comparing the exposure levels in treatment groups with clinical exposures level it has to be noted that AUC levels in mid-dose animals are around the clinical AUC levels (plasma AUC0-24h levels of 612.1/405.9 ng*h/ml for m/f mice, AUC0-12h 444 ng*h/ml in humans). In the rat study exposure levels measured in rat (Cmax males at 1.25 mg/kg/d 29.53 ng/ml at day 1, AUC0-24h

362.85ng*h/ml) were below the estimated therapeutic AUC0-12h of 444 ng*h/ml in humans. Safety margin could not be established.

Reproduction Toxicity

1) Fertility and early embryonic development in rats (ISA02-02)

Effects of mix-ISA247 on male fertility were assessed in a dedicated study. No adverse effects were noted on mating and fertility parameters at any dose tested (2.5, 10, 25 mg/kg/day). Several adverse findings were observed at 25 mg/kg/day, including decreased organ weights and ratios to terminal body weight for left cauda epididymis, left and right epididymis, seminal vesicles and prostate. A NOAEL of 10 mg/kg/day was determined for male reproductive organ toxicity, providing an approximate 12.5-fold safety margin with respect to clinical dose. Mating and fertility parameters remained unaffected in females up to the highest mix-ISA247 dose tested (25 mg/kg/day), providing an approximate safety margin of 30-fold compared to clinical dose.

2) Embryo-foetal development and maternal toxicity (ISA00-23, ISA01-12,ISA00-24, ISA01-13, ISA04-04, ISA04-05)

In rats, maternal toxicity was observed at 25 mg/kg/day mix-ISA247 dose, as red perioral substance, decreased food consumption and body weight gain, decreased ovarian:brain weight ratio, increased brain:body weight and adrenal:body weight ratio. Considering the observed effects at doses above or equal 2.5 mg/kg/day, i.e. increased incidence of scant faeces, excess salivation, urine-stained abdominal fur and alopecia, maternal NOAEL was 2.5 mg/kg/day (1.3-fold the exposure expected in humans). Developmental toxicity findings were noted in dams dosed 25 mg/kg/day as increased number of resorptions, increased percentage of dead or resorbed conceptuses per litter and increased number of early and late resorptions. In addition, there was a decrease in litter size, number of live foetuses and placental and foetal weights. Pups from dams in this high-dose group presented decreased metatarsal ossification at 25 mg/kg/day, considered a reversible delay related to the reduced foetal weights. The NOAEL for developmental toxicity was considered to be 10 mg/kg/day mix-ISA247 dose (14.1-fold the human exposure at therapeutic dose).

In the definitive embryo-foetal development study in rabbits performed with mix-ISA247 as test item, dams showed increased number of total resorptions, increased percentage of dead or resorbed conceptuses per litter at 20 mg/kg/day. Decreased litter size and number of live fetuses were noted at the high-dose group, while placental weights and fetal body weights were observed from 10 mg/kg/day dose. Pups in the mid- and high-dose groups (10 and 20 mg/kg/day) presented reduced metatarsal ossification. Maternal and developmental NOAEL was considered to be 2 mg/kg/day (2.5-fold the clinical dose).

Considering the rabbit as the more sensitive species, an embryo-foetal development study was conducted with voclosporin as test item to bridge the results in the reproductive toxicity program between the two test items. Soft stool and dried or wet brown material on the fur was noted in all animals and was considered to be vehicle-related due to its lipophilic properties. Maternal toxicity was revealed as decreased food consumption (only at 20 mg/kg/day), decreased uterine weight and lower

foetal body weight observed at 20 mg/kg/day. Foetal toxicity was noted as unossified sternabrae numbers in the 5 and 20 mg/kg/day dose groups and unossified hyoid body and/or arches in the 20 mg/kg/dose group. Maternal and developmental NOAEL for voclosporin in rabbits was considered to be 1 mg/kg/day (only 0.02-fold the exposure expected in humans).

3) Pre- and postnatal development in rats including maternal function (ISA02-03)

In the rat pre-and post-natal study, the high dose level of mix-ISA247 (25 mg/kg/day) caused severe maternal toxicity and also developmental toxicity characterized by decreased number of total pups delivered, liveborn pups and surviving pups per litter. Increased umbilical hernias were observed in the mid- and high-dose pups (F1, 10 and 25 mg/kg/day). Reproductive parameters in F2 generation were unaffected at all doses tested. The NOAEL for F0 maternal and developmental toxicity was considered 10 mg/kg/day (12.5-fold the clinical dose), while the NOAEL for F1 and F2 generation was above the maximum dose tested, 25 mg/kg/day (>30-fold the clinical dose).

Toxicokinetic data

Systemic exposure (Cmax and AUC values) to mix-ISA247 (cis- and trans- isomers combined) was dose-related in all species tested. There was no accumulation in any species following repeated daily dosing. Sex-related differences were observed in the 28-day, 13-week and 26-week rat studies with higher Cmax and AUC values in males than in females. When comparing exposures (AUC(0-24h)) at all doses, voclosporin exposure was greater than cis-ISA 247, in fact, CsA>voclosporin>mix-ISA247>cis-ISA247.

Exposure to voclosporin in monkeys was dose-related. Voclosporin demonstrated greater exposure on Day 1 than 10 in males and females. Based on AUC(0-24hr) data, female monkeys experienced greater voclosporin exposure than males which has been observed in other monkey studies (39-week oral repeat dose toxicity study). Exposure to voclosporin and its metabolites generally decreased in monkeys upon repeat dosing.

The margins of exposure at the NOAEL doses in the pivotal rat and monkey studies relative to estimated exposure at the proposed therapeutic dose of 0.4 mg/kg twice daily are presented in table below.

Study	NOAEL (mg/kg/day)	Mean AUC (0-24hr) ± SD (ng·hr/mL)	Estimated Therapeutic AUC (0-12hr) ± SD (ng·hr/mL)	Margin of Exposure[a]
13-Week Rat (ISA 03-03)	2.5 [b,e]	716.2[c]	444 ± 193[d]	1.61
39-Week Monkey (ISA 02-01)	25 [b]	781.9 ± 359.1[f]	444 ± 193[d]	1.76
	150 [e]	5113.4 ± 1676.6[f]	444 ± 193[d]	11.52

a. Animal-to-human exposure multiples were determined by dividing steady state AUC(0-24 hr) values (various dose levels) in animals by a mean steady state AUC(0-12 hr), 444 ng•hr/mL, in humans following administration of 0.4 mg/kg Q12H.
b. Overall study NOAEL
c. Voclosporin (males and females combined; no SD due to pooled samples)
d. Combined voclosporin data from drug interaction studies at 0.4 mg/kg Q12H (LX 211-06 (n=24) and LX 211-07 (n=20))
e. NOAEL for renal findings.
f. Mix-ISA247 (males and females combined).

Local Tolerance

ISA08-10, a dermal local tolerance study was performed with voclosporin (powder moistened in saline) in rabbits using a patch test. No erythema or oedema was observed in any animal at any timepoint (24, 48 and 72 hours).

ISA08-12, a delayed dermal contact hypersensitivity study was conducted with voclosporin in guinea pigs according to the Buehler method. No dermal irritation (erythema and oedema) was noted following voclosporin challenge.

ISA08-11, an eye irritation study was conducted with voclosporin in rabbits, by instillation of moistened powder into one eye. Only a slight transient ocular irritation (conjunctival redness chemosis and discharge at 1 hour post-dose) was noted, but no irritation involving the cornea was observed in any treated eye up to 72 hours.

Other toxicity studies

Voclosporin was tested in co-administration with prednisone in a 13-week repeat-dose toxicity study in rats. Mortality noted in the mid and high voclosporin dose groups (10 and 25 mg/kg/day) with prednisone 0.5 mg/kg/day was associated to a secondary infection process to the immunosuppressive action of both agents. No new toxic effects were noted when compared to the known effect of each of the test items assayed separately. A slight difference in cataracts onset was observed. A possible accumulation of prednisone/prednisolone was observed in males following dosing of voclosporin (25 mg/kg) + prednisone (0.5 mg/kg) for 10 weeks.

Immunotoxicity

In agreement with the Scientific Advice given in January 2008 further immunotoxicity studies were not considered necessary since immunosupression is an expected and desired property of the drug substance.

Impurities

Due to the fact that voclosporin was not the test item assayed in most of the toxicology non-clinical programme studies the need to qualify voclosporin drug substance or drug product impurities was discussed. It was acknowledged that no additional impurities require qualification as they were below the qualification threshold of 0.5%. The assessment of one impurity (RRT1.24) is ongoing.

Photosafety

In the nonclinical studies radioactivity was detected in skin and eye after oral administration of [14C]-labelled voclosporin to albino and pigmented rats. Voclosporin does not absorb light in the wavelength of 290-700 nm and has little potential to bind to melanin. Therefore, as discussed and confirmed by the CHMP, it would not require a phototoxicity evaluation.

Other studies

Current MAA does not include a paediatric indication. In the agreed PIP, the proposed studies for the subsets of the paediatric population concerned by the paediatric development (from 2 years to less than 18 years) include a juvenile animal toxicity study. This study is ongoing.

2.3.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): voclosporin			
CAS-number (if available): 515814-01-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	5.5	Potential PBT:**Y**
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, **refined** (prevalence 4/10000)	0.0056	µg/L	> 0.01 threshold (**N**)
Other concerns (e.g. chemical class)			(**N**)

Voclosporin PEC surfacewater value is below the action limit of 0.01 ug/l after the refinement of the calculation (orphan medicinal product). As log Kow exceeds 4.5 the PBT potential was discussed. The CHMP agreed that in view of the structure and metabolism of the product no persistence and bioaccumulation in the environment is expected. Overall, voclosporin is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Voclosporin is a cyclic undecapeptid structurally similar to cyclosporine A (CsA) except for a modification to the amino acid one region. It consists of two geometric isomers; a trans- isomer and a cis- isomer, depending on the orientation of the modified functional group at amino acid one. During development the trans-cis-mixture was switched from early 45-50% trans-, 50-55% cis- to an trans-enriched form (≥90% trans-isomer, ≤10% cis-isomer), which is the active substance of Luveniq. The early nonclinical program was completed with mix-ISA247 (45-50% trans-, 50-55% cis-), however, toxicology studies to bridge mix-ISA247 and voclosporin data were conducted.

Whereas *in vitro* voclosporin and mix-ISA247 demonstrated greater potency in calcineurin inhibition and functional T-cell assays (cytokine production, expression of T-cell activation surface antigens) when directly compared to CsA, no superiority of voclosporin was seen in the pivotal experimental autoimmune uveitis (EAU) model in rats. Both compounds reversed clinical signs of uveitis, but due to the different route of administration (i.p.) and significantly higher doses (40 mg/kg) used, no conclusion for the intended clinical use could be drawn.

In vitro results of a hERG assay in CHO cells indicated that mix-ISA247, cis-ISA247 and voclosporin inhibited repolarising currents through hERG K+ channels at concentrations well in excess of the estimated clinical Cmax of 0.1 µM (~120 ng/ml). Moreover, *in vivo* voclosporin and mix-ISA247 prolonged the QT/QTc interval in cynomolgus monkeys at a dose of 200 mg/kg, which resulted in Cmax about 5-times higher compared to the estimated clinical Cmax of 0.1 µM (~120 ng/ml). As the mechanism of QT prolongation is still unknown and effects of voclosporin exposure level due to drug

interactions might occur, the applicant was requested to comment on the need for further preclinical studies and its therapeutic relevance. The sponsor provided arguments against a causal evidence for hypomagnesaemia. Whereas possible effects on repolarising K+ channels other than hERG channels and on the trafficking of hERG channels can still not be excluded, this is not prohibitive for a positive opinion and could be addressed in future studies post-authorisation.

There was no evidence of ISA247 accumulation following repeat dosing for 10 days in rats. Voclosporin and mix-ISA247 were extensively metabolised by CYP450. Voclosporine was shown to be CYP3A4 and P-gp inhibitor. It crossed the placental barrier in rats.

Both isomers exhibit a comparable toxicological profile, differences in severity of toxicological effects following administration of the trans- isomer were linked to pharmacokinetic differences. Thus higher bioavailibilty of the trans- isomer compared to cis-isomer resulted in higher exposure and secondary more severe toxic effects. At the same dose level, CsA resulted in higher exposure.

The noted adverse effects in animals, e.g. gingival hyperplasia, neurological effects, soft/loose faeces, diarrhoea, nephrotoxicity are known effects of immunosuppressant drugs, and are considered "class effects"; no new toxicological findings were observed. However, to some extent the noted effects are surprising at the low exposure levels. The applicant discussed the increased incidences of lymphomas in mice, pancreatic islet cell tumours in male rats and granular cell tumours in cervix and vagina of rats together with the differences in effects seen between saline and vehicle control groups. They were either attributable to pharmacodynamic action of voclosporine (immunosuppresion) or were considered as spurious findings without clinical relevance as they were present in both, control and test groups. Reasons for the reduced, albeit not statistically significant, survival rates in mice and rats in carcinogenicity studies remain unclear. However, it is not regarded to be of clinical relevance.

Mix-ISA247 did not show any genotoxic potential in the standard test battery for genotoxicity. Additionally, the final formulation of voclosporin was studied in bacterial reverse mutation assay and mammalian (CHO) cell cytogenetic assay. Results of both of these assays were negative.

Studies of fertility, embryonic development and peri/post-natal reproductive toxicity were conducted with mix-ISA247. Based on adverse maternal and foetal toxic effects, the overall reproductive and developmental toxicity NOAEL for mix-ISA247 was 2 mg/kg/day. The voclosporin teratogenicity study in rabbits resulted in a NOAEL only 0.02-fold the expected exposure in humans. Foetal toxicity was only observed at doses associated with maternal toxicity. The reproductive and developmental toxicity of voclosporin is expected to be comparable to that of mix-ISA247 based on the teratology bridging study with voclosporin in rabbits.

Voclosporin is not expected to pose a risk to the environment based on the revised ERA with included PBT assessment.

2.3.7. Conclusion on non-clinical aspects

Overall, there seem to be no major differences in immunosuppressive properties and toxicological profile between voclosporin and CsA. Possible pharmacokinetic drug interactions with CYP 3A4 and/or PgP-inhibitors have to be taken into consideration (increased voclosporin exposure), but can be sufficiently addressed in the product information (for more information see discussion on clinical pharmacology). Some uncertainties related to species-specific events that are currently not known for CsA are not prohibitive for a positive opinion and could be addressed in future studies post-authorisation.

2.4. Clinical aspects

2.4.1. Introduction

The indication applied for was chronic non-infectious uveitis involving the intermediate and posterior segments of the eye.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

The efficacy and safety of voclosporin has been assessed in two pivotal controlled Phase 2/3 clinical studies LX211-01 and LX211-02. Additionally, in studies 01 and 02 the placebo-controlled phase was followed by an optional 6-moth extension to evaluate the long-term effects of voclosporin.

Study ID	Design/ Posology	Duration	Primary Endpoint
LX211-01 Active Sight Threatening, Non-Infectious Intermediate-, Anterior and Intermediate-, Posterior-, or Pan-Uveitis	Randomised, PBO controlled, DB blinded, Parallel groups: Voclosporin 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg BID and Placebo	• 24 weeks of core treatment • 24 weeks of optional extension	Mean change from baseline in graded vitreous haze after 16 and 24 weeks of therapy or at time of rescue, if earlier
LX211-02 Clinically Quiescent Sight Threatening, Non-Infectious, Intermediate-, Anterior and Intermediate-, Posterior-, or Pan-Uveitis	Randomised , PBO controlled, DB blinded, Parallel groups: Voclosporin 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg BID and Placebo	• 26 weeks of core treatment • 24 weeks of optional extension	Proportion of subjects who experienced inflammatory exacerbation at any time during the 26 weeks

A third study, LX211-03, was conducted to examine the efficacy of voclosporin in non-infectious anterior uveitis, which is considered to be a different indication. Approval for this indication was not sought at this time.

2.4.2. Pharmacokinetics

Twenty clinical pharmacology studies provided general pharmacokinetic information. Of those four studies assessed bioavailability/bioequivalence, two studies investigated intrinsic factors affecting pharmacokinetics including renal and liver dysfunction, three studies focused on pharmacokinetic interactions, two studies were QTc investigations, and four were studies conducted in other indications, e.g. psoriasis and renal transplant. Remaining five studies investigated single and multiple dose pharmacokinetics of ISA247 or voclosporin.

Several analytical methods have been developed and used in the different pharmacokinetic studies including isomer-specific LC-APCI/MS and LC-API/MS/MS, non-isomer specific LC/MS/MS, or

HPLC/MS/MS for quatification of voclosporine and metabolites. Voclosporine pharmacokinetic parameters were dertermined in whole blood while ISAtx247 was determined also in plasma. As voclosporin partitions extensively into RBCs whole blood was considered to be the most appropriate biological matrix for its quantification. The bioanalytical methods were adequately validated. However, the CHMP requested the applicant to perform a cross-validation of bioanalytical methods to further support the conclusions from population pharmacokinetic studies.

Absorption

Based on the results from Mass Balance Study (LX211-05) and assumption that the identified and unidentified voclosporin metabolites resulted from oxidation (following absorption), the total oral absorption of voclosporin was estimated to be 83% and was consistent with the estimated oral absorption of cyclosporine (~86%) (Wu, Benet, et al, 1995).

Absolute bioavailability studies (i.e. a comparison with the intravenous route of administration) have not been performed. Relative bioavailability studies have been performed to compare two dosage forms (oral solution and capsules) and the effect of food (see below).

Bioequivalence

The bioequivalence between the two formulations employed during the development programme, a soft-gelatin capsule which contains voclosporin in a multi-component vehicle and a non-encapsulated solution was investigated.

Study ISA04-01

An Open-Label four Way Crossover, Bioequivalence Study Comparing Liquid Versus Capsule Formulations of Orally Administered trans-ISA247 100 mg in Water or Apple Juice in Fasted Normal Healthy Volunteers

The four treatments were 100 mg single doses administered as 2 × 50 mg capsules with water or apple juice and 2 ml × 50 mg/ml solution with water or apple juice. Nineteen (19) healthy adult volunteer subjects (15 males and 4 females) were enrolled and 13 subjects completed all four periods of the study. All doses were administered after an overnight fast. Treatment phases were separated by a 10-day washout period. Blood samples were collected for 72 hours after dosing and analysed for trans-voclosporin and cis-voclosporin using an isomer specific validated LC/MS/MS method. Standard methods were used to calculate and analyse pharmacokinetic parameters.

The equivalence between oral solution and capsules for the Cmax, AUC0-t and AUCinf of cis-ISA247 when taken with apple juice or water could not be demonstrated. However the CHMP did not consider this finding as clinically relevant given that the cis- enantiomer is not active. In addition, a higher intra-subject variability was observed which might have precluded demonstration of equivalence with a small sample size. For the trans-isomer and the mixture of enantiomers the 90% confidence intervals for Cmax, AUC0-t, and AUCinf, solution-to-capsule, were within the 80.00% to 125.00% equivalence window after administration in water or apple juice, demonstrating bioequivalence between the two formulations regardless of vehicle. Apple juice had no apparent effect on the absorption of voclosporin from the capsule. However, absorption from the oral solution was somewhat lower when administered with apple juice (Cmax CI [77.1-96.7]). It was not considered clinically relevant as the dosing recommendations propose intake with water.

Protocol deviations were not considered to affect the study outcome.

Another, supportive, study ISA00-15 with ISAtx247 at 200 mg demonstrated bioequivalence between oral solution and soft capsule when taken with apple juice or water.

The evidence of equivalence obtained for the 100 mg strength can be extrapolated to the strength to be marketed (50 mg) because the composition is qualitatively identical and quantitatively proportional, both strengths are manufactured with the same strength and a higher dose is considered more discriminative to detect differences.

Food effect

The effects of fasting, consumption of a low-fat and a high-fat breakfast on the absorption of voclosporin from the oral solution after administration of 1.5 mg/kg with 50 ml of apple juice to healthy subjects were examined in study ISA04-02. This was Phase I, single centre, randomised, single-dose, open-label, three-way crossover study. Treatment phases were separated by washout periods of 12 days. Eighteen (18) healthy adult volunteer subjects (12 males and 6 females) enrolled into and 15 subjects completed all three periods of the study. Blood samples were collected for 72 hours after dosing and analysed for trans-voclosporin and cis-voclosporin using an isomer specific validated LC/APCI/MS method. Standard methods were used to calculate and analyse pharmacokinetic parameters.

Administration of voclosporin with either a low-fat or high-fat breakfast resulted in a decrease in the mean voclosporin (trans- isomer) whole blood concentrations. There were decreases in the mean values for Cmax, AUC0-t and AUCinf. The geometric least squares mean ratios ranged from 71.44% for Cmax to 85.04% for AUC0-t, low fat-to-fasted, and 47.47% for Cmax to 75.09% for AUC0-t, high fat-to-fasted and the lower limits of all confidence intervals were < 80.00%, indicating an effect of food on the extent of absorption. The mean Tmax increased from 1.77 h under fasted conditions to 1.90 h and 2.32 h with a low- and high-fat breakfast, respectively. Overall there was a rank-order relationship between the fat content and the decrease in the rate and extent of voclosporin absorption.

Protocol deviations and amendments were not considered to affect the study outcome.

Another, supportive, study (ISA00-12) demonstrated a minor food effect on Cmax without a food effect on AUC. This might have been due to the fact that a non-isomer-specific analytical method was employed.

Distribution

Mass balance study LX211-05, PK studies ISA03-10, ISA03-12,{ ISA211-05} and safety studies (QT) ISA03-11 and ISA05-03

After single doses (studies ISA03-10 and ISA03-11), the mean whole blood concentrations of voclosporin increased in a dose-related manner over doses ranging from 0.25 mg/kg to 4.5 mg/kg as did mean values for Cmax and AUCinf. After multiple doses of 0.25 mg/kg to 1.5 mg/kg BID for 10.5 days (study ISA03-12) and 0.3 mg/kg to 1.5 mg/kg BID for 6.5 days (study ISA05-03), there was a dose-related increase in the mean voclosporin whole blood concentrations and mean values for Cmax and AUC through 12 hours [AUC(0-12)] at steady-state.

Mass balance study LX211-05 showed that mean Cmax and AUCinf values for the trans- isomer of voclosporin were greater than 90% of the values for total voclosporin, whereas the mean Cmax and AUC(inf) values for the cis- isomer of voclosporin in blood were less than 10% of the values for total voclosporin indicating that majority of voclosporine circulating in blood was the trans- isomer.

A two-compartment PK model with first-order absorption was assumed for voclosporin. The population PK analysis based on 5 phase I and two phase 3 studies demonstrated volumes of distribution for the V1/F and V2/F compartments as 61.7 L and 2130 L, respectively with high inter-individual variability (IIV) on V1/F, reaching 61.1%.

As described in the non-clinical pharmacokinetic section (study ISA08-29), voclosporin is highly bound to plasma proteins in humans (96.97 ± 0.29%) and animals (97.35 ± 0.24% to 98.34 ± 0.32%). Data from another study examining effects of temperature on voclosporine distribution in human plasma (ISA09-26) demonstrated that voclosporin partitioned extensively into red blood cells.

Elimination

The data from the single ascending dose study ISA03-10 with higher doses of voclosporin (1.5 mg/kg to 4.5 mg/kg) indicated that the elimination half-life (t 1/2) ranged from 12.8 ± 1.34 to 18.1 ± 2.13 hours. In the ascending multiple dose study ISA03-12 evaluating lower doses from 0.25 to 1.5 mg/kg the mean t 1/2 ranged from 30.1 to 36.5 hours after the last dose on day 10.

The *in vivo* metabolism of voclosporin in humans was examined using pooled whole blood, urine, and faeces samples from Mass Balance Study (study 08680). Voclosporin is extensively metabolised by the liver following oral administration to humans. The main isoenzymes involved in the vocosporin metabolism are CYP3A4/5. All 20 of the identified and tentatively identified metabolites resulted from oxidation. These metabolites accounted for approximately 38% of the administered dose in pooled 0-24h human blood samples (excluding parent drug and the radioactive impurity). An additional 45.4% of the dose was associated with numerous unidentified metabolites. It is assumed that these unidentified metabolites (each of which is less than 2.3% of the dose) most likely resulted from further oxidation of primary voclosporin metabolites.

After oral administration of [14C]-voclosporin, renal excretion was limited as only approximately 2.11% of the dose recovered in the urine. Unchanged [14C]-voclosporin accounted for 0.25% of the administered dose recovered in the 0 to 48h pooled urine sample. Seven (7) metabolites, M1 (IM1-DIOL-1), M2 (IM4n9), M3 (IM1w), M4 (IM9), M5 (IM4), M6 (IM4n), and M19 (unidentified) were detected. After oral administration of [14C]-voclosporin approximately 88% of the dose was recovered in the faeces, pooled within each subject collection during the 0-72, 0-120, or 0-144-hour post-dose time period. Unchanged [14C]-voclosporin was a minor radioactive component, accounting for about 5% of the administered dose. This study also demonstrated that voclosporin did not undergo metabolic degradation when incubated (aerobic incubation) for 24 hours at ~37ºC in human faeces, suggesting that the metabolites in faeces come from hepatic metabolism followed by biliary excretion. Nineteen (19) minor metabolites, M1 to M18, were tentatively identified, each accounting for less than 5% of the dose in the pooled faecal samples.

In vitro metabolism studies with human samples indicated that CYP3A4/5 was the major contributor to the voclosporin metabolism (study ISA01-06), voclosporin in concentrations up to 4uM did not induce P450 isoenzymes (study ISA08-03), however it directly and competitively inhibited CYP3A4/5 as measured by midazolam hydroxylation, with an IC50 value of 1.2uM (study ISA08-20).

No data on genetic polymorphism was reported (see discussion for more detail).

Elimination was also characterised in the popPK analysis. The final covariate model included the influence of total daily dose, height and alkaline phosphatase on CL/F, and height on CLdistr/F. Consequently, for a 170 cm tall patient with psoriasis, values of alkaline phosphatase of 80 UI and a total dose of 60 mg of voclosporin, the estimated values ("typical" values) were CL/F=57.5 L/hr,

V1/F=61.7 L, V2/F=2130 L, and CLdistr/F=53.5 L/hr. Inter-individual variability (CV%) related to these parameters showed values of 38%, 61.1%, 19.7% and 37.2%, respectively.

No inter-conversion between enantiomers was observed both in vitro in human whole blood (study ISA03-08) and *in vivo* in a multiple dose ascending study (ISA09-11).

Dose proportionality and time dependencies

Based on the results from studies with single and multiple ascending doses of voclosporin (studies ISA03-10, ISA03-11, ISA03-12, ISA05-03) the pharmacokinetics appear to be slightly nonlinear after oral administration of doses ranging from 0.25 to 4.5 mg/kg. These findings were confirmed by the popPK model. Studies with multiple doses demonstrated that clearance did not vary with time. No time dependent changes in blood voclosporin pharmacokinetics were observed across the dose levels of 0.25 – 1.5 mg/kg.

Special populations

Intra- and inter-individual variability

As described earlier the inter-subject variability detected in the popPK model was large and varied between 20 and 60% for different parameters.

Impaired renal function

Study ISA07-08

Thirty-three (33) male and female subjects were placed into four (4) groups based on renal function as defined by glomerular filtration rate as estimated by creatinine clearance (CLcr) (Cockroft-Gault). The Normal renal function and Mild and Moderate impairment groups received voclosporin 0.4 mg/kg as a single dose on Day 1 and Day 10, and voclosporin 0.4 mg/kg BID on Days 3 through 9 while subjects with Severe Impairment received only a single dose of voclosporin 0.4 mg/kg on Day 1. Results from the study indicated that there was no significant effect of mild to moderate renal impairment on voclosporin exposure after single or multiple dosing while severe renal impairment resulted in an approximately 1.5-fold increase in overall exposure with no increase in peak concentration after a single dose.

Impaired hepatic function

Study ISA07-09

The objective of this study was to determine the pharmacokinetic and pharmacodynamic profile of voclosporin and selected metabolites in subjects with hepatic impairment after single or multiple doses.

Eighteen (18) male and female subjects were placed into three groups based on hepatic function: Normal hepatic function, Child-Pugh A (Mild Impairment), and Child-Pugh B (Moderate Impairment). The Normal and Child-Pugh A subjects received voclosporin 0.4 mg/kg (given as 10 mg soft gelatin capsules) as a single dose on Day 1 and Day 10, and voclosporin 0.4 mg/kg BID on Days 3 through 9. Child-Pugh B subjects received only a single dose of voclosporin 0.4 mg/kg on Day 1. In Child-Pugh A subjects there was a 1.5-fold increase in the geometric mean Cmax and a 1.7-fold increase in the geometric mean AUC(0-48) compared to Normal subjects. For Child-Pugh B subjects, the increases in the geometric mean Cmax and AUC(0-48) were 1.5- and 1.8-fold, respectively.

Other populations

Only 40% approximately of all individuals included in the popPK analysis were female. Gender was tested as a covariate of CL/F in the popPK analysis. It showed a certain degree of influence on CL/F which disappeared after including height a covariate of CL/F. Weight was tested as a covariate of CL/F in the popPK analysis. It showed a certain degree of influence on CL/F which disappeared after including total daily dose on CL/F, suggesting that weight could be a confounding factor.

Percentage of Caucasian patients was almost 90% in the majority of PK studies; hence, it is quite difficult to evaluate race influence on any PK parameter.

Pharmacokinetics in paediatrics was not investigated. A paediatric investigation plan was agreed deferring the start of clinical trials in the paediatric population until CHMP opinion granting the marketing authorisation in the adult population. There were no formal studies in geriatric patients.

Pharmacokinetic interaction studies

The potential of voclosporin to interact as a substrate for and/or an inhibitor of the P-glycoprotein (Pgp) efflux transporter in Caco-2 cell monolayers was investigated in study ISA08-02. Voclosporin inhibited the active efflux of [3H]-digoxin (positive control) by 91% at a nominal concentration of 4 µM. Although an IC50 for the inhibition of [3H]-digoxin transport could not be determined from the data obtained, the results indicated that voclosporin may be an inhibitor of Pgp.

Study LX211-06 was conducted to determine the effect of ketoconazole on the pharmacokinetics of voclosporin when both drugs were at steady state. Twenty-four (24) healthy male and female volunteers received voclosporin 0.4 mg/kg Q12H on Days 1 through 10 and voclosporin 0.4 mg/kg every 12 hours (Q12H) + ketoconazole 400 mg once daily (QD) on Days 11 through 20. Eleven subjects completed the study. There were corresponding increases in both Cmax and AUC(0-12) i.e. the geometric least squares mean ratios, voclosporin + ketoconazole-to-voclosporin alone, were 645% and 1,855%, respectively, demonstrating a significant drug-drug interaction due to the inhibition of CYP3A4/5 and/or Pgp.

Study LX211-07 was conducted to determine the effect of verapamil on the pharmacokinetics of voclosporin when both drugs were at steady state. Twenty-four (24) healthy male and female volunteers received voclosporin 0.4 mg/kg Q12H on Days 1 through 10 and voclosporin 0.4 mg/kg Q12H + verapamil 80 mg every eight hours (Q8H) on Days 11 through 20. Twenty subjects completed the study. Based on the increases in pre-dose concentrations, Cmax, and AUC(0-12), concomitant administration of voclosporin with verapamil, a Pgp inhibitor, resulted in an approximate 3-fold increase in voclosporin exposure, confirming that voclosporin is a substrate for Pgp.

Study LX211-08 was conducted to determine the effect of voclosporin on the pharmacokinetics of digoxin when both drugs were at steady state. Twenty-four (24) healthy male and female volunteers received digoxin 0.5 mg on Day 1 followed by multiple oral doses of digoxin 0.25 mg QD for 17 consecutive days (Day 2 to Day 18). Subjects were also administered voclosporin 0.4 mg/kg Q12H for consecutive days (Day 8 to Day 18). There was an increase in the mean plasma concentrations of digoxin when it was concomitantly administered with voclosporin (both Cmax and AUC(0-24)). Inhibition of Pgp reduced the excretion of digoxin into the gastrointestinal tract as well as excretion by the kidney. The renal clearance of digoxin when administered alone, 148 ± 34.7 mL/min, was reduced to 128 ± 34.7 mL/min when co-administered with voclosporin. Although the digoxin AUC(0-24) was increased due to Pgp inhibition, renal clearance (CLr) was decreased to about the same extent, resulting in comparable 24-hour urinary excretion of digoxin [Ue(0-24)] — 54.7 ± 11.4% alone and 58.7 ± 14.1% when voclosporin was co-administered.

Based on the structural similarity to cyclosporine it is possible that voclosporin is substrate and/or inhibitor of other transport proteins than P-gp (e.g. OATPs). Interaction potential with respect to transport proteins would be addressed post-authorisation.

Pharmacokinetics using human biomaterials

In vitro studies using human biomaterials are described in the relevant sections above.

2.4.3. Pharmacodynamics

Mechanism of action

Voclosporin, a calcineurin (CN) inhibitor, is structurally similar to cyclosporine A (CsA) except for a modification to the amino acid one region. This alteration changes the binding of voclosporin to CN, affecting potency of this molecule when compared to CsA. CN inhibitors have been shown to reversibly inhibit immunocompetent lymphocytes, particularly T-lymphocytes. In addition, they have been shown to inhibit lymphokine production and release. CsA mediates its suppressive effects on T-lymphocytes by binding to a ubiquitous intracellular protein, cyclophilin. This complex, in turn, inhibits the calcium- and calmodulin-dependent serine-threonine phosphatase activity of the CN enzyme. CN inhibition then prevents the activation of various transcription factors necessary for the induction of cytokine genes (IL-2, IFN-γ, IL-4 and GM-CSF) during T cell activation.

Primary and Secondary pharmacology

Voclosporin shares its molecular target and putative mode of action with other calcineurin phosphatase inhibitors. Its immunosuppressive activity is being investigated in uveitis, prevention of the solid organ transplant rejection and for the treatment of plaque psoriasis.

Relationship between plasma concentration and effect

The relationship between CN inhibition (CNi), as measured by the maximum percent change in CNi (Emax), and steady-state exposure to voclosporin, as measured by Cmax on Day 13, was examined in healthy volunteers (study ISA03-12). There was a dose-related increase in Cmax over the range of doses studied. Emax for CNi also increased with increasing dose but the data suggest that at doses above 1 mg/kg BID saturation of the immunophilin binding site can occur.

Relationships between pharmacodynamics (CN inhibition) and pharmacokinetics (concurrent whole blood voclosporin concentration) were examined in two Phase 3 studies, in patients with plaque psoriasis (study ISA04-03 and study ISA05-25). Percent of CN inhibition appeared to be related to whole blood voclosporin concentration. The PK/PD relationship from study ISA04-03 was used in the selection of dosages used in the uveitis clinical trials. The 0.4 mg/kg dose was the one recommended for the pivotal trial and two additional doses (0.2 and 0.6 mg/kg) were selected to cover a broader range of CN inhibition (30%, 50% and 70%).

Pharmacodynamic interactions with other medicinal products or substances

Not assessed

2.4.4. Discussion on clinical pharmacology

The total oral absorption of voclosporin was estimated to be 83% based on the analysis of results from the Mass Balance Study (LX211-05) in accordance with the Drug Disposition Classification System, as requested by the CHMP. It was consistent with the estimated oral absorption of cyclosporine (~86%).

The bioequivalence between the two formulations used during the development programme, a soft-gelatin capsule with voclosporin in a multi-component vehicle and a non-encapsulated solution was established for the trans-isomer and the mixture of enantiomers. However, absorption from the oral solution was somewhat lower when administered with apple juice (Cmax CI [77.1-96.7]). This was not considered clinically relevant as the dosing recommendations propose intake with water. The bioavailability of voclosporine was influenced by the fat content of the food. A 15% reduction in AUC was observed when taken with a non-high-fat meal and a 25% reduction in AUC was found when taken with high-fat meal. This has been adequately addressed in the recommendations on the administration of voclosporin. Voclosporin is metabolised to a high extent. It appeared to be a competitive inhibitor of CYP3A4/5. Due to voclosporin elimination pathway, clinically relevant drug-drug interactions could be expected. For example, an unusually marked increase in exposure, more than 18-fold, has been observed when voclosporin was co-administered with a potent CYP3A and P-gp inhibitor (ketoconazole). As voclosporin is a narrow therapeutic index medicine, an increase in exposure would be of concern. The Committee felt that it might not be possible to identify and avoid all CYP3A4 inhibitors during the treatment with voclosporin.

Different expression of CYP3A4, CYP3A5 and P-glycoprotein causes patient-to-patient variability in the absorption, metabolism and tissue distribution of calcineurin inhibitors which may lead to differing drug concentrations within the systemic circulation and at target sites, influencing drug efficacy, an individual's susceptibility to drug interactions, or drug toxicity. No data on genetic polymorphism on CYP3A4/5 (mainly CYP 3A4) was reported in the dossier. The need for further studies to address the co-administration of voclosporin with mild/moderate/potent CYP3A4/5 inhibitors was discussed. The Committee acknowledged that such a study would not influence daily management of patients if therapeutic drug monitoring (TDM) was performed for these patients.

Voclosporin was highly bound to plasma proteins in humans (96.97 ± 0.29%) and partitioned extensively to RBC. Therefore, the whole blood was considered to be the most appropriate biological matrix, compared to plasma, for quantifying voclosporin, and for the purpose of the Therapeutic Drug Monitoring (TDM).

In vivo data suggested that unchanged voclosporin was the major circulating component (37%) compared to its main metabolites. In the response to the CHMP question about the relative contribution of metabolites to the total immunosuppressive effect it has been clarified that IM9 contributes most to the total immunosuppressive effect of voclosporin, but its contribution is estimated to be less than 6%. The immunosuppressive contribution of the other metabolites was considered to be negligible. As a consequence, CHMP concluded that there would be no need to measure metabolites in addition to parent drug in TDM in daily clinical practice.

The basic pharmacokinetics of voclosporin after oral administration in healthy volunteers was examined after single doses and multiple doses. The population PK analysis included data from two Phase 3 studies in plaque psoriasis patients, however neither patients with uveitis nor those undergoing renal transplantation were included in the model. The Committee would have preferred if PK characteristics had been assessed in the intended population, i.e. in patients with non-infectious uveitis. The applicant was requested to clarify whether voclosporin PK was not significantly different in patients with uveitis. After assessing the applicant's responses the Committee acknowledged that the disease was unlikely to impact PK unless concomitant therapy or co-morbidity was present.

Elimination was well characterised in the final popPK model. As the final model included the height as a factor influencing the elimination, the applicant was requested to present estimates of weight as size measure to better judge the adequacy of the weight-based dosing (especially at the low- and high-end of body weights observed in the studied population), and to discuss the extent to which the between-subject variability was expected to be reduced by body weight-based dosing. In addition, data in obese subjects and a discussion regarding the appropriateness of the dose in these subjects were also requested. In response, further information on the weight-based model and its adequacy in predicting drug exposure was presented. The applicant acknowledged that the data did not provide evidence that dosing by body weight would reduce inter-subject variability with respect to either efficacy or safety. Dosing recommendations for obese patients have also been discussed. As dosing based on a mg/kg basis may lead to overexposure in such patients a maximum dose of 40 mg/kg was also recommended. From a safety perspective the proposed cut-off was acknowledged. However, from an efficacy perspective, large, but non-obese patients may be under-dosed. In their responses the applicant stated that the proposed limit of 40 mg BID should not be adjusted at this time even in patients who weighted more than 110 kg, as there was no additional benefit to treating patients with a higher dose. Further, there might be an increased risk for decreased renal function that would dictate a more conservative dose in these patients and which did not support dosing them on a mg/kg basis. This information would be reflected in the dosing recommendations. The Committee agreed with the applicant that "supportive" data on efficacy and safety in heavier patients could be obtained in a Post Authorisation Safety Study (PASS).

With regards to special populations, data indicated that there was no significant effect of mild to moderate renal impairment on voclosporin exposure after single or multiple dosing but that severe renal impairment may result in an approximately 1.5-fold increase in overall exposure. In response to the question whether dose recommendations in patients with renal impairment were adequate taking also into account possible renal toxicity in patients with normal renal function, it has been pointed out that dose reduction was not performed in clinical studies in patients with non-infectious uveitis but in patients with plaque psoriasis where a reduction of 25% was recommended if a patient experienced a confirmed ≥ 30% rise in serum creatinine from baseline. Patients with estimated GFR below 60 ml/min were excluded from the trials in non-infectious uveitis. This resulted in proposed recommendations that voclosporin should be used with caution in patients with severe renal failure. The CHMP felt that the dosing recommendations in renally-impaired population have not been reflected appropriately in the product information and that intensive monitoring of renal function (required at least at the beginning of therapy) would impose a high burden for patients and clinicians. This issue was also discussed at the oral explanation and remained open.

Similarly, increases in exposure were observed in patients with hepatic impairment. In Child-Pugh A subjects there was a 1.5-fold increase in the geometric mean Cmax and a 1.7-fold increase in the geometric mean AUC(0-48) compared to Normal subjects. For Child-Pugh B subjects, the increases in the geometric mean Cmax and AUC(0-48) were 1.5- and 1.8-fold, respectively. Dosing recommendations and detailed instructions for monitoring were included in the product information and endorsed by the CHMP provided further readjustment in the wording was done. Use of voclosporin is not recommended for patients with severe hepatic impairment.

An evaluation of the potential pharmacodynamic interactions of voclosporin and commonly co-administered medicinal products (e.g. systemic corticosteroids) in patients with uveitis has not been performed. The lack of the data would be reflected in the product information.

The exposure-safety relations have not been explored and the upper limit for acceptable exposure has not been identified. As voclosporin trough levels are considered a poor predictor of renal adverse

effects, routine monitoring of renal function was considered sufficient to address the risk of renal toxicity.

2.4.5. Conclusions on clinical pharmacology

The applicant has addressed the remaining issues pertaining to clinical pharmacology either trough product information modifications or commitments although it was felt that the intensive monitoring recommended in the product information may impose a high burden for patients and physicians. Still pending was the exact strategy to generate data on interactions with mild to moderate CYP3A4/5 inhibitors post-authorisation.

2.5. Clinical efficacy

2.5.1. Dose response studies

As mentioned earlier, the selection of voclosporine doses for pivotal studies was based on plaque psoriasis studies mainly study ISA04-03. The results showed that the dose of 0.4 mg/kg BID was likely to be both efficacious and well-tolerated, and that that doses of voclosporin 0.2 mg/kg BID and 0.6 mg/kg BID would provide a range including a clinically relevant dose (0.4 mg/kg BID), a low therapeutic dose (0.2 mg/kg BID), and a dose with potentially enhanced efficacy (0.6 mg/kg BID).

2.5.2. Main studies

LX211-01 A Double-Masked, Placebo-Controlled, Parallel-Group, Multi-Center, Dose-Ranging Study to Assess the Efficacy and Safety of LX211 as Therapy in Subjects with Active Sight Threatening, Non-Infectious Intermediate-, Anterior and Intermediate-, Posterior-, or Pan-Uveitis

LX211-02 A Double-Masked, Placebo-Controlled, Multi-Center, Parallel-Group, Dose-Ranging Study to Assess the Efficacy and Safety of LX211 as Therapy in Subjects with Clinically Quiescent Sight Threatening, Non-Infectious, Intermediate-, Anterior and Intermediate-, Posterior-, or Pan-Uveitis

Methods

Both studies were classical randomised, double-masked, placebo-controlled, multi-centre, parallel-group, dose-ranging trials with the blinded phase of 24 weeks in the study LX211-01 and 26 weeks in the study LX211-02. Blinded phases were followed by the optional 24-week extension.

The SUN Working Group scale was used to measure vitreous haze grade (Jabs et al. 2005).

0	0.5+	1+	2+	3+	4+
Clear	Trace	Few opacities, mild blurring of optic nerve and retinal vessels	Significant blurring of optic nerve and retinal vessels but still visible	Optic nerve visible, borders blurred, no retinal vessels seen	Dense opacity obscuring optic nerve head

The primary efficacy endpoint in the study LX211-02 was defined and analysed according to the data available in the public domain for pivotal trials for fluocinolone acetonide intravitreal implant (Retisert), i.e. subjects who discontinued prior to reaching a study endpoint for reasons not related to ocular inflammation (e.g., renal adverse event, withdrawal of consent) were classified as having experienced an inflammatory exacerbation.

Study Participants

Study LX211-01 was conducted at 43 investigational sites: 21 sites in North America, 12 sites in Europe, and 10 sites in India.

Subjects must have had uncontrolled uveitis, as evidenced by Grade 2+ or higher vitreous haze, in at least one eye for at least 2 weeks prior to randomisation. Uveitis therapy prior to study entry must have conformed to one of the following: prednisone monotherapy at a dose of ≥ 10 mg/day (or equivalent) for ≥ 2 weeks prior to randomisation; ≥ 2 injections of corticosteroid (intravitreal or periocular) within the past 8 months, but not within 2 weeks of randomisation; subjects for whom corticosteroid therapy (systemic or local) was medically inappropriate or who refused corticosteroid therapy. Subjects could also have been receiving systemic corticosteroid therapy; monotherapy with azathioprine, mycophenolate mofetil, mycophenolic acid or methotrexate for at least 2 weeks prior to randomisation; prednisone plus one immunomodulatory agent including ciclosporin, tacrolimus, azathioprine, mycophenolate mofetil, mycophenolic acid and methotrexate for at least 2 weeks prior to randomisation. Main exclusion criteria were: uveitis of infectious aetiology; any implantable corticosteroid-eluting device; treatment with an immune suppression regimen that included an alkylating agent within the previous 90 days; subjects who received treatment with a monoclonal antibody or any other biologic therapy within the previous 30 days or alemtuzumab within the previous 12 months.

Study LX211-02 was conducted at 46 investigational sites: 20 sites in North America, 17 sites in Europe, and 9 sites in India.

Subjects were required to have been diagnosed with non-infectious intermediate-, anterior and intermediate-, posterior- or pan-uveitis at least 3 months prior to enrolment, had been treated during that period to control intraocular inflammatory disease but who were clinically quiescent in both eyes at enrolment. Minimum prescribed therapy upon enrolment was one or more of the following: systemic prednisone or equivalent averaging ≥ 10 mg/day; at least 2 periocular/intravitreal corticosteroid administrations within the previous 8 months (but not within 6 weeks of randomisation); at least one, but not more than 2, immunomodulatory drugs including ciclosporin, tacrolimus, azathioprine, mycophenolate mofetil, mycophenolic acid, methotrexate. Subjects must also have had best corrected visual acuity (BCVA) in the worst involved eye of 20/400 or better (Early Treatment Diabetic Retinopathy Study [ETDRS] logMAR < 1.34). Subjects were not excluded from study entry if they were receiving treatment with topical corticosteroids for control of anterior inflammation.

Treatments

Subjects were randomly assigned to receive voclosporin 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg, or placebo, per os (PO), twice a day (BID).

In study LX211-01 subjects using oral corticosteroids at baseline were to be tapered to ≤ 5 mg/day of prednisone or equivalent by week 16. Subjects using topical corticosteroids were to be tapered to zero

by week 12. Treatment with topical anti-inflammatory therapy was allowed during the study, at the discretion of the investigator, for subjects who did not qualify for rescue on the basis of change in the vitreous haze (VH) grade but who developed active anterior chamber inflammation. Subjects who experienced either a deterioration of at least 1 grade in VH at week 4 or showed no improvement from baseline at week 8 were to receive rescue therapy. Subjects could also be rescued at any time if the investigator considered this to be necessary for the subject's welfare.

Study LX211-02 enrolled subjects whose ocular inflammation was considered to be controlled on a therapeutic regimen including an immunomodulatory agent (IMT) and/or oral corticosteroids. Treatment with IMT was withdrawn prior to the randomisation and was replaced by the study drug. Subjects on topical/oral corticosteroids were weaned off to <5 mg/day of prednisone or equivalent by week 16. Subjects who experienced a study endpoint; i.e., inflammatory exacerbation, received rescue therapy, and the study drug was stopped. However, they could receive rescue medication for another indication of inflammatory exacerbation that did not meet the protocol criteria (e.g., macular oedema).

Objectives

Study LX211-01 assessed the safety and efficacy of LX211 as compared to placebo in subjects with active non-infectious intermediate-, anterior and intermediate-, posterior- or pan-uveitis requiring systemic immunosuppression.

Study LX211-02 evaluated the safety and efficacy of LX211 as compared to placebo as treatment and maintenance therapy in subjects with currently clinically quiescent non-infectious intermediate-, anterior and intermediate-, posterior- or pan-uveitis requiring systemic immune suppression.

Outcomes/endpoints

Primary and secondary endpoints assessed in pivotal studies are presented below.

Study LX211-01	**Study LX211-02**
Primary efficacy endpoints	
The co-primary efficacy endpoints were: • mean change from baseline in graded vitreous haze for the designated study eye after 16 weeks of therapy or at time of rescue, if earlier • mean change from baseline in graded vitreous haze for the designated study eye after 24 weeks of therapy or at time of rescue, if earlier	The primary efficacy endpoint was the proportion of subjects who experienced inflammatory exacerbation at any time during the 26 weeks of treatment as defined by a clinically significant deterioration in either eye of one or more of the following: • Vitreous haze: an increase of ≥ 2 grades from baseline • Anterior chamber cells: an increase of ≥ 2 grades from baseline • Visual acuity: a change from baseline of ≥ +0.3 logMAR in best corrected visual acuity (BCVA)
Secondary efficacy endpoints	
• mean change from baseline in BCVA score in the designated study eye after 24 weeks of therapy or at time of rescue, if earlier • change from baseline in macular thickness (assessed by OCT) at Week 24 or at time of rescue, if earlier	• mean change from baseline in oral corticosteroid use at Week 26 or at end of treatment (in subjects who were treated with oral corticosteroids at baseline) • mean change from baseline in BCVA score in the designated study eye at Week 26 or at

	time of rescue, if earlier
Additional efficacy variables	
• change from baseline in oral and topical corticosteroid usage in subjects using corticosteroids at baseline` • change from baseline in area of macular hyperfluorescence (assessed by fluorescein angiography) for the study eye and the fellow eye at Weeks 16 and 24 • change from baseline in Quality of Life instrument scores[a] • change from baseline in anterior chamber cell score in the designated study eye at Week 16 and Week 24 or at time of rescue, if earlier	• change from baseline in Quality of Life instrument scores[a]

a: Quality of Life scales were: NEI VFQ-25, EQ-5D, EQ-VAS, and SF-36
OCT = optical coherence tomography, NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire (25 questions), EQ-5D = Euro Quality of Life-5 domains, EQ-VAS = Euro Quality of Life –visual analog scale, SF-36 = 36-Item Short Form Health Survey
Note: Information in this table is from the statistical analysis plans for Study LX211-01 and Study LX211-02.

Sample size

The provisional sample size was intended to provide 90% power for the detection of a true mean difference of 1 in graded vitreous haze (LX211-01) or a difference in inflammatory recurrence rates (LX211-02) between the placebo and active treatment (α=0.05, 2-tailed, corrected for multiple treatment comparisons). Assuming a standard deviation of σ=1.25, true recurrence rate for placebo subjects of 60% and that the relative risk of recurrence in an LX211 group of 1/3, a total sample size of 210 (LX211-01) and 220 (LX211-02) was indicated. The final determination of sample size was to have been guided by the interim analysis.

Randomisation

In both studies subjects were randomised in a 2:2:2:1 ratio to voclosporin 0.2, 0.4 or 0.6 mg/kg or placebo. Blocking occurred at the centre level. Randomisation was administered through an Interactive Web Response System (IWRS), accessed by the investigator or authorised designee as each eligible subject was identified.

Blinding (masking)

Both studies were double-blind. To maintain full masking, drug product was packaged in blister cards that combined the appropriate number of active and placebo capsules to provide 7 dose configurations: 0, 10, 20, 30, 40, 50 and 60 mg. Masking of the study drug assignments was preserved throughout the course of the core treatment period. The Sponsor, Investigators, all subjects, Contract Research Organizations (CROs) and all other relevant service providers remained masked to the treatment assignments until all subjects completed participation in the core treatment period, the database for Visits 1 through 8 was locked, and the statistical analysis for the core treatment period was completed.

Statistical methods

All statistical tests were conducted against a two-sided alternative hypothesis at the 0.05 level of significance. Intent-to-Treat (ITT) Population covered subjects who were randomised to a treatment group and provided any post-baseline data. Per Protocol (PP) Population excluded subjects who violated inclusion/exclusion criteria or who deviated from the protocol in a manner that had an effect on the assessment of efficacy. All Subjects Treated Population covered subjects who received at least one dose of study medication in the extension treatment period. Subjects who discontinued for any reason were considered to be treatment failures with respect to the primary efficacy endpoint. For secondary efficacy endpoints that were not analysed using time-to-event methodology, last observation-carried-forward (LOCF) was to be used for imputation of missing values for efficacy variables. The Data Monitoring Committee (DMC) was responsible for the conduct of the sample size re-estimation. The multiplicity of primary and secondary endpoints across treatment groups was controlled by a closed testing procedure. Based on the recommendation of the DMC regarding the high incidence of decreased renal function in the 0.6 mg/kg group, the applicant decided not to seek marketing approval for that dose. Accordingly, the statistical adjustment for multiple comparisons was modified to eliminate consideration of the 0.6 mg/kg arm for multiple comparisons. However, p-values for the 0.6 mg/kg dose are provided for descriptive purposes and completeness. The amendment of the SAP only affected the primary endpoint (see below for further discussion).

Results

Participant flow

Study	Dose	No pts randomised	No pts treated with study medication	No pts completed core treatment period	No pts completed extension treatment period
LX211-01	Total 0.2 mg/kg 0.4 mg/kg 0.6 mg/kg placebo	218 65 64 61 28	217* 64 64 61 28	92(42.2%) 28 28 22 14	32 13 10 5 4
LX211-02	Total 0.2 mg/kg 0.4 mg/kg 0.6 mg/kg placebo	232 69 66 66 31	230** 68 66 65 31	108 31 36 27 14	38 15 14 8 1

*One patient from dose group 0.2 mg/kg withdrew consent after randomisation

**Two of the 232 subjects who were randomised did not receive study medication.

In study LX211-01 126 subjects (58%) discontinued prior to the end of the core treatment period of whom 87 (26% of randomised subjects) were rescued. An additional 56 subjects discontinued due to adverse events; however, this number includes 31 subjects for whom, by convention, symptoms of ocular inflammation requiring rescue medication at the discontinuation visit were recorded as AEs.

In study 211-02 124 subjects (53%) discontinued prematurely from the core treatment period of whom 57 (24.6% of randomized subjects) were rescued. A total of 67 subjects discontinued due to AEs; however, this number includes 44 subjects who were marked as discontinuing due to an AE plus

23 subjects for whom, by convention, symptoms of ocular inflammation requiring rescue medication at the discontinuation visit were recorded as AEs.

Recruitment

Study LX2111-01: First subject was enrolled in the core treatment period on 15 February 2007 (First subject in); last subject completed the extension treatment period on 13 May 2009 (Last subject, last visit 10).

Study LX211-02: First subject was enrolled in the core treatment period on 02 May 2007 (First subject in); last subject completed the extension treatment period on 18 May 2009 (Last subject, last visit 10).

Conduct of the study

As mentioned earlier, due to increased renal toxicity in the higher dose group 0.6 mg/kg BID, DMC recommended the discontinuation of all subjects in this group in all uveitis clinical trials. This recommendation was later on revised and the DMC allowed subjects from the 0.6 mg/kg group in all 3 protocols to remain in the extension treatment period if they were not noted as having decreased renal function, and if they had fewer than 12 weeks of participation left. As mentioned earlier the increased renal toxicity observed with the 0.6 mg/kg group affected the conduct of the study. As a consequence, the SAP was modified and this dose was excluded from the comparisons. At the same time, the definition of "response rate" was amended to allow the inclusion of other parameters, e.g. change in VH grade of <0.5+ and <1+. This was clarified by the applicant. Therefore, it was acknowledged that the alternative definitions of the response rate were used only in the *post-hoc* analysis and did not make part of the agreed SAP.

The two pivotal trials LX211-01 and LX211-02 were subject of GCP inspections conducted in the context of this marketing authorisation procedure. Critical and major findings were observed during the inspections of two investigator sites and the CRO site, related in particular to the quantification and recording of the renal function (Glomerular Filtration Rate, GFR). For further information see discussion.

Baseline data

The mean age was 43 years, mean weight 71 kg, mean height 164 cm, BMI 26. Females were slightly more prevalent than males (61 and 64% respectively). A significant proportion, 44%, of the subjects enrolled were of the South Asian origin (Indian) therefore the CHMP has requested the applicant to discuss the impact of demographic differences on efficacy and safety of voclosporin. In their responses the applicant acknowledged that the efficacy results were less positive in the South Asian population than in the European and North American populations. A higher incidence of renal and hypertension events were observed in the Indian population.

Numbers analysed

Definitions of an ITT, Safety and PP populations can be found in section Statistical methods.

LX211-01	Placebo (N=28) n (%)	LX211 0.2 mg/kg (N=65a) n (%)	LX211 0.4 mg/kg (N=64) n (%)	LX211 0.6 mg/kg (N=61) n (%)	Total (N=218) n (%)

Intent-to-Treat (ITT) Population	28 (100.0%)	64 (98.5%)	64 (100.0%)	61 (100.0%)	217 (99.5%)
Safety Population	28 (100.0%)	64 (98.5%)	64 (100.0%)	61 (100.0%)	217 (99.5%)
Per-Protocol (PP) Population	25 (89.3%)	56 (86.2%)	59 (92.2%)	53 (86.9%)	193 (88.5%)

LX211-02	Placebo (N=31) n (%)	LX211 0.2 mg/kg (N=69) n (%)	LX211 0.4 mg/kg (N=66) n (%)	LX211 0.6 mg/kg (N=66) n (%)	Total (N=232) n (%)
Intent-to-Treat (ITT) Population	31 (100.0%)	69 (100.0%)	66 (100.0%)	66 (100.0%)	232 (100.0%)
Safety Population	31 (100.0%)	68 (98.6%)	66 (100.0%)	65 (98.5%)	230 (99.1%)
Per-Protocol (PP) Population	28 (90.3%)	59 (85.5%)	51 (77.3%)	56 (84.8%)	194 (83.6%)

Outcomes and estimation

Study LX211-01

Mean Change from Baseline in Vitreous Haze by Visit in ITT Population (co-primary endpoint) is presented below.

Mean ± Std Error	**Placebo (N=28)**	**LX211 0.2mg/kg (N=64)**	**LX211 0.4 mg/kg (N=64)**	**LX211 0.6 mg/kg (N=61)**
Baseline p-value vs. placebo 95% CI	2.06 ± 0.09 ---	2.05 ± 0.06 0.912 [-0.22;0.20]	2.21 ± 0.06 0.166 [-0.06;0.36]	2.09 ± 0.06 0.799 [-0.19;0.24]
Week 16 **p-value vs. placebo** **95% CI**	-0.53 ± 0.20 **---**	-0.93 ± 0.13 0.090 [-0.86;0.06]	**-1.15 ± 0.13** **0.008**** **[-1.08;-0.16]**	**-1.07 ± 0.13** **0.023*** **[-1.00;-0.07]**
Week 20 p-value vs. placebo 95% CI	-0.52 ± 0.19 ---	-0.85 ± 0.13 0.147 ---	-1.14 ± 0.13 0.007** ---	-1.03 ± 0.13 0.028* ---
Week 24 **p-value vs. placebo** **95% CI**	-0.55 ± 0.20 ---	-0.82 ± 0.13 0.256 [-0.73;0.20]	**-1.08 ± 0.13** **0.027*** **[-0.99;-0.06]**	**-1.06 ± 0.14** **0.034*** **[-0.97;-0.04]**

Note: p-values from 2-way ANOVA using treatment and region as fixed effects, 2-tailed, unadjusted for multiplicity, LOCF imputation (* $p < 0.05$, ** $p < 0.01$)

Results showed that voclosporin 0.4 mg/kg BID reduced intermediate or posterior segment ocular inflammation in patients with active inflammation as measured by the co-primary endpoint, VH grade. However, the effect on vitreous haze, although statistically significant, was modest. The study was powered to detect a true mean difference of 1 unit between active treatment and placebo. The estimated mean differences between 0.4 mg/kg and placebo were 0.62 units at Week 16 and 0.52 units at Week 24. The LX211 0.6 mg/kg dose demonstrated a similar level of efficacy.

The clinical relevance of the statistical significance of the co-primary endpoint was considered questionable, as only 92 (42.2%) subjects completed the core treatment period. In total, 126 subjects (58%) discontinued prior to the end of the core treatment period of whom 87 (26% of randomized subjects) were rescued. The percentage of subjects requiring oral corticosteroids was higher in all

voclosporin groups (0.2 mg/kg – 80%; 0.4 mg/kg – 60%; 0.6 mg/kg – 82%) as compared to placebo (57%). This was considered as a severe deficiency of the study. Additional 56 subjects discontinued due to adverse events.

There were no statistically significant changes in any of the active treatment groups compared with placebo in secondary efficacy endpoints, best corrected visual acuity (BCVA) and macular thickness in the core treatment period. However for BCVA, subjects had generally good vision at baseline and therefore an improvement was unlikely to have been observed. Fewer than 60% of all subjects had valid OCT readings at baseline (macular thickening was not an eligibility criterion in the LX211 protocols) and of these, only 60% of the subjects (75/126) presented with macular thickness in excess of >250 µm at baseline, thus, limiting the potential to discern for demonstration of improvement of this parameter.

For the additional efficacy variables, no statistically significant differences were found in any of the QoL instruments nor were statistically significant decreases or increases in macular leakage found between any voclosporin treatment groups as compared with placebo.

In the 24-week extension treatment period, all voclosporin treatment groups as well as the placebo group experienced further decreases from baseline in graded VH scores at Week 36 and Week 48. Decreases from baseline in graded anterior chamber cells occurred in most of the voclosporin treatment groups as well as the placebo group at Week 36 and Week 48. BCVA improved in all groups at Week 36 and Week 48.

Study LX211-02

Proportion of Subjects Experiencing an Inflammatory Exacerbation (or early discontinuation) is presented below.

	Placebo (N=31) n (%)	**LX211 0.2 mg/kg (N=69)** n (%)	**LX211 0.4 mg/kg (N=66)** n (%)	**LX211 0.6 mg/kg (N=66)** n (%)
Inflammatory Exacerbation (or early discontinuation)	16 (51.6%)	37 (53.6%)	31 (47.0%)	34 (51.5%)
95% Confidence Interval		[0.464;2.532]	[0.353;1.951]	[0.424;2.340]
p-value vs. Placebo&		0.853	0.671	0.993
Nature of event				
≥2 Grade Increase in Vitreous Haze	1 (3.2%)	4 (5.8%)	2 (3.0%)	1 (1.5%)
≥2 Grade Increase in Anterior Chamber Cells	6 (19.4%)	10 (14.5%)	6 (9.1%)	5 (7.6%)
≥0.3 Increase in logMAR	2 (6.5%)	9 (13.0%)	2 (3.0%)	2 (3.0%)
Investigator Initiated Rescue Treatment#	5 (16.1%)	8 (11.6%)	5 (7.6%)	6 (9.1%)
Discontinuation: Confirmed 30% Decrease in eGFR	0	2 (2.9%)	3 (4.5%)	4 (6.1%)
Discontinuation due to Adverse Event	2 (6.5%)	5 (7.2%)	9 (13.6%)	13 (19.7%)
Discontinuation due to Other Reason	2 (6.5%)	4 (5.8%)	6 (9.1%)	5 (7.6%)

&Subjects may be counted in more than one exacerbation criterion category
#Subject did not meet rescue criteria, but investigator initiated rescue medication
Note: Percentages are based on the number of subjects in each treatment group.

A higher than expected dose-dependent discontinuation rate due to adverse events occurred in the study, resulting in non significance for the primary endpoint (patients who experienced inflammatory exacerbation at any time during the week 26) and in all secondary endpoints including oral corticosteroid use and BCVA in the core treatment period. However, BCVA was improved in the LX211 0.2 mg/kg and 0.4 mg/kg groups compared with baseline at Week 38 and Week 50. No statistically significant differences were found in any of the additional endpoints, i.e. QoL-related aspects (NEI VFQ-25, EQ-5D, EQ-VAS, and SF-36) between voclosporin and placebo. Therefore, it was concluded that the effect of voclosporin on quiescent uveitis was not demonstrated.

Ancillary analyses

Sensitivity analysis (pre-specified in the SAP) of study LX211-02 data using the Kaplan-Meier method was conducted in which the data from subjects who discontinued or who were lost to follow-up prior to experiencing a study endpoint were censored at that date. The paired comparison for voclosporin 0.4 mg/kg BID vs. placebo was marginally statistically significant (p=0.044). To further address the issue of non-informativeness of censoring in the Kaplan-Meier analysis, the applicant attempted to determine if and when any of discontinued/lost-to-follow-up subjects experienced an inflammatory exacerbation within the 25 week time period. As subject examinations were no longer being conducted under the dictates of the protocol, the investigator's judgment was accepted for purposes of this analysis. Additional data were retrieved for 35 of the 47 remaining subjects (3, 6, 13, 13 in the placebo and 0.2, 0.4, 0.6 mg/kg arms, respectively). The inclusion of these data in the Kaplan-Meier analysis had minimal impact on the estimates for the placebo, 0.2 mg/kg and 0.4 mg/kg arms.

In addition, a *post hoc* Cochran-Mantel-Haenszel (CMH) analysis was conducted in which inflammatory exacerbation was not imputed for subjects who discontinued from the study prior to achieving an endpoint. This analysis resulted in a marginally significant difference between voclosporin 0.4 mg/kg and placebo control (p=0.047).

Nonetheless, the study LX211-02 was considered as a failed study as the proposed analyses showed a borderline significant result which could not be maintained after adjustment for the multiple analyses. Moreover, uninformative censoring was assumed making it impossible to determine from the available data whether the censored subjects in a given treatment arm would have been more likely to experience an exacerbation had they remained in the study than those who were not censored.

In addition, a subgroup analysis of study LX211-01 data by gender, race and different forms of non-infectious uveitis was requested by the CHMP in particular in the light of the fact that patients of Indian origin represented more than 30% of the study population. It was concluded that the available data are insufficient to determine whether uveitis of different etiology prevalent in India as compared to Europe may have influenced efficacy results in the study.

Summary of main studies

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

Summary of Efficacy for trial *LX211-01*

Title: A DOUBLE-MASKED, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTI-CENTER, DOSE-RANGING STUDY WITH AN OPTIONAL EXTENSION TO ASSESS THE EFFICACY AND SAFETY OF LX211 AS THERAPY IN SUBJECTS WITH ACTIVE SIGHT-THREATENING, NON-INFECTIOUS INTERMEDIATE-, ANTERIOR AND INTERMEDIATE-, POSTERIOR- OR PAN-UVEITIS			
Study identifier	Study LX211-01 EudraCT no: 2006-006543-31		
Design	This was a Phase 2/3, multi-center, prospective, double-masked, placebo-controlled, randomized, parallel-group study of LX211 for treatment of non-infectious intermediate-, anterior and intermediate-, posterior- or pan-uveitis in subjects with active inflammation. Following screening, subjects were randomized in a 2:2:2:1 ratio among the LX211 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg and placebo groups at the center level. Subjects were to take study drug orally, twice a day (BID). Assessments of subjects for efficacy and safety took place at regular intervals over a 24-week period. Subjects who completed the 24-week core treatment period had the option to continue their assigned treatment for an additional 24 weeks (i.e., extension treatment period). The total duration of subject participation was up to 48 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1 year, 9 months Not applicable 1 year, 7 months
Hypothesis	Superiority versus placebo comparator		
Treatments groups	Placebo (PLA) p.o. BID		N=28; 24 week core treatment period
	LX211 0.2 mg/kg (0.2) p.o. BID		N=65; 24 week core treatment period
	LX211 0.4 mg/kg (0.4) p.o. BID		N=64; 24 week core treatment period
	LX211 0.6 mg/kg (0.6) p.o. BID		N=61; 24 week core treatment period
Endpoints and definitions	Co-primary endpoint	Vitreous Haze (VH)	• Change from baseline in graded VH for the designated study eye at Week 16/End of Treatment (EOT) • Change from baseline in graded VH for the designated study eye at Week 24/EOT
	Secondary endpoint	Best Corrected Visual Acuity (BCVA)	Change from baseline in BCVA at Week 24/End of Treatment (EOT)
	Secondary endpoint	Optical Coherence Tomography (OCT)	Change from baseline in macular thickness assessed by OCT at Week 24/EOT
Database lock	15 June 2009		
Results and Analysis LX211 0.4 mg/kg BID demonstrated statistically significant superiority ($p<0.05$, 2-tailed) to placebo at both Weeks 16 and 24, thus meeting the protocol-specified primary efficacy criterion. Statistically significant superiority was also achieved for the LX211 0.6 mg/kg group at both timepoints, while the LX211 0.2 mg/kg group did not differ significantly from placebo at either time point.			

The secondary endpoints, change from baseline in BVCA and change from baseline in macular thickness, showed minimal change from baseline in all treatment groups.				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The co-primary endpoints were mean change from baseline at Week 16/EOT and at Week 24/EOT for the ITT population. For a dose group to be declared successful, statistical significance ($p < 0.05$, 2-tailed) was required at both time points.			
Time-point Parameter	**Placebo (N=28)**	**LX211 0.2 mg/kg (N=64)**	**LX211 0.4 mg/kg (N=64)**	**LX211 0.6 mg/kg (N=61)**
Baseline LS Mean	2.1	2.1	2.2	2.1
SE	0.09	0.06	0.06	0.06
Change from Baseline at Week 16/End of Treatment				
LS mean	-0.5	-0.9	-1.2	-1.1
SE	0.20	0.13	0.13	0.13
LS Mean Difference to Placebo		-0.40	-0.62	-0.54
95% Confidence Interval		-0.86, 0.06	-1.08, -0.16	-1.00, -0.07
p-value[a]		0.090	0.008	0.023
Change from Baseline at Week 24/End of Treatment				
LS mean	-0.6	-0.8	-1.1	-1.1
SE	0.20	0.13	0.13	0.14
LS Mean Difference to Placebo		-0.27	-0.52	-0.51
95% Confidence Interval		-0.73, 0.20	-0.99, -0.06	-0.97, -0.04
p-value[a]		0.256	0.027	0.034
[a]: p-value from pairwise comparisons between each of the LX211 groups and the placebo group				
Notes	The initiation of rescue therapy was permitted by protocol if the investigator judged that a risk of inflammatory damage to a subject's eyes was present. The protocol required that the subject be discontinued from study medication prior to rescue to avoid possible safety issues related to overimmunosuppression. This requirement led to a substantial loss of subjects prior to study end. The time to rescue therapy was longer in patients receiving LX211 0.4 mg/kg compared to those randomized to placebo – median time to rescue in patients receiving LX211 was 148 days versus 83 days in patients receiving placebo. Moreover, the degree of inflammation at time of rescue in patients receiving LX211 0.4 mg/kg was lower (mean VH grade: -0.50) compared to placebo recipients (mean VH grade: +0.36), i.e. a difference of 0.86 units of VH.			

Summary of Efficacy for trial *LX211-02*

Title: A Double-Masked, Placebo-Controlled, Multi-Center, Parallel- Group, Dose-Ranging Study with an Optional Extension to Assess the Efficacy and Safety of LX211 as Therapy in Subjects with Clinically Quiescent Sight-Threatening, Non-Infectious, Intermediate-, Anterior and Intermediate-, Posterior- or Pan-Uveitis			
Study identifier	Study LX211-02 EudraCT no.: 2006-006544-66		
Design	This was a Phase 2/3, multi-center, double-masked, placebo-controlled, randomized, parallel-group study of LX211 for control of inflammation associated with clinically quiescent non-infectious intermediate-, anterior and intermediate-, posterior-, or pan-uveitis both during and following tapered withdrawal of immunosuppressive and corticosteroid therapy in clinically stable subjects. Following screening, subjects were randomized in a 2:2:2:1 ratio among the LX211 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg and placebo groups at the center level. Subjects were to take study drug orally, twice a day (BID). Assessments of subjects for efficacy and safety took place at regular intervals over a 26-week period. Subjects who completed the 26-week core treatment period had the option to continue their assigned treatment for an additional 24 weeks (i.e., extension treatment period). The total duration of subject participation was up to 50 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 year, 7 months Not applicable 1 year, 4 months	
Hypothesis	Superiority versus placebo comparator		
Treatments groups	Placebo (PLA) p.o. BID	N=31; 26 week core treatment period	
	LX211 0.2 mg/kg (0.2) p.o. BID	N=69; 26 week core treatment period	
	LX211 0.4 mg/kg (0.4) p.o. BID	N=66; 26 week core treatment period	
	LX211 0.6 mg/kg (0.6) p.o. BID	N=66; 26 week core treatment period	
Endpoints and definitions	Primary Endpoint	The proportion of subjects who experienced inflammatory exacerbation as defined by a clinically significant deterioration in either eye in one or more of the following variables: • Vitreous Haze: an increase of ≥ 2 grades from baseline • Anterior Chamber cells: an increase of ≥ 2 grades from baseline • Visual acuity: a change of ≥ +0.3 logMAR from baseline in BCVA	
	Secondary Endpoint	Change from baseline in oral corticosteroid use at Week 26/End of Treatment (EOT) in subjects who were treated with oral corticosteroids at baseline	
	Secondary Endpoint	Change from baseline in BCVA at Week 26/time of rescue	
	Secondary Endpoint	Change from baseline in Quality of Life (QoL) at Week 26 or at time of rescue, if earlier in • NEI VFQ-25 • EQ-5D • SF-36	
	Secondary Endpoint	Time to occurrence of inflammatory exacerbation	
Database lock	19 June 2009		

Results and Analysis

As shown below, approximately 50% of the subjects in each of the 4 treatment arms experienced either adefined inflammatory event or early discontinuation from study drug during the 26 weeks of the core study period, with none of the 3 LX211 arms differing significantly from the placebo control arm in this regard.

Significant differences among treatment groups were not found with respect to changes from baseline in oral corticosteroid use, BCVA and the 3 QoL measures. Time-to occurrence of inflammatory exacerbation was significantly longer in the LX 211 0.4 mg/arm than in the placebo arm (p=0.044, 2tailed by log rank test).

Analysis description	**Primary Analysis**			
Analysis population and time point description	The primary efficacy endpoint of this study was the occurrence of inflammatory exacerbation in either eye at any time during the 26 weeks following randomization on the ITT population			
	Placebo (N=31)	**LX211 0.2 mg/kg (N=69)**	**LX211 0.4 mg/kg (N=66)**	**LX211 0.6 mg/kg (N=66)**
	n (%)	n (%)	n (%)	n (%)
Subjects Experiencing an Inflammatory Exacerbation or Early Discontinuation	16 (51.6%)	37 (53.6%)	31 (47.0%)	34 (51.5%)
CMH Statistics:				
Odds Ratio[a]		1.084	0.830	0.996
95% Confidence Interval		0.464, 2.532	0.353, 1.951	0.424, 2.340
p-value for Breslow-Day	0.664			
p-value vs. Placebo[b]		0.853	0.671	0.993
a: The odds ratio is LX211:Placebo i.e. odds ratio values < 1 indicate that LX211 is superior to Placebo b: Subjects may be counted in more than one exacerbation criterion category				
Notes	The time-to-event analysis (Kaplan-Meier) specified in the SAP addressed the possibility that subjects might discontinue from the study in a dose-related manner due to AEs unrelated to inflammatory exacerbation. Data from subjects who discontinued or were lost to follow-up prior to experiencing a study endpoint were censored at that date. Kaplan-Meier estimates for the proportion of subjects experiencing recurrence of inflammatory exacerbation within 26 weeks were 0.44 for placebo, 0.40 for LX211 0.2 mg/kg, 0.22 for LX211 0.4 mg/kg and 0.24 for LX211 0.6 mg/kg. The rate of inflammatory exacerbation for the 0.4 mg/kg group was 50% lower than that for placebo, a difference that is statistically significant (p<0.05).			

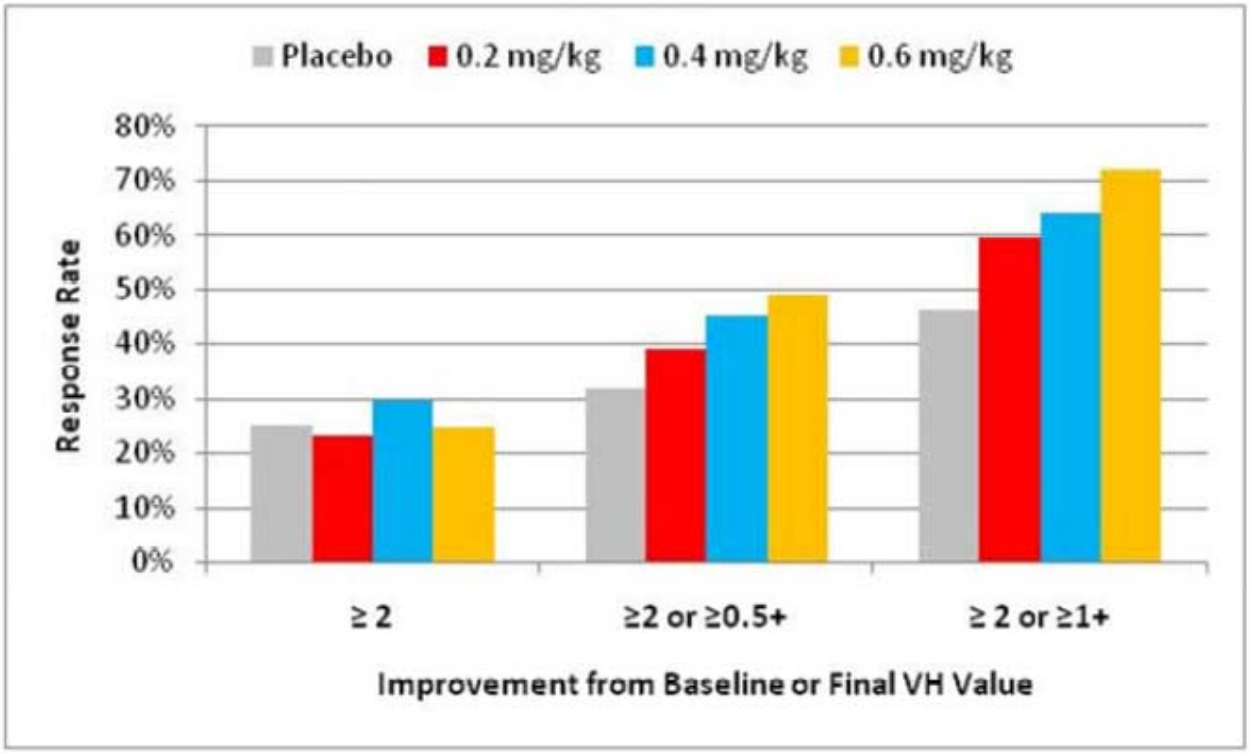
Analysis performed across trials (pooled analyses and meta-analysis)

Additionally, the applicant performed a responder analysis (first analysis) including the proportion of subjects from study LX211-01 who experienced improvement in vitreous haze grade as defined by 3 different criteria:

• ≥ 2 grade improvement: Includes subjects who experienced a 3-category improvement in vitreous haze. Of note, approximately 84% of subjects enrolled in Study LX211-01 had a baseline vitreous haze score of 2+.

• ≥ 2 or ≤ 0.5+: Includes subjects who experienced a 2-category or better improvement in vitreous haze and is consistent with criteria for clinical improvement as outlined by the Standardization of Uveitis Nomenclature (SUN) Working Group.

• ≥ 2 or ≤ 1+: Includes subjects who improved by 1 category or more.



The results of this analysis showed that:.

• Vitreous haze was reduced to ≤ 1+ in 64% of patients in the voclosporin 0.4 mg/kg group, as compared to 46% in the placebo group (third column, p=0.022 for Cochran-Armitage Test of Trend).

• Vitreous haze was reduced to ≤ 0.5+ in 45% of patients in the voclosporin 0.4 mg/kg group, as compared to 32% in the placebo group (second column, p=0.104 for Cochran-Armitage Test of Trend).

• Vitreous haze was reduced to ≤ 2+ in 30% of patients in the voclosporin 0.4 mg/kg group, as compared to 25% in the placebo group (first column, p=0.994 for Cochran-Armitage Test of Trend).

In the course of the assessment the CHMP requested a responder analyses with different cut-offs for vitreous haze values in study LX211-01 (e.g. patients achieving a vitreous haze grade ≤ 0.5+, the

proportion of subjects with a decrease in VH with ≥ 1 and/or≥ 2 grades while on ≤ 5mg prednisolone or equivalent).

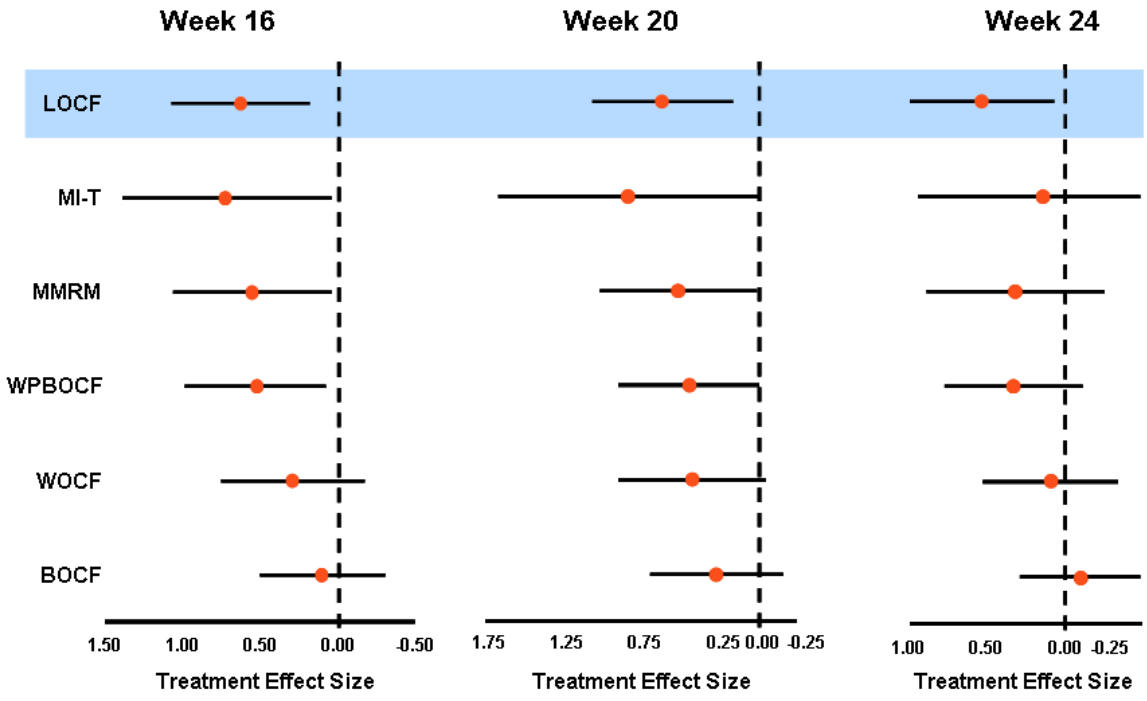
A summary of the requested, second analysis is presented below.

Responder Analyses for Vitreous Haze

Category 1	Control (n=28)	Voclosporin 0.2 mg/kg (n=64)	Voclosporin 0.4 mg/kg (n=64)	Voclosporin 0.6 mg/kg (n=61)
Score ≤ 0.5+	8 (28.6%)	22 (34.4%)	28 (43.8%)	27 (44.3%)
Improvement≥ 1	13 (46.4%)	36 (56.3%)	45 (70.3%)	41 (67.2%)
Improvement≥ 2	7 (25.0%)	14 (21.9%)	19 (29.7%)	13 (21.3%)

Additionally, the committee requested sensitivity analysis using different imputation methods in which patients withdrawing from treatment due to lack of efficacy or AEs were included as failures.

Results of these analyses are presented below.



Legend: Last Observation Carried Forward (LOCF), Multiple Imputation by Treatment (MI-T), Mixed Model for Repeated Measures (MMRM), Worst Post-baseline Observation Carried Forward (WPBOCF), Worst Observation Carried Forward (WOCF), Baseline Observation Carried Forward (BOCF)

Clinical studies in special populations

For information on studies in special populations please see Pharmacokinetic sections of this report.

Supportive study

No supportive studies have been conducted in the applied for indication. Study LX211-03 was performed to examine the efficacy of voclosporin in the treatment of anterior uveitis in subjects who required systemic immunosuppression for control of their disease, which is a different disease entity. It was a multi-centre, double-masked, placebo-controlled, randomised, parallel group study of LX211 for treatment of non-infectious anterior, anterior and intermediate or pan-uveitis in subjects with active inflammation. Forty-six centres enrolled 108 subjects, who were randomized in a 2:2:2:1 ratio among the LX211 0.2 mg/kg, 0.4 mg/kg, 0.6 mg/kg and placebo groups at the centre level. Subjects' assessments took place at regular intervals over a 24-week period for efficacy and safety. Subjects who completed the 24-week core protocol had the option to continue their assigned treatment for an additional 24 weeks, if the investigator so recommended.

The study did not meet its primary endpoint and none of the secondary endpoints. All treatment groups, including placebo experienced improvement in mean change from baseline in anterior chamber inflammation. Information from this study was used to support that safety data base.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal studies design was a randomised, double-blind placebo controlled trial; however there was no active comparator group. This was considered to be a major drawback of the design, as the absence of active control group hampered meaningful interpretation of the outcome of the studies. In their responses the applicant claimed that corticosteroids used in the 'placebo' group in Study LX211-01 represented the 'standard of care', that there was limited clinical data regarding the efficacy of cyclosporin and that there were safety concerns when cyclosporine was used in the treatment of noninfectious uveitis. Consequently, the Committee acknowledged that although a head to head comparison with ciclosporin would be of value an active comparator study would not be required.

The interpretation of the results was also difficult due to the fact that all patients including placebo group were treated with oral steroids tapered to a daily dose of 5 mg or less of prednisone. The CHMP felt that such therapeutic paradigm did not reflect the proposed first-line therapy. The applicant was requested to justify the additional treatment with steroids in both placebo and treatment groups. In their response the applicant stated that study followed the current guidelines for the treatment of noninfectious uveitis involving the intermediate and posterior segments of the eye recommending addition of an immunosuppressive agent to the systemic corticosteroid and subsequent tapering off of oral steroids. This line of argumentation was accepted by the CHMP, however the Committee requested the applicant to restrict the indication to the second line therapy in patients with in whom corticosteroids do not provide adequate control or could not be tapered below 10 mg/day of prednisolone (or equivalent).

A significant proportion, 44%, of the subjects enrolled were of the South Asian origin (Indian) therefore the CHMP requested the applicant to discuss the impact of demographic differences on efficacy and safety of voclosporin. In their responses the applicant acknowledged that the efficacy results were less positive in the South Asian population than in the European and North American populations.

The two pivotal trials LX211-01 and LX211-02 were subject of GCP inspections conducted in the context of this marketing authorisation procedure. Critical and major findings were observed during the inspections of two investigator sites and the CRO site, related in particular to the quantification and recording of the renal function (Glomerular Filtration Rate, GFR).

The applicant has performed analyses requested by the CHMP as well as another primary efficacy analysis of trial LX211-01 without data from one of the inspected investigational sites. The exclusion of the data from that site had no significant impact on the primary efficacy results. Furthermore the applicant performed a primary efficacy analysis of trial LX211-01 without data from all Indian investigational sites, which lead to a significant change in the results for the proposed label dose 0.4 mg/kg BID, and showed an influence of the overall results in favour of placebo. The CHMP concluded that although severe GCP deficiencies were observed and appropriate CAPAs were strongly recommended an additional impact on data validity was not expected, however supportive evidence of the PP analysis in favour of voclosporin was diminished.

Efficacy data and additional analyses

The CHMP has discussed in detail the following efficacy aspects of the main studies: the outcome of the primary and secondary endpoints.

Study LX211-02 was considered as unsuccessful. The planned primary analysis failed (p=0.67). Moreover, uninformative censoring was assumed making it impossible to determine the inflammatory status of the censored subjects. While the sensitivity analyses showed a borderline significant result it could not be maintained after adjustment for the multiple analyses.

Therefore, careful consideration was given to the robustness of data from study LX211-01 including the possible impact of high numbers of patients withdrawn from treatment or needing rescue medication. The clinical relevance of the observed effects including the steroid sparing effects was considered.

- Outcome of the primary and secondary endpoints, robustness of data and clinical relevance of the endpoints:

Several additional analyses were requested including responder analyses with different cut-offs for changes in vitreous haze, and sensitivity analysis using different imputation methods in which patients withdrawing from treatment due to lack of efficacy or AEs were included as failures.

In the responses to the question on the clinical relevance of findings in study LX211-01 the applicant referred to the first responder analyses performed and published data. The responder analysis showed statistically significant decrease in VH grade of more than 1 in 64% of patients in the voclosporin 0.4 mg/kg group, as compared to 46% in the placebo group. Moreover, to support further the relevance of the changes in VH the applicant quoted the randomised, double-masked study in posterior uveitis conducted by the National Eye Institute. This study compared high doses of prednisolone (64 mg/day) and ciclosporin (10-15 mg/kg/day) as monotherapy in 56 subjects. Based on the applicant's analysis of the NEI study data the mean vitreous haze value observed after three months of treatment was a reduction from baseline of approximately 0.75 units for prednisolone and approximately 0.75 for ciclosporin. Also according to the applicant, fewer than half of the subjects in either the ciclosporin or prednisolone arms showed improvements of ≥ 2 grades. Therefore the applicant considered the effects observed in study LX211-01, mean improvement from baseline in VH of 1.3 achieved in the 0.4 mg/kg group, as clinically relevant, in particular as it was maintained at the designated 16 and 24 week primary endpoints. The responder analysis requested by the CHMP (the second analysis) with different cut-offs for changes in vitreous haze indicated that a higher proportion of patients in 0.4 mg/kg group experienced decrease in the vitreous haze grade as compared to placebo. The applicant presented also comprehensive sensitivity analyses with respect to missing data imputation.

The committee acknowledged presented data, however remained of the opinion that study LX211-01, the only pivotal study, did not present robust and convincing enough results to support voclosporin

efficacy in the claimed indication including the indication restricted to the second line therapy. The positive treatment effect was not consistently shown for both co-primary endpoints. After 24 weeks of treatment only the LOCF analysis was significant. Due to the fact that voclosprorin was inferior to placebo in completing patients, as indicated by the BOCF analysis, the LOCF analysis could not be regarded as the main evidence of efficacy. Even after 16 weeks of treatment, both, the BOCF and the WOCF analysis did not show superiority over placebo. Since values carried forward in the LOCF analysis were much higher in the placebo group than in active treatment group, LOCF was still considered to be anticonservative and potentially biased in favour of voclosporin. In addition to the remaining limitations in the robustness of data the Committee considered that the reduction in VH endpoint did not immediately translate into improvement of patients' vision. It remained uncertain whether the reduction in VH could be regarded as a reliable predictor of the clinical course as there was no clinical improvement perceivable by the patients during the course of the study.

- The possible impact of high numbers of patients withdrawn from treatment or needing rescue medication:

It was carefully considered whether the high proportion of subjects withdrawn from treatment or needing rescue medication (more than 60%), the meaning of the maximum effect reached early in the treatment, the lack of predefined rules for the start of rescue medication, and the handling of these patients in the efficacy analysis may have introduced a potential bias.

In their responses the applicant agreed that the loss of subjects to rescue was difficult to avoid since physicians had the potential to intervene with high dose oral or injected corticosteroids to rapidly reduce inflammation and thus preserve vision. This made it increasingly difficult to demonstrate a difference in an active therapy vs. placebo as the clinical trial progressed, in particular because the discontinuation rate (including the initiation of rescue medication) reached 55-63% in the active treatment groups at week 24. Therefore, the applicant felt that the early effect of therapy seen at 8 and 12 weeks was important in establishing the efficacy of voclosporin. The applicant confirmed that not all of the rules for the start of rescue medication were predefined. The CHMP acknowledged that this would not introduce a bias if all treatment arms were managed in the same way. However, treatment arms could have been managed differently, if treatment allocation could have been unblinded for some patients, particularly due to decreased GFR values. Moreover, rescue medication was initiated for placebo patients at higher VH scores than for patients treated with voclosporin. The VH scores that were measured at the start of the rescue medication were used in the LOCF analysis. Considering a certain intra-subject variability the values that were carried forward may have been biased upwards for placebo or downwards for the active treatments. A potential bias introduced in the LOCF analysis, even if it was small, was considered to be of mayor concern since the degree of statistical significance was not considerable, and the results of those subjects who completed treatment without rescue medication were in favour of placebo. Additionally, the two definitive rescue rules defined in the protocol were not followed in several subjects in placebo and 0.4 mg/kg voclosporin groups.

- The steroid-sparing effect:

The robustness and relevance of the steroid sparing effect were considered by the Committee. All patients were to be tapered off to less than 5 mg/day of prednisone or equivalent by week 16. The applicant clarified that the 'ability to spare steroids' was defined as the proportion of subjects requiring rescue by the end of the tapering period; i.e., Week 16. In the subset of subjects who were using ≥ 10 mg/day corticosteroid at baseline, a clear dose-related decrease in rescue rate was observed. The rescue rate at Week 16 in the 0.4 mg/kg group was less than half that observed in the placebo group (0.22 vs. 0.50). The benefit of a reduced need for steroids was appreciated. It was also considered that whereas the reduction in steroid treatment doses can be *expected* to reduce the adverse effects of

steroid treatment, no data were presented actually demonstrating a reduction in steroid-related adverse effects *perceivable* for the patients during the course of the studies.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Luveniq was not demonstrated for quiescent uveitis (study LX211-02). For chronic non-infectious active uveitis, concerns and uncertainties remain regarding the limited robustness of the efficacy data and the magnitude of the effect in the only pivotal study LX211-01. It has not been convincingly demonstrated that the pharmacological activity and the possible modest efficacy of Luveniq would translate into a clear and clinically relevant and sustainable benefit for the patients with chronic non-infectious active uveitis, which would outweigh the uncertainties and risks.

2.6. Clinical safety

Patient exposure

Data from all subjects who received one or more doses of study medication were included in the Integrated Summary of Safety (ISS). A total of 2110 subjects were exposed to voclosporin in the clinical development programme. Four hundred thirteen subjects received placebo.

The data from the 5 phase 2/3 studies were integrated in 3 Cohorts: core treatment period of the uveitis studies (LX211-01, -02 and -03) [Cohort 1]; core treatment periods of both uveitis (LX211-01, -02 and -03) and psoriasis (ISA04-03, ISA05-02, ISA05-25) studies [Cohort 2]; uveitis and psoriasis studies, including both the core and extended treatment periods [Cohort 3].

Analysis Sets for Integrated Data in Uveitis and Psoriasis Studies (Safety Population)

Treatment Period	Analysis Set	Placebo	Voclosporin 0.2 mg/kg	Voclosporin 0.3 mg/kg	Voclosporin 0.4 mg/kg	Voclosporin 0.2-0.4 mg/kg	Voclosporin 0.6 mg/kg
Core	Cohort 1*	73	167	--	159	326	156
	PY	25.6	58.8	--	57.5	116.2	50.3
	Cohort 2†	316	274	113	660	1047	156
	PY	76.9	81.1	25.4	167.8	274.3	50.3
Core and Extension	Cohort 3†	316	274	348§	765¶	1250‡	156
	PY	84.9	117.8	255.4	416.9	790.1	59.9

PY = person-year exposure
* Integrated protocols: LX211-01, LX211-02, and LX211-03
† Integrated protocols: LX211-01, LX211-02, LX211-03, ISA04-03, ISA05-02, and ISA05-25
§ Includes Cohort 2 total plus subjects randomized to placebo in Study ISA04-03 who were switched per protocol after 12 weeks to voclosporin 0.3 mg/kg and those randomized to voclosporin 0.2 or 0.4 mg/kg who received voclosporin 0.3 mg/kg in the extension study ISA05-02.
Includes Cohort 2 total plus subjects randomized to placebo in Study ISA05-25 who were switched per protocol after 12 weeks to voclosporin 0.4 mg/kg.
‡ Includes Cohort 2 total plus subjects randomized to placebo in the double-blind psoriasis studies who were switched after 12 weeks to voclosporin 0.3 mg/kg in Study ISA04-03 or 0.4 mg/kg in Study ISA05-25.

Total voclosporin exposure in Phase 2/3 studies was 850 person-years (PY), compared to 84.5 person-years exposure in placebo, a 10-fold difference. In interpreting the safety data, especially for events that were common in the population (e.g., infections, decreased renal function, hypertension), unequal exposures across treatment groups due to pre-specified randomisation schedules could result in more events in the voclosporin group due to exposure differences alone. For this reason incidences based on 100 person-year exposure (100 PY) that take exposure differences into account, were also included in some of the safety analyses. Two hundred and eighty three (283), and 182 subjects were exposed to voclosporin for >36 weeks, and >52 weeks in phase 2/3 studies, respectively.

The addition of the psoriasis studies, which included subjects demographically similar to the uveitis population (with the exception of subjects of South Asian origin), provided more information on the recommended dose of 0.4 mg/kg BID in a higher number of patients (Cohorts 2 and 3). Cohort 3 provided insight into the safety profile following a longer exposure to voclosporin.

This extent of exposure was considered adequate to identify common and less frequent safety findings in particular in the light of the orphan status of the condition.

Although demographics and baseline characteristics were generally well matched across treatment groups in each of the 3 Cohorts, there were baseline differences in the Indian population compared to North American and European populations. At baseline, subjects of the Indian origin had lower mean height, weight, BMI, serum creatinine (sCr), BUN, albumin, magnesium and higher alkaline phosphatase values compared to the other regions. The applicant was requested to clarify the generalisability of the data obtained outside Europe to the European population. For more detail please see discussion.

Adverse events

Percentages of subjects with any AE were similar across voclosporin dose groups (83.0%-85.6%) and lower in the placebo group (80.8%). Most AEs were mild or moderate in severity; percentages of subjects with any severe AE were similar for the placebo and voclosporin 0.2-0.4 mg/kg dose groups and higher in the voclosporin 0.6 mg/kg group. Percentages of subjects with drug-related AEs and with AEs leading to discontinuation showed dose-related increases across the voclosporin dose groups.

Overall Summary of Treatment-Emergent Adverse Events (Proportions of Subjects, n [%]): Uveitis Studies/Core Treatment Period (Cohort 1 of Safety Population) is presented below.

Adverse Event Category	Placebo N = 73	Voclosporin 0.2 mg/kg N = 167	Voclosporin 0.4 mg/kg N = 159	Voclosporin 0.6 mg/kg N = 156	Voclosporin 0.2-0.4 mg/kg N = 326
Any adverse event	59 (80.8)	143 (85.6)	132 (83.0)	131 (84.0)	275 (84.4)
Maximum AE severity*					
Mild	31 (42.5)	69 (41.3)	62 (39.0)	48 (30.8)	131 (40.2)
Moderate	23 (31.5)	61 (36.5)	59 (37.1)	66 (42.3)	120 (36.8)
Severe	5 (6.8)	13 (7.8)	11 (6.9)	17 (10.9)	24 (7.4)
Relatedness to study drug*					
Unrelated	33 (45.2)	88 (52.7)	58 (36.5)	45 (28.8)	146 (44.8)
Related	26 (35.6)	55 (32.9)	74 (46.5)	86 (55.1)	129 (39.6)
AEs leading to discontinuation	16 (21.9)	36 (21.6)	42 (26.4)	60 (38.5)	78 (23.9)
Serious AEs	2 (2.7)	9 (5.4)	9 (5.7)	11 (7.1)	18 (5.5)
AEs leading to death	0	0	0	0	0

* Subjects are counted once in this analysis at the highest severity/closest relationship assessed for any AE reported.
† AEs for which the action taken was reported as permanent withdrawal of study drug; subjects with these AEs could have other reasons for discontinuation reported on study termination CRFs.

Adverse Events i.e. Individual PTs by SOC, reported for ≥ 2% of subjects in any treatment group (Proportions of Subjects, n [%]) in uveitis studies (Cohort 1 - Core Treatment Period Safety Population) are presented below.

System Organ Class Preferred Term*	Placebo N = 73	Voclosporin 0.2 mg/kg N = 167	Voclosporin 0.4 mg/kg N = 159	Voclosporin 0.6 mg/kg N = 156	Voclosporin 0.2-0.4 mg/kg N = 326
Any Adverse Event	59 (80.8)	143 (85.6)	132 (83.0)	131 (84.0)	275 (84.4)
Eye disorders	38 (52.1)	82 (49.1)	59 (37.1)	59 (37.8)	141 (43.3)
Anterior chamber cell	5 (6.8)	10 (6.0)	6 (3.8)	5 (3.2)	16 (4.9)
Cataract	12 (16.4)	20 (12.0)	12 (7.5)	12 (7.7)	32 (9.8)
Cataract nuclear	2 (2.7)	0	2 (1.3)	0	2 (0.6)
Cataract subcapsular	6 (8.2)	10 (6.0)	8 (5.0)	2 (1.3)	18 (5.5)
Conjunctival haemorrhage	0	4 (2.4)	3 (1.9)	1 (0.6)	7 (2.1)
Eye irritation	0	1 (0.6)	5 (3.1)	2 (1.3)	6 (1.8)
Eye pain	5 (6.8)	11 (6.6)	5 (3.1)	6 (3.8)	16 (4.9)
Macular oedema	1 (1.4)	9 (5.4)	4 (2.5)	10 (6.4)	13 (4.0)
Myodesopsia	0	5 (3.0)	2 (1.3)	4 (2.6)	7 (2.1)
Ocular hyperaemia	2 (2.7)	5 (3.0)	5 (3.1)	1 (0.6)	10 (3.1)
Posterior capsule opacification	2 (2.7)	1 (0.6)	2 (1.3)	1 (0.6)	3 (0.9)
Uveitis	6 (8.2)	7 (4.2)	6 (3.8)	7 (4.5)	13 (4.0)
Vision blurred	0	10 (6.0)	3 (1.9)	6 (3.8)	13 (4.0)
Visual acuity reduced	10 (13.7)	26 (15.6)	17 (10.7)	15 (9.6)	43 (13.2)
Vitritis	8 (11.0)	10 (6.0)	9 (5.7)	9 (5.8)	19 (5.8)

Gastrointestinal disorders	14 (19.2)	38 (22.8)	44 (27.7)	50 (32.1)	82 (25.2)
Abdominal discomfort	2 (2.7)	2 (1.2)	2 (1.3)	3 (1.9)	4 (1.2)
Abdominal distension	0	4 (2.4)	1 (0.6)	2 (1.3)	5 (1.5)
Abdominal pain	0	3 (1.8)	4 (2.5)	3 (1.9)	7 (2.1)
Abdominal pain upper	1 (1.4)	2 (1.2)	0	6 (3.8)	2 (0.6)
Constipation	1 (1.4)	2 (1.2)	6 (3.8)	2 (1.3)	8 (2.5)
Diarrhoea	4 (5.5)	14 (8.4)	14 (8.8)	11 (7.1)	28 (8.6)
Dyspepsia	2 (2.7)	3 (1.8)	4 (2.5)	5 (3.2)	7 (2.1)
Gastrointestinal disorder	2 (2.7)	1 (0.6)	2 (1.3)	2 (1.3)	3 (0.9)
Gingival hyperplasia	0	1 (0.6)	5 (3.1)	1 (0.6)	6 (1.8)
Nausea	5 (6.8)	3 (1.8)	8 (5.0)	12 (7.7)	11 (3.4)
Vomiting	2 (2.7)	2 (1.2)	6 (3.8)	1 (0.6)	8 (2.5)
General disorders and administration site conditions	10 (13.7)	23 (13.8)	33 (20.8)	33 (21.2)	56 (17.2)
Asthenia	1 (1.4)	2 (1.2)	4 (2.5)	3 (1.9)	6 (1.8)
Fatigue	1 (1.4)	7 (4.2)	4 (2.5)	8 (5.1)	11 (3.4)
Oedema peripheral	1 (1.4)	6 (3.6)	6 (3.8)	6 (3.8)	12 (3.7)
Pyrexia	3 (4.1)	7 (4.2)	12 (7.5)	11 (7.1)	19 (5.8)
Infections and infestations	16 (21.9)	41 (24.6)	28 (17.6)	23 (14.7)	69 (21.2)
Influenza	3 (4.1)	1 (0.6)	1 (0.6)	1 (0.6)	2 (0.6)
Nasopharyngitis	2 (2.7)	18 (10.8)	8 (5.0)	6 (3.8)	26 (8.0)
Sinusitis	2 (2.7)	2 (1.2)	0	4 (2.6)	2 (0.6)
Upper respiratory tract infection	1 (1.4)	5 (3.0)	3 (1.9)	0	8 (2.5)
Urinary tract infection	1 (1.4)	6 (3.6)	5 (3.1)	2 (1.3)	11 (3.4)

System Organ Class Preferred Term*	Placebo N = 73	Voclosporin 0.2 mg/kg N = 167	Voclosporin 0.4 mg/kg N = 159	Voclosporin 0.6 mg/kg N = 156	Voclosporin 0.2-0.4 mg/kg N = 326
Investigations	18 (24.7)	40 (24.0)	42 (26.4)	52 (33.3)	82 (25.2)
Blood triglycerides increased	2 (2.7)	0	1 (0.6)	1 (0.6)	1 (0.3)
Glomerular filtration rate decreased	7 (9.6)	13 (7.8)	24 (15.1)	39 (25.0)	37 (11.3)
Intraocular pressure increased	2 (2.7)	5 (3.0)	7 (4.4)	7 (4.5)	12 (3.7)
Visual acuity tests abnormal	4 (5.5)	13 (7.8)	5 (3.1)	4 (2.6)	18 (5.5)
Musculoskeletal and connective tissue disorders	9 (12.3)	31 (18.6)	29 (18.2)	30 (19.2)	60 (18.4)
Arthralgia	2 (2.7)	8 (4.8)	10 (6.3)	7 (4.5)	18 (5.5)
Back pain	4 (5.5)	8 (4.8)	5 (3.1)	6 (3.8)	13 (4.0)
Muscle spasms	1 (1.4)	1 (0.6)	4 (2.5)	4 (2.6)	5 (1.5)
Myalgia	0	5 (3.0)	1 (0.6)	4 (2.6)	6 (1.8)
Pain in extremity	1 (1.4)	3 (1.8)	5 (3.1)	8 (5.1)	8 (2.5)
Nervous system disorders	14 (19.2)	34 (20.4)	29 (18.2)	42 (26.9)	63 (19.3)
Dizziness	3 (4.1)	0	3 (1.9)	4 (2.6)	3 (0.9)
Headache	6 (8.2)	21 (12.6)	14 (8.8)	26 (16.7)	35 (10.7)
Paraesthesia	2 (2.7)	3 (1.8)	4 (2.5)	5 (3.2)	7 (2.1)
Psychiatric disorders	4 (5.5)	8 (4.8)	6 (3.8)	5 (3.2)	14 (4.3)
Anxiety	1 (1.4)	4 (2.4)	2 (1.3)	0	6 (1.8)
Depression	1 (1.4)	4 (2.4)	2 (1.3)	1 (0.6)	6 (1.8)
Renal and urinary disorders	1 (1.4)	1 (0.6)	8 (5.0)	9 (5.8)	9 (2.8)
Pollakiuria	0	0	5 (3.1)	2 (1.3)	5 (1.5)
Respiratory, thoracic and mediastinal disorders	7 (9.6)	12 (7.2)	10 (6.3)	9 (5.8)	22 (6.7)
Cough	1 (1.4)	8 (4.8)	3 (1.9)	4 (2.6)	11 (3.4)
Wheezing	2 (2.7)	0	0	0	0
Skin and subcutaneous tissue disorders	9 (12.3)	19 (11.4)	21 (13.2)	28 (17.9)	40 (12.3)
Alopecia	2 (2.7)	1 (0.6)	4 (2.5)	0	5 (1.5)
Hirsutism	0	2 (1.2)	7 (4.4)	11 (7.1)	9 (2.8)
Hyperhidrosis	2 (2.7)	1 (0.6)	0	1 (0.6)	1 (0.3)
Hypertrichosis	0	0	0	4 (2.6)	0
Rash	1 (1.4)	3 (1.8)	4 (2.5)	0	7 (2.1)
Swelling face	0	4 (2.4)	4 (2.5)	5 (3.2)	8 (2.5)
Vascular disorders	4 (5.5)	11 (6.6)	23 (14.5)	25 (16.0)	34 (10.4)
Hypertension	3 (4.1)	8 (4.8)	22 (13.8)	22 (14.1)	30 (9.2)

Integrated protocols: LX211-01, LX211-02, LX211-03

* Coded using MedDRA Version 12.0.

Common adverse drug reactions (i.e., potentially treatment-related) based on an AE rate in Cohort 1 of >5% in any voclosporin group and > 2 X the rate in placebo are presented below.

Preferred Term*	Placebo N = 73	Voclosporin 0.2 mg/kg N = 167	Voclosporin 0.4 mg/kg N = 159	Voclosporin 0.6 mg/kg N = 156	Voclosporin 0.2-0.4 mg/kg N = 326
Macular oedema	1 (1.4)	9 (5.4)	4 (2.5)	10 (6.4)	13 (4.0)
Nasopharyngitis	2 (2.7)	18 (10.8)	8 (5.0)	6 (3.8)	26 (8.0)
Glomerular filtration rate decreased†	7 (9.6)	13 (7.8)	24 (15.1)	39 (25.0)	37 (11.3)
Arthralgia	2 (2.7)	8 (4.8)	10 (6.3)	7 (4.5)	18 (5.5)
Pain in extremity	1 (1.4)	3 (1.8)	5 (3.1)	8 (5.1)	8 (2.5)
Headache	6 (8.2)	21 (12.6)	14 (8.8)	26 (16.7)	35 (10.7)
Hirsutism	0	2 (1.2)	7 (4.4)	11 (7.1)	9 (2.8)
Hypertension	3 (4.1)	8 (4.8)	22 (13.8)	22 (14.1)	30 (9.2)

Integrated protocols: LX211-01, LX211-02; LX211-03

* Coded using MedDRA Version 12.0.

† Includes AEs reported by investigator that were not supported by confirmed laboratory results

These events were either expected events associated with calcineurin inhibitors (CNIs) (i.e., GFR decreased, headache, hirsutism and hypertension) or non-specific events: nasopharyngitis, arthralgia and pain in extremity. Macular oedema was only seen in the uveitis studies. A dose relationship was evident for the events of decreased GFR, hirsutism, and hypertension and suggestive of pain in extremity. The rates of most ocular related AEs were inversely proportional to dose with the 0.6 mg/kg BID dose, in general showing the lowest rates of these events. The voclosporin 0.6 mg/kg BID dose however, was associated with more serious and severe events and higher rates of treatment discontinuations compared to lower voclosporin doses.

Class effects of CNIs other than renal and hypertension events, which are discussed in detail further down in the report, also include the risk of infection, malignancies and neurotoxicity. The table below summarises by Cohort the rate and incidence/100 PY of the SOCs of Infections and Infestations; Neoplasms Benign, Malignant and Unspecified (Inc Cysts and Polyps); and Nervous System Disorders. No relevant differences across treatment groups were seen.

Overall summary of infections, nervous system events and neoplasms (proportions of subjects, n [%]): all analysis cohorts (safety population).

Analysis Cohort	Placebo	Voclosporin 0.2 mg/kg	Voclosporin 0.3 mg/kg	Voclosporin 0.4 mg/kg	Voclosporin 0.2-0.4 mg/kg	Voclosporin 0.6 mg/kg
Cohort 1	**N = 73**	**N = 167**	**--**	**N = 159**	**N = 326**	**N = 156**
Infections and Infestations [per 100 PY]	16 (21.9) [62.5]	41 (24.6) [69.7]	--	28 (17.6) [48.7]	69 (21.2) [59.4]	23 (14.7) [45.7]
Neoplasms Benign, Malignant and Unspecified (Inc Cysts and Polyps) [per 100 PY]	1 (1.4) [3.9]	0	--	2 (1.3) [3.5]	2 (0.6) [1.7]	1 (0.6) [2.0]
Nervous System Disorders [per 100 PY]	14 (19.2) [54.7]	34 (20.4) [57.8]	--	29 (18.2) [50.4]	63 (19.3) [54.2]	42 (26.9) [83.5]
Cohort 2	**N = 316**	**N = 274**	**N = 113**	**N = 660**	**N = 1047**	**N = 156**
Infections and Infestations [per 100 PY]	77 (24.4) [100.1]	83 (30.3) [102.3]	51 (45.1) [200.8]	154 (23.3) [91.8]	288 (27.5) [100.5]	23 (14.7) [45.7]
Neoplasms Benign, Malignant and Unspecified (Inc Cysts and Polyps) [per 100 PY]	2 (0.6) [2.6]	1 (0.4) [1.2]	0	3 (0.5) [1.8]	4 (0.4) [1.5]	1 (0.6) [2.0]
Nervous System Disorders [per 100 PY]	45 (14.2) [58.5]	53 (19.3) [65.4]	18 (15.9) [70.9]	114 (17.3) [67.8]	185 (17.7) [67.4]	42 (26.9) [83.5]
Cohort 3	**N = 316***	**N = 274***	**N = 348***	**N = 765***	**N = 1250†**	**N = 156**
Infections and Infestations [per 100 PY]	78 (24.7) [91.9]	98 (35.8) [83.2]	156 (44.8) [61.1]	252 (32.9) [60.4]	474 (37.9) [59.9]	24 (15.4) [40.1]
Neoplasms Benign, Malignant and Unspecified (Inc Cysts and Polyps) [per 100 PY]	2 (0.6) [2.4]	2 (0.7) [1.7]	5 (1.4) [2.0]	7 (0.9) [1.7]	13 (1.0) [1.6]	1 (0.6) [1.7]
Nervous System Disorders [per 100 PY]	46 (14.6) [54.2]	63 (23.0) [53.5]	47 (13.5) [18.4]	153 (20.0) [36.7]	258 (20.6) [32.7]	43 (27.6) [71.8]

Integrated protocols: LX211-01, LX211-02, and LX211-03 (plus ISA04-03, ISA05-02, and ISA05-25 in Cohorts 2 and 3)

* Subjects receiving multiple treatments are counted once for each treatment.

† Subjects receiving more than one of the dosages included are counted once.

PY = person-years

Although the rate for infections overall showed no relevant differences across treatment groups, the preferred term nasopharyngitis met the criteria in Cohort 1 for a "potential" ADR based on a rate of 10.8% (0.2 mg/kg BID) compared to placebo (2.7%); but no dose response was noted (0.4 mg/kg BID = 5.0%; 0.6 mg/kg BID = 3.8%). These events were non-serious, mild to moderate in intensity and resulted in no treatment discontinuations. There were no opportunistic infections reported. This event was not accompanied by a higher incidence of infectious diseases and no dose pattern has been confirmed.

No lymphomas were reported in any treatment group, and the rate for skin cancer shown with long-term exposure (Cohort 3) was low in both the placebo (0.3%) and voclosporin groups (0.2% - all voclosporin dose groups combined).

Seizures were reported in a subject who was subsequently diagnosed with cerebral vasculitis. No other cases of treatment emergent convulsions have been reported. A case of gliosis was also reported.

Limited PY exposure precluded any conclusion on class effects such as neoplasms or nervous system events.

Adverse events of interest

Decreased renal function

Analysis focused on Cohort 1 and included all subjects with confirmed ≥ 30% decreases from baseline in eGFR, predefined in the protocols, and subjects with reported AEs/SAEs with combined terms of decreased/reduced GFR, low GFR, worsening/impaired renal function and acute renal failure.

Dose-related increases in renal function impairment were shown for voclosporin 0.4 mg/kg (8.2%), and 0.6 mg/kg (18.6%) groups, while placebo and 0.2 mg/kg groups presented similar rates (4.1% and 4.2%, respectively). Similar results were seen in Cohort 2 and 3. Low baseline serum creatinine (sCr) values, the male gender, South Asian/Indian origin, and post-baseline hypertension were factors associated with increased risk. Time to onset was in general <4 months and time to recovery ranged from 3-4 months in most cases; longer in subjects from sites in India with baseline sCr values <0.7 mg/dl. All subjects had recovery documented, indicating the reversibility of the renal changes.

Subjects with decreased renal function tended to have blood pressure increases, and some also reported concomitant oedema-related events. The laboratory analyses showed dose-related increases in serum creatinine, BUN, and uric acid; and dose-related decreases in magnesium. Relatively few subjects with normal baseline values had post-baseline values that reached clinical limits. The rates for subjects with renal-related AEs, AEs leading to discontinuation and SAEs were dose-related. Of the 7 SAEs reported, 6 were in the 0.6 mg/kg dose group.

Hypertension

Subjects with new onset or aggravated hypertension by baseline hypertension status: uveitis studies/ (core treatment period – Cohort 1 of safety population) are presented in the table below.

	Placebo		Voclosporin 0.2 mg/kg		Voclosporin 0.4 mg/kg		Voclosporin 0.6 mg/kg	
Baseline Status*	N	n (%) [n/100 PY]	N	n (%) [n/100 PY]	N	n (%) [n/100 PY]	N	n (%) [n/100 PY]
Non-hypertensive†	47	2 (4.3) [12.3]	87	18 (20.7) [57.5]	104	25 (24.0) [69.8]	96	25 (26.0) [77.4]
Controlled hypertension§	3	3 (100.0) [200.0]	10	6 (60.0) [193.5]	7	4 (57.1) [148.1]	11	6 (54.5) [200.0]
Uncontrolled hypertension¶	23	11 (47.8) [139.2]	70	51 (72.9) [209.0]	48	36 (75.0) [190.5]	49	37 (75.5) [248.3]
Total	73	16 (21.9) [62.5]	167	76 (45.5) [129.3]	159	65 (40.8) [113.0]	156	68 (43.6) [135.2]

Integrated protocols: LX211-01, LX211-02, LX211-03
* As defined in ISS Section 1.1.3.2.1
† New-onset hypertension for this subgroup is defined as occurrence of a hypertension AE, or initiation of antihypertension medication, or elevated BP (SBP ≥140 mmHg and/or DBP ≥90 mmHg) at 2 post-baseline assessments (consecutive or not).
§ Aggravated hypertension for this subgroup is defined as occurrence of a hypertension AE, or initiation or increase in dose or dosing frequency of anti-hypertension medication, or any occurrence of elevated BP (SBP ≥140 mmHg and/or DBP ≥90 mmHg) post-baseline.
¶ Aggravated hypertension for this subgroup is defined as occurrence of a hypertension AE, or initiation or increase in dose or dosing frequency of anti-hypertension medication, or any increase from baseline of ≥20 mmHg in SBP or ≥10 mmHg in DBP, or any occurrence of elevated BP (SBP ≥140 mmHg and/or DBP ≥90 mmHg) after a resolution (any post-baseline visit with SBP <140 mmHg and DBP <90 mmHg).

An association between AE reporting rates and voclosporin therapy was seen in the 0.4 and 0.6 mg/kg voclosporin treatment groups. Subjects of South Asian race/Indian origin were at greater risk than subjects from North America and Europe.

Four SAEs were reported during the core treatment period – 2 each in the 0.4 and 0.6 mg/kg voclosporin treatment groups. About 25% of subjects in the uveitis studies not hypertensive at baseline developed a new-onset hypertension in the voclosporin 0.4 mg/kg group. Most cases of new-onset hypertension occurred ≤ 2 months post-baseline, and all within 4 months post initiation of treatment. Most did not result in study drug discontinuation or initiation of antihypertensive medications. Half or more cases in each treatment group resolved with additional follow-up. Mean duration of resolved hypertension ranged from 98-219 days (including additional follow-up data) in the voclosporin groups, with no consistent dose-related trend seen.

Results for Cohorts 2 and 3 were similar and consistent with the results seen for Cohort 1. In the Cohort 3 which contained subjects with exposure of up to 60 weeks <1% of new onset hypertension cases occurred after 6 months. For subjects with uncontrolled hypertension at baseline, 2% of cases of aggravated hypertension occurred after 6 months in each of the 0.4 and 0.6 mg/kg voclosporin groups; 12% of subjects in the 0.2 mg/kg group experienced aggravated hypertension after 6 months. For Cohort 3, recovery rates were similar across treatment groups and ranged from 52.9-70% in the placebo group and 50-77.3% in the voclosporin group (all doses combined).

Cardiac and cerebrovascular risk

There were 4 Anti-Platelet Trialists' Collaboration (APTC) events reported across all safety cohorts: 1 cerebral infarction; 2 myocardial infarctions; 1 angina but no increased cardiovascular risk overall was evident in subjects exposed to voclosporin. Three cases occurred in subjects without pre-existing or new onset hypertension (1 cerebral infarction, 1 MI and 1 angina), while 1MI occurred in a subject with pre-existing hypertension.

The incidence/100 PY in any voclosporin treatment group for cardiac events, including those considered serious, and/or leading to premature termination was similar to, or less than placebo. No dose-relationship was evident.

Four cases of atrial fibrillation and 1 case of atrial flutter were reported in subjects exposed to voclosporin. The background rate (based on medical history) for these events in the study population was 0.17-0.23%, a rate similar to that seen in subjects exposed to voclosporin (0.36%). No clear association between these events and changes in magnesium, blood pressure or any other factor was evident. The clinical significance of this finding was considered to be unknown.

Ocular safety

The rate of macular oedema in Cohort 1 was 5.4% (0.2 mg/kg), 2.5% (0.4 mg/kg), and 6.4% (0.6 mg/kg) as compared to 1.4% in placebo. Macular oedema therefore met the criteria established for a "potential" ADR, i.e., a rate of >5% in any voclosporin group and > 2X the rate in placebo. However, the result of tests for dose-related trend did not approach statistical significance. Macular oedema was reported in the medical histories in 6.5% of the uveitis study population indicating that this was not an uncommon finding. Optical coherence tomography measuring macular thickness was done in uveitis studies LX211-01 and LX211-03 and showed no differences in the mean change from baseline in the voclosporin groups versus placebo after 24 weeks of voclosporin treatment. In addition, analysis of the area of macular leakage using fluorescein angiography in LX211-01 revealed no differences in the mean change from baseline between the voclosporin groups versus placebo after 24 weeks of voclosporin treatment.

Serious adverse event/deaths/other significant events

Most serious adverse events (SAEs) were reported in no more than one subject. The most common SAEs reported in voclosporin subjects (Cohort 3) were decreased GFR (5 subjects); hypertension (4 subjects); pyelonephritis (2) and paresthesia (2 subjects) and were dose-related. The SAE rate did not appear to increase with increased duration of exposure as seen in the incidence of SAE/100 PY for Cohort 3.

There were two deaths that occurred during the treatment period. One was due to a road accident, another death occurred post-treatment in a subject with bile duct cancer.

Four SAEs of special interest (haemolytic uremic syndrome, gliosis, acute febrile neutrophilic dermatosis and cerebral vasculitis) were identified. All of the 4 events either improved or resolved without sequelae. For three (except acute febrile neutrophilic dermatosis) out of four SAEs a causal relationship to voclosporin treatment could not be ruled out.

Four SAEs were reported in the Phase 1 clinical trials, i.e. active tuberculosis infection and human immunodeficiency virus (HIV) infection, pericarditis, increase in blood pressure. Except for the HIV infection all other SAEs were judged to be possibly related to voclosporin treatment.

Laboratory findings

A dose-related trend toward decreases in red blood cell parameters (i.e., erythrocytes, haematocrit and haemoglobin) could not be ruled out but these changes were associated with infrequent reports of anaemia related AEs. None of these events were severe, led to discontinuation, or were serious adverse events. Although a drug effect could not be ruled out, these findings did not appear to be clinically significant.

Dose-related increases were also noted for sCr, blood urea nitrogen (BUN), creatinine, and uric acid; and dose-related decreases were seen for magnesium. A trend towards increases in potassium and decreases in sodium values could not be entirely ruled out, although these findings were less consistent.

A dose-related increase in alkaline phosphatase was noted, but no subject had values that went above critical limits. In some analyses, there was a trend toward increased total bilirubin values after exposure to voclosporin but this was not a consistent finding. Mild transient elevations of alkaline phosphatase occasionally accompanied by slight elevations in serum bilirubin and aminotransferase activity suggestive of mild cholestatic liver injury have been reported with exposure to ciclosporin A. These abnormalities were usually asymptomatic and self-limiting. Mild cholestatic changes associated with vocloporin treatment cannot be ruled out. Clinically significant (> 3 x ULN) elevations of transaminases were rare, and there were no cases meeting the criteria of “Hy’s law” identified.

With the exception of decreases in red blood cell parameters, the observed laboratory changes were not unexpected and have been reported with calcineurin inhibitors.

In a phase 1 study assessing voclosporin effects on QT intervals (ISA03-11), single doses of voclosporin (0.3 mg/kg, 0.5 mg/kg, or 1.5 mg/kg BID), were associated with a dose-related rise in QTcF.

Safety in special populations

Drug-Demographic Studies

No specific drug-demographic studies were performed. As mentioned above subjects of South Asian/Indian origin were at greater risk of developing both decreased renal function and hypertension. Males also seemed to be at greater risk than females in developing changes in renal function. The effect of age could not be determined since most of the study population was between the ages of 18 and 65.

Drug-Disease Interaction Studies

As discussed earlier, the administration of voclosporin to subjects with mild to moderate renal impairment did not significantly affect exposure to voclosporin after a single 0.4 mg/kg dose or after administration of 0.4 mg/kg BID for 8 days. Administration of voclosporin to subjects with severe renal impairment resulted in a 1.5-fold increase in exposure with no significant increase in peak concentrations after administration of a single 0.4 mg/kg dose.

Similarly, administration of voclosporin to subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment resulted in an approximately 1.5-fold to 2-fold increase in voclosporin exposure after single doses of 0.4 mg/kg BID.

Other Safety Findings

One accidental overdose case was reported in a 65-year old male renal transplant subject who accidentally took a single dose of 150 mg (equivalent to 2.2 mg/kg). The subject was subsequently hospitalised for observation due to tremors and tachycardia. He recovered without complications 2 days later and was discharged.

Although no adverse maternal or foetal effects were identified due to voclosporin exposure during pregnancy, voclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. It is not known whether voclosporin is excreted in human milk, but placental transfer and lacteal excretion study in rats indicated that voclosporin was secreted in breast milk. Therefore, use of voclosporin while breast feeding is not recommended.

From the safety data collected to date, there is no evidence to suggest voclosporin treatment is associated with abuse potential, or inability to drive or operate machinery. There is also no evidence suggesting that stopping treatment with voclosporin is associated with any withdrawal or rebound effects.

Safety related to drug-drug interactions and other interactions

As discussed earlier, there was a substantial increase in the blood concentrations of voclosporin when it was concomitantly administered with ketoconazole 400 mg, a strong inhibitor of CYP3A4/5 and an inhibitor of P-gp. There were also large increases in both Cmax (6-fold) and AUC (19-fold), which demonstrated a significant drug-drug interaction. Although the results of this study did not allow for a determination of the specific mechanism for the drug-drug interaction, due to the magnitude of the increase in voclosporin exposure, it was likely a combination of CYP 3A4/5 and P-gp inhibition. Associated increases in sCr and decreased magnesium levels were also observed. None of these findings were reported as serious and values returned to within normal limits post-treatment.

There was an increase in the mean whole blood concentrations of voclosporin when it was concomitantly administered with verapamil 80 mg, a P-gp inhibitor. There were corresponding increases in both the Cmax (2-fold) and the AUC (2.7-fold) of voclosporin, which demonstrated a significant drug-drug interaction.

In another study digoxin, a substrate of P-gp, was co-administered with voclosporin, and the pharmacokinetics of each were examined when both drugs were at steady state. Co-administration of voclosporin 0.4 mg/kg daily with digoxin (0.5 mg on the first day followed by 0.25 mg daily) resulted in an increase in mean plasma concentrations of digoxin, with corresponding increases in both Cmax (1.5-fold) and AUC (1.2-fold). Overall, these results demonstrated a statistically significant drug-drug interaction, and confirmed that voclosporin is both a substrate and an inhibitor of Pgp.

Discontinuation due to adverse events

Overall summary of adverse events leading to discontinuation of study drug (proportions of subjects, n [%]) is presented below.

Analysis Cohort	**Placebo**	**Voclosporin 0.2 mg/kg**	**Voclosporin 0.3 mg/kg**	**Voclosporin 0.4 mg/kg**	**Voclosporin 0.2-0.4 mg/kg**	**Voclosporin 0.6 mg/kg**
Cohort 1	**N = 73** (%)	**N = 167** (%)	**--**	**N = 159** (%)	**N = 326** (%)	**N = 156** (%)
Any AE leading to discontinuation	16 (21.9)	36 (21.6)	--	42 (26.4)	78 (23.9)	60 (38.5)
Any AE leading to discontinuation/100 PYE	62.5	61.2	--	73.0	67.1	119.3
Cohort 2	**N = 316**	**N = 274**	**N = 113**	**N = 660**	**N = 1047**	**N = 156**
Any AE leading to discontinuation	24 (7.6)	44 (16.1)	4 (3.5)	55 (8.3)	103 (9.8)	60 (38.5)
Any AE leading to discontinuation/100PYE	31.2	54.3	15.7	32.8	37.6	119.3
Cohort 3	**N = 316***	**N = 274***	**N = 348***	**N = 765***	**N = 1250†**	**N = 156**
Any AE leading to discontinuation	30 (9.5)	54 (19.7)	33 (9.5)	86 (11.2)	173 (13.8)	70 (44.9)
Any AE leading to discontinuation/100 PYE	35.3	45.8	12.9	20.6	21.9	116.9

PY=person-years exposure

Integrated protocols: LX211-01, LX211-02, and LX211-03 (plus ISA04-03, ISA05-02, and ISA05-2 in Cohorts 2 and 3)

* Subjects receiving multiple treatments are counted once for each treatment.

† Subjects receiving more than one of the dosages included are counted once.

More subjects in the placebo and 0.2 mg/kg group compared to the 0.4 mg/kg and 0.6 mg/kg groups discontinued due to a lack of efficacy, while the 0.6 mg/kg dose group had the greatest rate of discontinuations due to adverse events. The most frequently reported events leading to discontinuation were eye-related but were in general reported more frequently in the placebo group (19%) with lower rates observed in the voclosporin groups (14%, 14% and 12% respectively). The decrease in the glomerular filtration rate was the most frequent, dose-related, non-ocular AE leading to discontinuation, with a 5% rate observed with the dose intended to market (0.4 mg/kg).

As only 56 out of the 92 subjects who completed the core treatment period in study LX211-01 entered the extension period, the applicant was requested to explain how many of the patients were excluded based on safety. It was clarified that a reduction in eGFR precluded the inclusion of 18 subjects in the extension phase. Subjects of Indian origin were more affected than those from other regions.

Post marketing experience

There is no post-marketing experience with voclosporin as it has not been authorised yet.

2.6.1. Discussion on clinical safety

The overall safety data base is reasonable considering the prevalence of the indication. Nevertheless risk estimates will have to be calculated with caution as both exposure and number of patients receiving the intended dose for uveitis is limited to 159 subjects, with a person-year exposure of 57.5. When considering the addition of studies in psoriasis, baseline characteristics change, as the proportion of South Asian population significantly decreases. Indian population, which accounts for more than 44% of the uveitis studies population, had lower mean height, weight, BMI, serum creatinine (sCr), BUN, albumin, magnesium and higher alkaline phosphatase levels compared to the other regions. This has impacted on the incidence and interpretation of some adverse events, e.g. decrease in renal function, hypertension. In addition, GCP findings indicated that the conduct of the study may have significantly impacted interpretation of the results, even though the applicant provided reassurance that the clinical investigators were experienced in the diagnosis and management of patients with uveitis, clinical trials and GCP requirements. In particular the recording and reporting of GFR has been affected, which might have endangered the patients' safety. The applicant has clarified the potential reasons behind these findings and showed that no other parameters were affected by local analytic practices. The clarifications and the additional safety analyses provided by the applicant did not show any additional negative impact on the validity of the clinical trial data and were considered satisfactory.

The exposure-safety relationship was explored. The applicant agreed that in the setting of renal impairment, exposure of voclosporin may be increased and that additional instructions are needed on the handling and avoidance of renal adverse drug reactions. However, the applicant argued that therapeutic drug monitoring based on trough voclosporin concentrations would not be an adequate measure of renal function and that it could not be accurately timed in an outpatient setting. The applicant has also adequately justified that the direct measurement of GFR via urinary clearance of inulin or comparable methods was not feasible for the routine monitoring of uveitis patients. This justification was found acceptable. The applicant claimed that changes in serial serum creatinine measurements were appropriate indicators of suspected renal dysfunction and proposed that serial measurements of serum creatinine would be monitored in preference to a calculated GFR together with changes in blood urea nitrogen (BUN), complete blood count (CBC), serum magnesium, potassium and uric acid. These parameters should be evaluated a minimum of every 2 weeks during the initial 3 months of therapy, then monthly for three months (if stable) and then every 3 months thereafter. CBC should be collected quarterly.

The recommendations for and practicability of the monitoring of renal function were discussed during the oral explanation as it was felt that proposed monitoring parameters and frequencies represented very demanding requirements, which warranted assessment in the context of the benefit of the product. The applicant explained that uveitis specialists routinely monitor laboratory parameters, hence monitoring would not be difficult and would be aligned with routine uveitis follow-up. Additionally it was mentioned that high dose corticosteroid therapy also required extensive routine monitoring, consequently voclosporin therapy would not substantially increase the burden of monitoring. The CHMP did not conclude on this issue in the light of the negative opinion.

The most frequent non-specific AEs observed in the uveitis studies were unremarkable. When compared with the placebo group, a clearly higher incidence of nasopharyngitis was observed in the active treatment groups. This event was not followed by a higher incidence of infectious diseases and no dose pattern has been confirmed.

Of note are some well-known class effects such as decreased renal function and hypertension, where a dose-effect relationship is established. The applicant acknowledged that the proportion of patients in the uveitis studies who showed decreased renal function was 8.2% at the proposed market dose of 0.4 mg/kg BID, as compared to 4.1% of those in the control group, even though those values might have been affected by evaluations in Indian patients, and that increased blood pressure was also a common adverse event associated with systemic corticosteroids and calcineurin inhibitors use. About 25% of subjects in the uveitis studies not hypertensive at baseline developed a new-onset hypertension in the voclosporin 0.4 mg/kg group. Since the two main adverse events associated with voclosporin, increased blood pressure and decreased renal function, could be detected easily, it was felt that patients would not be put at excessive risk when treated with voclosporin.

Limited PY exposure precludes any conclusion on other class effects such as neoplasms or nervous system events.

After further discussion it was clarified that the incidence of flutter, atrial fibrillation and QTc prolongations did not seem to be a source of concern, however it was agreed that this risk required further monitoring. For macular oedema the causality was difficult to establish as the sample was too limited to draw meaningful conclusions.

Long-term safety data were limited due to a high rate of discontinuation in the clinical trials. A possibility of requesting PASS to address this issue was discussed.

2.6.2. Conclusions on the clinical safety

Luveniq safety profile was similar to other calcineurin inhibitors with class effects such as renal toxicity, hypertension, or nervous system events. Increased voclosporin toxicity would be expected in renally impaired patients and patients with hepatic impairment. Limitations in long-term safety data could be addressed post- authorisation.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

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

The CHMP, having considered the data submitted in the application, was of the opinion that it was not appropriate to conclude on pharmacovigilance and risk minimisation activities at the time of adoption of CHMP opinion and in view of benefit-risk balance conclusions and CHMP recommendations.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of voclosporin for uveitis was assessed in two controlled, dose-ranging, randomised, multi-centre trials with a subject population that included a variety of aetiologies involving the intermediate and posterior ocular segments. In study LX211-01 only, the 0.4 mg/kg BID dose provided statistically significant efficacy (co-primary endpoint, vitreous haze) and withdrawal of immunosuppressive therapy and/or the use of 5 mg/day or less of prednisone was possible, following a tapering period reflected in the protocol. Neither relevant improvement nor loss of vision was observed in any of the groups.

Uncertainty in the knowledge about the beneficial effects

Only one pivotal study (LX-211-01) in chronic non-infectious active uveitis was statistically significant in the co-primary endpoint (vitreous haze, VH). A formal statistical significance clearly exceeding 0.05 as required for a marketing authorisation application based on one pivotal study has not been achieved. The evidence for efficacy is limited because a very high number of patients (exceeding 60%) of the voclosporin arm needed rescue therapy. The results in patients which finalised the only "successful" study without rescue therapy are not significant for the co-primary endpoint with a slight advantage to placebo at week 24. There is not enough information to consider the effect on VH as clinically relevant.

Voclosporin was not investigated in second-line monotherapy, therefore the efficacy of voclosporin therapy in this indication is not known. In study LX211-01 a true estimation of the magnitude of the treatment effect was not possible as corticosteroids were used following a tapering administration until week 16, the first time-point in which efficacy was assessed. Administration of corticosteroids at a low level (5 mg/day or less) was kept during the whole study period, including the second efficacy assessment time-point at week 24.

Distribution of the study population across regions was not well balanced. One country, India, contributed with nearly 44% of the study participants. Differences in demographic characteristics, metabolism and local analytical routines may have had a relevant impact on efficacy and safety.

The treatment and management of patients according to the warnings and restrictions of the proposed product information may be difficult to apply to uveitis patients requiring clinicians to change the current clinical management of the patients. The efficacy observed in the pivotal clinical study may be further reduced in a real world setting with a less than perfect adherence to the proposed recommendations.

Risks

Unfavourable effects

The most important treatment-related findings were those related to a decreased renal function and/or hypertension.

About 25% of subjects in the uveitis studies not hypertensive at baseline developed a new-onset hypertension in the voclosporin 0.4 mg/kg group. In the placebo group only 4.3% of the subjects showed a new-onset hypertension. Follow-up data revealed that only 56% of the voclosporin-treated subjects recovered, in 24% it was necessary to initiate an antihypertensive medication.

Dose-related decreases in renal function (decrease from baseline in eGFR) were seen in both short-term and long-term treatment. Time to onset was generally less than 4 months. Recovery of renal function was observed in all cases. Time to recovery ranged from 3 to 4 months in most cases.

Uncertainty in the knowledge about the unfavourable effects

It remains unclear how frequently the de novo hypertension will be reversible and how many patients will require continued antihypertensive treatment.

Subgroup analyses for the effects on renal function showed that low baseline sCr values, male gender, South Asian/Indian ethnicity, and subjects with post-baseline hypertension were factors associated with increased risk. Validation of the formula to estimate GFR from serum chemistry analytes in the Indian population is missing. The Indian population showed lower mean height, weight, BMI, sCr, BUN, albumin, magnesium and increased alkaline phosphatase values compared to North Americans/Europeans. These factors may have contributed to the increased risk for decreased renal function and hypertension seen in this group. Of note, in patients receiving 0.4 mg/kg BID no confirmed decreases of > 30% in eGFR were observed in either North America or Europe.

Increased voclosporin exposure was noted in subjects with renal and hepatic impairment. Dose recommendations are proposed for patients developing renal damage and for patients with mild and moderate hepatic damage. However, clinical data are currently not available.

Voclosporin is a substrate of CYP3A4/5 and a substrate/inhibitor of P-glycoprotein (P-gp). Therefore, clinically relevant drug-drug interactions are expected. The available data is very limited regarding co-administration with CYP3A4/5 inhibitors. Further drug-drug interaction studies are needed to develop clear dosing recommendations for situations when co-administration with CYP3A4/5 inhibitors cannot be avoided.

The results of studies where ECG was performed suggest that the overall risk of repolarisation abnormalities for voclosporin at the intended therapeutic dose may be low, but contradictory results observed in a single dose study may need further clarification.

From the non-clinical studies, there are some uncertainties related to presumably species specific events that are currently not known for CsA.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

For patients with chronic non-infectious uveitis there are very limited authorised therapeutic options beyond the treatment with steroids. Continued inflammation results in progredient worsening of visual acuity ending in blindness and has most severe consequences in all parts of the patients' lives.

The most important benefit of voclosporin is the anti-inflammatory effect. It resulted in an improvement in VH with the limitations and uncertainties described above. VH is an important indicator or predictor of a clinical benefit. There are, however, no data to demonstrate to what extent (if any) the effects on VH are translated in benefits the patients actually perceive, e.g. an improvement in visual acuity, avoidance or delay of blindness.

An additional important benefit of voclosporin treatment is a steroid-sparing effect. Though steroids are effective in quickly controlling inflammation, higher doses cannot be used long-term without serious side effects. If steroid doses can be tapered to ≤5 mg/day of prednisone or equivalent most serious adverse effects of steroids are avoided; however, no data were presented on the frequency and severity of the steroid-related adverse effects that can be prevented by voclosporin in patients with chronic non-infectious active uveitis.

The risks of voclosporin appear similar to other calcineurin-inhibitors. Data are limited both with regard to number of patients and treatment duration, resulting in considerable uncertainty about the frequency of serious long-term risks (e.g. neoplasms) or possible rare voclosporin-specific risks. The development of de-novo hypertension was observed in the studies with voclosporin. As the hypertension is frequently irreversible this is regarded as the most important risk observed in the studies. A voclosporin-induced decrease in renal function is usually fully reversible after discontinuation of voclosporin treatment.

Benefit-risk balance

Discussion on the benefit-risk balance

A combination of voclosporin with corticosteroids has demonstrated some positive effect in the treatment of chronic non-infectious active uveitis and the most appropriate dosing regimen seems to be the 0.4 mg/kg BID dose.

Pharmacological activity has been demonstrated in only one pivotal study, with several methodological shortcomings and high uncertainty. A formal statistical significance required for a marketing authorisation application based on one pivotal study has not been achieved for both co-primary endpoints, i.e. statistically evidence considerably stronger than $p<0.05$ has not been shown.

Voclosporin is a narrow therapeutic window product with increased exposure in renal and hepatic impairment. Unfavourable effects were mostly class effects of calcineurin inhibitors, including the possibly irreversible de-novo induction of hypertension and reversibly decreased renal function. In addition, increased voclosporin exposure was noted in subjects with renal and hepatic impairment. Clinically relevant drug-drug interactions cannot be ruled out.

No head-to-head comparison with another second-line active comparator has been performed. In an indirect comparison, the available data neither suggested better efficacy nor better safety than for existing treatments with a considerable degree of uncertainty regarding benefits and risks of voclosporin. In the light of the relatively weak level of evidence for clinical efficacy and the safety profile with serious risks and considerable uncertainty, the benefit risk balance cannot be deemed favourable in the proposed indication at this time.

As the efficacy study in quiescent uveitis was considered as unsuccessful the benefit risk balance appears negative for clinically quiescent uveitis.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Luveniq in the treatment of chronic non-infectious uveitis involving the intermediate or posterior segment of the eye, the CHMP considers by consensus that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The Marketing Authorisation Application for Luveniq (voclosporin) is based on one pivotal study. In cases where the confirmatory evidence is provided by one pivotal study only, this study has to be exceptionally compelling. The Luveniq pivotal study did not show the required statistical evidence considerably stronger than $p<0.05$, nor was it accompanied by precise estimates of treatment effects, and sensitivity analyses questioned the robustness of the results. Whether or to what extent the effect on vitreous haze is clinically relevant, i.e. translates in benefits actually perceived by the patients remains uncertain.

- Taking into account that the efficacy was not convincingly demonstrated and in light of the safety profile of voclosporine the positive benefit-risk balance in the applied for indication has not been established.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and conditions to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.