22 May 2014
EMA/CHMP/81205/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Envarsus

International non-proprietary name: tacrolimus

Procedure No. EMEA/H/C/002655/0000

Note

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

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Product information

Name of the medicinal product:	Envarsus
Applicant:	Chiesi Farmaceutici S.p.A. Via Palermo 26/A 43122 Parma ITALY
Active substance:	tacrolimus monohydrate
International Nonproprietary Name:	tacrolimus
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants, calcineurin inhibitors (L04AD02)
Therapeutic indication(s):	Prophylaxis of transplant rejection in adult kidney or liver allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.
Pharmaceutical form(s):	Prolonged-release tablet
Strength(s):	0.75 mg, 1 mg and 4 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/alu)
Package size(s):	30 tablets, 60 tablets and 90 tablets

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List of abbreviations

ADME	Absorption and bioavailability, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical therapeutic chemical classification
AUC	Area under the plasma concentration/time curve
AUC0-12	Area under the plasma concentration/time curve from time 0 to 12 hours
AUC0-24	Area under the plasma concentration/time curve from time 0 to 24 hours
AUC0-t	Area under the plasma concentration/time curve from time 0 to the last measurable time point
AUC0-∞	Area under the plasma concentration/time curve from time 0 to infinity
AUC%Extrap	Percentage of AUC0-∞ that is due to extrapolation from tlast to infinity
AUCτ	Area under the plasma concentration/time curve during a dosage interval
b.i.d.	Twice-a-day [Lat. Bis in die]
BMI	Body mass index
BPAR	Biopsy proven acute rejection
Cavg	Average plasma concentration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent (oral) clearance
Cmax	Maximum concentration observed in plasma
Cmin	Trough concentrations
CV	Coefficient of variation
C12	Concentration observed 12 hours after dosing
C24	Concentration observed 24 hours after dosing
CYP	Cytochrome P450
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
Fluctuation	Degree of concentration fluctuation at steady state
Form.	Formulation
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
Kel	First order terminal elimination rate constant
ICH	International Conference on Harmonisation
IL	Interleukin
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MA	Marketing authorisation
MAA	Marketing authorisation application
MELD	Model for end stage liver disease
MMF	Mycophenolate mofetil
NC	Not calculated
NF-AT	Nuclear factor of activated T-cells
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
q.d.	Once daily [Lat. Quaque die]
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
Swing	Degree of concentration swing at steady state [(Cmax - Cmin)/Cmin]
t½	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
Tlag	Lag time
Tmax	Time to reach Cmax
TEAE	Treatment emergent adverse event
URTI	Upper respiratory tract infection
UTI	Urinary tract infection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Chiesi Farmaceutici S.p.A. submitted on 29 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Envarsus, through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 February 2012.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference medicinal product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: "prophylaxis of transplant rejection in adult kidney allograft recipients".

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, a bridging study with the reference medicinal product and appropriate non-clinical and clinical data.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 January 2008 and 18 March 2010. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturer(s) responsible for batch release

CHIESI FARMACEUTICI S.P.A.
VIA SAN LEONARDO 96
43122
PARMA
ITALY

Rottendorf Pharma GmbH
Ostenfelder Strasse 51-61
D-59320 Ennigerloh
Germany
Veloxis Pharmaceuticals A/S
Bøge Allé 5, 2. th., Hørsholm, 2970, Denmark

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 29 April 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 August 2013.
- During the meeting on 19 September 2013, 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 26 September 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 January 2014.
- During the CHMP meeting on 20 March 2014, 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 List of Outstanding Issues on 16 April 2014.
- During the meeting on 22 May 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Envarsus.

2. Scientific discussion

2.1. Introduction

Problem statement

Tacrolimus (ATC code: L04AD02) is a potent immunosuppressive agent approved for the prophylaxis of organ rejection (Prograf - first approved product (liver, kidney or heart allograft recipients) and subsequently Advagraf (kidney or liver allograft recipients)) (both MAH is Astellas). Advagraf is a tacrolimus sustained release capsule formulation approved in the EU in 2007.

This is a centralised marketing authorisation application for Envarsus (0.75 mg, 1 mg and 4 mg) which is a prolonged release formulation of tacrolimus designed for once daily oral administration. This application is made under Article 10(3) of Directive 2001/83/EC with Advagraf (EU/1/07/387/001-026) as European reference medicinal product. The applicant has submitted data to bridge with the reference medicinal product Advagraf (Study 1017). This study supports the bridge under article 10(3) of Directive 2001/83/EC with the reference medicinal product. Furthermore the applicant has submitted additional data to support the differences with the reference medicinal product (different strengths, different pharmaceutical form) including several clinical studies in order to support the efficacy and safety of Envarsus (LCP-Tacro)) in comparison to the clinical comparator Prograf, an authorised and widely used tacrolimus product. Prograf (immediate release tacrolimus UK PL00166/0206 MAH Astellas Pharma Europe B.V.) authorised in the EU in 1999 is used as the clinical comparator in the studies' supporting the differences versus the reference medicinal product (hereinafter 'additional data'). Advagraf and Prograf are part of the same global marketing authorisation according to article 6 of Directive 2001/83/EC.

About the product

Tacrolimus blocks T-cell activation and proliferation by inhibiting the activity of the calcium-activated serine threonine phosphatase, Calcineurin. Tacrolimus reduces the expression of several cytokine genes that are normally induced on T-cell activation. These include interleukin-2, whose synthesis by T-lymphocytes is an important growth signal for T cells (Vicari-Christensen et al., 2009). The suppression of T-cell activation by tacrolimus inhibits the subsequent generation of cytotoxic lymphocytes and thereby down-regulates the processes leading to acute graft rejection.

Although the pharmacotherapeutic mainstay in post-transplant immunosuppression, the PK profile of tacrolimus is characterized by high degree of inter- and intra-individual variability (Venkataramanan et al., 1995). Therefore, standard dosing is not an accurate predictor of actual drug exposure. In clinical practice, tacrolimus dose adjustments are required based on monitoring of tacrolimus trough blood concentrations, which correlate well with the area under the concentration-time curve (AUC) and provide an acceptable measure of exposure.

Type of application and aspect on development

This application has been submitted in accordance with Article 10(3) of the Directive 2001/83/EC– hybrid application – application for a medicinal product referring to a so-called reference medicinal product with a Marketing Authorisation in a Member State or in the Union on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC and which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA.

The European reference medicinal product authorised is Advagraf: Prolonged-release capsule, hard; Marketing authorisation number: Astellas Pharma Europe B.V.; Marketing authorisation number: EU/1/07/387/001-026 date of authorisation: 23.04.2007

Studies supporting the differences versus the reference medicinal product (hereinafter 'additional data') includes the 'standard-of-care' Prograf as clinical comparator (immediate release tacrolimus UK PL00166/0206 MAH Astellas Pharma Europe B.V. authorised in the EU in 1999) as Advagraf and Prograf are part of the same global marketing authorisation according to article 6 of Directive 2001/83/EC.

Scientific Advice was sought twice from the CHMP. In 2008, with respect to the proposed q.d. dosing of LCP-Tacro, the CHMP agreed that the data available at that time supported q.d. dosing and stated that "reduced PK variability may lead to a possible therapeutic advantage in terms of reduced need for dose monitoring". Additionally, the CHMP was generally in agreement with the proposed clinical Phase 2 and Phase 3 development programmes in support of a Marketing Authorisation Application (MAA) (CHMP Scientific Advice, January 2008).

In March 2010, the CHMP indicated that data from clinical Phase 1 and Phase 2 studies alone are not anticipated to be sufficiently robust to establish therapeutic equivalence of LCP-Tacro to the standard-of-care Prograf in the respective patient populations. However, this was based upon review of the protocols for planned clinical Phase 2 and 3 studies only. Further evidence is now available and included in the present MAA by inclusion of the Phase 2 study results from Study LCP-Tacro 2017 and data from the pivotal clinical Phase 3 Study LCP-Tacro 3001. The CHMP also clearly stated "that the proposal to submit phase III studies after the grant of MAA is not acceptable since the phase II studies do not appear to be sufficiently robust in establishing equivalence of LCP-Tacro in relevant patient populations, in particular *de novo* transplant patients. The inclusion of Study 3001 in the initial MAA package is unlikely to overcome this problem". Further evidence is now available and included in the present MAA by inclusion of the data from the pivotal clinical Phase 3 Study LCP-Tacro 3002.

The CHMP also indicated that the size of the proposed safety database for appears acceptable to support a MAA and that "extrapolation to the wider tacrolimus bibliographic data would be feasible" (CHMP Scientific Advice, March 2010).

During the procedure, the Applicant has changed the proposed invented name from Tacrolimus Veloxis to Envarsus.

2.2. Quality aspects

2.2.1. Introduction

Envarsus is presented as prolonged-release tablets containing 0.765mg, 1.02mg and 4.08mg of tacrolimus monohydrate which are equivalent to 0.75mg, 1mg and 4mg of tacrolimus, respectively as active substance.

Other ingredients are: hypromellose, lactose monohydrate, polyethylene glycol, poloxamer, magnesium stearate, tartaric acid, butylated hydroxytoluene and dimethicone

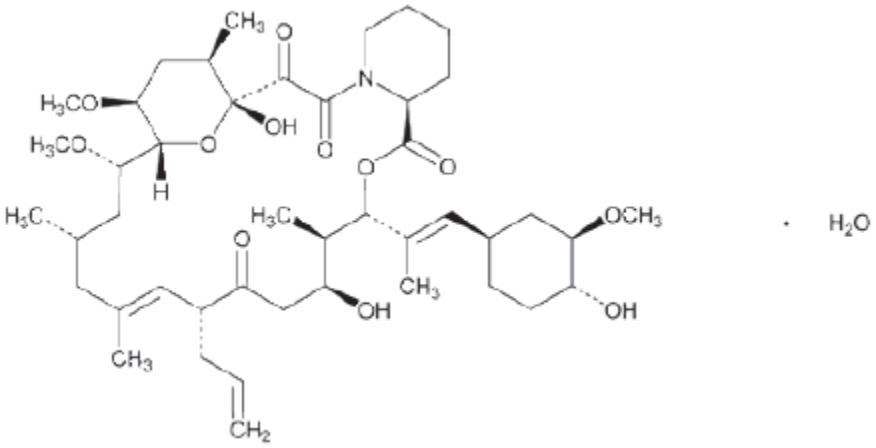
The product is available in PVC blisters, packed in an aluminium foil wrapper containing a desiccant.

2.2.2. Active Substance

The chemical name of tacrolimus monohydrate is:

(1R,9S,12S,13R,14S,17R,21S,23S,24R,25S,27R)-1,14-dihydroxy-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-23,25-dimethoxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetronemonohydrate

and has the following structure:



Tacrolimus is a well-known active substance which is not described in the European Pharmacopoeia. Tacrolimus is white to off-white powder; it is soluble in methanol, ethanol, acetone, ethyl acetate and chloroform. It is insoluble in water. Tacrolimus is an optically active molecule. The results obtained across batches confirm the right stereochemistry of the molecule.

The structural elucidation of Tacrolimus is evidenced based on the route of manufacture and Elemental Analysis, Infrared Spectroscopy (IR), (1H NMR), (13C NMR), and Mass Spectroscopy. Other characteristics like crystalline nature and polymorphism have been demonstrated by using Differential Scanning Calorimetry (DSC) and Powder X Ray Diffraction (XRD).

In the solid state tacrolimus exists as one conformer, in aqueous solutions tacrolimus epimerises to two tautomers, reaching an equilibrium containing three forms. This is considered an inherent property of the molecule, and the tautomeric forms do not alter the efficacy and safety of tacrolimus. Pharmacological activities of tautomer I and II have been reported to be similar to that of tacrolimus, and the immunosuppressive activity of tacrolimus was found to be associated with the cis-trans conversion.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

An ASMF is used for information on the drug substance. The structure of tacrolimus has been adequately proven and its physico-chemical properties sufficiently described. The synthesis of tacrolimus is well described. The manufacturing process has been differentiated as process A and process B. Manufacturing process validation data has been provided for both processes.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification has been established in-house by the ASMF holder and the applicant. Both specifications include tests for description, identification (IR, HPLC), water content (Ph Eur), Residue on ignition (Ph Eur), specific optical rotation (Ph Eur), residual solvents (GC), heavy metals (Ph Eur), related substances and assay (HPLC).

All methods and acceptance criteria included in the drug substance specifications of the ASMF holder and applicant have been described and justified and are acceptable.

Batch analysis data and certificate of analysis (CoA's) have been presented by the active substance manufacturer demonstrating compliance with the drug substance specification for three commercial scale batches of the original manufacturing process and of three commercial scale batches of the optimized process.

Stability

Stability data was provided for three process A batches of the active substance at 25ºC/60% RH (60 months) and 40ºC/75% RH (6 months) and three process B batches of the active substance at long term conditions 25ºC/60% RH (12 months) and accelerated conditions 40ºC/75% RH (6 months) as per ICH guidelines. The batches were stored in packaging material used for routine storage and distribution of the active substance (double transparent low density polyethylene (LDPE) bags closed with plastic ties. A silica gel sachet is placed between the two LDPE bags and does not come into contact with the drug substance. The sealed LDPE bags are then placed inside aluminium containers).

The following parameters were tested: Description, identification (IR, XRD), water content (KF), specific optical rotation (Ph. Eur), content of tautomers (HPLC), Assay (HPLC) and related substances (HPLC).

Both process A and process B batches remain stable at long term conditions; no significant changes and specific trends have been observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The product is developed as a prolonged-release formulation. Pharmaceutical development is described with special regard to formulation development especially with respect to the development of the erodible matrix containing hypromellose as the release controlling polymer.

The purpose of the formulation was to obtain a stable formulation (a solid dispersion of tacrolimus in a polymer matrix of polyglycols) with the purpose of increasing the bioavailability of this poorly water-soluble active substance. The product was formulated to achieve once daily dosing with reduced strengths as compared to the immediate release reference medicinal product formulation requiring twice daily dosage.

The applicant used the MeltDose technology to develop the product in the form of prolonged-release tablets. The MeltDose technology produces granules suitable for direct compaction into tablets. The extended release properties of this tablet formulation make it suitable for a once a- day dosing. The drug release is extended by means of an erodible matrix containing hypromellose as the release controlling polymer.

Three tablet strengths are intended to be marketed. The 0.75mg strength is the lowest proposed strength that will be marketed. However, the applicant did not carried out any bioequivalence studies to confirm the adequacy of the dose and provided only supportive dissolution studies. After the assessment of the 0.75mg strength vis-à-vis development program it can be stated that the formulation of the 0.75mg strength is virtually identical to the 1mg formulation with the only differences being that the vehicle ingredients are increased in the 0.75mg strength to compensate for the lower amount of active.

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation

The lowest strength for which a bioequivalence study was carried out was the 0.5mg strength (not marketed) (formulation D) bioequivalence was shown.

The formulation and manufacturing parameters that can affect the performance of the finished product in regard to the *in vitro* dissolution profile of tacrolimus were investigated. Excipients were selected based on their compatibility with the active substance, manufacturability, and impact on performance of the finished product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging is PVC blisters containing 10 prolonged-release tablets. 3 blisters are packed together in an aluminium foil wrapper containing a desiccant. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

The applicant provided a BSE statement form the manufacturer of Lactose Monohydrate and a declaration from the manufacturer of Magnesium Stearate stating that Magnesium Stearate is of plant origin.

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process is considered as a non-standard process in view of the MeltDose technology used. The manufacturing process for tacrolimus prolonged-release tablets consists of the following steps: melting and dissolving active substance, fluid bed granulation, sieving of granules, mixing of granules with extra granular excipients and compression into tablets. The first steps, melting and dissolving API, fluid bed granulation and sieving, are identical for all strengths. The process is adequately described and the critical process parameters have been discussed. Appropriate IPC have been put in place. For the validation of the manufacturing process for tacrolimus prolonged-release tablets, 3 consecutive batches of each of the commercial strengths were manufactured in commercial scale and tested according to the proposed release specification which is acceptable. The applicant also carried out additional testing to further confirm that the process is suitably qualified to be used for commercial manufacture.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The specification was elaborated in accordance with Ph. Eur. general monographs: “Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use”. The applied methods are based on Ph. Eur. or are in-house methods.

The control of finished product quality is done via in-house specifications. The product specification includes tests for appearance (visual), identification (HPLC; colorimetric test), assay of tacrolimus

(HPLC), assay of BHT (HPLC) uniformity of dosage units (HPLC), degradation products (HPLC), dissolution (HPLC), water content (KF), and microbial test (Ph Eur). The release and shelf life specifications differ with regard to uniformity of dosage, assay of BHT and identification.

The analytical methods were adequately described and validated. Batch analytical data were presented for six commercial batches (2 batches per strength) produced by the proposed commercial manufacturing process, demonstrating compliance with the release specification and confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial batches per strength stored at 25°C/60%RH (30-36 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months) according to the ICH guidelines were provided. The batches were stored in the primary packaging for commercial supply.

During stability studies the following parameters are controlled: appearance, assay of the active substance (HPLC), related substances (HPLC), dissolution (HPLC), moisture content (KF) and microbiological purity (Ph. Eur). The ranges of controlled parameters are appropriate for verification of quality and stability of the drug product

Photo-stability studies were also carried-out in accordance to ICH guideline Q1B. One batch per strength was placed on the stability study. Results of the studies confirmed that Tacrolimus prolonged-release tablets are sensitive to light and should be protected from light during storage.

The applicant also carried out in-use stability studies on tacrolimus prolonged release tablets which were carried out on blister cards which have been removed from the aluminium bag and the desiccant discarded. Two studies were carried out, the first covering a 30 day test point whilst the second covered a three month test period. In order to comply with the requirements of the Note for Guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99) to test at least one batch towards the end of its shelf-life, a 24 months old drug product batch was selected for the in-use stability study, which was completed at the 3 month test station. In the first in-use study 12-months old drug product was used.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of tacrolimus are well known. The new formulation is not expected to alter the pharmacology of tacrolimus (such as the immunosuppressant characteristics and actions on non-immune systems which have been thoroughly evaluated as part of the previous MA for tacrolimus), no further non-clinical studies were provided by the applicant and this was deemed acceptable by the CHMP. The non-clinical overview based on literature review provided by the applicant is, thus, appropriate to support the non-clinical aspects of this MAA.

2.3.2. Pharmacology

Tacrolimus is a well-known macrolide immuno-suppressant. Its pharmacology in the prevention and treatment of organ transplant rejection is well documented in the literature. No new pharmacodynamic studies have been performed in relation to this application. A summary review of the most salient pharmacology studies is presented as part of this assessment.

Primary pharmacodynamic studies

Tacrolimus has been demonstrated to act via several mechanisms of actions with the central mechanism for its immunosuppressive action being the inhibition of the activated serine threonine phosphatase, calcineurin, in T-lymphocytes. The molecular mechanism of tacrolimus has been extensively studied and reviewed in the literature. In essence this involves the inhibition of the activated serine threonine phosphatase, calcineurin, in T-lymphocytes which is the central mechanism for the immunosuppressive action of tacrolimus (Plosker and Foster, 2000; Scott et al, 2003).

Immunosuppressive Action

Tacrolimus is a highly potent immunosuppressive agent and has proven activity and efficacy in both *in vitro* and *in vivo* studies. *In vitro* tacrolimus has been demonstrated to inhibit the proliferative responses of lymphocytes to allogen and mitogen stimulation, the cytotoxic T-cell generation, the expression of the IL-2 receptor and the production of IL-2, IL-3 and IFN- γ (Kino et al, 1987; Scott et al, 2003). The immunosuppressive efficacy of tacrolimus has been demonstrated in various animal models of transplantation (Collier et al., 1987; Muarase et al, 1987; Ochiai et al, 1987; Inamura et al., 1988; Todo et al, 1987, 1988; Jiang et al, 1999; Kinugasa et al., 2008). Most of these studies have now been superseded by clinical data.

Actions in Non Immune Tissues

Adverse side effects of tacrolimus including neurotoxicity and post-transplant diabetes are suggested to result from the inhibition of calcineurin. Calcineurin and FKBP12 are abundant in the central nervous system and evidence has been provided that calcineurin mediated NF-AT activation is also necessary for gene transcription within nerve cells. Thus inhibition of calcineurin could form the basis for the

pathophysiology of neurotoxicity observed in patients on calcineurin inhibitor therapy (Tan and Robinson, 2006).

Calcineurin inhibition may also contribute to post-transplant diabetes by diminishing β-cell survival and replication (Soleimanpour et al, 2010). Following treatment with tacrolimus, human β-cell apoptosis was significantly increased. Tacrolimus significantly decreased rodent β-cell replication, no human β-cell replication was observed. The relevance of calcineurin in β-cell growth and function was further demonstrated in a murine model of β-cell specific calcineurin deletion (Heit et al, 2006). The mice displayed a phenotype of age-dependent diabetes and decreased β-cell proliferation. Expression of numerous genes known to be critical for β-cell function and proliferation was reduced.

Tacrolimus-induced TGF-ß hyperexpression has been implicated in the nephrotoxicity observed with the clinical use of tacrolimus (Plosker and Foster, 2000). Further possible mechanisms for the development of a nephrotoxicity include modulation of cyclic adenosine monophosphate (cAMP) dependent signaling and activation of NFκB in fibroblasts and mesangial cells.

Safety pharmacology programme

The impact of tacrolimus administration upon the cardiovascular system was investigated by both *in vitro* and *in vivo* animal studies.

Electrophysiologiological Effects

In vitro in human embryonic kidney 293 cells supra-therapeutic concentrations of tacrolimus (>0.1 µmol/l) inhibited the hERG potassium channel with a maximum inhibition of 28% at 10 µmol/l (Kise et al, 2009).

In isolated rat ventricular myocytes it has been demonstrated that tacrolimus has the potential to directly inhibit the transient outward potassium current (I_{to}) and the delayed rectifier potassium current (I_k) and prolongs the action potential (DuBuell, et al, 1997). Prolongation of the action potential by tacrolimus was suggested to be more complex as previously reported by Fauconnier et al, 2005. In single rat ventricular cells using the whole cell clamp method to record action potentials and ionic currents, the prolongation of the action potential was demonstrated to result from an inhibition of three distinct potassium currents: the delayed rectifier current (I_k >80%), the transient outward current (I_{to} <20%) and the inward rectifier current (I_{k1} >40%). In addition, a use dependent increase in Ca^{++} entry, initiated by frequency dependent facilitation of I_{CaL} has permissive effects for the occurrence of early after depolarizations with a contribution of I_{NaCa}.

In vivo a sustained QTc prolongation was induced in guinea pigs by tacrolimus administered intravenously at drug concentrations corresponding to its therapeutic range (Minematsu et al, 1999). In line with this finding, the QTc interval and $MAP_{90(sinus)}$ were prolonged by tacrolimus in a dose-related manner in the halothane-anesthetized dog (Kise et al 2009).

Clinical case reports exist in the literature suggesting tacrolimus to be associated with a prolongation of the QT interval, an increase in QTc dispersion or torsade de point in transplant patients (Johnson et al, 1992; Hodak et al, 1998; Gerhardt et al, 2001; Nishimura et al, 2002).

Haemodynamic effects

Tacrolimus was demonstrated to increase mean arterial blood pressure in the conscious rat (Gardiner et al, 2004). Hypertension is one of the most common adverse events that occur in patients treated with tacrolimus (Plosker and Foster, 2000), which is reflected in the product information.

2.3.3. Pharmacokinetics

No non-clinical studies have been conducted to evaluate the pharmacokinetic profile of LCP-Tacro tablets. The pharmacokinetics parameters and profile for LCP-Tacro tablets were evaluated as part of the development program in two Phase 1 studies in healthy volunteers and four Phase 2 studies in kidney and liver transplant patients. Distribution, metabolism, and excretion of tacrolimus or potential pharmacokinetic drug interactions with tacrolimus are well described in the literature and are briefly summarized below.

Absorption

Data from the literature has shown that tacrolimus is able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed. Absorption is variable and the mean oral bioavailability of tacrolimus is in the range of 20%-25% (individual range in adult patients 6%-43%).

No absorption studies were conducted by the applicant and this is acceptable to the CHMP.

Distribution

Data from animal studies described in the literature has shown that tacrolimus is distributed extensively in the body into most tissues including the lungs, spleen, heart, kidney, pancreas, brain, muscle and liver (Scott et al, 2003). In renal and liver transplant patients receiving intravenous tacrolimus, the volume of distribution was 1.41 and 0.85 L/kg.

No distribution studies were conducted by the applicant and this is acceptable to the CHMP.

Metabolism

Data from literature has shown that tacrolimus is extensively metabolized in the liver and small intestine and so far eight metabolites have been identified (Iwasaki et al, 2007). Metabolite formation is qualitatively similar across species. Formation of the major metabolite (M-1) is the first step and main pathway of tacrolimus metabolism. Tacrolimus is predominantly metabolized by the CYP3A subfamily including rat CYP3A2 and human CYP3A4 and CYP3A5 (M-1 formation and total metabolism). Other human CYPs such as the 1A, 2A, 2C, 2D and 2E subfamilies do not metabolize tacrolimus and M-1.

Using a mixed lymphocyte reaction system, metabolite M-II is active while the major metabolite M-1 and other metabolites showed only weak or negligible activity (Iwasaki et al, 2007).

Several single nucleotide polymorphisms (SNPs) have been identified in the genes encoding for CYP3A4 and CYP3A5 and recent studies focused on the relationship of the CYP3A5 genotype and the dose selection of tacrolimus (Staaz et al, 2010 a, b). However, to date, it is not clear whether pharmacogenetic profiling can be a useful clinical tool for personalizing immunosuppressant therapy.

No metabolism studies were conducted by the applicant and this is acceptable to the CHMP.

Excretion

Data from literature has shown that following intravenous injection of 14C-labelled tacrolimus to rats, 95% of the dose was excreted in the faeces (Iwasaki et al, 2007). In bile duct cannulated rats excretion of radioactivity was mainly in the bile (82% of the dose) suggesting that the bile is the main route of elimination. Less than 0.4% of unchanged tacrolimus was detected in the urine, bile and faeces of rats after intravenous and oral administration.

No excretion studies were conducted by the applicant and this is acceptable to the CHMP.

Pharmacokinetic drug interactions

Tacrolimus is a substrate of CYP3A4/5 and p-glycoprotein (Iwasaki et al, 2007).

Concomitant use of inhibitors or inducers of the hepatic and intestinal microsomal CYP3A isoenzymes may affect tacrolimus metabolism and may cause an increase or decrease of tacrolimus blood level which may impact the efficacy or the toxicity of the compound. Therefore, the monitoring of tacrolimus blood levels is recommended when compounds which have the potential to alter the CYP3A metabolism are used concomitantly and to adjust the dose as appropriate.

The potential interactions between tacrolimus and CYP3A inhibitors or inducers have been extensively reviewed (Iwasaki, 2007; Scott et al, 2003). CYP3A4 inhibitors and induces potentially leading to increased or decreased tacrolimus blood levels.

Tacrolimus in addition has been described as an inhibitor of CYP3A (Amundsen et al, 2012) and may affect the metabolism of other medicinal products.

Tacrolimus is extensively bound to plasma proteins (approximately 99%) and interactions may occur with compounds which are also highly protein-bound (Nagase et al, 1994).

2.3.4. Toxicology

The toxicity of tacrolimus has been previously well described in the literature. Therefore, no new toxicity studies were conducted by the applicant with the prolonged release formulation of tacrolimus, which is accepted by the CHMP.

Single dose toxicity

No single dose toxicity studies were conducted by the applicant which was considered acceptable by the CHMP.

Repeat dose toxicity

Signs of general toxicity as well as the target organs of toxicity have been identified. Target organs of toxicity include the kidneys, the pancreas, the heart, the nervous system, the eyes and the lymphoid organs.

Kidneys: The kidneys have been identified as major target organs of tacrolimus toxicity (Ohara et al., 1990). In oral repeat dose toxicity studies in the rat (13-week), histopathological findings included mineralisation at the corticomedullary junction and basophilic staining of cortical tubules. These findings were associated with an increase in blood urea nitrogen (BUN) levels. In baboons, BUN was also increased following repeated oral administration of tacrolimus (13- week) and an interstitial inflammation with basophilic staining of the tubule was observed. In the cynomolgus monkey repeat intramuscular administration of tacrolimus (90 days) induced mesangelial cell proliferation and acute tubular necrosis which was associated with an increase in serum urea (Wijnen et al, 1992). The acute initial phase of tacrolimus-induced nephrotoxicity was suggested to be reversible and to consist of a reduction of the glomerular filtration rate and a reduction of the renal blood flow (constriction of the renal arteriole) caused by an increase in vasoconstrictor factors such as thromboxane and the activation of the renin-angiotensin system (Mitamura et al, 1994; Finn, 1999; Nakatani et al, 2003). Furthermore, evidence was provided that also reductions of vasodilator factors including nitric oxide contribute to tacrolimus induced glomerular vascular dysfunction (Wang et al, 2001).

Pancreas: Repeat administration of tacrolimus to experimental animals caused glucose intolerance and toxic changes in the pancreas consisting of cytoplasmic swelling, vacuolization, and apoptosis of ß-cells (Ohara et al., 1990; Ericszon et al, 1992; Hirano et al, 1992; Wijnen et al., 1992; Larsen et al., 2006, Hernandez-Fisac et al, 2007). These effects were demonstrated to be reversible following dose reduction or following a recovery period. Tacrolimus was shown to decrease insulin content, to impair insulin secretion and insulin transcription in pancreatic islets and ß-cell lines (Oetjen et al, 2003; Uchizono et al, 2004; Radu et al, 2005; Hernandez-Fisac et al, 2007; Øzbay et al, 2011).

Heart: Although no signs of cardiotoxicity were observed in previous repeat dose toxicity studies conducted in rats (13-week, orally, up to 3.2 mg/kg/day), dogs (2-week orally up to 1 mg/kg/day) and baboons (4-week, intravenously, up to 2 mg/kg/day and 13-week, orally, up to 36 mg/kg/day) (Ohara et al, 1990), cardiotoxic effects were found in rabbits following 4-week intravenous administration of tacrolimus at dose levels of 0.1, 0.2 and 0.4 mg/kg/day (Nomoto et al, 1994). The findings consisted of a dose-dependent myocarditis and few cases of severe myocardial necrosis in the high and medium dose group. The myocardial lesions when mild were reversible following a recovery period of 28 days. Significant left ventricular dilatation was evident even in the low-dose group. The finding was similar in degree to the high dose group. Cardiomyopathy was also observed in the Cynomolgus monkey following repeated intramuscular administration of tacrolimus (Wijnen et al., 1992).

Nervous System: Neurotoxic events were reported following repeat administration of tacrolimus to rats (Sakamoto et al, 2000). In Rhesus monkeys, repeat oral administration of tacrolimus (up to 25 mg/kg/day) caused fine tremors beginning at 6 to 12 weeks of dosing without histopathological correlates (Kindt et al., 1999).

Eyes: Cataracts developed in rats following repeat oral dosing of tacrolimus (Ohara et al, 1990). This has been attributed to an accumulation of sorbitol in the lens secondary to the diabetogenic effects of tacrolimus (Ishida et al., 1997).

Lymphoid Organs: Due to the immunosuppressive action of tacrolimus atrophy of lymphoid tissues was observed in experimental animals following repeat administration (Ohara et al, 1990, Wijnen et al., 1992). Over the past decade of clinical use with tacrolimus, clinical side effects have been associated with the kidney, pancreas/glycaemic control, eye and heart in treated patients and appear consistent with the findings of the repeat-dose studies (Plosker and Foster, 2000; Scott et al, 2003)

Genotoxicity

No mutagenic or clastogenic effect induced by tacrolimus was detected in a standard battery of genotoxicity testing including bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, and *in vivo* clastogenicity assays in mice. In addition, tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes (Prograf Label, 2012).

A published report showed that tacrolimus increased micronuclei in human lymphocyte cultures (Oliveira et al, 2004). However, the test was not fully performed according to OECD 487. Criteria, such as the number of cultures, the maximum concentrations, concentration-related increases or a reproducible increase in the number of cells containing micronuclei, or considerations whether the observed values are within or outside of the historical control range, were not provided or discussed. Therefore, the biological relevance of this result cannot be judged. In the light of the negative *in vivo* clastogenicity assays in mice it is concluded that tacrolimus has no clastogenic potential.

Carcinogenicity

According to the data provided, no dose-response relationship of the tumour incidence was observed in an 80-week mouse study and a 104-week rat study. The doses tested were 4 to 10.8 times the clinical dose (0.075 to 0.2 mg/kg/day) when corrected for body surface area.

However, in a 24-month dermal carcinogenicity study in mice an increased incidence of lymphoma which was associated with high systemic exposure was detected following daily application with 0.1% tacrolimus ointment (Protopic label, 2011). Tacrolimus also increased lymphomas in mouse herpes virus (RadLV+) mice providing evidence that viral carcinogenesis can play an important role in the neoplasms associated with immunosuppressive drugs (Mistrikova et al, 1999).

A statistically significant reduction in time to skin tumour (squamous cell carcinomas) development and an increase in the number of tumours were observed in a photocarcinogenicity study in albino hairless mice which were chronically treated with tacrolimus ointment. It is unknown whether this was a local or systemic effect (Protopic label, 2011).

Furthermore, tacrolimus induced a dose-dependent metastatic progression in a mouse model of renal cancer cell pulmonary metastasis (Maluccio et al, 2003).

It has been well documented that long-term immunosuppression significantly increases the risk for the development of neoplasms in transplanted patients. Malignancies which have been particularly associated with the use of immunosuppressive drugs include lymphoma/lymphoproliferative disorders, Kaposi sarcoma and squamous cell carcinoma (Bugelski et al, 2010). The etiology of post-transplant malignancies likely involves impaired immune surveillance mechanisms and a depressed antiviral immune activity. In addition, direct tumourigenic effects were discussed in the literature (Hojo et al, 1999; Maluccio et al, 2003; Datta et al, 2009; Suthanthiran et al, 2009). For example, calcineurin inhibitors including tacrolimus were demonstrated to enhance transforming growth factor- ß1 (TGF-ß1) expression, induce TGF-ß1 secretion by tumour cells and promoted tumour progression in T-cell, B-cell and NK-cell deficient SCID-beige mice.

Reproduction Toxicity

Treatment with tacrolimus adversely affected male and female reproduction and caused embryo-foetal toxicity in rats and rabbits (Saegusa et al., 1992, Hisatomi et al, 1996).

In the fertility study in rats a higher rate of pre-implantation loss, lower pup viability, increased number of undelivered pups and birth defects were observed in the high dose group at a dose level of 3.2 mg/kg/day (Saegusa et al., 1992). In the embryo-foetal toxicity study in rats, foetal weight was reduced and there was a greater incidence of skeletal variations in the high dose group (3.2 mg/kg/day). In rabbits, abortion occurred at the intermediate dose (0.32 mg/kg/day) and the high dose (1.0 mg/kg/day) level. In a study on peri- and postnatal development in rats viability and growth of the offsprings from the high dose group was reduced and were related to the maternal toxicity of tacrolimus.

Tacrolimus dose-dependently decreased sperm counts and motility in male mature rats, but did not affect serum testosterone levels following a daily subcutaneous dose of 1 or 3 mg/kg/day for 2 weeks (Hisatomi et al, 1996). There were no histopathological findings in the testis, seminal vesicle or prostate in any treated rats. Intraductal eosinophilic globules, probably degeneration of the sperm cells, were observed in the epididymis of the 3 mg/kg/day group. The effects on sperm counts and motility returned to the control levels after stopping of the drug. When the tacrolimus treated males were mated with drug naive females, no effects on copulation or fertility index were observed, but a decrease in the number of live foetuses associated with implantation loss was observed in the 3 mg/kg/day group which were attributed to the decrease of sperm counts and motility.

Limited data from organ transplant recipients showed no evidence of an increased risk of adverse reactions on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. As discussed by McKay and Josephson, 2008, the impact of immunosuppressive exposure on the developing foetus is often measured by the presence of structural malformation at birth; however, calcineurin inhibitors may also exert other effects not apparent at birth. For example, calcineurin inhibitors were shown to inhibit elimination of self-reactive T-cells during thymic development leading to autoimmunity in animal models. Furthermore, the high level of calcineurin and FKBP12 in the foetal brain and the functional changes induced by stimulation with tacrolimus raises concerns about potential neurocognitive deficits.

Toxicokinetic data

Local Tolerance

No local tolerance studies have been conducted with the applied tacrolimus formulation. These studies are not deemed necessary by the CHMP since the tacrolimus dose level/concentration in the gastrointestinal tract is not expected to exceed that obtained following administration of the clinical comparator Prograf. Furthermore, excipients of the tacrolimus prolonged-release tablets conform to the European Pharmacopoeia and are used at common dose levels.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP4447/00], a justification for the absence of an environmental risk assessment (ERA) has been provided. The applicant stated that LCP-Tacro tablets will replace similar products already marketed in the European Union/European Economic Area. Thus, an increase of the environmental exposure is not expected with this medicinal product.

The justification was considered acceptable by the CHMP.

2.3.6. Discussion on non-clinical aspects

Tacrolimus is a well-known macrolide immuno-suppressant. Its pharmacology in the prevention and treatment of organ transplant rejection is well documented in the literature. Tacrolimus has been demonstrated to act via several mechanisms of actions with the central mechanism for its immunosuppressive action being the inhibition of the activated serine threonine phosphatase, calcineurin, in T-lymphocytes. No new pharmacodynamic, safety or drug interaction studies have been performed by the applicant in relation to this application. The absence of new studies is considered acceptable by the CHMP as the pharmacodynamics of tacrolimus have been extensively characterised within the literature and various models of organ transplantation as well as being clinically well established and used worldwide for more than a decade as an immunosuppressive agent. No new pharmacodynamic drug interaction studies have been submitted. Pharmacodynamic drug interactions with tacrolimus are known and well documented in the reference product's product information. No new pre-clinical pharmacokinetic or drug interaction studies have been submitted in relation to LCP-Tacro. The applicant has submitted existing published literature in support of the pharmacokinetics and pharmacodynamics of LCP-Tacro.

These data suggest that tacrolimus has the potential to prolong the QT interval. Despite the absence of these types of events in the LCP-Tacro clinical development program, this finding has been addressed in the product information as follows: "Tacrolimus may prolong the QT interval but at this time lacks

substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome".

No new repeat dose toxicity studies have been submitted in relation to LCP-Tacro. The toxicity of tacrolimus has been previously well characterised in relation to signs of general toxicity as well as the identification of the target organs of toxicity including the kidney, pancreas, eyes, nervous system and the heart as well as lymphoid organs. Due to the immunosuppressive action of tacrolimus atrophy of lymphoid tissues was observed in experimental animals following repeat administration. In line with these findings, the product information mentions the following: "The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus".

The adverse effects of tacrolimus on reproduction and development in experimental animals are adequately addressed in the product information.

Due to the developmental and reproductive toxicity of tacrolimus in experimental animals and the lack of sufficient epidemiological data, tacrolimus treatment in pregnant women is only recommended when the perceived benefit justifies the potential risk to the foetus (as mentioned in the product information).

2.3.7. Conclusion on the non-clinical aspects

The non-clinical literature data provided by the Applicant was considered adequate to support this application for the Prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.

Tacrolimus is a well-known macrolide immuno-suppressant. Its pharmacology in the prevention and treatment of organ transplant rejection is well documented in the literature. No new pharmacodynamic studies have been performed in relation to this application which is acceptable to the CHMP.

The toxicity of tacrolimus both pre-clinical and clinical has previously been well characterised with the organs of toxicity identified and no new toxicity concerns are expected with LCP-Tacro. Animal data clearly indicate that systemic treatment with tacrolimus adversely affects male and female reproduction. With respect to reproductive toxicity and carcinogenicity, LCP-Tacro does not differ from the reference medicinal product and the proposed wordings in the product information are considered to adequately address these concerns.

The justification for the absence of an environmental risk assessment is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

The Applicant has conducted four early pilot studies, two Phase 1 studies in adult healthy volunteers, three Phase 1 bioavailability studies in adult healthy volunteers with LCP-Tacro versus either Advagraf or Prograf, and four Phase 2 studies in adult kidney and liver transplant patients which have investigated the pharmacokinetics of tacrolimus from LCP-Tacro tablets.

The four early pilot studies were designed to test the inter-subject variability, relative bioavailability and/or pharmacokinetic profiles of different test formulations of LCP-Tacro 2 mg tablets versus the marketed clinical reference product, Prograf capsules (LCP-Tacro PK-001, LCP-Tacro PK-002, and LCP-Tacro PK-004) or to evaluate the colon absorption of LCP-Tacro 2 mg tablets (LCP-Tacro PK-003).

The first Phase 1 study, LCP-Tacro 1013, was designed to evaluate the dose linearity of tacrolimus pharmacokinetic parameters after administration of LCP-Tacro tablets at three dose levels (5 mg, 7 mg and 10 mg). The second Phase 1 study, LCP-Tacro 1014, investigated the effect of morning administration compared with evening administration of a single LCP-Tacro 2mg tablet on the pharmacokinetics of tacrolimus.

The three Phase 1 bioavailability studies, were two-way crossover multiple dose studies designed either to compare the bioavailability of LCP-Tacro tablets with the marketed clinical reference product Prograf (LCP-Tacro 1012, LCP-Tacro 1016) or with Advagraf (LCP-Tacro 1017).

The first two Phase 2 studies (LCP-Tacro 2011 and LCP-Tacro 2012) were designed to establish the comparative bioavailability of tacrolimus from LCP-Tacro tablets once daily (q.d.) compared with Prograf capsules twice daily (b.i.d.) in stable kidney and liver transplant patients, respectively. The studies were also designed to validate the dose conversion ratio for substituting LCP-Tacro for Prograf in Phase 3 studies. Patients who completed the liver study (LCP-Tacro 2012) were eligible to enter a 1-year extension study, where they received LCP-Tacro for up to 1 year.

The Applicant also conducted two, prospective, open-label, randomized, parallel group studies to determine the pharmacokinetics of LCP-Tacro in *de novo* kidney and liver transplant patients (LCP-Tacro 2017 and LCP-Tacro 2018, respectively). Following completion of the pharmacokinetic assessments in study LCP-Tacro 2017 and 2018, patients in these studies continued to receive either LCP-Tacro or Prograf for up to 360 days for the evaluation of additional secondary efficacy and safety parameters respectively.

In addition to the above, the Applicant has conducted a further nine Phase 1 studies (comparative bioavailability and bioequivalence studies) in healthy male and female volunteers.

Seven comparative bioavailability/bioequivalence studies were conducted to investigate: one vs. two LCP-Tacro tablets dosing units (Study LCP-Tacro 1018); one to establish the relative bioavailability of differently sized low- and high-dose LCP-Tacro tablets (Study LCP-Tacro 1024); one to demonstrate bioequivalence between different formulations used in the clinical development programme of LCP-Tacro tablets, namely Formulations D, E, and F in comparison with the final formulation (Formulation G) (Studies LCP-Tacro 1019, LCP-Tacro 1020, LCP-Tacro 1021, LCP-Tacro 1022, and LCP-Tacro 1023).

One food effect study was also conducted to determine the effect of food on the PK of tacrolimus after administration of LCP-Tacro tablets (Study LCP-Tacro 1011).

The relative bioavailability of LCP-Tacro tablets has been compared to matched doses of the marketed immediate-release Prograf capsules in studies LCP-Tacro 1015 LCP-Tacro 1012,LCP-Tacro 1016 (both steady state studies) and the modified-release product Advagraf in study LCP-Tacro 1017).

To support the application two pivotal phase III studies in stable and *de novo* kidney transplant patients (3001 & 3002) have also been submitted.

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.

Table 1 Tabular overview of clinical studies

Study No.	Developmental Need; Objectives	Study Drugs

Early Clinical Pilot Trials		
LCP-Tacro PK-001	PK (inter-subject variability, relative BA, PK profiles)	T1: Tacrolimus tablet 2 mg IR T2: Tacrolimus tablet 2 mg IR-EC T3: Tacrolimus tablet 2 mg CR-GMS R: Prograf 1-mg capsule
LCP-Tacro PK-002	PK; Safety	Tacrolimus tablet 2 mg HMPC (Form A) Prograf 1-mg capsule
LCP-Tacro PK-003	PK (transit time, PK profile, site of release, inter- and intra-subject variability)	LCP-Tacro tablet (Form A), radiolabelled (^{153}Sm)
LCP-Tacro PK-004	PK (bioavailability); Safety	LCP-Tacro 2-mg tablets q.d.(Form A) Prograf 1-mg capsules b.i.d.
Clinical Phase 1		
LCP-Tacro 1011	PK (BA, food effect)	LCP-Tacro 5-mg tablets (fasted/fed) (Form B) Prograf 5-mg capsules (fasted)
LCP-Tacro 1012	PK (comparative BA LCP- Tacro vs. Prograf); Safety	Treatment A: LCP-Tacro 2-mg tablets q.d. (Form B) Treatment B:Prograf 1-mg capsules b.i.d.
LCP-Tacro 1013	PK (dose linearity LCP- Tacro tablets 5, 7 and 10 mg doses)	Treatment A: LCP-Tacro 5-mg tablet (Form C) Treatment B: LCP-Tacro 5-mg tablet + LCP-Tacro 2-mg tablet (Form C) Treatment C: LCP-Tacro 5-mg tablet (Form C)
LCP-Tacro 1014	PK (chronoPK; morning vs. evening administration)	Treatment A: LCP-Tacro 2-mg tablet (evening dose) (Form C) Treatment B: LCP-Tacro 2-mg tablet (morning dose) (Form C)
LCP-Tacro 1015	PK (comparative BA LCP- Tacro vs. Prograf); Safety	Treatment A: LCP-Tacro 1-mg tablet (Form C) Treatment B: Prograf 1-mg capsule
LCP-Tacro 1016	PK (comparative BA LCP- Tacro q.d. vs. Prograf 0.5 mg capsules b.i.d.); Safety	Treatment A: LCP-Tacro 1-mg tablets q.d. (Form C) Treatment B: Prograf 0.5-mg capsules b.i.d.
LCP-Tacro 1017	PK (comparative BA: LCP-Tacro q.d. vs. Advagraf 1 mg capsules q.d.); Safety	Treatment A: one LCP-Tacro 2-mg tablet q.d. (Form. C) Treatment B: two Advagraf 1-mg capsules q.d.
LCP-Tacro 1018	PK (comparative BA: LCP-Tacro 0.5mg tablets vs. LCP-Tacro 1mg tablets); Safety	Treatment A: two LCP-Tacro 0.5-mg tablets (Form. D) Treatment B: one LCP-Tacro 1-mg tablet (Form. C)
LCP-Tacro 1019	PK (comparative BA / BEat steady-state: LCP-Tacro1.5mg tablets q.d., LCP- Tacro 1mg tablets q.d., LCP-Tacro 1-mg tablets q.d.)	Treatment A: two LCP-Tacro 1.5-mg tablets (Form. E) q.d. Treatment B: three LCP-Tacro 1-mg tablets (Form. E) q.d. Treatment C: three LCP-Tacro 1-mg tablets (Form. D) q.d.
LCP-Tacro 1020	PK (comparative BA / BE of LCP-Tacro 1-mg tablets (Form. F vs. D) at steady- state)	Treatment A: one LCP-Tacro 1-mg tablet (Form. F) q.d. Treatment B: one LCP-Tacro 1-mg tablet (Form. D) q.d.
LCP-Tacro 1021	PK (comparative BA / BE of LCP-Tacro 5-mg tablets (Form. F vs. Form. D) at steady-state)	Treatment A: one LCP-Tacro 5-mg tablet (Form. D) q.d. Treatment B: one LCP-Tacro 5-mg tablet (Form. F) q.d.

LCP-Tacro 1022	PK (comparative BA/BE of LCP-Tacro 2 mg tablets (Form. G vs. Form. F) at steady-state)	Treatment A: one LCP-Tacro 2-mg tablet (Form. F) q.d. Treatment B: one LCP-Tacro 5-mg tablet (Form. G) q.d.
LCP-Tacro 1023	PK (comparative BA/BE of LCP-Tacro 4-mg tablets (Form. G vs. Form. F) at steady-state)	Treatment A: one LCP-Tacro 4-mg tablet (Form. G) q.d. Treatment B: one LCP-Tacro 4-mg tablet (Form. F) q.d.
LCP-Tacro 1024	PK (comparative BA of high-low-dose strengths of LCP-Tacro tablets at steady-state); Safety	Test: one LCP-Tacro 4-mg tablet (Form. F) q.d. Reference: four LCP-Tacro 1-mg tablets (Form. F) q.d.

Clinical Phase 2

LCP-Tacro 2011	PK (steady-state tacrolimus exposure (AUC_{0-24}) and trough levels (C_{24}) in stable kidney transplant patients converted from Prograf capsules to LCP-Tacro tablets); Safety (incl. efficacy-relevant outcomes: graft failure and death, acute allograft rejection)	Study Period 1 (Days 0-7): Fixed-dose Prograf capsules (b.i.d.) Study Period 2 (Days 8-14): On Day 8, patients were converted to fixed dose LCP-Tacro tablets (q.d.) using a dose conversion ratio ranging from 0.66-0.80 (Form. C). Study Period 3 (Day 15-21): Patients remained on LCP-Tacro (q.d.) until Day 21 (Formulation C). Dose adjustment allowed on Day 15 if tacrolimus trough levels changed by > 25% (up or down)
LCP-Tacro 2012	PK (steady-state tacrolimus exposure (AUC_{0-24}) and trough levels (C_{24}) in stable liver transplant patients converted from Prograf capsules to LCP-Tacro tablets); Safety	Study Period 1 (Days 0-7): Fixed-dose Prograf capsules (b.i.d.) Study Period 2 (Days 8-14): On Day 8, patients were converted to fixed-dose LCP-Tacro tablets (q.d.) using a dose conversion ratio ranging from 0.66-0.80 (Forms C and D). Study Period 3 (Day 15-21): Patients remained on LCP-Tacro (q.d.) until Day 21 (Forms C and D). Dose adjustment allowed on Day 15 if tacrolimus trough levels changed by >25% (up or down)
LCP-Tacro 2012E	Safety (long-term; LCP-Tacro for maintenance immunosuppression in stable liver transplant recipients converted from Prograf capsules); PK	LCP-Tacro tablets (q.d.), dosed to maintain tacrolimus whole blood trough levels between ~5 and 15 ng/mL (Forms C and D).
LCP-Tacro 2017	PK (LCP-Tacro (AUC_{0-24} and C_{max}) and 24-hour trough levels (C_{24}) early after transplantation (within the first 14 days) in adult *de novo* kidney transplant recipients); Proportion of patients achieving sufficient tacrolimus whole blood trough levels (7 to 20 ng/mL) during first 14 days post-transplantation; Efficacy; Safety	PK Phase (Days 1-14): LCP-Tacro tablets (q.d.) (Form. D); Starting dose: 0.14 mg/kg (0.17 mg/kg for Black patients) vs. Prograf capsules (b.i.d.); Starting dose: 0.1 mg/kg every 12 hours (0.2 mg/kg total daily dose) Maintenance Phase (Days 15-360): Patients remained on their assigned medication until Day 360

LCP-Tacro 2018	PK (LCP-Tacro (AUC_{0-24} and C_{max}) and 24-hour trough levels (C_{24}) early after transplantation (within the first 14 days) in adult *de novo* liver transplant recipients); Proportion of patients achieving sufficient tacrolimus whole blood trough levels (5 to 20 ng/mL) during first 14 days post-transplantation; Efficacy; Safety	PK Phase (Days 1-14): LCP-Tacro tablets (q.d.) (Form. D); Starting dose: 0.07-0.11 mg/kg (0.09-0.13 mg/kg for Black patients) vs. Prograf capsules (b.i.d.); Starting dose: 0.1-0.15 mg/kg every 12 hours (0.2-3 mg/kg total daily dose). Maintenance Phase (Days 15-360): Patients remained on their assigned medication until Day 360
Clinical Phase 3		
LCP-Tacro 3001	Efficacy (LCP-Tacro tablets q.d. when used to replace Prograf capsules b.i.d. for maintenance immunosuppression for prevention of acute allograft rejection in adult renal transplant patients); Safety	Based on the results from Study LCP-Tacro 2011, patients were converted from Prograf capsules to LCP-Tacro tablets (Form. D) using a dose conversion multiplier of 0.7 (0.85 for Black patients). Following randomization, 163 patients were converted to LCP- Tacro tablets (q.d.) and 163 patients continued on Prograf capsules (b.i.d.).
LCP-Tacro 3002	Efficacy (LCP-Tacro tablets q.d. versus Prograf capsules b.i.d. for prevention of acute allograft rejection in adult *de novo* renal transplant patients); Safety	Double-blind, double-dummy, multicenter, prospective, randomised; Adult (18–70 years) *de novo* kidney transplant patients; Patients are randomised 1:1 to: LCP-Tacro tablets (q.d.) Starting dose 0.17 mg/kg/day or Prograf capsules (b.i.d.) Starting dose 0.1 mg/kg/day (Oral administration); 613 patients were enrolled into the study, 543 patients were randomly assigned to study drug: 268 to the LCP-Tacro group and 275 to the Prograf group.

2.4.2. Pharmacokinetics

Overview of Biopharmaceutics

The prolonged-release product LCP-Tacro has been developed to allow for once daily dosing using the MeltDose technology. MeltDose, as proposed by the applicant, is a validated drug-delivery technology platform aimed to enhance bioavailability of low water solubility drugs by obtaining a solid dispersion in a polymer matrix of polyglycols. The granules are suitable for direct compaction into tablets. The drug release is sustained by means of an erodible matrix containing hypromellose as release-controlling polymer. Hypromellose and magnesium stearate constitute the extra-granular phase in the tablet dosage form.

Bioanalytical Methods

A liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay was developed and validated for quantification of tacrolimus in human whole blood. The same basic method was used throughout the studies. Evaluation of this LC-MS/MS assay was carried out by the construction of an eight-point calibration curve (excluding zero concentration) which was validated with the concentration range of 0.200 to 25.600ng/mL ± 10% for tacrolimus in human whole blood. The slope and intercept of the calibration curves were determined through weighted linear regression analysis (1/conc2.). Two calibration curves and duplicate quality control (QC) samples (at three or four concentration levels, depending on the study) were analysed along with each batch of the study samples. Peak area ratios

were used to determine the concentration of the standards, QC samples, and the unknown study samples from the calibration curves. The lower limit of quantification (LLOQ) across most of the Phase 1 and Phase 2 studies was 0.200ng/mL.

For studies LCP-Tacro 1017, LCP-Tacro 1018, and LCP-Tacro 1019, additional information was provided in the corresponding study analytical reports on the solid phase extraction into an organic medium and (LCP-Tacro 1018 and LCP-Tacro 1019 only) subsequent evaporation and reconstitution of the mobile phase. Method sensitivity and selectivity were achieved by detecting distinct precursor to production mass transitions for tacrolimus (821.5 −>768.5) and the internal standard rapamycin (931.6−>864.7) at defined retention time under reversed phase chromatographic conditions.

The bioanalytical method was validated for precision and accuracy, linearity of the calibration curves, absolute recovery, selectivity, dilution integrity, carry over and matrix effects in line with the EMA guideline on the validation of the bioanalytical method (EMEA/CHMP/EWP/192217/2009). Other validation experiments included the determination of interference with over-the-counter (OTC) drugs (including but not limited to caffeine, ibuprofen, salicylic acid, acetylsalicylic acid, acetaminophen, and nicotine) and oral contraceptives. No interfering peaks were observed with any of the tested analytes.

Bioequivalence between LCP-Tacro Formulations C, D, F and Commercial Formulation G

Bioequivalence between the LCP-Tacro tablet formulations used in clinical trials (Formulations C, D, E and F) and the commercial Formulation G was established via the individual clinical Phase 1 comparative PK and bioavailability/bioequivalence studies linking the respective formulations. Apart from Study LCP-Tacro 1018 (single-dose), the main objective was to demonstrate bioequivalence between the respective formulations at steady-state under multiple-dose fasting conditions. In Study LCP-Tacro 1019, bioequivalence assessments were performed on two tablet strengths for Formulation E and of two different formulations (Formulations E and D). As Formulation E has never been further pursued in clinical trials, study 1019 is not further discussed here.

Bioequivalence of Formulations C and D and Formulations D and F

Study LCP-Tacro 1018 evaluated the bioavailability of tacrolimus from a single oral dose of two LCP-Tacro 0.5-mg tablets (Formulation D) vs. one LCP-Tacro 1.0-mg tablet (Formulation C). This was a Phase 1, randomized, open-label, single-dose, two-way crossover study in 24 normal, healthy male and female volunteers, aged 18-50 years, all Caucasian, under fasting conditions.

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated by standard non-compartmental methods: AUC0-24, AUC0-t, AUC0-inf, AUC% Extrap, Cmax, Tmax, t½, Kel, and CL/F.

Results

The peak and overall systemic exposures of tacrolimus were comparable between the two treatments with no statistical differences observed: geometric mean ratios (two LCP-Tacro 0.5-mg tablets/one LCP-Tacro 1.0-mg tablet) of AUC0-24, AUC0-t, AUC0-inf, and Cmax ranged from 99.00-107.27%. In addition, the 90% confidence intervals (CIs) for comparison between dose strength for AUC0-24 and AUC0-t were within EMA-recommended 90- 111% acceptance ranges for bioequivalence (EMA/618604/2008 Rev. 8) and AUC0-inf was only just outside; 90% CIs for the comparison of Cmax were within the recommended 80-125% range. Therefore, two LCP-Tacro 0.5 mg tablets and one LCP-Tacro 1 mg tablet of Formulation C and D, respectively, exhibited similar bioavailability.

Table 5 Pharmacokinetic Parameters for Tacrolimus (Study LCP-Tacro 1018)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	2 × LCP-Tacro 0.5 mg Tablets (A) (n=23)	1 × LCP-Tacro 1 mg Tablet (B) (n=23)
AUC_{0-24} (ng·hr/mL)	26.07 (31.62) 27.29 ± 8.63	25.87 (31.31) 27.10 ± 8.48
AUC_{0-t} (ng·hr/mL)	48.42 (49.31) 53.49 ± 26.38	48.75 (43.78) 53.68 ± 23.50
AUC_{0-inf} (ng·hr/mL)	70.20 (41.59) 75.58 ± 31.44 †	71.14 (32.67) 74.42 ± 24.31 †
$AUC_{\%Extrap}$	20.20 ± 9.75	20.25 ± 8.88 ‡
C_{max} (ng/mL)	1.97 (33.41) 2.08 ± 0.69	1.83 (35.64) 1.94 ± 0.69
T_{max} (hr)*	9.00 (6.02 – 16.00)	7.00 (2.00 – 12.00)
$t_{½}$ (hr)	28.45 ± 12.01 †	30.23 ± 9.60 †
K_{el} (hr^{-1})	3.19E-02 ± 2.54E-02 †	2.51E-02 ± 8.15E-03 †
CL/F (L/hr)	15.50 ± 7.80 †	14.66 ± 4.29 †

* median (min – max)
† n = 14
‡ n = 22

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR TACROLIMUS:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC_{0-24}	93.52% to 108.10%	100.55%	14.34%
AUC_{0-t}	90.24% to 108.61%	99.00%	18.40%
AUC_{0-inf}	91.22% to 114.91%	102.38%	15.70%
C_{max}	95.41% to 120.60%	107.27%	23.37%

Studies LCP-Tacro 1020 and LCP-Tacro 1021 were conducted to demonstrate bioequivalence of LCP-Tacro 1-mg and 5-mg tablets (Formulation F vs. Formulation D), respectively.

LCP-Tacro 1020: a Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP-Tacro 1 mg Tablets (Formulation F) Versus LCP-Tacro 1 mg Tablets (Formulation D) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated: Primary- AUC0-24, AUCτ and Cmax.

Secondary parameters- Tmax, Cpd, C24, Cmin, Cavg, % Fluctuation,% Swing, Accumulation ratio (R) (AUC τ (Day 8) / AUC0-24 (Day 1)), Cmax/Cmin, AUC τ /Cmin.

Results

On day 1, the single dose pharmacokinetics of tacrolimus from LCP-Tacro Formulations D and F were comparable, although the extent of exposure was slightly higher with Formulation D compared with Formulation F, based on AUC0-24 and Cmax. For both formulations, maximum tacrolimus concentrations were achieved 8 hours following drug administration. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 33-45%.

On average, tacrolimus concentrations at the end of the first dosing day (C24) were comparable between Formulations D and F.

Table 6 Pharmacokinetic Parameters for Tacrolimus on Day 1 (Study LCP-Tacro 1020)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 1-mg Tablet (Formulation F) (n=45)	LCP-Tacro 1-mg Tablet (Formulation D) (n=45)
AUC_{0-24} (ng·h/mL)	22.81 (33.24) 24.04 ± 7.99[b]	26.39 (34.92) 28.23 ± 9.86[b]
C_{24} (ng/mL)	0.89 (40.67) 0.97 ± 0.39[b]	0.92 (44.67) 1.04 ± 0.46[b]
C_{max} (ng/mL)	1.51 (34.87) 1.61 ± 0.56	1.86 (35.44) 1.99 ± 0.71
T_{max} (h) [a]	8.00 (3.00 – 14.03)	8.00 (1.00 – 16.02)

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1020, Table 11.4.1
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)
[b] n=44

The multiple dose pharmacokinetics of tacrolimus on Day 8 were similar, although the extent of exposure was approximately 10% lower for formulation F compared with Formulation D, based on AUC_T. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 10-43%.

Table 7 Pharmacokinetic Parameters for Tacrolimus on Day 8 (Study LCP-Tacro 1020)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 1-mg Tablet (Formulation F) (n=44)	LCP-Tacro 1-mg Tablet (Formulation D) (n=44)
AUC_τ (ng·h/mL)	56.79 (27.93) 59.35 ± 16.58	62.90 (27.58) 65.50 ± 18.06
AUC_τ/C_{min}	33.11 (10.40) 33.27 ± 3.46	32.43 (10.37) 32.60 ± 3.38
C_{avg} (ng/mL)	2.37 (27.91) 2.47 ± 0.69	2.62 (27.58) 2.73 ± 0.75
C_{max} (ng/mL)	3.20 (27.38) 3.34 ± 0.92	3.35 (25.61) 3.47 ± 0.89
C_{max}/C_{min}	1.87 (20.11) 1.90 ± 0.38	1.73 (17.72) 1.75 ± 0.31
C_{min} (ng/mL)	1.72 (32.88) 1.82 ± 0.60	1.94 (31.59) 2.05 ± 0.65
T_{max} (h) [a]	8.00 (4.00 – 16.00)	8.00 (0.00 – 24.00)
C_{pd} (ng/mL) [c]	1.88 (31.88) 1.99 ± 0.63	2.17 (33.48) 2.30 ± 0.77[b]
Degree of fluctuation (%)	60.39 (32.15) 63.48 ± 20.41	50.95 (32.68) 54.02 ± 17.65
Degree of swing (%)	83.28 (42.41) 90.23 ± 38.26	68.85 (41.20) 75.50 ± 31.10
R	2.53 (20.27) 2.58 ± 0.52[b]	2.38 (28.22) 2.47 ± 0.70

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1020, Table 11.4.2
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)
[b] n=43

Table 8 Relative Bioavailability of LCP-Tacro 1-mg Tablets Formulation F and Formulation D in the Fasted State on Day 8 (Study LCP-Tacro 1020)

Comparison	Parameter	90% CI	Ratio of Means (%)	Intra-Subject CV (%)
LCP-Tacro 1-mg Tablet (Formulation F) *vs.* LCP-Tacro 1-mg Tablet (Formulation D)	AUC_{τ}	85.22 – 95.65	90.28	16.21
	C_{max}	89.81 – 101.80	95.62	17.60

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1020, Table 11.4.3
CI=confidence interval; CV=coefficient of variation

The bioavailability of tacrolimus from LCP-Tacro 1-mg tablets Formulation F and Formulation D was similar on Day 1 and Day 8. On Day 8, formulations F and D were bioequivalent for Cmax and approached bioequivalence for AUCτ.

The single dose and multiple dose pharmacokinetics of tacrolimus following daily administration of one LCP-Tacro 1 mg tablet (Formulation F) and one LCP-Tacro 1-mg tablet (Formulation D) were comparable.

For Formulation F, the extent of exposure was lower, based on AUC0-24 and Cmax (single dose pharmacokinetics) and AUCτ (multiple dose pharmacokinetics).

The variability in tacrolimus pharmacokinetics following administration of Formulations D and F was moderate and ranged from 33-45% on Day 1 and 10-43% on Day 8.

LCP-Tacro 1021: a Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP-Tacro 5 mg Tablets (Formulation F) Versus LCP-Tacro 5 mg Tablets (Formulation D) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.

Bioequivalence was assessed by comparing the Cmax and AUCτ of tacrolimus from the two LCP-Tacro 5-mg tablet formulations (Formulation F and D) on Day 8.

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated:

Primary- AUC0-24, AUCτ, Cmax.

Secondary parameters- Tmax, Cpd ,C24, Cmin, Cavg, % Fluctuation,% Swing, Accumulation ratio (R) (AUC τ (Day 8) / AUC0-24 (Day 1)), Cmax/Cmin, AUC τ /Cmin.

Steady-State Assessment: The achievement of steady-state was assessed by comparing the pre-dose concentrations (Day 8 vs. 7, Day 7 vs. 6 and Day 6 vs. 5) for each treatment.

Results

On Day 1, the single dose pharmacokinetics of tacrolimus from LCP-Tacro Formulations D and F were comparable. For both formulations, maximum tacrolimus concentrations were achieved 6 hours following drug administration. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 27-42%. On average, tacrolimus concentrations at the end of the first dosing day (C24) were slightly lower following administration of Formulations D compared with Formulation F.

Table 9 Pharmacokinetic Parameters for Tacrolimus on Day 1 (Study LCP-Tacro 1021)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 5-mg Tablet (Formulation F) (n=39)	LCP-Tacro 5-mg Tablet (Formulation D) (n=39)
AUC_{0-24} (ng·h/mL)	140.69 (29.09) 146.57 ± 42.63	130.40 (28.76) 136.43 ± 39.23
C_{24} (ng/mL)	4.23 (35.24) 4.49 ± 1.58	3.55 (41.63) 3.87 ± 1.61
C_{max} (ng/mL)	10.65 (31.31) 11.16 ± 3.49	11.29 (27.39) 11.78 ± 3.23
T_{max} (h) [a]	6.00 (1.00 – 12.00)	6.00 (1.50 – 12.12)

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1021, Table 11.4.1
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)

Steady-state tacrolimus concentrations were observed for both treatment groups on Day 8 following comparison of pre-dose concentrations on Days 5, 6 7 and 8. The mean pharmacokinetic parameters for tacrolimus on Day 8 are summarized in the table below.

Table 10 Pharmacokinetic Parameters for Tacrolimus on Day 8 (Study LCP-Tacro 1021)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 5-mg Tablet (Formulation F) (n=37)	LCP-Tacro 5-mg Tablet (Formulation D) (n=37)
AUC_{τ} (ng·h/mL)	284.10 (19.94) 290.78 ± 57.97	295.92 (19.63) 302.02 ± 59.30
AUC_{τ}/C_{min}	36.81 (15.22) 37.18 ± 5.66	37.72 (12.39) 37.99 ± 4.71
C_{avg}·(ng/mL)	11.84 (19.93) 12.12 ± 2.41	12.33 (19.61) 12.58 ± 2.47
C_{max} (ng/mL)	17.93 (22.91) 18.44 ± 4.22	19.62 (20.49) 20.03 ± 4.10
C_{max}/C_{min}	2.32 (21.72) 2.37 ± 0.52	2.50 (28.78) 2.58 ± 0.74
C_{min} (ng/mL)	7.72 (23.05) 7.95 ± 1.83	7.84 (24.62) 8.10 ± 1.99
T_{max} (h) [a]	6.00 (1.00 – 12.07)	6.05 (1.50 – 8.02)
C_{pd} (ng/mL) [c]	8.12 (23.81) 8.38 ± 1.99	8.33 (24.43) 8.59 ± 2.10
Degree of fluctuation (%)	83.78 (25.02) 86.64 ± 21.68	92.61 (34.68) 97.16 ± 33.69
Degree of swing (%)	128.47 (37.54) 137.35 ± 51.56	145.53 (46.95) 158.42 ± 74.38
R	2.03 (24.47) 2.09 ± 0.51	2.28 (28.00) 2.36 ± 0.66

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1021, Table 11.4.2
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)

The multiple-dose pharmacokinetics of tacrolimus on Day 8 were comparable, although the extent of exposure was approximately 9% lower for Formulation F compared with Formulation D, based on AUC_{T}. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 12-47%.

Under fasting conditions the results showed that the 90% CI of the geometric mean Cmax ratio was within the normal 80-125% acceptance range. The 90% CI of the geometric mean AUCT ratio was within the 90-111% acceptance range.

Table 11 Relative Bioavailability of LCP-Tacro 5-mg Tablets Formulation F and Formulation D in the Fasted State on Day 8 (Study LCP-Tacro 1021)

Comparison	Parameter	90% CI	Ratio of Means (%)	Intra-Subject CV (%)
LCP-Tacro 5-mg Tablet (Formulation F) *vs.* LCP-Tacro 5-mg Tablet (Formulation D)	AUC_τ	92.19 – 100.24	96.13	10.68
	C_{max}	86.20 – 97.13	95.50	15.29

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1021, Table 11.4.3
CI=confidence interval; CV=coefficient of variation

Bioequivalence of Formulations F and the Commercial Formulation G

The primary objective of Studies LCP-Tacro 1022 and LCP-Tacro 1023 was to demonstrate bioequivalence of two formulations of LCP-Tacro 2-mg and 4-mg tablets (commercial Formulation G vs. Formulation F), respectively. The two LCP-Tacro 2-mg and the two 4-mg LCP-Tacro tablet formulations were bioequivalent. The 90% CI of the geometric mean Cmax ratio was within the 80-125% acceptance range. Furthermore, the 90% CI of the geometric mean AUCT ratio was within the more stringent 90-111% acceptance range recommended by EMA.

LCP-Tacro 1022: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP-Tacro 2 mg Tablets (Formulation G) Versus LCP-Tacro 2 mg Tablets (Formulation F) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated:

Primary- AUC0-24, AUCT ,Cmax.

Secondary parameters- Tmax, Cpd, C24, Cmin, Cavg, % Fluctuation,% Swing, Accumulation ratio (R) (AUC τ (Day 8) / AUC0-24 (Day 1)), Cmax/Cmin, AUC τ /Cmin.

Results

On Day 1, the single dose pharmacokinetics of tacrolimus from LCP-Tacro Formulations F and G were comparable. For both formulations, maximum tacrolimus concentrations were achieved 8 hours following drug administration. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 29-37%. On average, tacrolimus concentrations at the end of the first dosing day (C24) were comparable between Formulations F and G.

Table 12 Pharmacokinetic Parameters for Tacrolimus on Day 1 (Study LCP-Tacro 1022)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro™ 2 mg Tablets (Formulation G) (B) (n=42)	LCP-Tacro™ 2 mg Tablets (Formulation F) (A) (n=43)
$AUC_{0\text{-}24}$ (ng·hr/mL)	50.38 (30.68) 52.55 ± 16.12	45.72 (29.60) 48.30 ± 14.30
C_{24} (ng/mL)	1.85 (29.57) 1.95 ± 0.58	1.79 (36.54) 1.97 ± 0.72
C_{max} (ng/mL)	3.32 (36.71) 3.52 ± 1.29	3.12 (37.12) 3.34 ± 1.24
T_{max} (hr)*	8.00 (1.00 - 23.83)	8.00 (1.50 - 23.87)

* median (min – max)

Steady-state tacrolimus concentrations were observed for both treatment groups on Day 8 following comparison of concentrations on Days 7 and 8. The mean pharmacokinetic parameters for tacrolimus on Day 8 are summarized in Table 13. The multiple-dose pharmacokinetics of tacrolimus on Day 8 was comparable between Formulations F and G. The median time to maximum blood concentrations of tacrolimus was slightly longer for Formulation F compared with Formulation G, although this was not statistically significant (8 hours vs. 7 hours; p=0.084). There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 13-63%.

Table 13 Pharmacokinetic Parameters for Tacrolimus on Day 8 (Study LCP-Tacro 1022)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro™ 2 mg Tablets (Formulation G) (B) (n=42)	LCP-Tacro™ 2 mg Tablets (Formulation F) (A) (n=43)
AUC_τ (ng·hr/mL)	105.36 (25.05) 108.68 ± 27.23	110.78 (24.82) 114.77 ± 28.48
AUC_τ/C_{min}	33.18 (16.33) 33.52 ± 5.47	32.86 (13.63) 33.14 ± 4.52
C_{avg} (ng/mL)	4.39 (25.05) 4.53 ± 1.13	4.62 (24.82) 4.78 ± 1.19
C_{max} (ng/mL)	5.92 (25.00) 6.12 ± 1.53	5.97 (23.18) 6.15 ± 1.43
C_{max}/C_{min}	1.87 (30.17) 1.93 ± 0.58	1.77 (21.04) 1.81 ± 0.38
C_{min} (ng/mL)	3.18 (29.98) 3.32 ± 1.00	3.37 (30.10) 3.55 ± 1.07
T_{max} (hr)*	7.00 (1.50 - 12.00)	8.00 (0.50 - 14.00)
C_{pd} (ng/mL)	3.38 (30.12) 3.54 ± 1.07	3.71 (28.98) 3.89 ± 1.13
Degree of Fluctuation (%)	57.68 (45.22) 63.56 ± 28.74	53.12 (33.31) 56.22 ± 18.73
Degree of Swing (%)	79.72 (62.48) 93.40 ± 58.36	72.74 (47.12) 80.65 ± 38.00
R	2.09 (30.08) 2.18 ± 0.66	2.42 (50.74) 2.62 ± 1.33

* median (min – max)

Table 14 Relative Bioavailability of LCP-Tacro 2 mg Tablets Formulation G and Formulation F in the Fasted State on Day 8 (Study LCP-Tacro 1022)

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV	Degree of Freedom
AUC_τ	90.06% to 102.16%	95.92%	17.20%	40
C_{max}	93.32% to 107.35%	100.09%	19.15%	40

LCP-Tacro 1023: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP-Tacro 4 mg Tablets (Formulation G) Versus LCP-Tacro 4 mg Tablets (Formulation F) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated by standard non compartmental methods:

Day 1: AUC0-24, Cmax, C24, and Tmax

Days 5, 6, and 7: Cpd

Day 8: AUCτ (τ=24), Cmax, Cmin, Cavg, Tmax, Cpd, % Fluctuation, % Swing, AUCτ/Cmin, Cmax/Cmin, and Accumulation Ratio (R).

Results

On day 1, the single dose pharmacokinetics of tacrolimus from LCP-Tacro Formulations G and F were comparable. For both formulations, maximum tacrolimus concentrations were achieved 6 hours

following drug administration. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 26-43%. Tacrolimus concentrations at the end of the first dosing day (C24) were comparable between Formulations G and F.

Table 15 Pharmacokinetic Parameters for Tacrolimus on Day 1 (Study LCP-Tacro 1023)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 4-mg Tablet (Formulation G) (n=43)	LCP-Tacro 4-mg Tablet (Formulation F) (n=40)
AUC_{0-24} (ng·h/mL)	117.74 (29.16) 123.43 ± 35.99	110.56 (33.97) 116.87 ± 39.70
C_{24} (ng/mL)	3.13 (39.57) 3.43 ± 1.36	3.12 (43.41) 3.42 ± 1.48
C_{max} (ng/mL)	10.04 (26.39) 10.41 ± 2.75	9.11 (32.41) 9.59 ± 3.11
T_{max} (h) [a]	6.00 (1.50 – 8.02)	6.00 (1.50 – 12.00)

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1023, Table 11.4.1
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)

Table 16 Pharmacokinetic Parameters for Tacrolimus on Day 8 (Study LCP-Tacro 1023)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 4-mg Tablet (Formulation G) (n=43)	LCP-Tacro 4-mg Tablet (Formulation F) (n=37)
AUC_{τ} (ng·h/mL)	255.05 (24.19) 262.77 ± 63.57	236.17 (26.47) 245.32 ± 64.95
AUC_{τ}/C_{min}	37.07 (12.51) 37.34 ± 4.67	35.67 (7.94) 35.78 ± 2.84
C_{avg}·(ng/mL)	10.63 (24.20) 10.95 ± 2.65	9.84 (26.47) 10.22 ± 2.71
C_{max} (ng/mL)	17.57 (22.81) 18.01 ± 4.11	16.38 (27.69) 17.05 ± 4.72
C_{max}/C_{min}	2.55 (25.40) 2.63 ± 0.67	2.47 (20.74) 2.52 ± 0.52
C_{min} (ng/mL)	6.88 (28.39) 7.18 ± 2.04	6.62 (28.34) 6.91 ± 1.96
T_{max} (h) [a]	6.00 (1.50 – 12.00)	6.00 (1.00 – 12.00)
C_{pd} (ng/mL) [c]	7.49 (27.84) 7.80 ± 2.17	7.04 (28.59) 7.36 ± 2.10
Degree of fluctuation (%)	97.90 (29.92) 102.23 ± 30.58	96.72 (29.57) 101.02 ± 29.88
Degree of swing (%)	151.21 (41.00) 162.76 ± 66.73	143.74 (34.36) 152.37 ± 52.35
R	2.17 (23.92) 2.22 ± 0.53	2.20 (24.28) 2.26 ± 0.55 [b]

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1023, Table 11.4.2; CV=coefficient of variation; SD=standard deviation; [a] median (min – max); [b] n=36

The mean pharmacokinetic parameters for tacrolimus on Day 8 are summarized in the table 16. The multiple dose pharmacokinetics of tacrolimus on Day 8 were similar, with no statistical difference in total

systemic exposure or Cmax (p>0.05). Median time to Cmax was 6.00 hours for both formulations. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 8-41%.

Table 17 Relative Bioavailability of LCP-Tacro 4-mg Tablet Formulations G and F in the Fasted State on Day 8 (Study LCP-Tacro 1023)

Comparison	Parameter	90% CI	Ratio of Means (%)	Intra-Subject CV (%)
LCP-Tacro 2 mg Tablet (Formulation G) *vs.* LCP-Tacro 2 mg Tablet (Formulation F)	AUC_t	100.64 – 110.81	105.60	12.08
	C_{max}	100.55 – 112.56	106.38	14.17

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1023, Table 11.4.1
CI=confidence interval; CV=coefficient of variation

A summary of the bioequivalence analysis outcomes throughout the comparative bioequivalence studies conducted between the Formulations C, D, F, and G is shown in the table below.

Table 18 Relative Bioavailability of LCP-Tacro Tablet Formulations C, D, F, and G

Study	Comparison	Parameter	Ratio of Means (%)	90% CI
#1018[a]	Form. C (1-mg tablets) vs. Form. D (0.5-mg tablets)	AUC_{0-24} AUC_{0-t} $AUC_{0-\infty}$	100.55 99.00 102.38	93.52 - 108.10 90.24 - 108.61 91.22 - 114.91
		C_{max}	107.27	95.41 - 120.60
#1020	Form. D (1-mg tablets)vs. Form. F (1-mg tablets)	AUC_t	90.28	85.22 – 95.65
		C_{max}	95.62	89.81 – 101.80
#1021	Form. D (5-mg tablets) vs. Form. F (5-mg tablets)	AUC_t	96.13	92.19 – 100.24
		C_{max}	95.50	86.20 – 97.13
#1022	Form. F (2-mg tablets) vs. Form. G (2-mg tablets)	AUC_t	95.92	90.06 – 102.16
		C_{max}	100.09	93.32 – 107.35
#1023	Form. F (4-mg tablets) vs. Form. G (4-mg tablets)	AUC_t	105.60	100.64 – 110.81
		C_{max}	106.38	100.55 – 112.56

Sources: Clinical Study Report LCP-Tacro 1018, Table 11.4.2; Clinical Study Report LCP-Tacro 1020, Table 11.4.3; Clinical Study Report LCP-Tacro 1021, Table 11.4.3; Clinical Study Report LCP-Tacro 1022, Table 11.4.3; Clinical Study Report LCP-Tacro 1023, Table 11.4.1. [a] Single-dose study; AUC=area under the concentration/time curve; CI=confidence interval; C_{max}=maximum concentration; Form.=Formulation

Bioequivalence between LCP Tacro low and high dose strengths (formulation F)

In order to assess the relative bioavailability of low (1 mg) and high dose strength (4 mg) tablets of LCP-Tacro (Formulation F), Study LCP-Tacro 1024 was conducted. The results demonstrated that the differences in the low-dose and high-dose strength formulations do not affect the bioavailability of tacrolimus from LCP-Tacro: LCP-Tacro 4-mg tablet and 1-mg tablet formulations were bioequivalent. The 90% CI of the geometric mean Cmax ratio was within the 80-125% acceptance range. The 90% CI of the clinically relevant geometric mean AUCt ratio was within the more stringent 90-111% acceptance range recommended (EMA/618604/2008 Rev. 8).

Study LCP-Tacro 1024: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Relative Bioavailability Study of LCP-Tacro 1 × 4 mg Tablet (Formulation F) Versus LCP-Tacro 4 × 1 mg Tablets (Formulation F) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects.

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated by standard non compartmental methods:

Day 1: AUC0-24, Cmax, C24, and Tmax

Days 5, 6, and 7: Cpd

Day 8: AUCτ (τ=24), Cmax, Cmin, Cavg, Tmax, Cpd, % Fluctuation, % Swing, AUCτ/Cmin, Cmax/Cmin, and Accumulation Ratio (R).

Results

On Day 1, the single dose pharmacokinetics of tacrolimus from LCP-Tacro Formulation F dosed as one × 4 mg tablet or as four × 1 mg tablets were comparable. For both doses of this formulation, maximum tacrolimus concentrations were achieved 8 hours following drug administration. There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 27-40%. On average, tacrolimus concentrations at the end of the first dosing day (C24) were slightly higher for the four ×1 mg tablets compared to the one × 4 mg tablets.

Table 19 Pharmacokinetic Parameters for Tacrolimus on Day 1 (Study LCP-Tacro 1024)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 1 × 4-mg Tablet (Formulation F) (n=45)	LCP-Tacro 4 × 1-mg Tablet (Formulation F) (n=46)
AUC_{0-24} (ng·h/mL)	117.65 (27.55) 122.29 ± 33.69	119.13 (30.43) 125.45 ± 38.18
C_{24} (ng/mL)	3.20 (33.78) 3.41 ± 1.15	3.89 (40.41) 4.28 ± 1.73
C_{max} (ng/mL)	9.93 (33.10) 10.50 ± 3.47	8.05 (28.32) 8.41 ± 2.38
T_{max} (h) [a]	6.00 (1.00 – 8.00)	8.00 (3.00 – 12.02)

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1024, Table 11.4.1
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)

The mean pharmacokinetic parameters for tacrolimus on Day 8 are summarized below. The multiple-dose pharmacokinetics of tacrolimus on Day 8 was similar in terms of AUCs. However, at steady-state, Cmax was higher after dosing with one 4 mg tablet than after dosing with four 1 mg tablets and trough plasma concentrations were lower; consequently, the peak/trough ratio was also greater. Median Tmax on Day 8 was 6.02 hours for one 4 mg tablet (range: 1.00-12.02 hours) and 7.00 hours for the four 1 mg tablets (range: 1.00-16.02 hours), (p=0.108). There was moderate variability in the tacrolimus pharmacokinetic parameters, with %CV estimates ranging from approximately 11-57%.

Table 20 Pharmacokinetic Parameters for Tacrolimus on Day 8 (Study LCP-Tacro 1024)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	LCP-Tacro 1 × 4-mg Tablet (Formulation F) (n=45)	LCP-Tacro 4 × 1-mg Tablet (Formulation F) (n=46)
AUC_τ (ng·h/mL)	260.29 (23.08) 267.12 ± 61.64	257.29 (24.67) 265.36 ± 65.47
AUC_τ/C_{min}	36.21 (10.97) 36.40 ± 3.99	34.16 (15.92) 34.52 ± 5.49
C_{avg} (ng/mL)	10.83 (23.90) 11.12 ± 2.57	10.71 (24.70) 11.05 ± 2.73
C_{max} (ng/mL)	17.28 (25.85) 17.85 ± 4.61	14.71 (23.48) 15.12 ± 3.55
C_{max}/C_{min}	2.40 (21.04) 2.45 ± 0.52	1.95 (28.80) 2.02 ± 0.58
C_{min} (ng/mL)	7.19 (25.68) 7.42 ± 1.91	7.53 (30.02) 7.91 ± 2.28
T_{max} (h) [a]	6.02 (1.00 – 12.02)	7.00 (1.00 – 16.02)
C_{pd} (ng/mL) [c]	7.94 (30.06) 8.30 ± 2.49	7.93 (29.99) 8.32 ± 2.50
Degree of fluctuation (%)	91.08 (26.14) 94.16 ± 24.61	63.53 (40.26) 67.75 ± 27.28
Degree of swing (%)	137.21 (35.52) 145.18 ± 51.58	90.32 (57.13) 101.64 ± 58.06
R	2.21 (23.55) 2.27 ± 0.54	2.16 (34.34) 2.27 ± 0.78

Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1024, Table 11.4.2
CV=coefficient of variation; SD=standard deviation
[a] median (min – max)

A summary of the bioequivalence analysis outcomes at day 8 between the low- and high-dose tablet strengths is given in table 21.

Table 21 Relative Bioavailability of LCP-Tacro 4-mg Tablets and LCP-Tacro 1-mg Tablets in the Fasted State on Day 8 (Study LCP-Tacro 1024)

Study	Comparison	Parameter	Ratio of Means (%)	90% CI
#1024	Form. F (4-mg tablets) vs. Form. F (1-mg tablets)	AUC_τ	102.19	97.18 – 107.46
		C_{max}	118.40	112.49 – 124.62

Source: Clinical Study Report LCP-Tacro 1024, Table 11.4.3. AUC=area under the concentration/time curve; CI=confidence interval; C_{max}=maximum concentration; Form.=Formulation

Influence of food

The PK of tacrolimus is known to be influenced by food; food effect has been demonstrated for Prograf and Advagraf and is documented in their respective product information. To evaluate food effect on the bioavailability of LCP-Tacro tablets (5 mg; Formulation B), the applicant conducted a randomised, open-label, three way cross-over, single-dose PK study (Study LCP-Tacro 1011). The objectives of this study were to determine and compare the rate and extent of absorption of tacrolimus from a test formulation of LCP-Tacro 5 mg Tablets versus the comparator Prograf 5 mg Capsules under fasting conditions and to evaluate the effect of food on the pharmacokinetics of LCP-Tacro 5 mg Tablets.

Study LCP-Tacro 1011

This was a randomized, open-label, single-dose, three-way crossover study in 27 normal, healthy non-smoking male and female volunteers, aged 18-65 years, all Caucasian. There were three 6-day study periods (Period I: September 10, 2006, period II: September 20, 2006, period III: September 30, 2006).

As expected for prolonged-release product, LCP-Tacro 5-mg tablets produced very similar overall systemic exposure, but lower peak exposure of tacrolimus, with delayed Tmax relative to the immediate-release product Prograf. These results indicated that, under fasting conditions, LCP-Tacro tablets produced similar systemic exposure of tacrolimus to that of Prograf, although the 90% CIs for the comparison of AUC0-t were just outside the acceptance range of 90-111% for bioequivalence. The geometric mean Cmax ratio was 45.24% (90% CI: 40.34-50.75%). This was expected, as after the administration of the LCP-Tacro prolonged-release product, Cmax was ~55% lower than Cmax observed after Prograf ($p<0.05$) and Tmax was significantly delayed by over 3 hours (median value of 5 hours vs. 1.3 hours). Due to the delayed absorption of LCP-Tacro tablets, ~25% lower mean AUC0-12 was observed from LCP-Tacro tablets than that of Prograf. There was no significant difference observed in t1/2 ($p>0.05$), both exhibited a terminal half-life of approximately 35 hours.

Table 22 Relative bioavailability of LCP-Tacro 5 mg in Fed and Fasted states and LCP-Tacro 5-mg and Prograf 5mg in the fasted state.

Comparison	Parameter	90% CI	Ratio of Means	Intra-Subject CV
LCP-Tacro 5-mg Tablet Fed (Treatment A) *vs.* LCP-Tacro 5-mg Tablet Fasted (Treatment B)	AUC_{0-12}	40.24% to 52.35%	48.13%	18.19%
	AUC_{0-24}	41.83% to 49.82%	45.65%	18.92%
	AUC_{0-t}	39.30% to 48.89%	43.83%	23.76%
	$AUC_{0-\infty}$	40.31% to 49.14%	44.50%	21.19%
	C_{max}	69.92% to 87.96%	78.42%	24.99%
LCP-Tacro 5-mg Tablet Fasted (Treatment B) *vs.* Prograf 5-mg Capsule Fasted (Treatment C)	AUC_{0-12}	68.68% to 81.25%	74.70%	18.19%
	AUC_{0-24}	83.36% to 99.29%	90.98%	18.92%
	AUC_{0-t}	92.13% to 114.62%	102.76%	23.76%
	$AUC_{0-\infty}$	95.99% to 117.02%	105.98%	21.19%
	C_{max}	40.34% to 50.75%	45.24%	24.99%

Source: Module 5.3.1.2 LCP-Tacro 1011 Clinical Study Report, Table 11.4.2 and Table 11.4.3
CI=confidence interval; CV=coefficient of variation

Food reduced the systemic exposure to tacrolimus by ~ 55% after the administration of the LCP-Tacro tablets. The food also decreased the peak plasma concentration of tacrolimus by ~22% (mean ratio: 78.42%; 90% CIs: 40.34-50.75%) but no effect was seen on the time to reach Cmax (a median of 5 hours under both fed and fasted conditions). The average terminal half-lives of tacrolimus from LCP-Tacro tablets under both fasted and fed conditions was also similar ($p>0.05$).

Table 23 Summary Statistics of Pharmacokinetic Parameters of Tacrolimus in Healthy Male and Female Subjects for Treatments A, B and C (Study LCP-Tacro 1011)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Treatment A LCP-Tacro 5-mg Tablet – Fed (n=26)	Treatment B LCP-Tacro 5-mg Tablet – Fasting (n=26)	Treatment C Prograf 5-mg Capsules – Fasting (n=26)
AUC_{0-12} (ng·h/mL)	46.88 (27.57) 48.72 ± 13.43	94.49 (25.66) 99.78 ± 25.61	130.40 (30.60) 137.59 ± 42.10
AUC_{0-24} (ng·h/mL)	70.58 (28.39) 73.65 ± 20.91	153.10 (28.33) 159.10 ± 45.08	169.96 (31.35) 180.01 ± 56.43
AUC_{0-t} (ng·h/mL)	131.56 (38.92) 141.85 ± 55.20	296.65 (35.72) 316.77 ± 113.14	292.05 (33.87) 313.41 ± 106.15
$AUC_{0-\infty}$ (ng·h/mL)	145.58 (37.85) 155.83 ± 58.98	328.17 (32.81) [a] 344.76 ± 113.10	308.64 (34.46) 330.89 ± 114.03
C_{max} (ng/mL)	10.86 (33.83) 11.43 ± 3.87	13.73 (30.01) 14.31 ± 4.29	30.59 (27.73) 31.76 ±8.81
T_{max} (h) [b]	5.00 (1.67 – 9.00)	5.00 (1.67 – 8.00)	1.33 (1.00 – 2.00)
t½ (h)	33.32 ± 6.40	35.12 ± 6.95 [a]	35.15 ± 8.39
K_{el} (h^{-1})	2.15E-02 ± 4.06E-03	2.06E-02 ± 4.43E-03 [a]	2.05E-02 ± 3.81E-03

Source: : Module 5.3.1.1 Clinical Study Report LCP-Tacro 1011, Table 11.4.1
a n = 25
b median (min – max)

Dose proportionality and time dependency

In order to investigate dose proportionality and chronopharmacokinetics of LCP-Tacro, the applicant conducted two clinical Phase 1 single-dose PK studies in healthy subjects (Studies LCP-Tacro 1013 [Formulation C], LCP-Tacro 1014 [Formulation C]). In addition, a systematic review of PK studies on LCP-Tacro tablets in terms of dose proportionality was also provided.

Dose proportionality

LCP-Tacro 1013: A Three-Way Crossover, Randomized, Open-Label, Single-Dose, Fasting, In-Vivo, Dose Linearity Study Of Tacrolimus Administered As LCP-Tacro Tablets At The Doses Of 5 mg, 7 mg, And 10 mg In Normal, Healthy, Non-Smoking Male And Female Subjects

There were 27 subjects dosed in Period I, 24 of whom completed the study. Two subjects were dismissed because of administrative reasons and 1 subject withdrew for personal reasons. Pharmacokinetic and statistical analyses were performed on 25 subjects—the 24 subjects who completed all 3 study periods and 1 subject (#002) for whom there was enough data for a meaningful analysis.

Table 24 Exposure-Related Pharmacokinetic Parameters for Tacrolimus After Single-Dose Administration of LCP-Tacro Tablets

Study 1013 Dose proportionality			(data are mean and s.d.)
	C_{max} (ng.mL)	C_{24} (ng.mL)	AUC_{0-t} (ng.h/mL)
LCP-Tacro 5mg n=25	12.21±4.84	3.91±1.74	303.67±133.61
LCP-Tacro 7mg n=24	16.73±5.22	6.11±2.54	450.00±173.66
LCP-Tacro 10mg N=25	24.91±7.15	8.63±3.43	649.08±224.16

Time dependency

Study LCP-Tacro 1014: A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Morning And Evening Chronopharmacokinetic Study Of LCP-Tacro 2 mg Tablets In Normal, Healthy, Non-Smoking Male And Female Subjects) demonstrated that there was no significant difference in PK parameters for tacrolimus following a single dose of one LCP-Tacro 2-mg tablet under fasting conditions in the morning or evening. Overall exposure over the dosing interval (AUC0-24) of morning vs. evening dosing demonstrated a mean ratio of 95.68% and a 90% CI of 84.25–108.65%.

The PK results for study LCP-Tacro 1014 are depicted below:

Table 25 Exposure-Related Pharmacokinetic Parameters for Tacrolimus After Single-Dose Administration of LCP-Tacro Tablets

Study 1014 Time dependency		(data are mean and s.d.)	
	C_{max} (ng.mL)	C_{24} (ng.mL)	AUC_{0-t} (ng.h/mL)
LCP-Tacro 2mg dose at 20.00	4.39±1.21	1.31±0.52	94.52±34.41
LCP-Tacro 2mg dose at 08.00	4.20±1.46	1.69±0.67	112.46±41.77
Ratio and 90%CI	109.65% (95.32%-126.14%)	80.74% (65.43%-99.64%)	86.81% (72.16%-104.43%)

Comparative Pharmacokinetics versus the clinical comparator Prograf and the European reference medicinal product Advagraf in Healthy Subjects

The relative bioavailability of LCP-Tacro tablets has been compared to matched doses of the authorised immediate-release Prograf capsules in studies LCP-Tacro 1015 [single dose Formulation C], LCP-Tacro 1012 [Formulation B], LCP-Tacro 1016 [Formulation C](both steady state studies) and the modified-release reference product Advagraf in study LCP-Tacro 1017 [Formulation C]).

Bioavailability of LCP-Tacro compared with Prograf after a single dose

The single-dose study (LCP-Tacro 1015) demonstrated the prolonged-release pharmacokinetics of tacrolimus from the LCP-Tacro 1 mg tablets.

Study LCP-Tacro 1015: A Two-Way Crossover, Open-Label, Single Dose, Fasting, Comparative Bioavailability Study of LCP-Tacro 1 mg Tablets Versus Prograf 1 mg Capsules in Normal, Healthy, Non-Smoking Male and Female Subjects.

There were two 6-day study periods. Subjects were randomized to receive one of the following treatments on Day 1 of each study period in a crossover design. There was at least a 2-week washout period between study treatments. The peak and total systemic exposures of tacrolimus were compared after a single oral dose of LCP-Tacro 1 mg tablets (Treatment A, test formulation) versus Prograf 1 mg capsules (Treatment B, comparator treatment).

Pharmacokinetics

The following pharmacokinetic parameters for tacrolimus were calculated by standard non-compartmental methods: AUC0-t, AUC0-inf, AUC0-12, AUC0-24, Cmax, C12, C24, Tmax, Kel, t½, CL/F, and AUC0-24/C24.

Results

In this single-dose study, the geometric mean ratio (LCP-Tacro/Prograf) for Cmax was ~62% lower than the comparator treatment (i.e., Prograf) whereas the geometric mean ratio for C24 was found to be ~165% higher for LCP-Tacro compared to Prograf. The statistical results also indicated that the geometric mean ratio (LCP-Tacro/Prograf) of AUC0-t was higher by ~88% for LCP-Tacro compared to

Prograf. As expected, the median Tmax of the prolonged release product was found to be significantly longer compared to that of the comparator treatment: 9.00 hours vs. 1.33 hours, respectively.

The $t_{1/2}$ of the test formulation [mean ± SD: 26.39 ± 6.57 hours] was similar to the comparator [mean ± SD: 28.61 ± 14.03 hours, p=0.2811] and were concurrent to those for marketed tacrolimus products. The elimination parameters and their descriptive statistics for all the subjects are listed separately. Furthermore, the significantly higher apparent clearance values (CL/F) in Prograf is evident due to lower AUC0-∞ values when compared to that from LCP-Tacro (p=0.0043).

Table 26 Pharmacokinetic Parameters for Tacrolimus after a Single Dose in Fasted Conditions (Study LCP-Tacro 1015)

Study 1015	N=17 (data are mean and s.d.)		
	C_{max} (ng.mL)	C_{24} (ng.mL)	AUC_{0-t} (ng.h/mL)
LCP-Tacro 1mg	2.54±1.03	1.04±0.36	61.74±24.24
Prograf 1mg	7.04±3.56	0.46±0.25	36.19±22.72
Ratio and 90% CI	37.63% (28.06-50.48%)	265.01 (203.04-345.90%)	187.42% (135.52-259.18)

Bioavailability of LCP-Tacro compared with Prograf after multiple doses
In the two steady-state PK and bioavailability Studies LCP-Tacro 1012 (one LCP-Tacro 2 mg tablet q.d. vs. one Prograf 1 mg capsule b.i.d.) and LCP-Tacro 1016 (one LCP-Tacro 1 mg tablet q.d. vs. one Prograf 0.5 mg capsule b.i.d.), subjects were dosed over 10 successive days.

Study LCP-Tacro 1012: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Relative Bioavailability Study of LCP-Tacro 2 mg Tablets (q.d.) Versus Prograf 1 mg Capsules (b.i.d.) in Normal, Healthy, Non-Smoking Male and Female Subjects.

The primary objective of this study was to evaluate and compare the bioavailability of tacrolimus from a test formulation of LCP-Tacro 2 mg Tablets taken once daily (q.d.) versus Prograf 1 mg Capsules taken twice daily (b.i.d.) under steady-state, fasting conditions.

Pharmacokinetics

Day 1: AUC0-12, AUC0-24 (Treatment A only), C12, C24, Cmax, and Tmax.

Day 10: AUCτ (τ=24), AUC0-12, AUC12-24, C12, Cmax, Cmin, Cavg, Tmax, t½, Kel, % Fluctuation, % Swing, AUCτ/Cmin, Cmax/Cmin, AUC12-24/Cmin, AUC0-12/C12, and Accumulation Ratio (R).

Results

Upon administration of LCP-Tacro 2 mg Tablets (q.d.) and Prograf 1 mg Capsules (b.i.d.) for 10 successive days, there were no significant differences observed in the morning pre-dose concentrations between Days 5, 6, 7, 8, 9, and 10, therefore steady state was maintained since Day 5. At steady state, the systemic exposure (AUC and Cmin) over the period of 24 hours of LCP-Tacro 2 mg Tablets (q.d.) was about 46% higher than that of Prograf 1 mg Capsules (b.i.d.). The higher AUC exposure of the test formulation could be partially explained by the lower exposure of 2nd dose of the reference treatment. As expected, the LCP-Tacro 2 mg Tablets (q.d.) had higher Cavg values and lower degree of fluctuation than that of the immediate-release Prograf 1 mg Capsules (b.i.d.). The time to peak concentration between the single and multiple doses of each individual formulation was similar for both treatments. Also there was no significant difference observed in elimination half-life between the 2 treatments at steady state.

Overall, LCP-Tacro 2 mg Tablets were well tolerated as a multiple-dose of 2 mg, administered under fasting conditions, and no significant safety issues emerged.

Table 27 Pharmacokinetic Parameters for Tacrolimus on Day 10 Under Fasted Conditions (Study LCP-Tacro 1012)

Study 1012 (data are mean and s.d.)	Day 10 LCP-Tacro 2mg q.d. N=25	Day 10 Prograf 1mg b.d n=25
Tmax(h)	6.00 (1.00-10.00)	1.50(1.00-13.00)
% degree of fluctuation	68.80±19.67	154.96±48.57
%degree of swing	93.06±30.86	211.26±80.91
Cmax/Cmin	1.93 ±0.31	3.11±0.81

Study LCP-Tacro 1016: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Comparative Bioavailability Study Of LCP-Tacro 1 mg Tablets (q.d.) Versus Prograf 0.5 mg Capsules (b.i.d.) In Normal, Healthy, Non-Smoking Male and Female Subjects.

The primary objective of this study was to evaluate the bioavailability of tacrolimus from a test formulation of LCP-Tacro 1 mg Tablets taken once daily (q.d.) versus Prograf 0.5 mg Capsules taken twice daily (b.i.d.) under steady-state, fasting conditions.

Pharmacokinetics

Day 1: AUC0-12, AUC0-24 (Treatment A only), C12, C24, Cmax, and Tmax

Day 10: AUC_{τ} (τ=24), AUC0-12, AUC12-24, C12, Cmax, Cmin, Cavg, Tmax, t½, Kel, % Fluctuation, % Swing, AUC_{τ}/Cmin, Cmax/Cmin, AUC12-24/Cmin, AUC0-12/C12, and Accumulation Ratio (R).

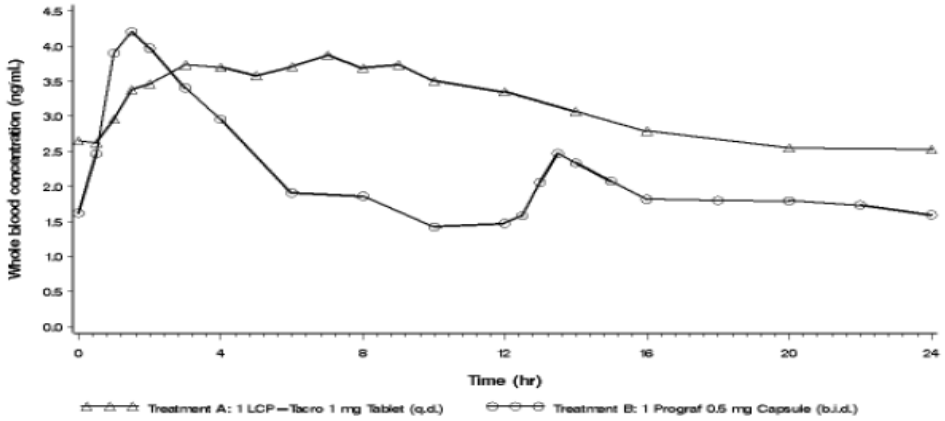
Results

Upon administration of LCP-Tacro 1 mg Tablets (q.d.) and Prograf 0.5 mg Capsules (b.i.d.) for 10 successive days, there were no significant differences observed in the morning pre-dose concentrations between Days 5, 6, 7, 8, 9, and 10, therefore steady state was maintained since Day 5. At steady state, the systemic exposure (AUC and Cmin) over the period of 24 hours of LCP-Tacro 1 mg Tablets (q.d.) was ~ 52% to 64% higher than that of Prograf 0.5 mg Capsules (b.i.d.). The higher AUC exposure of the test formulation could be partially explained by the lower exposure of the second dose of the comparator treatment. As expected, the LCP-Tacro 1 mg Tablets (q.d.) had higher Cavg values and lower degree of fluctuation than that of the immediate-release Prograf 0.5 mg Capsules (b.i.d.). The time to peak concentration between the single and multiple doses of each individual formulation was similar in both treatments. The elimination half-life of the test formulation was slightly longer (up to ~3 hrs) than that of the reference formulation at steady state conditions (36.89 ± 7.74 vs. 33.88 ± 7.51, p-value=0.0019). Overall, LCP-Tacro 1 mg Tablets (q.d.) were well tolerated as a multiple-dose of 1 mg, administered under fasting conditions, and no significant safety issues emerged.

Table 28 Pharmacokinetic Parameters of LCP-Tacro and Prograf on Day 1 and Day 10 of Dosing (Study LCP-Tacro 1016)

Study 1016	(data are mean and s.d.)			
	Day 1 LCP-Tacro 1mg q.d. N=17	Day 1 Prograf 0.5mg b.d n=15	Day 10 LCP-Tacro 1mg q.d. N=17	Day 10 Prograf 0.5mg b.d n=15
Tmax(h)	6.05(2.00-24.00)	1.50 (1.00-6.00)	6.00 (1.50-10.00)	1.55(1.00-8.00)
% degree of fluctuation	-	-	84.72±42.07	156.78±49.48
%degree of swing	-	-	97.31±64.18	204.54±78.14
Cmax/Cmin	-	-	1.97 ±0.64	3.05±0.78

Figure 1 **Mean Whole Blood Tacrolimus Concentration Versus Time, Linear Scale (upper panel), Semi-Log Scale (lower panel) (n=17) for Day 10**



Source: Module 5.3.1.2 Clinical Study Report LCP-Tacro 1016, Figure 11.4.2

Bioavailability of LCP-Tacro compared with Advagraf

Study LCP-Tacro 1017: A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Comparative Bioavailability Study of LCP-Tacro 2 mg Tablets (q.d.) Versus Advagraf 2 x 1 mg Capsules (q.d.) in Normal, Healthy, Non-Smoking Caucasian Male Subjects.

This study investigated the comparative PK with dosing of one LCP-Tacro 2-mg tablet q.d. (Formulation C) compared with two Advagraf 1 mg capsules q.d.

Pharmacokinetics

Day 1: AUC0-24, Cmax, C24, and Tmax.

Day 10: AUCτ (τ=24), Cmax, Cmin, Cavg, Tmax, t½, Kel, % Fluctuation, % Swing, AUCτ/Cmin, Cmax/Cmin and Accumulation Ratio (R).

Results

Upon administration of one LCP-Tacro 2 mg Tablet (q.d.) and two Advagraf 1 mg Capsules (q.d.) for 10 successive days, there were no significant differences observed in the predose concentrations between Days 5, 6, 7, 8, 9, and 10, therefore steady-state was maintained since Day 5. At steady-state, the systemic exposure (AUC and Cmin) over the period of 24 hours of 1 LCP-Tacro 2 mg Tablet (q.d.) was ~49% and ~66% higher than that of 2 Advagraf 1 mg Capsules (q.d.). Of particular interest is that the 1 LCP-Tacro 2 mg Tablet (q.d.) had higher Cavg values and a lower degree of fluctuation and swing than the 2 Advagraf 1 mg Capsules (q.d.). The time to peak concentration was longer for the test treatment, indicating the extended release product characteristics of the LCP-Tacro 2 mg Tablets. The elimination half-life of the test formulation was similar to that of the reference formulation at steady-state conditions. Overall, 1 LCP-Tacro 2 mg Tablet (q.d.) was well tolerated as a multiple-dose of 2 mg daily, administered under fasting conditions, and no significant safety issues emerged.

From the initial Day-1 dosing AUC and Cmin were significantly greater ($p < 0.0001$). At steady-state, the systemic exposure (AUC and Cmin) over the period of 24 hours of one LCP-Tacro 2 mg tablet (q.d.) was ~49% and ~66% higher than that of two Advagraf 1 mg capsules (q.d.).

The Pharmacokinetic Parameters for Tacrolimus on Day 10 (Study LCP-Tacro 1017) are shown in table 29.

Table 29 Pharmacokinetic Parameters for Tacrolimus on Day 10 (Study LCP-Tacro 1017)

Study 1017	N=20 (data are mean and s.d.)		
	C_{max} (ng.mL)	C_{min} (ng.mL)	AUC_t (ng.h/mL)
LCP-Tacro 2mg	8.39±2.89	4.66±1.71	142.27±49.41
Advagraf 2 x 1mg	7.00±2.04	2.80±0.98	94.15±28.24
Ratio and 90% CI	115.99% (105.33%-127.73%)	165.68% (152.29-108.25%)	148.79% (137.42%-161.111%)

Confirming the higher systemic exposure of LCP-Tacro, the Cavg of LCP-Tacro 2-mg tablets (q.d.) (5.93 ± 2.06) was ~50% higher than that of the Advagraf 1 mg capsules (q.d.) (3.92 ± 1.18); this difference was statistically significant ($p<0.05$). Cmax (mean ± SD) were 8.39 ± 2.89 and 7.00 ± 2.04 for LCP-Tacro and Advagraf, respectively ($p<0.05$).

The degree of fluctuation (64.7% ± 23.0) and degree of swing (85.5% ± 37.6) of LCP-Tacro were significantly lower than Advagraf (110.2% ± 28.2 and 158.5% ± 48.2, respectively) ($p<0.05$). A comparison of Tmax between treatments on Days 1 and 10 revealed that the time to peak concentration was much longer for LCP-Tacro compared to Advagraf. No significant difference was observed in Tmax between single and multiple doses of the same treatment ($p>0.05$).

Phase 2 Clinical Studies in Kidney Transplant Patients

Conversion setting

The proposed ratio for converting patients from their current maintenance dose of Prograf capsules twice daily to the corresponding dose of LCP-Tacro tablets once daily is based on the results of LCP-Tacro Study 2011.

LCP-Tacro Study 2011 was a Phase II, 3-sequence, open-label, multicenter, prospective study in stable kidney transplant patients to assess and compare the PK (AUC, Cmax and Cmin) and safety of LCP-Tacro tablets once daily versus Prograf capsules twice daily. A 24-hour PK profile was obtained in patients taking Prograf capsules twice daily under steady state conditions and then repeated under steady state conditions after conversion to LCP-Tacro tablets once daily at a fixed dose approximately 30% less than the total daily dose of Prograf.

Methodology

Stable kidney transplant patients who fulfilled all inclusion/exclusion (I/E) criteria were enrolled and kept on Prograf for 7 days. Following a 24-hour PK study on Day 7 to determine pharmacokinetics for Prograf, all patients were converted to once daily LCP-Tacro (Ratio 1:0.66-0.80) for 7 days with no dose changes allowed. On Day 14 a 24-hour LCP-Tacro PK study was performed. On Day 15 one predefined dose change was allowed if there was more than 25% change in the mean of 3 trough levels measured on Days 10 ± 1, 12 ± 1 (separated by at least 48 hours from the previous sample) and 14 compared to the mean of 3 trough levels measured on Days 0, 7 and 8 for each individual patient. Patients remained on the dose determined on Day 14 for another 7 days with no dose changes allowed. Another 24-hour LCP-Tacro PK study was performed on Day 21. On Day 22 patients were converted back to their original twice-daily dose of Prograf for a safety follow-up period of 30 days ending with a safety assessment at Day 52.

The following blood samples were drawn during this study:

For LCP-Tacro: Blood sampling points included: 0.00 (pre-dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 14.00, 16.00, 20.00 and 24.00 hours post dose, on Days 14 and 21. For Prograf:

Blood sampling points included: 0.00 (pre-dose), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 12.50, 13.00, 13.50, 14.00, 15.00, 16.00, 20.00 and 24.00 hours after the morning dose, on Day 7.

Pharmacokinetic Variables

The following pharmacokinetic parameters were determined for tacrolimus as available within both test and reference products and determined using SAS software: AUCT; Cmax; Tmax; Cmin; Cave; % fluctuation; % swing; Cmax/Cmin.

Results

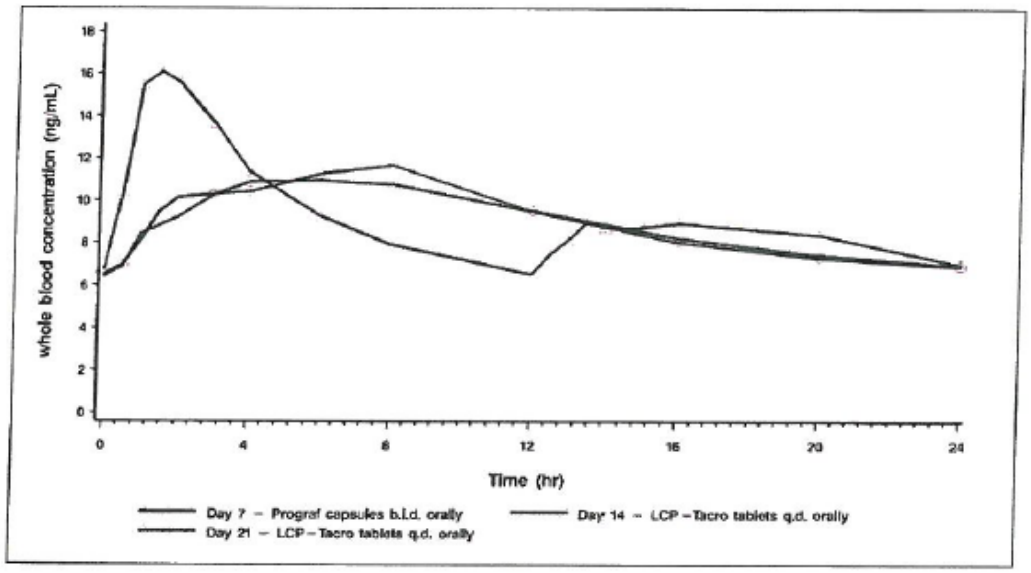
The average (± SD) of the dose conversion ratios used for converting the 47 patients in the per-protocol (PP) set from Prograf to LCP-Tacro was 0.71 ± 0.05 (median 0.70, range 0.67 to 0.80). Based on the results obtained, there was no significant difference between the AUC or the C_{min} obtained for Prograf versus LCP-Tacro after 1 week of dosing.

Table 30 Pharmacokinetic Parameters for LCP-Tacro and Prograf in Stable Kidney Transplant Patients (Study LCP-Tacro 2011)

Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Prograf Capsules (b.i.d.)	LCP-Tacro Tablets (q.d.)	
	Day 7 (n=47)	Day 14 (n=47)	Day 21 (n=46)
AUC_{0-24} (ng.h/mL)	212.12 (25.59) 218.82 ± 55.99	206.79 (29.27) 215.71 ± 63.14	209.05 (31.30) 218.03 ± 68.23
C_{max} (ng/mL)	17.66 (42.59) 19.14 ± 8.15	12.64 (36.02) 13.45 ± 4.84	13.05 (41.91) 13.94 ± 5.84
C_{min} (ng/mL)	6.82 (22.01) 7.00 ± 1.54	6.59 (33.41) 6.96 ± 2.32	6.64 (31.70) 6.94 ± 2.20
C_{avg} (ng/mL)	8.84 (25.59) 9.12 ± 2.33	8.62 (29.27) 8.99 ± 2.63	8.71 (31.29) 9.08 ± 2.84
T_{max} (h)[a]	1.82 (0.50 – 24.00)	6.00 (1.00 – 16.00)	6.00 (1.5 – 16.00)
Degree of Fluctuation (%)	127.41 ± 57.28	73.24 ± 44.96	77.04 ± 50.59
Degree of Swing (%)	174.55 ± 93.72	102.80 ± 75.24	110.07 ± 89.23
C_{max}/C_{min}	2.75 ± 0.94	2.03 ± 0.75	2.10 ± 0.89

Mean tacrolimus whole blood-concentration time profiles over 24 hours on Day 7 showed a characteristic fluctuation in tacrolimus concentration (approximately 6-16 ng/mL) with Prograf. In comparison, a smaller fluctuation in mean tacrolimus concentrations (approximately 7-12 ng/mL) was observed with LCP-Tacro on Day 14 and Day 21 (see Figure 2).

Figure 2 Mean Whole Blood Tacrolimus Concentration in Patients on Days 7, 14, and 21 years versus Time, Linear Scale (n=47)



***De Novo* Setting**

The Phase 2 randomized, open-label Study LCP-Tacro 2017 in 63 adult *de novo* kidney transplant patients evaluated the PK and safety of tacrolimus from LCP-Tacro tablets and Prograf capsules during the first 2 weeks after kidney transplantation. The study then compared the efficacy and safety of LCP-Tacro tablets and Prograf capsules over a further 50 weeks after kidney transplantation.

LCP-Tacro 2017: A Phase 2, Open-Label, Multi-Center, Randomized Trial to Demonstrate the Pharmacokinetics of LCP-Tacro Tablets Once Daily and Prograf Capsules Twice Daily in Adult *de novo* Kidney Transplant Patients.

This was a Phase II Open-Label, Multi-Center, Randomized Trial to Demonstrate the Pharmacokinetics of LCP-Tacro Tablets Once Daily and Prograf Capsules Twice Daily in Adult *de novo* Kidney transplant adult patients (18 – 65 yrs). The study was conducted in 9 sites in US. Three 24-hour whole blood concentration-time profiles were taken during the study: one following the first administration of tacrolimus, and two under steady state conditions at Day 7 and Day14. The primary endpoint was the systemic exposure $AUC_{0-24;}$ C_{min} of tacrolimus on Day 1, Day 7 & Day 14.

The mean daily dose of LCP-Tacro (n=32) decreased from 10.29 (3.32) mg on Days 1-7 to 10.27 (4.183) mg on Days 8-14, and mean total daily doses of Prograf (n=31) decreased from 10.88 (3.417) mg on Days 1-7 to 8.47 (4.208) mg on Days 8-14. Through blood levels in the early transplant period were higher for Prograf-treated patients than LCP-Tacro-treated patients; however, by Day 7 they were comparable and then lower at day 14.

A summary of the results from the pharmacokinetic assessments performed on Days 1, 7 and 14 is presented in Table 31.

Table 31 Pharmacokinetic Parameters of LCP-Tacro and Prograf in *de novo* Kidney Transplant Patients (Study LCP-Tacro 2017)

Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD					
	Day 1		Day 7		Day 14	
	LCP-Tacro (n=31)	Prograf (n=30)	LCP-Tacro (n=29)	Prograf (n=28)	LCP-Tacro (n=28)	Prograf (n=28)
AUC_{0-24} (ng.h/mL)[a]	107.31 (58.56) 131.04 ± 76.73[b]	232.21 (42.08) 252.59 ± 106.29[c]	295.50 (38.79) 319.85 ± 124.07[d]	267.16 (34.38) 286.69 ± 98.55	330.53 (32.18) 349.31 ± 112.41	240.72 (31.50) 255.22 ± 80.39
C_{max} (ng/mL)	9.52 (59.11) 11.56 ± 6.83	20.83 (47.41) 23.41 ± 11.10	23.11 (63.95) 27.41 ± 17.53	20.97 (52.99) 24.12 ± 12.78	25.65 (48.51) 28.21 ± 13.68	19.15 (32.04) 20.27 ± 6.49
C_{min} (ng/mL)	4.81 (65.68) 5.70 ± 3.74[b]	8.15 (48.09) 9.10 ± 4.38[c]	8.20 (46.38) 9.18 ± 4.26[d]	9.39 (49.92) 10.35 ± 5.16	9.51 (40.84) 10.37 ± 4.24	7.45 (38.57) 8.12 ± 3.13
C_{avg} (ng/mL)	5.46 ± 3.19[a]	10.55 ± 4.42[c]	13.32 ± 5.16[d]	11.91 ± 4.08	14.55 ± 4.66	10.63 ± 3.35
Degree of Fluctuation (%)	89.94 ± 65.58[b]	138.08 ± 77.30[c]	135.86 ± 121.35[d]	107.62 ± 76.80	131.07 ± 98.48	122.45 ± 59.91
Degree of Swing (%)[e]	118.25 ± 111.95[b]	187.77 ± 124.53[c]	230.76 ± 246.80[d]	152.79 ± 135.61	210.18 ± 182.42	174.49 ± 100.91
T_{max} (h)[e]	11.97 (4.02 – 24.00)	4.00 (0.98 – 24.00)	6.00 (1.52 – 12.10)	1.61 (0.50 – 24.00)	4.00 (1.33 – 8.07)	1.88 (0.50 – 14.05)

The proportion of patients achieving therapeutic trough tacrolimus levels (7-20 ng/ml) in the LCP-Tacro group was lower than the Prograf group on Day 1, was similar to the Prograf group on Day 7, and was higher than the Prograf group on Day 14 (table 32).

Table 32 Comparison of the Proportion of Patients Achieving Therapeutic Tacrolimus Trough Levels (mITT Set; Study LCP-Tacro 2017).

Number and Percentage of Patients Achieving Therapeutic Trough Tacrolimus Levels (7-20 ng/mL) – Pharmacokinetic mITT Population)

Day	Treatment Group	
	LCP-Tacro	Prograf
1	6/30 (20%)	19/29 (65.52%)
7	18/27 (66.67%)	21/28 (75%)
14	22/28 (78.57%)	16/28 (57.14%)

Biopsy Proven Acute Rejection

Three patients experienced BPAR 1-LCP-Tacro and 2-Prograf.There was no statistically significant difference between treatment groups in the cumulative incidence of freedom from BPAR.

Table 33 Kaplan-Meier Estimates of Cumulative Incidence of Freedom from BPAR at Day 180 and Day 365 - mITT Population

Day	Statistic	LCP-Tacro (N=32)	Prograf (N=31)
Day 180	Estimate	96.77%	93.32%
	95% CI	(79.23%, 99.54%)	(75.80%, 98.29%)
	P-value[a]	0.65	
Day 365	Estimate	96.77%	93.32%
	95% CI	(79.23%, 99.54%)	(75.80%, 98.29%)
	P-value[a]	0.65	

Phase 2 Clinical Studies in Liver Transplant Patients

LCP-Tacro 2012: A Phase 2, Open-Label, Multi-center Prospective, Conversion Study in Stable Liver Transplant Patients to Compare the Pharmacokinetics of LCP-Tacro Tablets Once-A-Day to Prograf Capsules Twice-A-Day.

The primary objective was:

To evaluate steady state tacrolimus exposure (AUC0-24) and trough levels (C24) in stable liver transplant patients converted from Prograf capsules to LCP-Tacro tablets using a three-sequence study design.

Study Design

This Phase 2, open-label, multi-center, prospective, conversion study enrolled 59 stable liver transplant patients (liver transplant at least 6 months before enrollment and serum creatinine <2.5 mg/dL) on oral Prograf therapy as part of their maintenance immunosuppression regimen. All patients were on a stable Prograf dose with trough levels of tacrolimus maintained at 5-12 ng/mL for at least 4 weeks before enrollment. The study population comprised 33 male and 26 female patients (aged 20-66 years; 46 Caucasian, 8 Black; 2 Asian, 1 Mixed Race, 1 Native Hawaiian, 1 Native American).

The three sequence study design was essentially identical to that for Study-LCP-Tacro 2011 in stable kidney transplant patients with the same dose conversion ratio (0.66-0.80) used to convert patients from Prograf (b.i.d.) to LCP-Tacro (q.d.). The only slight difference was that trough levels of tacrolimus were to be maintained at 5-12 ng/mL during Study Period 1.

Pharmacokinetic Results

Mean tacrolimus whole blood concentration time profiles over 24 hours show a characteristic fluctuation in tacrolimus concentration (approximately 6-16 ng/mL) with Prograf on Day 7. In comparison, a smaller fluctuation in mean tacrolimus concentrations (approximately 7-12 ng/mL) was observed with LCP-Tacro on Day 14 and Day 21.

The pharmacokinetic data for tacrolimus are summarized in Table 34.

Table 34 Pharmacokinetic Parameters for LCP-Tacro and Prograf in Stable Liver Transplant Patients (Study LCP-Tacro 2012)

Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Prograf Capsules (b.i.d.)	LCP-Tacro Tablets (q.d.)	
	Day 7 (n=57)	Day 14 (n=57)	Day 21 (n=56)
AUC_{0-24} (ng.h/mL)	196.43 (29.78) 205.14 ± 61.10	185.48 (30.25) 195.06 ± 59.00	202.29 (36.82) 215.66 ± 79.40
C_{max} (ng/mL)	16.86 (42.02) 18.45 ± 7.75	11.80 (32.66) 12.49 ± 4.06	12.62 (43.39) 13.70 ± 5.95
C_{min} (ng/mL)	6.40 (30.76) 6.72 ± 2.07	5.91 (37.38) 6.37 ± 2.38	6.37 (38.44) 6.85 ± 2.63
C_{avg} (ng/mL)	8.18 (29.77) 8.54 ± 2.54	7.72 (30.27) 8.12 ± 2.46	8.42 (36.82) 8.98 ± 3.31
T_{max} (h)	1.75 (145.46) 2.97 ± 4.31	5.32 (55.07) 6.31 ± 3.47	5.05 (55.84) 5.92 ± 3.31
Degree of Fluctuation (%)	120.97 (42.13) 133.34 ± 56.18	67.00 (59.50) 79.19 ± 47.12	65.33 (53.47) 76.58 ± 40.95
Degree of Swing (%)	154.59 (46.15) 174.87 ± 80.70	87.59 (74.14) 112.44 ± 83.36	86.44 (62.35) 107.97 ± 67.32
C_{max}/C_{min}	2.63 (29.36) 2.75 ± 0.81	2.00 (39.24) 2.12 ± 0.83	1.98 (32.37) 2.08 ± 0.67

The bioavailability of tacrolimus from LCP-Tacro and Prograf was similar (table 35).

Table 35 Relative Bioavailability of Tacrolimus from LCP-Tacro and Prograf in Stable Liver Transplant Patients (Study LCP-Tacro 2012)

Comparison	Parameter	90% CI	Ratio of Means (%)	Intra-Patient CV (%)
Day 14 vs. Day 7	AUC_{0-24}	85.16 – 104.70	94.43	34.28
	C_{max}	61.85 – 79.27	70.02	41.73
	C_{min}	82.12 – 103.69	92.28	39.00
Day 21 vs. Day 7	AUC_{0-24}	92.84 – 114.24	102.98	34.28
	C_{max}	66.08 – 84.80	74.86	41.73
	C_{min}	88.45 – 111.79	99.44	39.00
Day 21 vs. Day 14	AUC_{0-24}	98.31 – 120.98	109.06	34.28
	C_{max}	94.38 – 121.10	106.91	41.73
	C_{min}	95.85 – 121.15	107.76	39.00

Source: Module 5.3.3.2 Clinical Study Report LCP-Tacro 2012, Tables 12, 13 and 14
CI=confidence interval; CV=coefficient of variation

LCP-Tacro 2012E: A Phase 2, Open-label, Multi-center Extension Study for Patients Completing Study LCP-Tacro 2012

The objectives were to evaluate the long-term safety and tolerability of LCP-Tacro for maintenance immunosuppression therapy in stable liver transplant recipients converted from Prograf capsules and to assess the pharmacokinetic profile of LCP-Tacro after 6 months of therapy.

Study Design

Study LCP-Tacro 2012E (extension study) was an extension of Study LCP-Tacro 2012 (core study) in liver transplant patients. Patients who successfully completed the core study (N=57) were eligible to enter the extension study and were maintained on LCP-Tacro for an additional 50 weeks (a total of 52 weeks on LCP-Tacro). Eligible patients were enrolled in the extension study on the morning of Day 22 at the end of the core study.

Tacrolimus whole blood trough levels were to be maintained between approximately 5 and 15 ng/mL according to the standard of care at each center. The number of "weeks" in this study refers to the total number of weeks that patients had been on LCP-Tacro tablets and included the 2 weeks that patients received the study drug in the core study. Patients were instructed to take study drug in the morning. Since tacrolimus absorption is affected by food, patients were instructed to take LCP-Tacro either 1 hour before or at least 2 hours after meals. Patients who routinely took their study medication with meals prior to and during the core study were allowed to continue to do so during the extension study.

Results

Forty-nine (49) patients received at least 1 dose of study medication and 43/49 (87.8%) patients completed the extension study. A total of 6/49 (12.2%) patients withdrew early. The most common reason for early withdrawal was an AE (3/49 [6.1%] patients, elevated creatinine, headache, and metastatic carcinoma). Three other patients withdrew for the following reasons: administrative/other reason (moved out of state), non-compliance with protocol, and withdrawal of consent.

Table 36 Tacrolimus Pharmacokinetic Parameters on Day 14 (Study 2012) and Week 26 (Study 2012E)

Pharmacokinetic Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		Difference (90% CI) p value
	Week 26 (n=44)	Day 14 (n=44)	
AUC_{0-24} (ng·h/mL)	175.75 (35.54)	192.21 (28.11)	-0.08956 (-0.2136, 0.03446)
	186.94 ± 66.45	200.24 ± 56.29	0.1526 [a]
AUC_{0-12} (ng·h/mL)	100.24 (34.58)		
	106.39 ± 36.79 [b]		
C_{max} (ng/mL)	11.59 (36.09)	12.22 (32.14)	-0.05278 (-0.1908, 0.08528)
	12.41 ± 4.48	12.87 ± 4.13	0.4449 [a]
C_{min} (ng/mL)	5.36 (43.64)	6.11 (33.22)	-0.1312 (-0.2796, 0.01722)
	5.91 ± 2.58	6.48 ± 2.15	0.0817 [a]
C_{avg} (ng/mL)	7.32 (35.62)	8.01 (28.11)	-0.09054 (-0.2147, 0.03360)
	7.78 ± 2.77	8.34 ± 2.35	0.1486 [a]
C_{12} (ng/mL)	7.19 (43.52)		
	7.84 ± 3.41 [b]		
C_{24} (ng/mL)	5.36 (43.64)		
	5.91 ± 2.58		
T_{max} (h) [c]	4.99	6.01	-1.01 (-2.51, 0.26)
	(1.47 – 24.00)	(1.50 – 16.00)	0.243 [d]
%Fluctuation	76.72 (63.05)	68.24 (54.90)	10.8052 (-7.2044, 28.8147)
	89.45 ± 56.40	78.64 ± 43.18	0.2329 [a]
%Swing	105.97 (76.17)	89.40 (66.56)	23.8849 (-8.3343, 56.1041)
	134.49 ± 102.45	110.61 ± 73.61	0.1422 [a]
R	0.91 (43.29)		
	0.99 ± 0.43		

Source: : Module 5.3.1.2 Clinical Study Report LCP-Tacro 2012E, Table 11.

a p value based on ANOVA

b n=43

c median (min – max)

d p value based on Wilcoxon-Mann-Whitney test

Study 2018: A Phase 2, Open-label, Multicenter, Randomized Trial to Demonstrate the Pharmacokinetics LCP-Tacro Tablets Once Daily and Prograf Capsules Twice Daily in Adult *de novo* Liver Transplant Patients.

The primary objectives were to demonstrate the pharmacokinetics (AUC and Cmax) and 24-hour trough levels (Cmin) of LCP-Tacro early after transplantation (within the first 14 days) in adult *de novo* liver transplant recipients and to compare the proportion of patients in each treatment group achieving sufficient tacrolimus whole blood trough levels (5 to 20 ng/mL) during the first 14 days post-transplantation.

The secondary objectives were to compare the pharmacokinetics (AUC, Cmax and Cmin) on Days 1, 7 and 14 of LCP-Tacro with the pharmacokinetics of Prograf and to evaluate the efficacy and safety of LCP-Tacro compared to Prograf in the first 12 months after liver transplantation

Tacrolimus pharmacokinetic parameters were calculated using non-compartmental methods as follows: area under the plasma concentration-time curve (AUC_{0-24}), maximum plasma concentration (Cmax), average plasma concentration (C_{ave}) , plasma concentration 24 hours post dose (Cmin), time of maximum plasma concentration (Tmax), % Fluctuation, % Swing and Accumulation Ratio.

Results

A summary of the results from the pharmacokinetic assessments performed on Days 1, 7 and 24 is presented in Table 37.

Table 37 Pharmacokinetic Parameters of LCP-Tacro and Prograf in *de novo* Liver Transplant Patients (Study LCP-Tacro 2018)

Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD					
	Day 1		Day 7		Day 14	
	LCP-Tacro (n=29)	Prograf (n=28)	LCP-Tacro (n=23)	Prograf (n=26)	LCP-Tacro (n=21)	Prograf (n=23)
AUC_{0-24} (ng.h/mL)	59.57 (54.86) 68.18 ± 37.40	116.17 (54.51) 135.62 ± 73.92	231.94 (40.83) 251.29 ± 102.60	226.87 (41.56) 245.47 ± 102.03	254.24 (50.02) 279.59 ± 139.86	229.55 (33.12) 241.22 ± 79.90
C_{max} (ng/mL)	5.06 (58.15) 5.95 ± 3.46	11.13 (49.48) 12.70 ± 6.29	15.41 (46.04) 17.15 ± 7.90	19.24 (42.52) 21.10 ± 8.97	18.95 (46.64) 21.30 ± 9.93	19.61 (63.47) 22.95 ± 14.57
C_{min} (ng/mL)	2.55 (74.27) 3.22 ± 2.39	3.62 (63.97) 4.42 ± 2.83	6.67 (48.32) 7.33 ± 3.54	6.83 (53.29) 7.61 ± 4.06	6.68 (56.27) 7.41 ± 4.17	7.17 (34.95) 7.56 ± 2.64
C_{avg} (ng/mL)	2.84 ± 1.55	5.65 ± 3.08	10.45 ± 4.25	10.22 ± 4.24	11.66 ± 5.82	10.06 ± 3.33
Degree of Fluctuation (%)	95.25 ± 80.45	159.89 ± 86.33	92.70 ± 48.81	134.22 ± 51.77	121.82 ± 62.34	140.49 ± 81.52
Degree of Swing (%)[e]	137.92 ± 164.76	248.59 ± 183.80	147.75 ± 96.90	201.52 ± 105.38	204.95 ± 127.82	196.42 ± 131.51
T_{max} (h)[a]	12.00 (1.48 – 24.20)	2.67 (1.00 – 20.00)	4.00 (0.00 – 12.00)	1.51 (0.67 – 16.50)	4.00 (1.00 – 16.00)	2.00 (1.00 – 14.00)

Table 38 Overview of Clinical Phase 2 Studies on LCP-Tacro Tablets q.d. in Liver Transplant Patients

Study	Design	Patient Population	Treatments	No. Patients Randomised / Completed	Duration
Stable Liver Transplant Patients (Conversion Setting)					
LCP-Tacro 2012 Phase 2 USA (2008) *Completed*	Controlled, randomised, multicentre, open-label, 3-sequence	Adult (≥18 years) stable liver transplant patients	Study Period I: Prograf b.i.d. Study Period I+II: patients were converted from Prograf b.i.d. to LCP-Tacro tablets q.d. Conversion ratio: 0.66	59/57	3 weeks (21 days)

Study	Design	Patient Population	Treatments	No. Patients Randomised / Completed	Duration
			to 0.80 Oral administration		
LCP-Tacro 2012E Phase 2 Study Extension USA (2009) *Completed*	Open-label, multicentre; study extension		LCP-Tacro tablets q.d. according to tacrolimus exposure / trough level Oral administration	49*	Up to 12 months (+ 50 weeks)
***De novo* Liver Transplant Patients**					
LCP-Tacro 2018 Phase 2 USA (2010) *Completed*	Controlled, randomised, multicentre, open-label, parallel-group	Adult (≥18 years) *de novo* liver transplant patients	Patients were randomised 1:1 to: LCP-Tacro tablets (q.d.) Starting dose 0.07 – 0.11 mg/kg/day (0.09 – 0.13 mg/kg/day Black patients) or Prograf capsules (b.i.d.) Starting dose 0.10 – 0.15 mg/kg/day Oral administration	58/35	12 months (PK phase: 14 days)

[1] administered in combination with mycophenolate mofetil (MMF); b.i.d.: twice daily; PK: pharmacokinetics; q.d.: once daily; *No of patients entering study extension

2.4.3. Pharmacodynamics

The key pharmacodynamic action of tacrolimus is inhibition of cytokine gene transcription. It enters T-lymphocytes by non-specific mechanisms, and binds to a 12 kDa cis-trans rotamase, termed FK506 binding protein (FKBP12), in the cytoplasm. The tacrolimus-FKBP12 complex binds to the phosphatase calcineurin, and thereby inhibits the dephosphorylation of the nuclear factor of activated T-cells (N-FAT) preventing translocation of N-FAT into the nucleus of the T-lymphocyte. The inhibition of signal transduction pathways prevents transcription of a set of lymphokine genes, in particular those encoding interleukin (IL)-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, granulocyte macrophage colony stimulating factor, tumour necrosis factor-α, interferon-γ and the gene encoding the IL-2 receptor. Tacrolimus suppresses T-cell activation, and the subsequent generation of cytotoxic lymphocytes, thereby down-regulating processes leading to acute graft rejection. T-helper cell dependent B-cell proliferation is also affected.

Tacrolimus is a well-defined macrolide immuno-suppressant, its pharmacology in the prevention and treatment of organ transplant rejection is well documented in the literature. No new pharmacodynamic studies have been performed in relation to this application. The pharmacodynamics of tacrolimus have been extensively characterised within the literature and various models of organ transplantation as well

as being clinically well defined and used worldwide for more than a decade as an immunosuppressive agent.

2.4.4. Discussion on clinical pharmacology

Tacrolimus has been in clinical use for almost two decades and the general PK in transplant recipients and healthy subjects is well defined. No further specific studies on the ADME characteristics or PK in special populations of tacrolimus have been conducted by the applicant. This applies also to PD and drug interactions, both of which are well characterized and are reflected in the Prograf EU SmPC, 2012 and Advagraf EU SmPC, 2013. This was agreed by the CHMP.

The PK profile of LCP-Tacro tablets has been comprehensively investigated. Dose proportionality was demonstrated for LCP-Tacro tablets across the therapeutically relevant dose range (Study LCP-Tacro 1013) and is consistent with the dose proportional PK reported for tacrolimus following oral administration of Prograf and Advagraf in the dose range of 1.5 to 10 mg.

No significant difference in the tacrolimus PK following single-dose LCP-Tacro tablet administration was observed when given in the morning or in the evening, indicating an absence of a chronopharmacokinetic effect (Study LCP-Tacro 1014). Consistent throughout the Phase 1 studies conducted by the applicant, LCP-Tacro tablets (q.d.) have been demonstrated to provide greater bioavailability of tacrolimus compared with an equivalent dose of Prograf capsules (b.i.d.) or Advagraf (q.d.). In addition, Cmax and the Cmax/Cmin ratio were both significantly lower for LCP-Tacro compared with Prograf. A prolonged Tmax was observed for LCP-Tacro tablets compared with matched doses of Prograf or Advagraf. At steady state, systemic exposure to tacrolimus was approximately 46% higher following administration of LCP-Tacro tablets (q.d.) compared with matched doses of Prograf capsules (b.i.d.).

Available data on Prograf and Advagraf indicate that AUC and Cmin are predictive in terms of safety and efficacy, whereas Cmax is not. Higher Cavg (~50%), reduced peak trough fluctuation (Cmax/Cmin) and a longer Tmax were seen for the prolonged-release test product compared with both Prograf and Advagraf. In Study LCP-Tacro 1012, it was observed that the inter-subject variability in Cmin and Cavg of the LCP-Tacro tablet was ~12- 14% lower compared to Prograf.

The within method QC samples and their analysis for the bioanalytical validation of all of the Phase I, II and III studies in line with the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) have been provided during the procedure and are within the limits established. The analytical standard curves, precision of standards for tacrolimus (CV%), accuracy of standards for tacrolimus (% Nom conc) for LLOQ, LQC, MQC, HQC and Repeat Analysis have been provided and are deemed acceptable.

Allograft transplant patients maintained on twice daily Prograf (immediate-release) or once daily Advagraf (prolonged release) dosing requiring conversion to once daily Envarsus should be converted on a 1:0.7 (mg:mg) total daily dose basis, i.e. the Envarsus maintenance dose should be 30% less than the Prograf or Advagraf dose. In stable patients converted from tacrolimus immediate-release products (twice daily) to Envarsus (once daily) on a 1:0.7 (mg:mg) total daily dose basis, the mean systemic exposure to tacrolimus (AUC_{0-24}) was similar to that of immediate-release tacrolimus. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for Envarsus is similar to that of immediate-release tacrolimus. No studies have been conducted with conversion of patients from Advagraf to Envarsus; however, data from healthy volunteers would suggest that the same conversion rate is applicable as with the conversion from Prograf to Envarsus. When converting from tacrolimus immediate-release products (e.g. Prograf capsules) or from Advagraf prolonged-release capsules to Envarsus, trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained after the

switch. The CHMP noted that black patients may require a higher dose to achieve the targeted trough levels (as reflected in the product information).

The oral bioavailability of Envarsus was decreased when the product was administered after a meal. The extent of absorption was decreased by 55% and the maximum plasma concentration was decreased by 22% when taken directly after a high-fat meal. Therefore, Envarsus should generally be taken on an empty stomach to achieve maximal absorption as mentioned in the product information.

Study LCP-Tacro 2017 in *de novo* kidney transplant recipients showed that higher Cmax/Cmin and AUC profile is recorded with LCP-Tacro compared to Prograf. The results of study 2017 have therefore been used by the applicant to further support the proposed posology for LCP-Tacro. This study 2017 also reported that no patients experienced graft failure and no patients died during the study. Three patients experienced BPAR: one in the LCP-Tacro group and two in the Prograf group. For the mITT analysis set (n=63), there was no statistically significant difference in Kaplan-Meier estimates of the cumulative incidence freedom from BPAR between the LCP-Tacro and Prograf groups (96.8% vs. 93.3%: p=0.65); findings were essentially identical on Day 180 and Day 365.

In study 2017 supporting the PK of LCP-Tacro in *de novo* kidney transplant patients, the absolute doses of LCP-Tacro and Prograf administered seem to be equivalent. The mean daily dose on day 1 to 7 for LCP-Tacro was 10.29 mg (3.32), and the dose for Prograf was 10.88 mg (3.417). During the procedure, the applicant clarified the respective average daily tacrolimus doses normalized by patient weight during the first 14 days of study LCP-Tacro 2017 (Days 1-7; Days 8-14) as well as for the remainder of the study. The average daily doses normalized by patient weight showed that the mean (SD) daily dose of LCP-Tacro tablets in the mITT population decreased progressively from 0.12 (0.04) mg/kg on Days 1-7 to 0.07 (0.05) mg/kg on Days 181-360. The mean (SD) daily dose of Prograf decreased progressively from 0.13 (0.04) mg/kg on Days 1-7 to 0.08 (0.06) mg/kg on Days 181-360. PK results obtained from study 2017 indicated that LCP-Tacro dose regimens are improved by utilising a slightly higher Day-1 dose in the *de novo* setting. This has been consequently confirmed in phase III study 3002 using an LCP-starting dose of 0.17 mg/kg/day given as a single morning dose, followed by dosing according to the desired tacrolimus trough levels. This is acceptable to the CHMP since relative bioavailability studies with LCP-Tacro show higher plasma concentrations. In addition, results from study LCP-Tacro 2017 showed that a Day 1 dose of 0.14 mg/kg/day results in lower tacrolimus exposure as well as that a limited subset of patients tolerated well a Day 1 dose of 0.17 mg/kg/day. The results submitted clarified that the apparently equal mean doses for the two treatments in study 2017 are caused by differences in weight. Furthermore it has been clarified by the applicant that the dose for LCP-Tacro is not increased rapidly, but conversely decreased according to the desired tacrolimus trough levels. The dose corrected data indicated that by Day 14, LCP-Tacro therapy shows similar systemic exposure, peak systemic exposure and trough tacrolimus levels when compared to Prograf in adult *de novo* liver transplant recipients during the first 14 days post-transplantation.

The applicant proposed to use the highest dose of each dose range used in Study 2018, resulting in a starting dose recommendation of 0.11 to 0.13 mg/kg/d for *de novo* liver allograft recipients, based on the observed data (i.e., 30% lower Cmin values for Envarsus on day 1 compared to Prograf). This has been agreed by the CHMP and is in line with reference product.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of tacrolimus has been investigated extensively in the past, is well known and has been the subject of many publications.

The clinical development strategy was based on clinical pharmacokinetic studies evaluating the comparative pharmacokinetics of the European reference medicinal product Advagraf and LCP-Tacro as well as the clinical comparator Prograf and LCP-Tacro. This strategy is agreed by the CHMP.

Overall the CHMP concluded that higher C_{avg} (~50%), reduced peak trough fluctuation (C_{max}/C_{min}) and a longer T_{max} were seen for Envarsus when compared with both, tacrolimus immediate-release formulation (Prograf) and a tacrolimus once daily formulation (Advagraf). Mean values for C_{max}, percentage degree of fluctuation and percentage degree of swing were significantly lower with administration of Envarsus tablets.

A strong correlation exists between AUC and whole blood trough levels at steady-state for Envarsus. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

2.5. Clinical efficacy

2.5.1. Dose response studies

As tacrolimus efficacy is known to correlate with trough concentrations obtained during therapeutic drug monitoring, separate dose-response studies were not conducted. This was agreed by the CHMP.

The doses of LCP-Tacro used in the three completed Phase 2 and Phase 3 efficacy studies in kidney transplant patients (Study LCP-Tacro 2017, Studies LCP-Tacro 3001 and 3002) were primarily based on the findings of the Phase 2 PK Study LCP-Tacro 2011 and was also determined by Prograf dosing approved at the time the studies were conducted. Reflecting clinical practice at that time, in all completed clinical Phase 2 and Phase 3 studies on LCP-Tacro, dose adjustments of study drug were permitted to maintain tacrolimus whole blood levels within predefined ranges (4-15 ng/mL) as therapeutically recommended at the time of the respective study protocol generation.

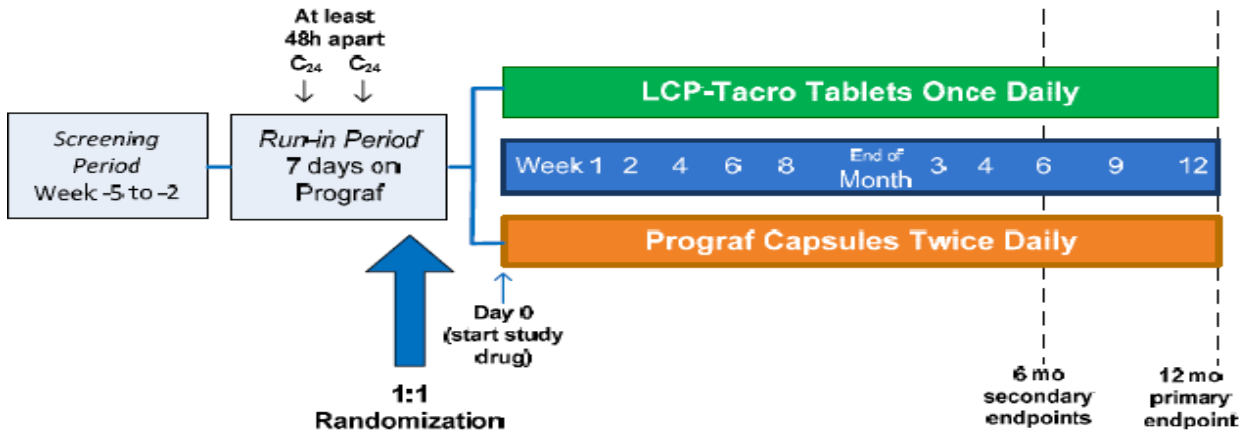
2.5.2. Main study(ies)

LCP-Tacro 3001: A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion From Prograf Capsules Twice Daily to LCP-Tacro Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients

Methods

Study LCP-3001 was a Phase 3, open label, multicenter, prospective, randomized, two-arm parallel group study in stable kidney transplant patients. Following a 7-day run-in period during which patients continued on their current dose of Prograf capsules (b.i.d.), patients were randomized 1:1 to receive a reduced dose of LCP-Tacro tablets (q.d.) or to continue on Prograf capsules (b.i.d.) for 12 months.

Study Flow Diagram:



Study Participants

The study population comprised 326 adult (≥18 years) stable kidney transplant patients (renal transplant 3 months to 5 years before enrollment) on oral Prograf capsules (b.i.d.), at a total daily dose of ≥2 mg/day, as part of their maintenance immunosuppression regimen.

Inclusion criteria were:

1. Men and women at least 18 years of age who are recipients of a kidney transplant between 3 months and 5 years before the screening date.

2. Patients taking oral Prograf capsules twice daily, at least 2 mg total dose per day, as part of their maintenance immunosuppression therapy, with tacrolimus trough levels of 5 to 15 ng/mL. Patients must maintain tacrolimus trough levels in this range during the 7-day Run-in Period to be eligible for randomization (based on two consecutive trough level measurements at least 48 hours apart).

3. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days before receiving study drug.

Exclusion Criteria included:

1. Recipients of any transplanted organ other than kidney

2. Recipients of a bone marrow transplant

3. Patients with an eGFR (MDRD7) < 30 mL/min at Screening

4. Patients with a spot protein: creatinine ratio > 0.5

5. Patients with a WBC count < 2.8 x 109/L unless the WBC count has been stable for at least 2 weeks and the absolute neutrophil count is > 1.0 x 109 /L

6. Patients unable to swallow study medication

7. Patients incapable of understanding the purposes and risks of the study, who cannot give written informed consent and who are unwilling or unable to comply with the study protocol requirements

8. Pregnant or nursing women

9. Patients with reproductive potential who are unwilling/unable to use a double-barrier method of contraception

Treatments

Patients on a stable dose of oral Prograf of at least 2 mg per day were randomly assigned to be converted from Prograf twice daily to oral LCP-Tacro once daily or to remain on maintenance therapy with oral Prograf twice daily. For patients randomly assigned to LCP-Tacro, initial dosing was 0.7 times the total daily dose of Prograf being taken by the patient just before conversion. Because of decreased bioavailability of LCP-Tacro, black patients were converted using a 0.85 conversion multiplier. All subsequent study drug dose adjustments were based on clinical assessment of the patient and maintenance of target tacrolimus whole blood trough levels within the predefined therapeutic range of 4 to 15 ng/mL. The duration of treatment was 360 days.

Reference Product

Only patients taking a stable total daily dose of at least 2 mg of Prograf were eligible for entry into the study. During the study, fractional total daily doses were only permitted for patients taking less than 5 mg per day (fractional total daily doses of 1.5, 2.5, 3.5 and 4.5 mg per day).

Prograf was to be administrated twice daily in 2 equally divided doses (or as close to equally divided as feasible), once in the morning and once in the evening, with an interval of 12 hours (±1 hour) between

the morning and evening doses. After initial dosing, patients taking Prograf had their dose adjusted to maintain tacrolimus whole blood trough levels within the predefined therapeutic range of 4 to 15 ng/mL for the duration of the study.

Objectives

The primary objective was to evaluate, the efficacy and safety of LCP-Tacro tablets administered once daily when used to replace Prograf capsules administered twice daily for maintenance immunosuppression for prevention of acute allograft rejection in adult renal transplant patients.

Outcomes/endpoints

A composite primary endpoint for non-inferiority was used for efficacy failure at 12 months after the first dose of study drug and included any patient experiencing any of the following within 12 months (by Day 360) after random assignment to treatment: death, graft failure (return to dialysis for >30 days, allograft nephrectomy, or retransplantation), biopsy-proven acute rejection (BPAR) (Banff grade ≥1A), or loss to follow-up. The primary efficacy endpoint analysis was performed using the modified intent-to-treat (mITT) set.

The secondary efficacy endpoints were based on the mITT set, except where specified, as follows:

- Incidence of efficacy failure (i.e., defined as any patient experiencing death, graft failure, BPAR, or lost to follow-up) in the mITT and in the PP populations within 6 months after first dose of study drug

- Incidence of efficacy failure in the PP set within 12 months after first dose of study drug

- Incidences of death or graft failure within 6 months and 12 months after first dose of study drug

- Incidences of BPAR (Banff grade ≥1A) within 6 months and 12 months after first dose of study drug

- Incidences of steroid-resistant acute rejection (as assessed by the need for antibody therapy for the treatment of acute rejection after a course of corticosteroids) within 6 months and 12 months after first dose of study drug

- Proportion of severity grades of the first episode of BPAR (by Banff grade) occurring within 6 months and 12 months after first dose of study drug

Sample size

A total of 409 patients were enrolled into the study, 83 of these patients were not randomly assigned to study treatment. Overall, 326 patients were randomly assigned to the study, 163 patients in each treatment group, and 296 patients completed the 12-month treatment period, 142 patients in the LCP-Tacro group and 154 patients in the Prograf group. One patient in each treatment group was randomly assigned and not dosed; thus, a total of 324 patients (99.4%) were included in the (mITT) set, 162 (99.4%) in each treatment group. Thirty patients (9.2%) discontinued from the study; of these, more patients in the LCP-Tacro treatment group (21 patients [12.9%]) discontinued from the study than in the Prograf treatment group (9 patients [5.5%]). Reasons for study discontinuation in the LCP-Tacro treatment group were AE (10 patients), voluntary discontinuation (7 patients), death (2 patients), and physician decision (2 patients). Reasons for study discontinuation in the Prograf treatment group were AE (3 patients), voluntary discontinuation (3 patients), protocol violations (2 patients) and lost to follow-up (1 patient).

Randomisation

Randomization was performed using a fixed-block randomization scheme. The randomization scheme was generated and reviewed by the study biostatistician and quality assurance staff and locked by them after approval. The investigational sites randomly assigned qualified patients through an IVRS. The IVRS

was contacted for randomization assignment once a patient satisfied the requirements for tacrolimus whole blood trough levels and pregnancy testing during the Run-in Period. The sites were to record the time of randomization.

Blinding (masking)

This was an open-label study.

Statistical methods

There were 5 data sets for analysis:

- The Enrolled Set included all patients who have signed the informed consent.
- The Randomized Set included all enrolled patients who have passed the run-in period and are subsequently randomized.
- The mITT Set included all randomized patients who receive at least one dose of either study drug (LCP-Tacro or Prograf). Patient who were randomized and took any incorrect treatment for the entire study were reported under their randomized treatment group for the mITT Set.
- The Safety Set included all randomized patients who receive at least one dose of either study drug (LCP-Tacro or Prograf). Patient who were randomized and took any incorrect treatment for the entire study were reported under the treatment they actually received for the Safety Set.
- The PP Set included all mITT patients who completed the study without any major protocol deviations. Unless otherwise specified, the PP Set was determined using the major deviations occurring within 12 months after the first dose of study drug. Major protocol deviations were reviewed on a case-by-case to determine eligibility for the per protocol analysis set before the database freeze.

The primary efficacy analysis was conducted at the 2-sided 0.05 significance level. All other analyses such as confidence intervals, statistical tests, and resulting p-values were reported as 2-sided and assessed and reported at the 0.05 significance level. No Type 1 error rate adjustments for multiple comparisons were made.

Primary Efficacy Endpoint Analysis

A composite primary endpoint for non-inferiority was used to define efficacy failure in the mITT population and included any patient experiencing any of the following within 12 months after receiving the first dose of either study drug: death, graft failure (return to dialysis for >30 days, allograft nephrectomy, or retransplantation), BPAR (Banff grade >1A), or lost to follow-up. Noninferiority of LCP-Tacro with respect to the composite primary endpoint was assessed using a (2-sided) 95% CI based on the risk difference for efficacy failure between the treatment groups (LCP-Tacro minus Prograf). If the upper bound of the 95% CI for the difference in efficacy failure was less than 0.09 in the mITT analysis set, then LCP-Tacro was considered non-inferior to Prograf. The 95% CI for the difference in efficacy failure rates were calculated using exact methods.

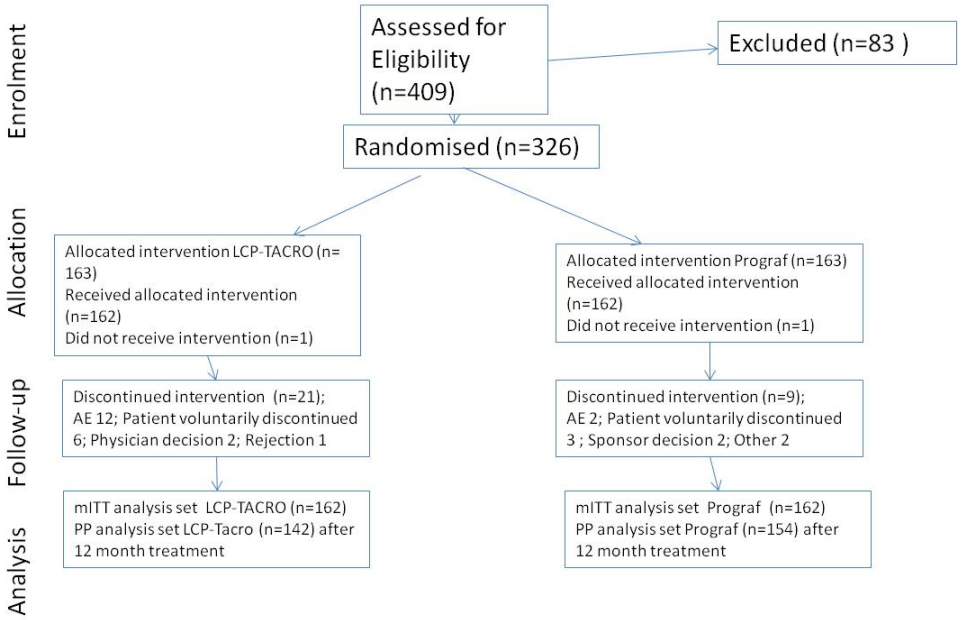
Primary Safety Endpoint Analysis

The primary safety endpoint was the differences between treatment groups at 12 months after randomization with respect to the incidence of AEs and the incidence of predefined potentially clinically significant laboratory measures that included: fasting plasma glucose level >200 mg/dL; platelets < 100 x 109 cells/L; WBC < 2.0 x 109 cells/L; transaminases >100 U/L; total cholesterol > 300 mg/dL; LDL cholesterol > 200 mg/dL; triglycerides > 500 mg/dL; and eGFR < 30 mL/min. Differences among treatment groups with respect to AE incidence and the incidence of predefined potentially clinically

significant laboratory values were assessed using the Fisher exact test. The primary safety assessment was performed on the mITT analysis set.

Results

Participant flow



Recruitment

Study Initiation Date: 23 December 2008

Study Completion Date: 07 February 2011

Conduct of the study

2 major amendments were made to the protocol. No major protocol deviations occurred.

Baseline data

Baseline patient characteristics are presented in the following tables:

Table 39 Demographic and Other Baseline Characteristics (Randomized Set)

	LCP-Tacro n=163	Prograf n=163	*P* value[a]	Total N=326
Age (years)[b]				
n	163	163		326
Mean (SD)	50.4 (11.71)	50.2 (13.49)	0.909	50.3 (12.61)
Median	51.0	52.0		52.0
Minimum, maximum	18, 73	18, 77		18, 77
Age categories (years)			0.190	
<65	146 (89.6%)	137 (84.0%)		283 (86.8%)
≥65	17 (10.4%)	26 (16.0%)		43 (13.2%)
Sex			0.098	
Male	117 (71.8%)	102 (62.6%)		219 (67.2%)
Female	46 (28.2%)	61 (37.4)		107 (32.8%)
Race			0.826	
White	120 (73.6%)	117 (71.8%)		237 (72.7%)
Black	36 (22.1%)	34 (20.9%)		70 (21.5%)
Asian	3 (1.8%)	3 (1.8%)		6 (1.8%)
American Indian or Alaska Native	0	1 (0.6%)		1 (0.3%)
Native Hawaiian or other Pacific Islander	0	1 (0.6%)		1 (0.3%)
Other[c]	4 (2.5%)	7 (4.3%)		11 (3.4%)
Ethnicity			0.768	
Hispanic or Latino	26 (16.0%)	29 (17.8%)		55 (16.9%)
Not Hispanic or Latino	137 (84.0%)	134 (82.2%)		271 (83.1%)
Height at Screening (cm)				
n	159	156		315
Mean (SD)	171.69 (9.485)	169.61 (10.538)	0.067	170.66 (10.059)
Median	172.40	170.00		171.00
Minimum, maximum	137.0, 192.9	149.5, 200.5		137.0, 200.5
Weight at Screening (kg)				
n	159	156		315
Mean (SD)	85.72 (18.564)	83.07(20.513)	0.230	84.41 (19.567)
Median	83.80	81.41		83.00
Minimum, maximum	47.5, 157.8	45.5, 150.6		45.5, 157.8

Table 39 continued

	LCP-Tacro n=163	Prograf n=163	*P* value[a]	Total N=326
Body mass index (kg/m^2)[d]				
n	159	156		315
Mean (SD)	29.01 (5.420)	28.73 (6.124)	0.676	28.87 (5.771)
Median	28.19	27.68		27.94
Minimum, maximum	18.4, 46.8	17.8, 53.0		17.8, 53.0
Diabetes history (both insulin dependent and non-insulin dependent)	61 (37.4%)	53 (32.5%)	0.416	114 (35.0%)
Previous rejection for the current graft	20 (12.3%)	23 (14.1%)	0.744	43 (13.2%)
Donor type			0.244	
Living	62 (38.0%)	51 (31.3%)		113 (34.7%)
Deceased	101 (62.0%)	112 (68.7%)		213 (65.3%)
Number of human leukocyte antigen (HLA) mismatches			0.502	
0	16 (9.8%)	15 (9.2%)		31 (9.5%)
1	10 (6.1%)	8 (4.9%)		18 (5.5%)
2	18 (11.0%)	11 (6.7%)		29 (8.9%)
≥3	119 (73.0%)	129 (79.1%)		248 (76.1%)
Subjects who had a previous transplant other than the current transplant	22 (13.5%)	20 (12.3%)	0.869	42 (12.9%)
Panel reactive antibody (%)				
n	141	138		279
Mean (SD)	10.3 (24.02)	8.8 (19.42)	0.566	9.6 (21.84)
Median	0.0	0.0		0.0
Minimum, maximum	0, 99	0, 98		0, 99
Panel reactive antibody (%)			>0.999	
<20	120 (73.6%)	117 (71.8%)		237 (72.7%)
≥20	21 (12.9%)	21 (12.9%)		42 (12.9%)
Missing	22 (13.5%)	25 (15.3%)		47 (14.4%)

Table 39 continued

	LCP-Tacro n=163	Prograf n=163	*P* value[a]	Total N=326
Days from transplant to informed consent				
n	163	162		325
Mean (SD)	779.7 (502.66)	659.7 (457.09)	0.025	719.9 (483.50)
Median	643.0	569.0		617.0
Minimum, maximum	115, 2005	82, 1821		82, 2005
Baseline Prograf dose (mg/day)				
n	162	162		324
Mean (SD)	6.09 (3.903)	5.34 (3.347)	0.063	5.71 (3.650)
Median	5.00	4.00		4.00
Minimum, maximum	2.0, 24.0	2.0, 24.0		2.0, 24.0
Baseline weight-adjusted Prograf dose (mg/kg/day)				
n	162	162		324
Mean (SD)	0.07 (0.052)	0.07 (0.040)	0.160	0.07 (0.046)
Median	0.06	0.06		0.06
Minimum, maximum	0.0, 0.3	0.0, 0.2		0.0, 0.3

Source data: Table 14.1.4 (Appendices 16.2.4.1 and 16.2.4.4)

Note: Percentages are based on the number of randomly assigned patients in each treatment group and the number of enrolled patients in the total column.

SD=standard deviation.

[a] *P* value was generated from t-test for continuous variables and Fisher exact tests for categorical variables.

[b] Age was calculated as the integer part of (date of informed consent – date of birth + 1)/365.25.

[c] Other race included the following: Indian (1 patient), Tonga (1 patient), Dominican (1 patient), Guyanese (1 patient), Hispanic (3 patients), Indian-subcontinent (1 patient), Philippine (1 patient), Indian (from India; 1 patient), and not specified (1 patient).

[d] Body mass index was calculated as ([weight in kg]/[{height in cm}/100]^2) at Screening

Numbers analysed

Approximately 302 patients at 50 sites were planned; a total of 409 patients at 47 sites were enrolled. A total of 324 patients received at least 1 dose of study drug and 296 patients completed the study without any major protocol deviations within 12 months (per-protocol PP set).

Outcomes and estimation

Outcomes from this study are presented in the following table:

Table 40 Primary Efficacy Failure Within 12 Months (mITT Set) – Locally Read BPAR

	LCP-Tacro n=162	Prograf n=162	*P* value[a]
Efficacy failure	4 (2.5%)	4 (2.5%)	>0.999
Death	2 (1.2%)	1 (0.6%)	>0.999
Graft failure	0	0	ND
Locally read BPAR	2 (1.2%)	2 (1.2%)	>0.999
Loss to follow-up	0	1 (0.6%)	>0.999
Efficacy Failure Treatment Difference[b]	0		
95% 2-sided CI	–4.21%, 4.21%		

Source data: Table 14.2.1.1 (Appendices 16.2.6.1, 16.2.6.2.1, 16.2.6.3, 16.2.6.4.1 and 16.2.6.4.2.)

Note: Percentages are based on the number of patients in the mITT set in each treatment group.

BPAR=biopsy-proven acute rejection; CI=confidence interval; ND=not defined; mITT=modified intent to treat.

[a] *P* value was calculated using Fisher exact test to compare LCP-Tacro to Prograf.

[b] Treatment difference was determined by LCP-Tacro minus Prograf. The 95% CI for the difference in efficacy failure rates were calculated via StatXact 8.0 using an exact method that is based on the

The incidence of efficacy failure was not different between Test (LCP-Tacro) and reference (Prograf), LCP-Tacro (4/162; 2.5%) and Prograf (4/162; 2.5%). The CIs constructed for the incidence differences

of LCP-Tacro indicate no statistical difference between treatment groups. With respect to efficacy failure, a treatment difference of 0% (95.2% confidence interval [CI]: -4.21% to 4.21%) was observed.

The primary efficacy failure within 12 months in the mITT set for centrally read BPAR is summarised as follows:

Table 41 Primary Efficacy Failure Within 12 Months (mITT Set) – Centrally Read BPAR

	LCP-Tacro n=162	Prograf n=162	*P* value[a]
Efficacy Failure	3 (1.9%)	6 (3.7%)	0.502
Death	2 (1.2%)	1 (0.6%)	>0.999
Graft failure	0	0	ND
Centrally read BPAR	1 (0.6%)	4 (2.5%)	0.371
Loss to follow-up	0	1 (0.6%)	>0.999
Efficacy Failure Treatment Difference[b]	–1.85%		
95% 2-sided CI	–6.51%,2.30%		

Source data: Table 14.2.1.2 (Appendices 16.2.6.1, 16.2.6.2.2, 16.2.6.3, 16.2.6.4.1 and 16.2.6.4.2)

Percentages are based on the number of patients in the mITT set in each treatment group

BPAR=biopsy-proven acute rejection; CI=confidence interval; ND=not defined; mITT=modified intent to treat.

[a] P value was calculated using Fisher exact test to compare LCP-Tacro to Prograf.

[b] Treatment difference was determined by LCP-Tacro minus Prograf. The 95% CI for the difference in efficacy failure rates were calculated via StatXact 8.0 using an exact method that is based on the standardized statistic and inverting a 2-sided test (Agresti and Min, 2001).

The overall efficacy failure rate was lower for LCP-Tacro (1.9%) than for Prograf (3.7%) and the treatment difference (CI) was -1.85% (-6.51%, 2.30%). No statistically significant difference was observed between LCP-Tacro and Prograf for the incidence rate of overall efficacy failure, death, graft failure, centrally read BPAR or loss to follow-up.

LCP-Tacro 3002: A Phase 3, Double-Blind, Double-Dummy, Multi-Center, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro Tablets, Once Daily, Compared to Prograf Capsules, Twice Daily, in Combination With Mycophenolate Mofetil for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients

Methods

This was a 2-arm parallel group, prospective, randomized, double-blind, double-dummy, multicenter Phase 3 clinical trial to establish the efficacy and safety of LCP-Tacro tablets once daily for the prevention of allograft rejection in adult male and female recipients of a *de novo* primary or secondary kidney transplant evaluated by a combined efficacy endpoint of death, acute rejection, graft loss, and patient loss. The study was designed to determine if the test drug, LCP-Tacro, was not inferior to an unacceptable extent to the comparator compound, Prograf.

Study Participants

The study population comprised 543 adult (≥18 years) primary or secondary kidney transplant patients. Recipients of another organ (liver, heart, lung, pancreas, or intestinal transplant) or bone marrow transplant were not eligible.

Inclusion Criteria

1. Signed ICF

2. Patient was between the ages of 18 and 70 years, inclusive

3. Patient was receiving a primary or secondary renal allograft from a deceased donor or non-HLA identical living donor

4. Patients had no known contraindications to the administration of IL-2 receptor antagonist induction therapy, MMF, corticosteroids, or tacrolimus

5. If patient was a WOCBP, she should have had a negative pregnancy test (serum or urine) with a sensitivity of a least 25 mIU/mL within 1 week prior to beginning therapy. Women of childbearing potential were willing to agree to contraceptive practices as detailed in the Contraception Guidelines. If patient was a WOCBP, she must have had a negative pregnancy test (serum or urine pregnancy test with a sensitivity of a least 25 mIU/mL) within 1 week before beginning therapy. Women of childbearing potential were willing to agree to contraceptive practices as detailed in the Contraception Guidelines.

6. Patient had a negative cross match test, and compatible (A, B, AB, or O) blood type

7. Patient was able to swallow tablets and capsules

Exclusion Criteria included:

1. Patient was a recipient of any non-renal transplant (solid organ or bone marrow) ever

2. Patient had a panel reactive antibody (PRA) >30%

3. Patients with any condition that may affect study drug absorption (e.g., gastrectomy or clinically significant diabetic gastroenteropathy)

4. Patient had a body mass index (BMI) <18 kg/m2 or >40 kg/m^2

5. Patient had a history of alcohol abuse with less than 6 months of sobriety

6. Patient had a history of recreational drug abuse with less than 6 months of documented abstinence

7. Patient had a 12-lead ECG at Screening demonstrating clinically relevant abnormalities (including QTc prolongation, reversible ischemia, and clinically symptomatic congestive heart failure or documented ejection fraction of less than 45%). Patient had a 12-lead ECG at Screening demonstrating clinically relevant abnormalities (including QT prolongation)

8. Patient was a WOCBP who was either pregnant, lactating, planning to become pregnant, or had a positive serum or urine pregnancy test

9. Patients with an oral temperature (before study drug)

Treatments

Patients were randomly assigned to receive 1 of 2 formulations of tacrolimus (LCP-Tacro or

Prograf) as follows:

Test treatment: LCP-Tacro tablets, once daily, orally; provided in 0.75-mg, 1.0-mg, and 4.0-mg dosage strengths.

Comparator treatment: Prograf capsules (tacrolimus), twice daily, orally; provided in 0.5-mg, 1-mg, and 5-mg dosage strengths.

All patients also received matching double-dummy placebo to maintain the blind.

LCP-Tacro was started at 0.17 mg/kg/day given as a single morning dose. Prograf was started at a total daily dose (TDD) of 0.1 mg/kg/day, given as 2 equally divided doses 12 hours apart (1 in the morning before noon and 1 in the evening). Subsequent doses of each study drug were adjusted to maintain trough concentrations of tacrolimus in whole blood within the target range of 6 to 11 ng/mL for the first 30 days, then 4 to 11 ng/mL for the remainder of the study.

Objectives

The objectives of the study were to evaluate the efficacy and safety of LCP-Tacro (tacrolimus) tablets administered once daily compared to Prograf (tacrolimus) capsules twice daily as immunosuppression for the prevention of acute allograft rejection in *de novo* adult kidney transplant recipients treated for a 12-month treatment period followed by a 12-month, blinded treatment extension period, and to show that LCP-Tacro tablets are not clinically inferior to Prograf capsules in the prevention of acute allograft rejection in *de novo* adult kidney transplant recipients.

Outcomes / endpoints

Primary

The primary efficacy endpoint was the incidence of treatment failures within 12 months, up to and including Day 365, after the randomization date. Treatment failure was a composite endpoint that included any of the following events: death, graft failure (initiation of chronic maintenance dialysis, current allograft nephrectomy, or re-transplantation), biopsy-proven acute rejection (BPAR) (Banff Grade $\geq$ 1A), or lost to follow-up. Patients who did not experience these events or discontinued the study for other reasons (including adverse events [AEs], withdrawn consent, physician decision, sponsor decision, unsatisfactory therapeutic effect, or noncompliance) were not counted as treatment failures.

Secondary

The incidence of each event within 12 months, up to and including Day 365 after the randomization date, was a secondary efficacy endpoint. The secondary efficacy endpoints were: 12-month all-cause mortality rate, 12-month graft failure rate, 12-month BPAR rate, 12-month incidence of death, or graft failure.

Other Efficacy

The other efficacy endpoints were:

- Twelve-month (Day 404, the upper limit of the day range for the Month 12 Visit, or 18 Mar 2013, whichever was earlier) incidence of clinically suspected and treated acute rejections
- Twelve-month (up to and including Day 365 after the randomization date) incidence of premature discontinuation for any reason
- Severity grades of the first episode of BPAR at Day 404, the upper limit of the day range for the Month 12 Visit, or 18 Mar 2013, whichever was earlier.
- Time-to-event (up to and including Day 365 after the randomization date) analysis of treatment failure, graft and patient survival, and time to first episode of BPAR.

Secondary safety endpoints included:

1. New-onset diabetes mellitus within 6 months and 12 months

2. Incidences of any opportunistic infection and any malignancy

3. Incidences of post-transplant lymphoproliferation disorder (PTLD) among all patients and within the patients who are EBV seronegative at the time of transplant

4. Mean change from Baseline (Day 30) in estimated creatinine clearance by estimated glomerular flow rate (eGFR) at Months 3, 6, and 12

5. Mean dose of study drug and mean tacrolimus whole blood trough level at each post randomization visit

6. Interpatient and intrapatient variability of tacrolimus whole blood trough levels

7. Change in clinical laboratories and vital signs at each time point

8. Incidence of 12-lead ECGs clinical findings at each time point

9. In patients not diabetic at time of transplant, mean change from (Baseline) Day 0 in

HbA1c at Days 90, 180 and 360

10. Incidence of clinically significant infection (confirmed by culture, biopsy, genomic or serologic findings) that requires hospitalization or systemic anti-infective treatment, or is otherwise deemed significant by the Investigator

11. Cytomegalovirus [CMV] disease will be assessed as 1) symptomatic CMV syndrome, 2) tissue-invasive CMV disease and 3) asymptomatic CMV).

12. Incidence of BK virus viremia at days 30, 90, 180 and 360

13. Incidence of BK virus nephropathy

Sample size

A total of 601 patients were enrolled into the study and 58 of these patients (9.7%) were not randomly assigned to study treatment. Of the 543 patients randomly assigned to study drug, 268 patients were in the LCP-Tacro group and 275 were in the Prograf group. Two patients in the LCP-Tacro group and 4 patients in the Prograf group were randomly assigned and not dosed. Overall, 425 patients (78.3%) completed the 12-month study drug treatment.

Randomisation

Randomization was performed using a fixed-block randomization scheme. The randomization scheme was generated before the initiation of the study by an independent statistician/programmer who was not a member of the study team; all investigators were not aware of the block size of the randomization scheme. Randomization was stratified by site and race (black vs. non-black).

Blinding (masking)

A double-blind, double-dummy study design was used to mask the placebo and active formulations. Consequently, both the investigator and patient did not know the treatment group to which the patient was assigned, thus reducing bias. To maintain blinding of both the investigator and the patient, all patients took tablets (LCP-Tacro/matching placebo) in the morning and capsules (over encapsulated Prograf to maintain the blind/matching placebo) twice daily.

Statistical methods

The primary analysis of the primary efficacy endpoint, treatment failure rate within 12 months after randomization, was summarized for the ITT set. The number and percentage of patients who experienced any event qualifying as treatment failure event was presented by treatment group. The noninferiority of LCP-Tacro with respect to treatment failure within 12 months was assessed using a 2-sided 95% confidence interval (CI) based on the difference in treatment failure rates between the treatment groups at 12 months, i.e., LCP-Tacro minus Prograf. The 95% confidence limits for the difference in treatment failure rates were calculated using the Newcombe-Wilson score method.

Results

Participant flow

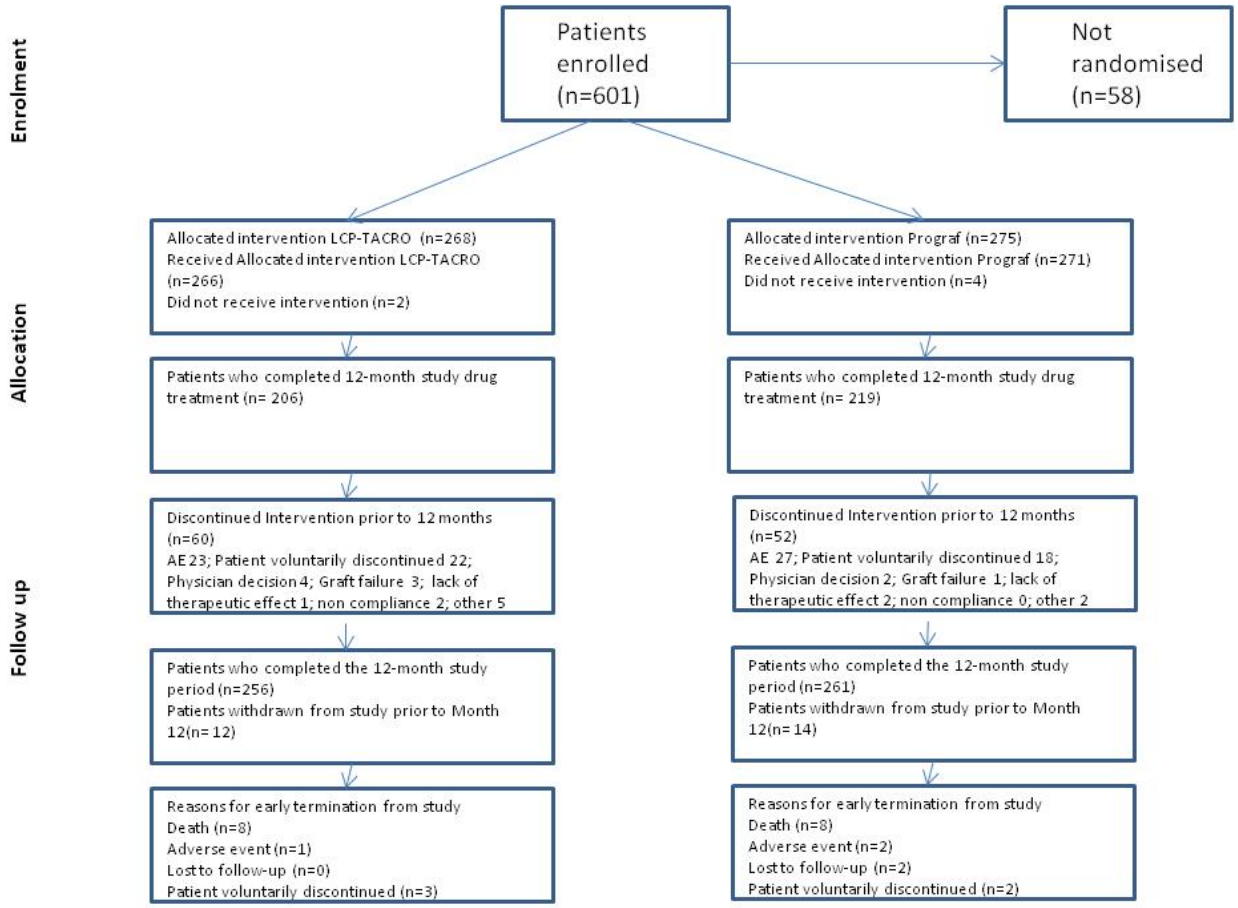


Table 42 Overall Disposition (All Patients Enrolled)

Parameter	Total Enrolled	Not Randomized	LCP-Tacro	Prograf (N=275)	Total
Patients	601	58 (9.7)[a]	n (%)	n (%)	n (%)
Patients randomized			268	275	543
Patients who received at least 1 dose of study[b]			266 (99.3)	271 (98.5)	537 (98.9)
Patients who completed 12-month study drug			206 (76.9)	219 (79.6)	425 (78.3)
Patients discontinued from study drug prior to Month 12[c]			60 (22.4)	52 (18.9)	112 (20.6)
Reasons for early discontinuation of study drug prior Month 12					
Graft failure			3 (1.1)	1 (0.4)	4 (0.7)
Rejection			0	0	0
Adverse event			23 (8.6)	27 (9.8)	50 (9.2)
Unsatisfactory therapeutic effect			1 (0.4)	2 (0.7)	3 (0.6)
Patient voluntarily discontinued			22 (8.2)	18 (6.5)	40 (7.4)
Physician decision			4 (1.5)	2 (0.7)	6 (1.1)
Sponsor decision			0	0	0
Noncompliance			2 (0.7)	0	2 (0.4)
Other			5 (1.9)	2 (0.7)	7 (1.3)
Patients who completed the 12-month study period			256 (95.5)	261 (94.9)	517 (95.2)
Patients withdrawn from study prior to Month 12[d]			12 (4.5)	14 (5.1)	26 (4.8)
Reasons for early termination from study					
Death			8 (3.0)	8 (2.9)	16 (2.9)
Adverse event			1 (0.4)	2 (0.7)	3 (0.6)
Lost to follow-up			0	2 (0.7)	2 (0.4)
Patient voluntarily discontinued			3 (1.1)	2 (0.7)	5 (0.9)

[a]Number of patients enrolled but not randomized, as a percentage of total enrolled. All other percentages are based on the total number of patients randomized to each treatment group.
[b] Includes the patients who received 1 dose of either drug (study drug or ctive control).
[c] Only includes the patients who discontinued on or before Day 365.
[d] Only includes the patients who withdrew from the study on or before Day 365. Each of these patients was continued to be followed for primary efficacy data even after they had withdrawn from the study.

Recruitment

Study Initiation Date: 13 Oct 2010 (first patient enrolled)

12-Month Study Completion Date: 20 Mar 2013 (last patient completed 12-month visit)

Conduct of the study

Overall, 21 patients (3.9%) had at least 1 major protocol deviation, 10 in the LCP-Tacro group and 11 in the Prograf group. Most of the protocol deviations were related to investigational product issues or randomization errors.

Baseline data

Table 43 Demographics (ITT Set)

Parameter	Statistics or Distribution	LCP-Tacro (N=268)	Prograf (N=275)	Total (N=543)
Age (years)	n	268	275	543
	Mean (SE)	44.8 (0.81)	46.9 (0.86)	45.8 (0.59)
	SD	13.29	14.2	13.8
	Minimum, maximum	18, 70	18, 70	18, 70
	Median	46.	50.	48.
	<65 years	252 (94.0)	247 (89.8)	499 (91.9)
	≥65 years	16 (6.0)	28 (10.2)	44 (8.1)
Sex – n (%)	Male	174 (64.9)	181 (65.8)	355 (65.4)
	Female	94 (35.1)	94 (34.2)	188 (34.6)
Race – n (%)	White	203 (75.7)	214 (77.8)	417 (76.8)
	Black or African	10 (3.7)	15 (5.5)	25 (4.6)
	Asian	10 (3.7)	10 (3.6)	20 (3.7)
	American Indian or Alaska	0	1 (0.4)	1 (0.2)
	Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)	2 (0.4)
	Other	44 (16.4)	34 (12.4)	78 (14.4)
Ethnicity – n (%)	Hispanic or Latino	74 (27.6)	79 (28.7)	153 (28.2)
	Non-Hispanic or Latino	194 (72.4)	196 (71.3)	390 (71.8)
Baseline BMI	n	266	274	540
	Mean (SE)	25.72	26.68	26.21
	SD	4.648	4.94	4.82
	Minimum, maximum	16.6, 38.2	15.6, 42.1	15.6, 42.1
	Median	25.22	26.4	25.8
	<30 kg/m^2	217 (81.0)	207 (75.3)	424 (78.1)
	≥30 kg/m^2	49 (18.3)	67 (24.4)	116 (21.4)
	Missing	2 (0.7)	1 (0.4)	3 (0.6)
Reproductive Status – n (%)	Without Childbearing Potential	36 (13.4)	55 (20.0)	91 (16.8)
	With Childbearing	58 (21.6)	39 (14.2)	97 (17.9)
	Not Applicable (Male Patients)	174 (64.9)	181 (65.8)	355 (65.4)

Abbreviation: BMI, body mass index.

a Body mass index was calculated as weight in kg at Baseline/(height in cm/100)^2. Baseline height and weight were considered to be the last measurements on or before the randomization date.

b Percentage was calculated based on the patients with previous transplant.

Table 44 Baseline Data and Transplant Information (ITT Set)

Parameter	Statistics or Distribution	LCP-Tacro (N=268)	Prograf (N=275)	Total (N=543)
Diabetes at the Time of Transplant? – n (%)	Yes	50 (18.7)	56 (20.4)	106 (19.5)
	No	218 (81.3)	219 (79.6)	437 (80.5)
Time From Transplant to First Dose (h)				
	n	26	271	537
	Mean (SE)	34.15	34.38	34.27
	SD	8.878	9.73	9.31
	Minimum, maximum	8.0, 60.5	6.5, 78.0	6.5, 78.0
	Median	34.00	34.0	34.0
CMV IgG – n (%)	Positive	175 (65.3)	191 (69.5)	366 (67.4)
	Negative	90 (33.6)	83 (30.2)	173 (31.9)
	Indeterminate	2 (0.7)	0	2 (0.4)
	Not Done	1 (0.4)	0	1 (0.2)
	Missing	0	1 (0.4)	1 (0.2)
EBV IgG – n (%)	Positive	210 (78.4)	212 (77.1)	422 (77.7)
	Negative	36 (13.4)	36 (13.1)	72 (13.3)
	Indeterminate	10 (3.7)	6 (2.2)	16 (2.9)
	Not Done	12 (4.5)	20 (7.3)	32 (5.9)
	Missing	0	1 (0.4)	1 (0.2)
PRA (%) – n (%)	n	26	274	542
	Mean (SE)	1.5 (0.31)	1.5 (0.36)	1.5 (0.24)
	SD	5.1	5.9	5.5
	Minimum, maximum	0, 31	0,	0,
	Median	0.	0.0	0.0
	<5%	243 (90.7)	253 (92.0)	496 (91.3)
	5-20%	18 (6.7)	14 (5.1)	32 (5.9)
	>20%	7 (2.6)	7 (2.5)	14 (2.6)
	Missing	0	1 (0.4)	1 (0.2)
Donor Type	Living	135 (50.4)	129 (46.9)	264 (48.6)
	Deceased	133 (49.6)	145 (52.7)	278 (51.2)
	Missing	0	1 (0.4)	1 (0.2)
HLA Mismatches				
HLA-A – n (%)	0	31 (11.6)	37 (13.5)	68 (12.5)
	1	129 (48.1)	135 (49.1)	264 (48.6)
	2	91 (34.0)	83 (30.2)	174 (32.0)
	3	0	1 (0.4)	1 (0.2)
	Unknown	17 (6.3)	18 (6.5)	35 (6.4)
	Missing	0	1 (0.4)	1 (0.2)
HLA-B – n (%)	0	32 (11.9)	21 (7.6)	53 (9.8)
	1	127 (47.4)	136 (49.5)	263 (48.4)
	2	91 (34.0)	97 (35.3)	188 (34.6)
	3	0	1 (0.4)	1 (0.2)
	Unknown	18 (6.7)	19 (6.9)	37 (6.8)
	Missing	0	1 (0.4)	1 (0.2)
HLA-DR – n (%)	0	45 (16.8)	51 (18.5)	96 (17.7)
	1	136 (50.7)	141 (51.3)	277 (51.0)
	2	67 (25.0)	62 (22.5)	129 (23.8)
	Unknown	20 (7.5)	20 (7.3)	40 (7.4)
	Missing	0	1 (0.4)	1 (0.2)
Previous Transplant – n (%)				
	Yes	11 (4.1)	11 (4.0)	22 (4.1)
	No	257 (95.9)	263 (95.6)	520 (95.8)
	Missing	0	1 (0.4)	1 (0.2)
Years From Last Transplant to Current Transplant				
	n	11	10	21
	Mean	11.66	10.95	11.32

SD	3.457	6.74	5.15
Minimum, maximum	4.9, 16.9	1.4, 24.4	1.4, 24.4
Median	12.02	9.9	11.6
Previous Transplant Donor Type[b] – n (%)			
Living	4 (36.4)	3 (27.3)	7 (31.8)
Decease	7 (63.6)	7 (63.6)	14 (63.6)
Had previous transplant, but type unknown	0	1 (9.1)	1 (4.5)

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; IgG, immunoglobulin G; PRA, panel reactive antibody.

a Body mass index was calculated as weight in kg at Baseline/(height in cm/100)^2. Baseline height and weight were considered to be the last measurements on or before the randomization date.

b Percentage was calculated based on the patients with previous transplant.

Numbers analysed

601 patients were enrolled. A total of 537 patients received at least 1 dose of study drug and 425 patients completed the study within 12 months.

Outcomes and estimation

Results for treatment failure and individual events defining treatment failure within 12 months after randomization are presented in Table 45.

The overall incidence of treatment failure was 18.3% for patients in the LCP-Tacro treatment group and 19.6% for patients in the Prograf treatment group. The treatment difference (CI) was -1.35% (-7.94% to 5.27%), below the noninferiority margin of 10%. No statistically significant difference was observed between the LCP-Tacro and Prograf treatment groups for the incidence rate of all-cause mortality, graft failure, BPAR, or lost to follow-up.

Table 45 Incidence of Treatment Failure and Individual Events Defining Treatment Failure Within 12 Months After Randomization (ITT Set)

Patients With Event	LCP-Tacro (N=268)	Prograf (N=275)	LCP-Tacro – Prograf (95% CI)[a]	*P* Value[b]
Treatment failure within 12 months after randomization	49 (18.3)	54 (19.6)	-1.35% (-7.94%, 5.27%)	–
All-cause mortality	8 (3.0)	8 (2.9)		>0.99
Graft failure	9 (3.4)	11 (4.0)	-0.64% (-4.05%,	0.821
BPAR	35 (13.1)	37 (13.5)	-0.39% (-6.14%,	0.900
Lost to follow-up	4 (1.5)	5 (1.8)	-0.33% (-2.86%, 2.18%)	>0.999

Abbreviation: BPAR, biopsy-proven acute rejection.

a Two-sided 95% confidence intervals were calculated using Newcombe-Wilson score intervals. For the primary efficacy endpoint (12-month treatment failure rate), the difference between groups was assessed via a non-inferiority approach with a non-inferiority margin of 10%.

b The *P* value was based on a 2-sided Fisher exact test to evaluate the difference between treatment groups in the incidence of events defining treatment failure (death, graft failure, BPAR, and lost to follow-up).

Secondary Endpoints

Kaplan-Meier estimates of event rates for the ITT set are presented in Table 46. Kaplan-Meier analysis of time to treatment failure is also displayed graphically in Figure 3. No statistically significant difference was observed between the 2 treatment groups in time-to-event distribution by log-rank P value for: treatment failure, first episode of BPAR, graft failure, all-cause mortality, graft failure or death, discontinuation from study or study drug, or discontinuation from study or study drug due to AEs. The

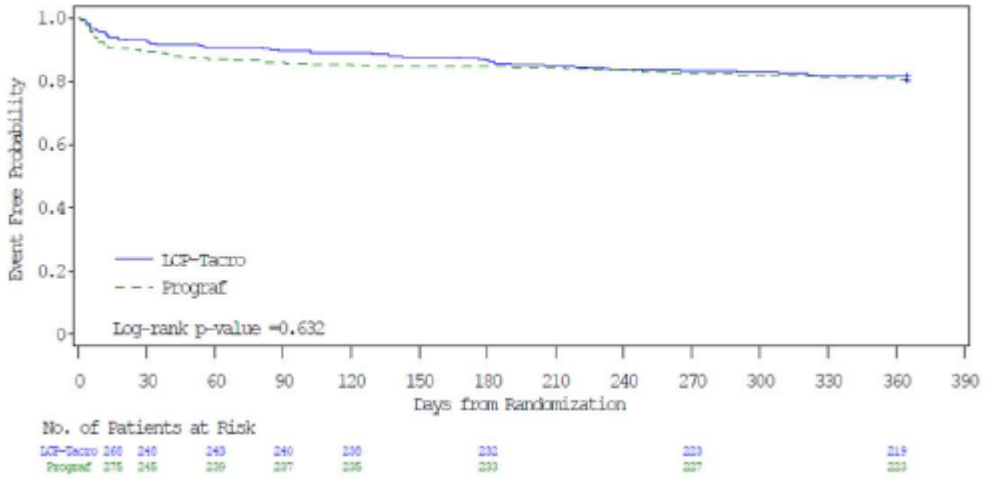
estimated hazard ratios and 95% CIs also did not indicate meaningful or statistically significant treatment differences in risks of failure.

Table 46 Kaplan-Meier Estimates of Event Rates: Time to Treatment Failure and Other Endpoints (First Episode of BPAR, Graft Failure, Death, and Premature Discontinuation) Within 12 Months After Randomization (ITT Set)

Event	Statistics[a]	LCP-Tacro (N=268)	Prograf (N=275)	Hazard Ratio (95% CI)
Treatment failure				
	Patients censored: n (%)	219 (81.7)	221 (80.4)	
	KM event rate at 12 months	0.183	0.196	0.910
	(95% CI)	(0.137, 0.229)	(0.149, 0.243)	(0.618, 1.340)
				Log-rank $P = 0.632$
First episode of BPAR				
	Patients censored: n (%)	233 (86.9)	238 (86.5)	
	KM event rate at 12 months	0.131	0.136	0.957
	(95% CI)	(0.091, 0.172)	(0.095, 0.177)	(0.603, 1.519)
				Log-rank $P = 0.852$
Graft failure				
	Patients censored: n (%)	259 (96.6)	264 (96.0)	
	KM event rate at 12 months	0.034	0.040	0.833
	(95% CI)	(0.012, 0.055)	(0.017, 0.063)	(0.345, 2.010)
				Log-rank $P = 0.684$
All-cause mortality				
	Patients censored: n (%)	260 (97.0)	267 (97.1)	
	KM event rate at 12 months	0.030	0.029	1.011
	(95% CI)	(0.010, 0.051)	(0.009, 0.050)	(0.380, 2.694)
				Log-rank $P = 0.982$
Graft failure or death (whichever occurs first)				
	Patients censored: n (%)	253 (94.4)	257 (93.5)	
	KM event rate at 12 months	0.056	0.066	0.844
	(95% CI)	(0.029, 0.084)	(0.036, 0.095)	(0.425, 1.674)
				Log-rank $P = 0.625$
Discontinuation from study or study drug (whichever occurs first)				
	Patients censored: n (%)	207 (77.2)	222 (80.7)	
	KM event rate at 12 months	0.228	0.193	1.180
	(95% CI)	(0.177, 0.278)	(0.146, 0.239)	(0.817, 1.705)
				Log-rank $P = 0.376$
Discontinuation from study or study drug (whichever occurs first) due to adverse events				
	Patients censored: N (%)	245 (91.4)	248 (90.2)	
	KM event rate at 12 months	0.086	0.098	0.862
	(95% CI)	(0.052, 0.120)	(0.063, 0.134)	(0.495, 1.504)
				Log-rank $P = 0.601$

Abbreviations: CI, confidence interval; KM, Kaplan-Meier.
a The KM event rate = Kaplan-Meier product-limit estimate of the cumulative probability of event at specified time point. The *P* value (2-tailed) is based on a log-rank test used to compare time-to-event distributions.
Source: Table 14.2.4.

Figure 3 Time to Treatment Failure – Kaplan-Meier Analysis (ITT Set)



No statistically significant difference was observed between the 2 treatment groups in the incidence of treatment failure when stratified by baseline, sex, race, age (i.e., <65 and ≥65 years), BMI, diabetes at the time of transplant, and geographic region. However, some differences occurred when the incidence of treatment failure was stratified by race, age, and geographic region (Table 47).

Table 47 Incidence of Treatment Failure Within 12 Month After Randomization: Analysis Stratified by Race, Age, and Geographic Region (ITT Set)

Subgroup	LCP-Tacro (N=268)		Prograf (N=275)		LCP-Tacro – Prograf (95% CI)[a]	*P* Value[b]
Baseline factor	N	n (%)	N	n (%)		
Overall	268	49 (18.3)	275	54 (19.6)	-1.35% (-7.94%, 5.27%)	0.694
Race						
Blacks	10	3 (30.0)	15	6 (40.0)	-10.00% (-40.95%, 26.42%)	0.691
Whites	203	36 (17.7)	214	40 (18.7)	-0.96% (-8.35%, 6.51%)	0.899
Other	55	10 (18.2)	46	8 (17.4)	0.79% (-14.75%, 15.51%)	>0.999
Age						
<65 years old	252	48 (19.0)	247	48 (19.4)	-0.39% (-7.32%, 6.53%)	>0.999
≥65 years old	16	1 (6.3)	28	6 (21.4)	-15.18% (-34.00%, 9.59%)	0.393
Geographic region						
US	67	12 (17.9)	70	10 (14.3)	3.62% (-8.83%, 16.18%)	0.645
Europe	130	22 (16.9)	131	22 (16.8)	0.13% (-9.02%, 9.29%)	>0.999
Latin America	57	8 (14.0)	59	17 (28.8)	-14.78% (-29.04%, 0.29%)	0.071
Asia Pacific	14	7 (50.0)	15	5 (33.3)	16.67% (-17.41%, 46.13%)	0.462

Abbreviation: CI, confidence interval.
a Percentages were based on the number of patients in each subgroup. The 95% confidence interval was calculated using the Newcombe-Wilson Score method.
b The *P* value was based on a Fisher exact test of treatment difference within each subgroup. The "overall" *P* value was based on the Cochran-Mantel-Haenszel test of treatment difference, controlling for baseline factors.

When stratified by race, the incidence of treatment failure was greater in blacks in the Prograf group compared with the LCP-Tacro group (40.0% vs. 30.0%), with a treatment difference

(CI) of -10.00% (-40.95%, 26.42%) (LCP-Tacro minus Prograf) (*P* = 0.691); although the clinical significance is unknown as the patient samples were small (10 and 15 black patients in the LCP-Tacro and Prograf groups, respectively).

When stratified by age, the incidence of treatment failure was greater in patients 65 years and older in the Prograf group compared with the LCP-Tacro group (21.4% vs. 6.3%), with a treatment difference (CI) of -15.18% (-34.00%, 9.59%) (LCP-Tacro minus Prograf) (*P* = 0.393); although the clinical significance is unknown as the patient samples were unequal and small (16 and 28 patients who were 65 years and older in the LCP-Tacro and Prograf groups, respectively).

When stratified by geographic region, the incidence of treatment failure within 12 months in Latin America was greater in the Prograf group compared with the LCP-Tacro group (28.8% vs. 14.0%), with a treatment difference (CI) of -14.78% (-29.04%, 0.29%) (LCP-Tacro minus Prograf) (*P* = 0.071). In Asia Pacific, the incidence of treatment failure was greater in the LCP-Tacro group compared with the Prograf group (50.0% vs. 33.3%), with a treatment difference (CI) of 16.67% (-17.41%, 46.13%) (LCP-Tacro minus Prograf) (*P* = 0.462); although the clinical significance is unknown as the patient samples were small (14 and 15 patients in the LCP-Tacro and Prograf groups, respectively).

Severity of the first episode of BPAR and incidence of clinically suspected and treated acute rejection episodes within 12 months after randomization for the ITT set is presented in Table 48. There was no statistically significant difference between the 2 treatment groups in the incidence of patients with clinically suspected and treated rejections, the number of BPAR episodes, or the severity of the first BPAR episode. Of the patients with 1 or more BPAR episodes or clinically suspected and treated rejection episodes, most had only 1 episode. Most of the first BPAR episodes were mild in severity.

Table 48 Severity of the First Episode of BPAR and Incidence of Clinically Suspected and Treated Acute Rejection Episodes Within 12 Months After Randomization (ITT Set)

Parameter	LCP-Tacro (N=268)	Prograf (N=275)	LCP-Tacro – Prograf (95% CI)[a]	*P* Value
Number (%) of patients with ≥1 rejections	37 (13.8)	43 (15.6)	-1.83% (-7.81%, 4.18%)	0.628[b]
Patients with 1 episode	33 (12.3)	37 (13.5)		
Patients with 2 episodes	3 (1.1)	6 (2.2)		
Patients with 3 episodes	1 (0.4)	0		
Patients with ≥4 episodes	0	0		
Patients with ≥1 BPAR	38 (14.2)	40 (14.5)	-0.37% (-6.30%,	>0.999[b]
Patients with 1 episode	29 (10.8)	32 (11.6)		
Patients with 2 episodes	6 (2.2)	6 (2.2)		
Patients with 3 episodes	2 (0.7)	2 (0.7)		
Patients with ≥4 episodes	1 (0.4)	0		
Severity of first BPAR episode (Banff criteria)				
Mild	30 (11.2)	31 (11.3)		0.984[c]
Moderate	7 (2.6)	8 (2.9)		
Severe	1 (0.4)	1 (0.4)		

Abbreviation: BPAR, biopsy-proven acute rejection.

Note: Mild is acute T-cell-mediated rejection Grade IA or IB; moderate is acute T-cell-mediated rejection Grade IIA or Grade IIB; and severe is acute T-cell-mediated rejection Grade III utilizing Banff 2007 criteria. BPAR events were based on the central biopsy reading. Events occurring prior to or on Study Day 404 or 18 Mar 2013, whichever is earlier, are included.

a The 2-sided Newcombe-Wilson score confidence intervals are presented.

b *P* value from Fisher exact test.

c *P* value from Cochran-Mantel-Haenszel test for general association.

Categorical analysis of treatment failure by time of occurrence for the ITT set is presented in Table 49. No statistically significant treatment differences were observed in the occurrences of treatment failure, graft failure, BPAR, or lost to follow-up when categorically analyzed by time of occurrence. A significant treatment difference was observed in the occurrence of death when analyzed by time (P = 0.007). All 8 deaths in the LCP-Tacro group occurred 92 days or more after randomization (i.e., 4 to 12 months) while 5 of the 8 deaths in the Prograf group occurred within 3 months of randomization.

Table 49 Categorical Analysis of Treatment Failure by Time of Occurrence (ITT Set)

Event	Time After Randomization[a]	LCP-Tacro (N=268)	Prograf (N=275)	*P* Value[b]
Treatment	Within 3 Months	28 (10.4)	39 (14.2)	0.12
	4-6 Months	10 (3.7)	3 (1.1)	
	7-9 Months	7 (2.6)	6 (2.2)	
	10-12 Months	4 (1.5)	6 (2.2)	
Death	Within 3 Months	0	5 (1.8)	0.00
	4-6 Months	5 (1.9)	0	
	7-9 Months	1 (0.4)	3 (1.1)	
	10-12 Months	2 (0.7)	0	
Graft failure	Within 3 Months	6 (2.2)	7 (2.5)	0.68
	4-6 Months	1 (0.4)	2 (0.7)	
	7-9 Months	2 (0.7)	1 (0.4)	
	10-12 Months	0	1 (0.4)	
BPAR	Within 3 Months	22 (8.2)	26 (9.5)	0.55
	4-6 Months	5 (1.9)	2 (0.7)	
	7-9 Months	4 (1.5)	3 (1.1)	
	10-12 Months	4 (1.5)	6 (2.2)	
Lost to follow-up	Within 3 Months	2 (0.7)	5 (1.8)	0.24

4-6 Months	0	0
7-9 Months	1 (0.4)	0
10-12 Months	1 (0.4)	0

Abbreviation: BPAR, biopsy-proven acute rejection.

a Times of BPAR and graft failure were those of the first episodes. Time of treatment failure was that of the first event. Patients are classified according to the number of days after randomization as: if ≤91, then "within 3 months," if 92 to 183, then "4-6 months," if 184 to 274, then "7-9 months," and if 275 to 365, then "10-12 months."

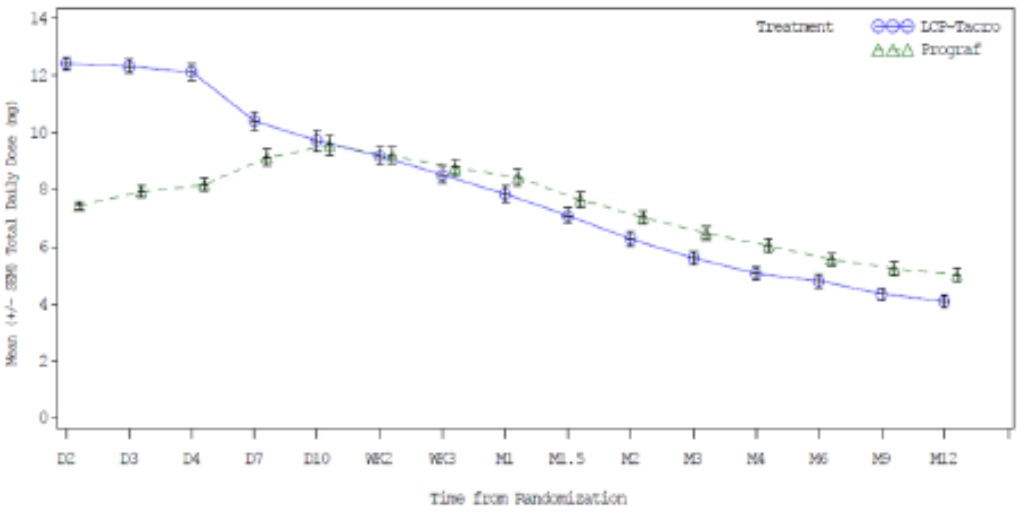
b *P* value from Cochran-Mantel-Haenszel test for general association.

Kaplan-Meier analyses showed comparable efficacy throughout the 12-month study period including the early post-operative days when patients are at greatest risk of organ rejection and graft failure. Within the first 3 months after transplant, when patients are at the greatest risk of rejection, no statistically significant difference was observed in term of treatment failure rates between LCP-Tacro and Prograf - 10.4% and 14.2%, respectively (P=0.124). No statistically significant difference was observed between the 2 treatment groups in the incidence of treatment failure also when stratified by baseline sex, race, age (i.e., <65 and ≥65 years), BMI, diabetes at the time of transplant, and geographic region.

Tacrolimus Total Daily Dose (TDD)

In the first week of dosing, TDD levels were higher in patients in the LCP-Tacro group compared with the Prograf group; on Days 2 through 4, mean LCP-Tacro TDD levels were approximately 12 mg compared with 7 to 8 mg in the Prograf group likely reflecting the higher starting dose of LCP-Tacro (0.17 mg/kg vs 0.10 mg/kg for Prograf). At Day 7, mean tacrolimus TDD levels were 10.4 and 9.1 mg in the LCP-Tacro and Prograf groups, respectively. Tacrolimus TDD levels were similar in both treatment groups from Day 10 through Week 3. From Month 1 through Month 12, tacrolimus TDD levels were lower in the LCP-Tacro group compared with the Prograf group and the difference increased continually over time. At the final visit on Month 12, mean levels in the LCP-Tacro group were 18.3% lower than in the Prograf group (4.09 mg in the LCP-Tacro group and 5.01 mg in the Prograf group) (see figure 4 below).

Figure 4 Mean (±SEM) Tacrolimus Total Daily Dose (mg) Over Time by Treatment Group (ITT Set; Study LCP-Tacro 3002).

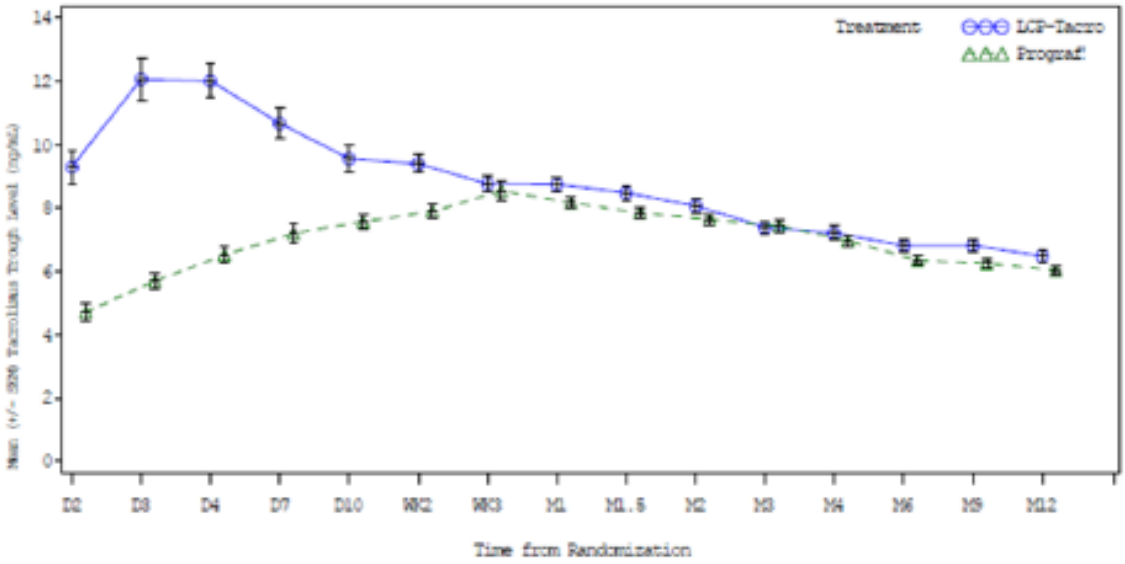


No meaningful differences between the treatment groups in mean tacrolimus total daily dose or tacrolimus trough levels were noted based on race or gender. The mean total dose (i.e., sum of all tacrolimus daily dose levels over 12 months) was 14.3% lower in the LCP-Tacro group (1659.5 mg) compared with the Prograf group (1935.8 mg), reflecting the lower daily dose of LCP-Tacro necessary to

provide comparable tacrolimus exposure. The average number of dose adjustments per month (after being normalized by exposure duration) was essentially the same (1.11) between the groups.

Tacrolimus Trough Levels (TTLs): TTLs over time between LCP-Tacro and Prograf are displayed in Figure 5.

Figure 5 Mean (±SEM) Tacrolimus Trough Level (ng/ml) Over Time by Treatment Group (ITT Set; Study LCP-Tacro 3002)



The overall mean tacrolimus trough levels (TTLs) were within the predefined therapeutic range in both treatment groups through Month 12. TTLs were notably greater in the LCP-Tacro group compared with the Prograf group in the first 2 weeks after dosing; thereafter, trough levels in the 2 groups were similar. The mean TTLs from Day 1 through Month 12 were greater in the LCP-Tacro group; when calculated as the average of all trough level records, mean levels were 8.8 ng/ml in the LCP-Tacro group compared with 7.0 ng/ml in the Prograf group. Median values were generally similar or slightly lower than mean values.

Proportion of Patients Achieving Therapeutic Tacrolimus Trough Levels

On Day 2, 36.6% of patients in the LCP-Tacro group and 18.5% of patients in the Prograf group were within the target tacrolimus trough range; the majority of Prograf patients (74.7%) had trough levels less than 6 ng/ml compared with 33.5% in the LCP-Tacro group. From Day 2 through Day 7, approximately 30% to 40% of patients were within the target range. Of the patients in the LCP-Tacro group who did not meet the target range in this time period, the majority had levels greater than 11 ng/ml, while the majority of patients in the Prograf group had levels below 6 ng/ml. By Day 10, approximately 50% of patients were within the target range and at Month 1, 57.1% and 70.3% of patients in the LCP-Tacro and Prograf groups, respectively, were within the target range. From Month 1.5 through Month 12, the majority of patients were within the post 30-day target range of 4 to 11 ng/ml and the proportions of patients in each range were similar between the treatment groups.

Dose Adjustments

The majority of patients had at least 1 dose adjustment during the first 12 months of the study (96.2% and 97.8% in the LCP-Tacro and Prograf groups, respectively). More patients had dose adjustments in the first 3 months after the first dose (>79% in both treatment groups) compared with after 3 months; at >3 to ≤6 months, 65.4% and 61.3% in LCP-Tacro and Prograf groups, respectively, and at >6 to ≤12 months, approximately half of all patients had dose adjustments. The average number of dose

adjustments per month (after being normalized by exposure duration) was essentially the same (1.11) between the groups. The majority of patients had an average of less than 1 dose adjustment per month (70.7% and 77.5% in the LCP-Tacro and Prograf groups, respectively); more patients in the LCP-Tacro group required 1 to less than 3 dose adjustments per month (23.3%) compared with the Prograf group (14.8%).

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).

Table 50 Summary of efficacy for trial 3001

Title: Study 3001 A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion From Prograf Capsules Twice Daily to LCP-Tacro Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients			
Study identifier	Study 3001		
Design	A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion From Prograf Capsules Twice Daily to LCP-Tacro Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		360 Days 7 days not applicable
Hypothesis	Non-inferiority		
Treatments groups	LCP-Tacro		Treatment: LCP-Tacro once daily. Duration 360 Days, 163 patients randomized
	Prograf		Treatment: Prograf b.i.d. Duration 360 Days, 163 patients randomized
Endpoints and definitions	Primary endpoint	Efficacy	A composite primary endpoint for non-inferiority was used for efficacy failure at 12 months after the first dose of study drug and included any patient experiencing any of the following within 12 months (by Day 360) after random assignment to treatment: death, graft failure (return to dialysis for >30 days, allograft nephrectomy, or retransplantation), biopsy-proven acute rejection (BPAR) (Banff grade ⩾1A), or loss to follow-up. The primary efficacy endpoint analysis was performed using the modified intent-to-treat (mITT) set.
	Secondary	Efficacy	The secondary efficacy endpoints were based on the mITT set, except where specified, as follows: Incidence of efficacy failure (i.e., defined as

			any patient experiencing death, graft failure, BPAR, or lost to follow-up) in the mITT and in the PP populations within 6 months after first dose of study drug Incidence of efficacy failure in the PP set within 12 months after first dose of study drug Incidences of death or graft failure within 6 months and 12 months after first dose of study drug Incidences of BPAR (Banff grade ⩾1A) within 6 months and 12 months after first dose of study drug Incidences of steroid-resistant acute rejection (as assessed by the need for antibody therapy for the treatment of acute rejection after a course of corticosteroids) within 6 months and 12 months after first dose of study drug Proportion of severity grades of the first episode of BPAR (by Banff grade) occurring within 6 months and 12 months after first dose of study drug Incidence of clinically suspected and treated rejection episodes (treated acute rejection despite the absence of confirmatory evidence on a biopsy) within 6 months and 12 months after first dose of study drug Incidence of premature discontinuation of randomly assigned study drug for any reason within 12 months after first dose of study drug
Database lock	The study database of study LCP-Tacro 3001 was locked on 27 May 2011; The study database study LCP-Tacro 3001 was unlocked on 14 June 2011; The study database study LCP-Tacro 3001 was re-locked on 16 June 2011. The study database was unlocked to correct data issues identified during preparation / review of the following study tabulations, listings and figures (TLFs). These issues included insertion of 2 missed biopsy records, corrections of study medication start and stop dates for 16 patients, correction of medication doses based on the updates of medication start and stop dates, as well as correction of vital sign dates and values for 5 patients. These corrections did not impact or affect the efficacy or safety analyses.		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified Intent to Treat time point: Day 360 of treatment from the date of randomization			
Descriptive statistics and estimate variability	Treatment group	LCP-Tacro	Prograf	
	Number of subjects	162	162	
	Overall efficacy failure (number) Death Graft failure Locally assessed BPAR Lost to follow-up	4 (2.5%) 2 (1.2%) 0 2 (1.2%) 0	4 (2.5%) 1 (0.6%) 0 2 (1.2%) 1 (0.6%)	

Effect estimate per comparison	Primary endpoint	Comparison groups	LCP-Tacro vs Prograf
		Efficacy Failure Treatment Difference	0
		95% 2-sided CI	–4.21%; 4.21%
		P-value	>0.9999

Notes	The 95% CI for the difference in efficacy failure rates were calculated using an exact method based on the standardized statistic and inverting a 2-sided test. Ref: Agresti A, Min Y. On small-sample confidence intervals for parameters in discrete distributions. Biometrics. 2001;57:963-971. *P* value was calculated using Fisher exact test to compare LCP-Tacro to Prograf

Analysis population and time point description	PP Analysis Set time point: Day 360 of treatment from the date of randomization			
Descriptive statistics and estimate variability	Treatment group	LCP-Tacro	Prograf	
	Number of subjects	142	154	

	Overall efficacy failure (number)	1 (0.7%)	2 (1.3%)	
	Death	0	0	
	Graft failure	0	0	
	Locally assessed BPAR	1 (0.7%)	2 (1.3%)	
	Lost to follow-up	0	0	

Effect estimate per comparison	Primary endpoint	Comparison groups	LCP-Tacro vs Prograf
		Efficacy Failure Treatment Difference	-0.59%
		95% 2-sided CI	-4.04%, 2.90%
		P-value	>0.9999
Notes	The 95% CI for the difference in efficacy failure rates were calculated using an exact method based on the standardized statistic and inverting a 2-sided test (Agresti and Min, 2001). *P* value was calculated using Fisher exact test to compare LCP-Tacro to Prograf.		

Secondary Analysis				
Analysis population and time point description	Secondary Endpoint Incidence of Efficacy Failure at 6 Months PP Analysis Set			
Descriptive statistics and estimate variability	Treatment group	LCP-Tacro	Prograf	
	Number of subjects	147	157	
	Overall efficacy failure (number)	0	1 (0.6%)	
	Death	0	0	
	Graft failure	0	0	
	Locally assessed BPAR	0	1 (0.6%)	
	Lost to follow-up	0	0	

Effect estimate per comparison	Secondary endpoint	Comparison groups	LCP-Tacro vs Prograf
		Efficacy Failure Treatment Difference	-0.64%
		95% 2-sided CI	-3.82%,2.12%
		P-value	>0.9999
Notes	The 95% CI for the difference in efficacy failure rates were calculated using an exact method based on the standardized statistic and inverting a 2-sided test (Agresti and Min, 2001).		

Analysis population and time point description	Modified Intent to Treat time point: 6 months of treatment from the date of randomization			
Descriptive statistics and	Treatment group	LCP-Tacro	Prograf	

estimate variability	Number of subjects	162	162	
	Overall efficacy failure (number) Death Graft failure Locally assessed BPAR Lost to follow-up	2 (1.2%) 1 (0.6%) 0 1 (0.6%) 0	1 (0.6%) 0 0 1 (0.6%) 0	

Effect estimate per comparison	Primary endpoint	Comparison groups	LCP-Tacro vs Prograf
		Efficacy Failure Treatment Difference	0.62
		95% 2-sided CI	-2.42%,4.14%
		P-value	>0.9999
Notes	The 95% CI for the difference in efficacy failure rates were calculated using an exact method based on the standardized statistic and inverting a 2-sided test. Ref: Agresti A, Min Y. On small-sample confidence intervals for parameters in discrete distributions. Biometrics. 2001;57:963-971.		

Table 51 Summary of efficacy for trial 3002

Title: Study 3002: A Phase 3, Double-Blind, Double-Dummy, Multi-Center, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro Tablets, Once Daily, Compared to Prograf Capsules, Twice Daily, in Combination With Mycophenolate Mofetil for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients		
Study identifier	Study 3002	
Design	LCP-Tacro 3002: A Phase 3, Double-Blind, Double-Dummy, Multi-Center, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro™ Tablets, Once Daily, Compared to Prograf Capsules, Twice Daily, in Combination With Mycophenolate Mofetil for the Prevention of Acute Allograft Rejection in De Novo Adult Kidney Transplant Recipients	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	360 Days 7 days 12 months (still ongoing)
Hypothesis	Non-inferiority	
Treatments groups	LCP-Tacro	Treatment: LCP-Tacro once daily. Duration 360 Days, 268 patients randomized
	Prograf	Treatment: Prograf b.i.d. Duration 360 Days, 275 patients randomized

Endpoints and definitions	Primary endpoint	Efficacy	A composite primary endpoint for non-inferiority was used for efficacy failure at 12 months after the first dose of study drug and included any patient experiencing any of the following within 12 months up to and including D365 after random assignment to treatment: death, graft failure (initiation of chronic maintenance dialysis, current allograft nephrectomy, or re-transplantation.), biopsy-proven acute rejection (BPAR) (Banff Grade ⩾1A), or lost to follow-up. Patients who did not experience these events or discontinued the study for other reasons (including adverse events [AEs], withdrawn consent, physician decision, sponsor decision, unsatisfactory therapeutic effect, or noncompliance) were not counted as treatment failures. The primary efficacy endpoint analysis was performed using the intent-to-treat (ITT) set.
	Secondary	Efficacy	The incidence of each event within 12 months, up to and including Day 365 after the randomization date, was a secondary efficacy endpoint. The secondary efficacy endpoints were: 12-month all-cause mortality rate, 12-month graft failure rate, 12-month BPAR rate, 12-month incidence of death, or graft failure. Other efficacy endpoints were: • Twelve-month (Day 404, the upper limit of the day range for the Month 12 Visit, or 18 Mar 2013, whichever was earlier) incidence of clinically suspected and treated acute rejections • Twelve-month (up to and including Day 365 after the randomization date) incidence of premature discontinuation for any reason • Severity grades of the first episode of BPAR at Day 404, the upper limit of the day range for the Month 12 Visit, or 18 Mar 2013, whichever was earlier. • Time-to-event (up to and including Day 365 after the randomization date) analysis of treatment failure, graft and patient survival, and time to first episode of BPAR.

Database lock	Not Available

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Incidence of Treatment Failure Within 12 Months After Randomization (Intent to Treat, ITT Set) time point: Day 360 of treatment from the date of randomization			
Descriptive statistics and estimate variability	Treatment group	LCP-Tacro	Prograf	
	Number of subjects	268	275	
	Overall efficacy failure (number)	49 (18.3%)	54 (19.6%)	

Effect estimate per comparison	Primary endpoint	Comparison groups	LCP-Tacro vs Prograf
		Efficacy Failure Treatment Difference	-1.35%
		95% 2-sided CI	–7.94%, 5.27%
		P-value	
Notes	Two-sided 95% confidence intervals were calculated using Newcombe-Wilson Score intervals. For the primary efficacy endpoint (12-Month Treatment Failure rate), the difference between groups was assessed via a non-inferiority approach with NI margin of 10%.		

Secondary Analysis				
Analysis population and time point description	Secondary Endpoints: 12-month all-cause mortality rate, 12-month graft failure rate, 12-month BPAR rate, 12-month incidence of death, or graft failure. 12 Months After Randomization (Intent to Treat, ITT Set)			
Descriptive statistics and estimate variability	Treatment group	LCP-Tacro	Prograf	
	Number of subjects	268	275	

	Death Graft failure BPAR Lost to follow-up	8 (3.0%) 9 (3.4%) 35 (13.1%) 4 (1.5%)	8 (2.9%) 11 (4.0%) 37 (13.5%) 5 (1.8%)	

Effect estimate per comparison	Secondary endpoint	Comparison groups	LCP-Tacro vs Prograf
		All cause mortality	0.08%
		95% 2-sided CI	-3.02%, 3.21%
		P-value	>0.9999
		Graft failure	-0.64%
		95% 2-sided CI	-4.05%, 2.75%
		P-value	0.821
		BPAR	-0.39%
		95% 2-sided CI	-6.14%, 5.38%
		P-value	0.900
		Lost to follow-up	-0.33%
		95% 2-sided CI	-2.86%, 2.18%
		P-value	>0.999
Notes	*P* value was calculated using Fisher exact test to compare LCP-Tacro to Prograf.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In order to demonstrate efficacy of LCP-Tacro in the claimed therapeutic indications, the applicant has conducted three clinical studies: two Phase 3 studies one in adult stable kidney transplant patients (Study LCP-Tacro 3001) and one Phase 3 and one Phase 2 studies in *de novo* adult kidney transplant patients (Studies LCP-Tacro 3002 & 2017). All studies presented by the applicant enrolled a population that are the intended target population to benefit from study drug. Design of studies 3001 & 3002 are a non-inferior open-label, multicenter, prospective, randomized efficacy and safety study in the either stable kidney transplant conversion setting or the *de novo* kidney transplant setting for the prevention of acute allograft rejection. These designs are acceptable to establish non-inferiority to Prograf in this patient population.

The choice of a composite primary endpoint for the main pivotal non-inferiority trial (study 3001) to study efficacy failure at 12 months after the first dose of study drug, included any patient experiencing any of the following within 12 months (by Day 360) after random assignment to treatment: death, graft failure (return to dialysis for >30 days, allograft nephrectomy, or retransplantation), biopsy-proven acute rejection (BPAR) (Banff grade ≥1A), or loss to follow-up, is in line with the relevant CHMP scientific advice and the primary endpoint used to support the efficacy for the reference medicinal product Advagraf . The choice of the secondary endpoints is relevant to support the non-inferiority claim of LCP-Tacro to comparator treatment with Prograf.

The treatment groups in main study 3001 are in accordance with the CHMP scientific advice given, with the intended treatment dose of LCP-Tacro to be 20% lower than that of Prograf. The outcomes reveal that patients can be successfully converted from Prograf to LCP-Tacro at a lower dose and with q.d. dosing. LCP-Tacro patients, on average, required a total daily dose about 20% lower than patients receiving Prograf. The duration of study was acceptable to demonstrate long term maintenance effect of LCP-Tacro in the conversion setting.

Similarly to Study 3001, the choice of a composite primary endpoint for pivotal non-inferiority trial 3002 to study efficacy failure at 12 months after the first dose of study drug as well as the secondary endpoints is considered acceptable by the CHMP.

Efficacy data and additional analyses

The results from the main study 3001 showed that in the conversion setting there was no clinical difference in treatment failure between LCP-Tacro (4/162; 2.5%) and Prograf (4/162; 2.5%). The CIs constructed for the incidence differences of LCP-Tacro indicated no statistical difference between treatment groups. With respect to efficacy failure, a treatment difference of 0% (95.2% confidence interval [CI]: -4.21% to 4.21%) was observed. Similar results for the PP set at 12 months were reported. The secondary endpoints (Incidence of Efficacy Failure at 6 Months mITT & 12 Months PP set) also showed no statistically significant difference in efficacy failure and its individual component between the 2 treatments. In addition, the incidences of death or graft failure and allograft rejections within 6 months in the mITT resulted in no statistically significance difference was observed between the 2 treatments for the mITT set at 6 months for death or graft failure, locally-read BPAR (Banff grade 1A), steroid-resistant acute rejection, clinically suspected and treated rejection episodes or severity of the first episode of BPAR (Banff grade), with an overall incidence of less than 1% for all endpoints. The same result was seen for the incidence of death or graft failure, allograft rejections, and premature discontinuation within 12 Months for the mITT set. No statistically significant difference was observed between the 2 treatments for the mITT set at 12 months for death or graft failure, locally-read BPAR (Banff grade 1A), steroid-resistant acute rejection, clinically suspected and treated rejection episodes or severity of the first episode of BPAR (Banff grade), with an overall incidence of 0% to 1.2% for all endpoints. The results from pivotal study 3001 showed that stable kidney transplanted patients can be adequately switched from Prograf to LCP-tacrolimus without a failure in efficacy.

Data to support efficacy in the claimed *de novo* kidney indication was provided by Study 3002 and Study 2017 as well as the pharmacokinetic profile of LCP-Tacro obtained from studies 1015, 1016 and 1017. The applicant claimed that the PK data can be considered a valid surrogate endpoint for both safety and efficacy for tacrolimus. The CHMP discussed the extensive PK data submitted and agreed that conversion factors have been established that allow switching between formulations as judged from trough concentrations which are in line with the clinical use of tacrolimus. In addition, Study 1017 between LCP-Tacro and Advagraf shows similar PKs profiles and any differences in the concentration time curves could be expected to lack any clinical relevance. The CHMP concluded that based on the extensive PK characterisation of LCP-Tacro and the clinical use of tacrolimus (i.e. clinical monitoring and dose adjustments to remain within effective plasma concentrations), clinically important differences between Advagraf and LCP-Tacro are not expected as the known differences, i.e. lack of bioequivalence with respect to AUC and Cmin (other PK variables not being considered clinically relevant) can be handled by conversion factors and monitoring.

Based on the above and the extensive clinical experience with Advagraf, the CHMP considered that the available pharmacokinetics data for LCP-Tacro in *de novo* and conversion renal transplant setting allow bridging both products with regards to the use in the treatment of acute rejection.

These considerations lead the CHMP to agree that all the PK data in this dossier could support the efficacy of LCP-Tacro in the *de novo* kidney setting. This hypothesis was confirmed further by a confirmatory phase III study in the *de novo* kidney setting (study 3002).

The results in study 3002 for primary efficacy failure rate within 12 months for the ITT set showed treatment failure rates of 18.3% for the LCP-Tacro treatment group and 19.6% for the Prograf treatment group, and the treatment difference (95% CI) was -1.35% (–7.94%, 5.27%), i.e. below the non-inferiority margin of 10.0%. The percentage of patients with one or greater than one episodes of clinically-suspected and treated rejections during the 360-day study was 13.8% for the Envarsus group (N=268) and 15.6% for the Prograf group (N=275). The event rate for centrally-read, biopsy-confirmed acute rejection (BPAR) during the 360-day study was 13.1% in the Envarsus group (N=268) and 13.5% in the Prograf group (N=275). No statistically significant difference was observed between the LCP-Tacro and Prograf treatment groups for the incidence rate of any of the individual events defining treatment failure (all-cause mortality, graft failure, BPAR, or lost to follow-up). No statistically significant difference was observed between the 2 treatment groups in time-to-event distribution by log-rank P value for treatment failure, first episode of BPAR, graft failure, all-cause mortality, graft failure or death, discontinuation from study or study drug, or discontinuation from study or study drug due to AEs. No statistically significant difference was observed between the 2 treatment groups in the incidence of treatment failure when stratified by baseline sex, race, age (i.e., <65 and 65 years), BMI, diabetes at the time of transplant, and geographic region. There was no statistically significant difference between the 2 treatment groups in the incidence of patients with clinically suspected and treated rejections, the number of BPAR episodes, or the severity of the first BPAR episode. Of the patients with 1 or more BPAR episodes or clinically suspected and treated rejection episodes, most had only 1 episode. Most of the first BPAR episodes were mild in severity. No statistically significant treatment differences were observed in the occurrences of treatment failure, graft failure, BPAR, or lost to follow-up when categorically analysed by time of occurrence.

The results from pivotal study 3002 showed that in *de novo* kidney transplanted patients LCP-Tacro is non-inferior to Prograf.

Data to support efficacy in the claimed liver transplant indication is provided by two clinical Phase 2 studies conducted in a total of 117 liver transplant recipients in study 2012, its extension 2012E, and study 2018. In the *de novo* liver transplant study, 29 subjects were treated with LCP-Tacro. The event rate of biopsy-confirmed acute rejection within the 360 day study period was 0% in the Envarsus group and 6.9% in the tacrolimus immediate-release group. Although no pivotal efficacy study to show the suitability of conversion from Prograf to LCP-Tacro in liver transplanted patients has been submitted, a phase 2 study (2012) and its extension (2012E) were provided showing that at day 21, the test product and LCP-Tacro are bioequivalent to Prograf as the CIs lie within the 80-125 CIs.

The CHMP discussed the extensive PK data submitted and agreed that conversion factors have been established that allow switching between formulations as judged from trough concentrations which are in line with the clinical use of tacrolimus. Furthermore, based on the extensive clinical experience with Advagraf, the CHMP considered that the available pharmacokinetics data for LCP-Tacro in *de novo* and conversion liver transplant setting allow bridging both products with regards to the use in the treatment of acute rejection.

The efficacy of tacrolimus as immunosuppressive rescue medication in solid organ transplant recipients is well defined. No specific studies on LCP-Tacro tablets as a rescue medication in case of allograft rejection resistant to treatment with other immunosuppressive medicinal products have been conducted by the applicant in support of this application. However, LCP-Tacro has demonstrated a robust correlation between trough blood levels and overall exposure, allowing for effective dose titration according to tacrolimus trough blood levels. Based on the outcomes of the clinical Phase 2 and 3 development programmes on LCP-Tacro tablets for the prevention of kidney or liver allograft rejection,

it can be concluded that LCP-Tacro tablets are efficacious in a solid organ rejection rescue medication setting. This data and the extensive clinical knowledge on tacrolimus-containing products support the therapeutic indication for LCP-Tacro tablets in the: *"Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients"* in line with the indications of the European reference medicinal product Advagraf and clinical comparator Prograf.

2.5.4. Conclusions on the clinical efficacy

LCP-Tacro efficacy in prophylaxis of transplant rejection in adult kidney allograft recipients is based on both a single pharmacokinetic phase 2 open-label trial as well as a confirmatory phase III study.

The activity of the clinical comparator Prograf in terms of prophylaxis of transplant rejection in adult kidney allograft recipients been demonstrated and is well characterised. The event rate for locally read biopsy-confirmed acute rejection (BPAR) during the 360 day study was 1.2% in the LCP-Tacro group (N=162) post conversion from Prograf at a dose ratio of 0.7:1 mg and 1.2% in the group maintained on Prograf (N=162). The efficacy failure rate as measured by the composite endpoint of death, graft loss, locally read BPAR and loss to follow-up was 2.5% in both the LCP-Tacro and Prograf groups. The treatment difference (LCP-Tacro - Prograf) was 0% (95% confidence interval [-4.21%, 4.21%]). The treatment failure rate using the same composite end-point with centrally read BPAR was 1.9% in the LCP-Tacro group and 3.7% in the Prograf group (95% confidence interval [-6.51%, 2.31%]).

In *de novo* kidney patients, the percentage of patients with one or greater than one episodes of clinically-suspected and treated rejections during the 360-day study was 13.8% for the Envarsus group (N=268) and 15.6% for the Prograf group (N=275). The event rate for centrally-read, biopsy-confirmed acute rejection (BPAR) during the 360-day study was 13.1% in the Envarsus group (N=268) and 13.5% in the Prograf group (N=275). The efficacy failure rate as measured by the composite endpoint of death, graft loss, centrally read BPAR and loss to follow-up was 18.3% in the Envarsus group and 19.6% in the Prograf group. The treatment difference (Envarsus-Prograf) was -1.35% (95% confidence interval [-7.94%, 5.27%]).

The pharmacokinetics, efficacy and safety of Envarsus and tacrolimus immediate-release capsules, both in combination with corticosteroids was compared in 117 liver transplant recipients, of whom 88 received treatment with Envarsus.
In the *de novo* liver transplant study, 29 subjects were treated with Envarsus. The event rate of biopsy-confirmed acute rejection within the 360 day study period was not significantly different between the Envarsus group and the tacrolimus immediate-release group. The overall incidence of fatal treatment emergent adverse events for the combined *de novo* and stable liver transplant population was not significantly different between the Envarsus group and the tacrolimus immediate-release group.

Initially, the applicant proposed a limited indication (for use in kidney transplant patients). During the assessment, the applicant has substantiated the extrapolation of the PK data available with LCP-Tacro in the *de novo* kidney patients and in the liver and transplantation setting (including rescue indication). Based on the extensive clinical experience with the clinical comparator Prograf and the European reference medicinal product Advagraf, the CHMP considered that the available pharmacokinetics data for LCP-Tacro from *de novo* and conversion renal and liver setting allow bridging both products with regards to the use in the treatment of acute rejection. This data and the extensive clinical knowledge on tacrolimus-containing products support the therapeutic indication for LCP-Tacro tablets in the: *"Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients"* in line with the European reference medicinal product Advagraf and the clinical comparator Prograf.

2.6. Clinical safety

The LCP-Tacro clinical development programme comprises: 14 clinical Phase 1 studies in 485 healthy volunteers; the Phase 1 studies tested 6 LCP-Tacro formulations and 7 doses; 4 clinical Phase 2 studies and one Phase 2 extension study with a total of 449 kidney transplant patients and 117 liver transplant patients; Two pivotal clinical Phase 3 Study LCP-Tacro 3001 & 3002 in kidney transplant patients.

Patient Exposure

6 multi-centre clinical studies (2 phase III study and 4 phase II studies) were performed in the USA (4 in kidney transplantation (studies 3001, 3002, 2011 & 2017) and 2 in liver transplantation (studies 2012 (including 2012e) & 2018) and Europe (2 phase III study in kidney transplantation), were used as the basis for analysis of ADRs for LCP-Tacro. This was primarily based on a total of 601 patients treated with LCP-Tacro in these 6 clinical studies (513 kidney-transplanted patients and 88 liver-transplanted patients). 162 patients treated in Phase III long term follow up study with 1 year analysis (study 3001). 268 patients treated in Phase III *de novo* kidney transplant study (study 3002). The experience gathered in all Phase II studies is included into this analysis. Patient population is depicted in the following table.

Table 52

Total estimated exposition of LCP-Tacro

	Patients enrolled	**Patients exposed**	**Patient exposed to the proposed dose range**	**Patient with long term safety data** (≥ 6 months)
Placebo-controlled	NA	NA	NA	NA
Active-controlled	NA	NA	NA	NA
Open studies	Kidney LCP-Tacro Study 3001 (n=163) Study 2011 (n=60) Study 2017 (n=32) Study 3002 (268) LIVER LCP-Tacro Study 2018 (n=29) Study 2012 (n=59)	Study 3001 N=162 Study 2011 (n=51) Study 2017 (n=32) Study 3002 (n=266) Study 2018 (n=29) Study 2012 (n=59)	Kidney (n=511) Liver (n=88)	Study 2011 (n=47) Study 2017 (n=22) Study 3001 (n=142) Study 3002 (n=206) Study 2018 (n=11) Study 2012 (n=44)
Post marketing	NA	NA	NA	NA
Compassionate use	NA	NA	NA	NA
TOTAL			333	266

The incidence of treatment-emergent AEs in the combined (i.e. studies 3001, 2011 and 2017) Phase 2/3 clinical kidney transplant studies was similar with 76.3% for LCP-Tacro (n=187 of 245 patients) and 72.2% for Prograf (n=177 of 251 patients). The incidence of treatment-emergent non-fatal serious AEs (SAEs) (reported for 99 patients [22.2%] overall: 50 patients [20.4%] in the LCP-Tacro group and 49 [19.5%] in the Prograf group) was also similar between LCP-Tacro and Prograf, whereas the AEs leading to discontinuation was higher with LCP-Tacro as compared to Prograf. In total, 21 (4.7%) patients discontinued the assigned treatment in Phase 2 / 3 kidney transplant studies due to AEs (14 [5.7%]

LCP-Tacro patients and 7 [2.8%] Prograf patients). There were no particular individual AEs or system organ classes associated with discontinuation; the only AE leading to more than one discontinuation was cardiac arrest.

For study 3002, the incidence of TEAEs was similar between the 2 treatment groups; 260 (97.0%) patients in the LCP-Tacro group and 269 (97.8%) patients in the Prograf group experienced TEAEs. The most frequently reported TEAEs (reported in 20% or more of patients overall) were: diarrhoea (33.5%), anaemia (28.7%), urinary tract infection (24.4%), hypertension (22.5%), constipation (24.4%), and peripheral oedema (20.7%). While most events occurred at a similar frequency in both treatment groups, constipation and peripheral oedema occurred more frequently in the Prograf group compared with the LCP-Tacro group: constipation (24.4% vs. 18.3%) and peripheral oedema (20.7% vs. 15.7%).

Table 53 Overview of Treatment Emergent Adverse Events per Study – Safety Analysis Set (Studies LCP–Tacro 3001, LCP-Tacro 2017)

Conversion Setting - Clinical Phase 3 Study LCP-Tacro 3001 (12-month study)			
Category	**LCP-Tacro** (N=162)	**Prograf** (N=162)	**Total** (N=324)
Any AE	135 (83.3%)	133 (82.1%)	268 (82.7%)
Any AE Related to Study Drug	35 (21.6%)	21 (13.0%)	56 (17.3%)
Serious non-fatal AEs	36 (22.2%)	26 (16.0%)	62 (19.1%)
AE leading to death	2 (1.2%)	0	2 (0.6%)
AEs Leading to Study Drug Discontinuation	13 (8.0%)	2 (1.2%)	15 (4.6%)
***De Novo* Setting - Clinical Phase 2 Study LCP-Tacro 2017 (12-month study)**			
	LCP-Tacro (N=32)	**Prograf** (N=31)	**Total** (N=63)
Any AE	32 (100%)	30 (96.8%)	62 (98.4%)
Any AE Related to Study Drug	15 (46.9%)	15 (48.4%)	30 (47.6%)
Serious non-fatal AEs	15 (46.9%)	21 (67.7%)	36 (57.1%)
AEs leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs Leading to Study Drug Discontinuation	2 (6.3%)	2 (6.5%)	4 ()

Note: n represents number of patients contributing to summary. AE=adverse event.
Source: CSR LCP-Tacro 3001; Table 11-2; CSR LCP-Tacro 2017; Table 19

The Phase 2 clinical PK Study LCP-Tacro 2011 was a 3-sequence trial, including 59 stable kidney transplant patients. Study duration was 21 days (7 days on Prograf [b.i.d.], 14 days on LCP-Tacro q.d.]). Overall, 10 patients experienced AEs in Period I (Prograf period), 15 patients in Period II (LCP-Tacro period), 6 patients in Period III (LCP-Tacro period), and 4 patients during the follow-up period. No individual AE preferred term occurred in more than 2 patients in any treatment period. Three patients had SAEs and all of them were considered unrelated to treatment. Three patients discontinued due to AEs that were unrelated to treatment. No patients experienced graft loss or allograft rejection. There were no deaths during the study. Eight patients experienced events that were considered possibly related to LCP-Tacro.

The most commonly reported AEs (reported for at least 5% of patients) are listed as follows:

Table 54 Most Common Treatment Emergent Adverse Events (at Least 5% of Patients) Across the Combined Stable and *De Novo* Kidney Transplant Clinical Phase 2/3 Studies (Pooled Safety Analysis Set – Veloxis LCP-Tacro ISS TFLs Combined Kidney Subset, 2012)

	Total[2] (N=445)		LCP-Tacro (N=245)		Prograf (N=251)	
Preferred Term[1]	No. of Events	Freq. (%)	No. of events	Freq. (%)	No. of Events	Freq. (%)
Diarrhoea	92	72 (16.2)	52	38 (15.5)	40	34 (13.5)
UTI	98	60 (13.5)	40	26 (10.6)	58	34 (13.5)
Blood Creatinine Increased	55	49 (11.0)	31	28 (11.4)	24	21 (8.4)
Nausea	65	48 (10.8)	37	25 (10.2)	28	23 (9.2)
Oedema Peripheral	46	41 (9.2)	21	20 (8.2)	25	21 (8.4)
Constipation	42	39 (8.8)	25	23 (9.4)	17	16 (6.4)
Headache	44	38 (8.5)	26	23 (9.4)	18	15 (6.0)
URTI	43	38 (8.5)	19	17 (6.9)	24	21 (8.4)
Hypertension	44	36 (8.1)	22	18 (7.3)	22	18 (7.2)
Nasopharyngitis	42	36 (8.1)	18	17 (6.9)	24	19 (7.6)
Anaemia	40	33 (7.4)	19	17 (6.9)	21	16 (6.4)
Vomiting	34	27 (6.1)	24	18 (7.3)	10	9 (3.6)
Diabetes Mellitus	26	26 (5.8)	15	15 (6.1)	11	11 (4.4)
Hypomagnes-aemia	28	25 (5.6)	16	14 (5.7)	12	11 (4.4)
Leukopenia	31	25 (5.6)	15	14 (5.7)	16	11 (4.4)
Abdominal Pain	24	23 (5.2)	13	13 (5.3)	11	10 (4.0)
Dizziness	24	23 (5.2)	15	14 (5.7)	9	9 (3.6)
Insomnia	23	21 (4.7)	16	14 (5.7)	7	7 (2.8)
Hypophosphat-aemia	22	20 (4.5)	15	13 (5.3)	7	7 (2.8)

Pooled Studies LCP-Tacro 2011, LCP-Tacro 2017, LCP-Tacro 3001. [1] MedDRA version 12.1 was used for all studies. [2] Study LCP-Tacro 2011 had 2 treatment groups; subjects from those studies could be included in both groups if they had both treatments but they were counted only once in the 'Total'. Freq.=Frequency (frequency is calculated as the percentage of patients with the TEAE reported); URTI= Upper respiratory tract infection; UTI=urinary tract infection. Source: Veloxis LCP-Tacro ISS TFLs Combined Kidney Subset, 2012: Table 4.4.2

Diarrhoea, UTI, blood creatinine increased and nausea were the most common AEs reported for patients in Phase 2/ 3 clinical kidney transplant studies. No large differences were observed for LCP-Tacro and Prograf groups. The majority of AEs were mild or moderate.

The integrated safety data pool of liver transplant patients (stable and *de novo* combined) included all liver transplant recipients treated with study medication from the completed Phase 2 clinical Study LCP-Tacro 2012, its extension Study LCP-Tacro 2012E, and Study LCP-Tacro 2018. The safety analysis set comprised a total of 117 liver transplant patients, of which 88 each were treated with LCP-Tacro and Prograf, respectively. None of the liver transplant patients were exposed to Advagraf. The proportion of patients who completed study in the respective treatment groups across the pooled clinical Phase 2 studies was comparable (LCP-Tacro: 79.5%, Prograf: 85.2%). The overall exposure of liver transplant patients to LCP-Tacro was substantially higher as compared to Prograf, with a cumulative exposure of 64.6 patient-years as compared to 21.2 person-years, reflecting a longer duration of exposure to LCP-Tacro in the LCP-Tacro 2012E extension study.

Serious adverse events and deaths

Deaths

In study 3001, there were 4 deaths in total. 2 patients in the LCP-Tacro group died of cardiac arrest. Both patients had a history of cardiac disease. Neither of the deaths was suspected of being related to study drug. Additionally, 2 patients died during the follow-up period, both of whom were discontinued from the study due to AEs: 1 patient in the LCP-Tacro group died of cardiac arrest approximately 4 months after discontinuing the study and 1 patient in the Prograf group died of lung cancer approximately 5 months after discontinuing the study.

In study 2018 (in Liver *de novo* patients) 4 patients died during the study. Two patients in the LCP-Tacro group (diarrhoea and ventricular dysfunction) and 2 patients in the Prograf group (sepsis and cytomegalovirus (CMV) infection and cardiorespiratory arrest). One patient in the Prograf group, discontinued due to an AE (C. difficile infection). The other 3 patients died prior to study completion or withdrawal. None of these events were suspected by the investigator to be related to study medication.

In study 3002, a total of 17 deaths occurred during the study: 12 treatment emergent and 5 non-treatment emergent. The 12 patients experienced treatment-emergent SAEs that resulted in death for the ITT set.

Overall, most causes of death in patients who experienced treatment-emergent SAEs were related to the cardiopulmonary system and included cardiorespiratory/respiratory distress, acute respiratory distress syndrome, acute myocardial infarction, cardiorespiratory failure, and bilateral pneumonia. Other causes were sepsis in 3 patients and suicide and B cell lymphoma in 1 patient each. Of the 12 deaths, 5 were in patients in the LCP-Tacro group and 7 were in patients in the Prograf group. None of the fatal SAEs in the LCP-Tacro group were suspected to be related to study drug. Three of the 7 patients who died in the Prograf group experienced events considered by the investigator to be related to study drug: sepsis in two patients; and pneumonia, acute respiratory distress syndrome, sepsis, and cardiac failure in another patient.

For studies LCP-Tacro 2012, its extension Study LCP-Tacro 2012E, and Study LCP-Tacro 2018 (Liver transplant setting), fatal SAEs comprised 3 events in two subjects, which all occurred in the Prograf group: cardio-respiratory arrest, CMV infection and sepsis.

Serious AEs

Study 3001

In study 3001 36 (22.2%) patients in the LCP-Tacro group experienced an SAE. There was no pattern in terms of the type of SAEs by Preferred Term or number of days post-randomization when the SAE occurred in either treatment group. Most of the SAEs were not suspected to be related to study drug. The events in 8 (2.5%) patients were suspected to be related to study drug, 4 (2.5%) patients in the LCP-Tacro group and 4 (2.5%) patients in the Prograf group. The suspected events in the LCP-Tacro group included Grade 2 cytomegalovirus infection, Grade 2 diabetes mellitus, Grade 2 drug toxicity, Grade 2 polyomavirus-associated nephropathy and Grade 2 Epstein-Barr virus infection. The 4 suspected events in the Prograf group included Grade 3 UTI, Grade 2 increased blood creatinine, Grade 2 UTI and Grade 2 urosepsis.

Treatment emergent fatal adverse events occurred in 1.2% of Envarsus patients and 0.6% of Prograf patients.

Study 3002

Twelve patients experienced fatal treatment-emergent serious adverse events (SAEs): 5 (1.9%) patients in the LCP-Tacro group and 7 (2.5%) patients in the Prograf group. Overall, most causes of death for patients with fatal SAEs were related to the cardiopulmonary system. None in the LCP-Tacro group were suspected of being related to study drug.

Table 55 Serious TEAEs Occurring in More Than 1 Patient Overall by Preferred Term (Safety Set)

	LCP-Tacro n=162	Prograf n=162	Total N=324
Number of patients with at least 1 serious TEAE	36 (22.2%)	26 (16.0%)	62 (19.1%)
Urinary tract infection	3 (1.9%)	4 (2.5%)	7 (2.2%)
Blood creatinine increased	1 (0.6%)	2 (1.2%)	3 (0.9%)
Gastroenteritis	1 (0.6%)	2 (1.2%)	3 (0.9%)
Pneumonia	1 (0.6%)	2 (1.2%)	3 (0.9%)
Cellulitis	2 (1.2%)	0	2 (0.6%)
Diverticulitis	0	2 (1.2%)	2 (0.6%)
Osteomyelitis	2 (1.2%)	0	2 (0.6%)
Renal cancer	2 (1.2%)	0	2 (0.6%)
Angina pectoris	2 (1.2%)	0	2 (0.6%)
Cardiac arrest	2 (1.2%)	0	2 (0.6%)
Diarrhea	2 (1.2%)	0	2 (0.6%)
Deep vein thrombosis	1 (0.6%)	1 (0.6%)	2 (0.6%)

Source data: Table 14.3.1.6 (Appendix 16.2.7.2)

Notes: TEAE was defined as any AE that started after the first dose and within 30 days of the final dose of study drug. A patient was counted once if the patient reported one or more events.
Percentages were based on the number of safety set patients in each treatment group.
If relationship was missing, the AE was included as "suspected."

AE=adverse event; TEAE=treatment-emergent adverse event.

Study 3002

More than half of all patients experienced at least 1 SAE: 143 (53.4%) patients in the LCP-Tacro group and 162 (58.9%) patients in the Prograf group. SAEs experienced by more than 5% of patients in any treatment group were urinary tract infection, kidney transplant rejection, and complications of transplanted kidney. Urinary tract infection was reported slightly more commonly in the LCP-Tacro group (9.3%) compared with the Prograf group (6.9%), while kidney transplant rejection (4.2% and 8.0% in the LCP-Tacro and Prograf groups, respectively) and complications of transplanted kidney (3.0% and 6.5% in the LCP-Tacro and Prograf groups, respectively) were reported more commonly in the Prograf group compared with the LCP-Tacro group.

Study 2011

Three SAEs occurred during the study 2011 in 3 patients: 1 patient was receiving 3 mg LPC-Tacro QD at the time of the event (AE: Angina Pectoris), 1 patient was receiving 4 mg Prograf BID as part of Study Period I at the time of the event (AE: small intestine obstruction), 1 patient had completed the study and had resumed prophylactic treatment with 4 mg BID Prograf (AE: pyrexia). None of these SAEs were considered to be related to the study drugs. Overall both the nature and number of SAEs as well as significant AEs did not raise safety concerns regarding the use of LCP-Tacro. Since study 2011 was a short trial it is not unexpected that the incidence of SAEs was low.

Study 2017

SAEs were most commonly reported in the SOCs of Blood and Lymphatic System Disorders; Gastrointestinal Disorders; Infections and Infestations; Injury, Poisoning, and Procedural Complications; Metabolism and Nutrition Disorders; and Renal and Urinary Disorders. The observed SAEs are consistent with the events expected in this patient population.

Fifteen patients in the LCP-Tacro group and 21 patients in the Prograf group experienced SAEs. Most of the SAEs were considered to be unrelated to study medication by the investigator. Four patients (3 in the LCP-Tacro group and 1 in the Prograf one) experienced SAEs that the investigator considered to be related (suspected) to study medication.

Table 56

Serious Adverse Events Occurring in ≥1 Patient Overall (n [%]) – mITT Population

Preferred Term	LCP-Tacro (N=32)	Prograf (N=31)	Overall (N=63)
All Adverse Events	15 (46.9%)	21 (67.7%)	36 (57.1%)
Anaemia	1 (3.%)	3 (9.7%)	4 (6.3%)
Abdominal pain	2 (6.3%)	1 (3.2%)	3 (4.%)
Complications of transplanted kidney	1 (3.%)	2 (6.5%)	3 (4.%)
Dehydration	2 (6.3%)	1 (3.2%)	3 (4.%)
Urinary tract infection	2 (6.3%)	1 (3.2%)	3 (4.%)
Vomiting	2 (6.3%)	0 (0.0%)	2 (3.2%)
Gastroenteritis	1 (3.%)	1 (3.2%)	2 (3.2%)
Hydronephrosis	1 (3.%)	1 (3.2%)	2 (3.2%)
Pneumonia	1 (3.%)	1 (3.2%)	2 (3.2%)
Renal failure acute	0 (0.0%)	2 (6.5%)	2 (3.2%)

Source: Table 14.3.1.3

Note: Percentages were based on the total number of patients in the mITT analysis dataset (N). Any patient with multiple events in a Preferred Term (PT) was counted only once for that PT.

Study 2017 Rejection

Rejection

Seven patients overall experienced rejection AEs (preferred terms: kidney transplant rejection and transplant rejection). Three patients overall experienced kidney transplant rejection (1 patient on LCP-Tacro and 2 patients on Prograf) that were biopsy proven. Four patients experienced transplant rejection (1 patient on LCP-Tacro and 3 patients on Prograf) that was antibody-mediated.

None of these events was serious, severe, or resulted in a patient discontinuing the study. The investigator did not consider any of the kidney transplant rejection events to be related (suspected) to study medication. The investigator considered 1 of the transplant rejection events (1 patient on Prograf) to be related to study medication. This patient had previously discontinued study medication on Day 70 because of dehydration that was suspected of being secondary to myfortic intolerance and was diagnosed with moderate transplant rejection on Day 78. The event resolved without sequelae.

Laboratory findings

Generally, the clinical laboratory findings in kidney transplant recipients were similar in transplant recipients administered either Prograf or LCP-Tacro in Study 3001. However, it is noted that although not statistically significant, numerically, patients on LCP-Tacro had an increased FBG and blood lipid profile (cholesterol, LDL and TG) within 12 months as compared to Prograf.

Table 57 Incidence of Predefined Potentially Clinically Significant Laboratory Test Within 12 Months of Randomization Across the Combined Stable and De Novo Kidney Transplant Clinical Phase 2/3 Studies (Pooled Safety Analysis Set – Veloxis LCP-Tacro ISS TFLs Combined Kidney Subset, 2012)

	LCP-Tacro (N=245) New Onset / At Risk[1]		Prograf (N=251) New Onset / At Risk[1]		
Criteria	No. of Events	Freq. (%)	No. of Events	Freq. (%)	Difference (%) 95% CI[3]
Fasting plasma glucose >= 200 mg/dL	57	27/228 (11.842%)	37	17/229 (7.424%)	4.419 (-1.053%, 9.978%)
Platelet count < 100 x10^9 cells/L	6	5/241 (2.075%)	5	4/248 (1.613%)	0.462 (-2.269%, 3.325%)
White blood cell (WBC) count < 2.0 x10^9 cells/L	12	8/244 (3.279%)	5	4/251 (1.594%)	1.685 (-1.230%, 4.892%)
ALT (Alanine Transaminase) >= 100 U/L	3	2/242 (0.826%)	5	4/250 (1.600%)	-0.774 (-3.287%, 1.575%)
AST (Aspartate Transaminase) >= 100 U/L	4	2/243 (0.823%)	3	3/250 (1.200%)	-0.377 (-2.722%, 1.893%)
Total cholesterol >= 300 mg/dL[2]	5	4/161 (2.484%)	1	1/162 (0.617%)	1.867 (-1.312%, 5.630%)
Low density lipoprotein cholesterol >= 200 mg/dL[2]	2	2/162 (1.235%)	1	1/162 (0.617%)	0.617 (-2.319%, 3.812%)
Triglycerides >= 500 mg/dL[2]	2	2/160 (1.250%)	0	0/161 (0.000%)	1.250 (-1.251%, 4.443%)
Estimated glomerular filtration rate < 30 mL/min based on MDRD7	6	5/216 (2.315%)	12	7/219 (3.196%)	-0.882 (-4.393%, 2.527%)

Pooled Studies LCP-2011, LCP-2017, LCP-3001. [1] At Risk = subjects whose baseline value did not meet the criteria; New-onset: subjects who had at least one post baseline test value met the criteria. [2] In studies 2011 and 2017 lipids profile was not collected; hence, total cholesterol, low density lipoprotein cholesterol, and triglycerides analysis were based on study 3001 only. [3] Difference was calculated as LCP-Tacro minus Prograf; 2-sided 95% confidence intervals for the difference were calculated based on the Newcombe-Wilson score intervals.
CI=confidence interval; Freq.=Frequency (frequency is calculated as the percentage of patients with the TEAE reported).
Source: Veloxis LCP-Tacro ISS TFLs Combined Kidney Subset, 2012: Table 4.11.2

Safety in special populations

Ethnicity

Special studies to evaluate safety in different ethnic population have not been performed with LCP-Tacro. However, study 3001 has studied the efficacy and safety of LCP-Tacro in black patients as well as Caucasians. When converting from tacrolimus immediate-release products (e.g. Prograf capsules) or from Advagraf prolonged-release capsules to Envarsus, trough levels should be measured prior to conversion and within two weeks after conversion. Dose The CHMP noted that should be noted that black patients may require a higher dose to achieve the targeted trough levels.

Immunological events

No antibody production was noticed.

Discontinuation due to AES

Incidences for discontinuations due to AES.

Discontinuations due to AES were noted during development as common (in Phase I Database for LCP-Tacro) with 24/485 (4.4%) for LCP-Tacro vs. 3/90 (3.3%) for Prograf.

Table 58 Overall Summary of Treatment-Emergent Adverse Events Across Phase 1 Studies in Healthy Subjects (Pooled Safety Analysis Set – Veloxis LCP-Tacro ISS TFLs Combined Phase 1 Subset, 2012)

	Total[1] (N=485)		LCP-Tacro (N=480)		Prograf (N=90)		Advagraf (N=23)	
	No. of Events	Freq. (%)	No. of events	Freq. (%)	No. of Events	Freq. (%)	No. of Events	Freq. (%)
Any TEAEs	708	250 (51.5)	657	232 (48.3)	45	23 (25.6)	6	5 (21.7)
Any TEAEs Related to Study Drug	534	203 (41.9)	512	192 (40.0)	17	11 (12.2)	5	4 (17.4)
Serious non-fatal TEAEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Fatal TEAEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
AEs leading to Study Drug Discontinu-ation	-	24 (4.9)	-	21 (4.4)	-	3 (3.3)	-	2 (8.7)

Pooled Studies LCP-1011, LCP-1012, LCP-1013, LCP-1014, LCP-1015, LCP-1016, LCP-1017, LCP-1018, LCP-1019, LCP-1020, LCP-1021, LCP-1022, LCP-1023, LCP-1024. [1] Studies LCP-1011, LCP-1012, LCP-1013, LCP-1014, LCP-1015, LCP-1016, LCP-1017 had 2 treatment groups; subjects from those studies could be included in both groups if they had both treatments but they were counted only once in the 'Total'. Freq.=Frequency (frequency is calculated as the percentage of patients with the TEAE reported), TEAE=treatment-emergent adverse event.
Source: Veloxis LCP-Tacro ISS TFLs Combined Phase 1 Subset, 2012: Table 4.2.4, Table 1.1.4

The frequency of TEAEs by System Organ Class (SOC) affecting at least 5% of subjects across the pooled Phase 1 studies was as follows (Veloxis LCP-Tacro ISS TFL Combined Phase 1 Subset, 2012):

- Gastrointestinal disorders (LCP-Tacro: 17.3%, Prograf: 6.7%, Advagraf: 8.7%);
- General disorders and administration site conditions (LCP-Tacro: 5.0%, Prograf: 2.2%, Advagraf: 4.3%);
- Infections and infestations (LCP-Tacro: 4.2%, Prograf: 4.4%, Advagraf: 0.0%);
- Injury, poisoning and procedural complications (LCP-Tacro: 3.1%, Prograf: 2.2%, Advagraf: 0.0%);
- Investigations (LCP-Tacro: 16.7%, Prograf: 6.7%, Advagraf: 8.7%);
- Musculoskeletal and connective tissue disorders (LCP-Tacro: 4.6%, Prograf: 3.3%, Advagraf: 0.0%);
- Nervous system disorders (LCP-Tacro: 14.8%, Prograf: 8.9%, Advagraf: 0.0%)
- Discontinuations due to AES are noted during development as common (in Phase II Database for LCP-Tacro). With 8/88 (9.1%) for LCP-Tacro vs. 3/88 (3.4%) for Prograf.

Table 59 Overall Summary of Adverse Event Reporting – Subjects with Liver Transplant Safety Analysis Set

Pooled Studies LCP2012, LCP2012E, LPC2018

	Total [1] (N=117)		LCP_Tacro (N=88)		Prograf (N=88)	
Category	Number of Events	Frequency Subjects (%)	Number of Events	Frequency Subjects (%)	Number of Events	Frequency Subjects (%)
Any TEAEs	1134	108 (92.3)	681	77 (87.5)	453	40 (45.5)
Any TEAEs related to Study Drugs	152	57 (48.7)	97	44 (50.0)	55	13 (14.8)
Serious Non-Fatal Treatment Emergent Adverse Event	58	35 (29.9)	39	23 (26.1)	19	12 (13.6)
Fatal Treatment Emergent Adverse Events	3	2 (1.7)	0	0	3	2 (2.3)
Adverse Events Leading Study Drug Treatment Discontinuation	11	11 (9.4)	8	8 (9.1)	3	3 (3.4)

Study 3001

Discontinuation of patients due to AEs in the LCP-Tacro treatment group vs. Prograf was 10 patients and 3 patients respectively (10/163 vs. 3/163). Reasons for discontinuation are given in the table below.

Table 60 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term Safety Set

	LCP-Tacro (N=162)	Prograf (N=162)	Total (N=324)
Total Number of Treatment-Emergent Adverse Events	13	2	15
Number of Patients With at Least One Treatment-Emergent Adverse Event	13 (8.0%)	2 (1.2%)	15 (4.6%)
Infections and infestations	2 (1.2%)	1 (0.6%)	3 (0.9%)
BK virus infection	0	1 (0.6%)	1 (0.3%)
Polyomavirus-associated nephropathy	1 (0.6%)	0	1 (0.3%)
Vulval cellulitis	1 (0.6%)	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2%)	1 (0.6%)	3 (0.9%)
Hepatic neoplasm	1 (0.6%)	0	1 (0.3%)
Renal cancer	1 (0.6%)	0	1 (0.3%)
Renal cell carcinoma recurrent	0	1 (0.6%)	1 (0.3%)
Cardiac disorders	2 (1.2%)	0	2 (0.6%)
Cardiac arrest	2 (1.2%)	0	2 (0.6%)

2.6.1. Discussion on clinical safety

The incidence of AEs suspected to be causally related to study drug was low, with no substantial difference between LCP-Tacro and the clinical comparator. Among the most common AEs, the frequency of headache, diarrhoea, peripheral oedema, and fatigue was in excess for LCP-Tacro as compared to Prograf. AEs were mild or moderate in the majority of cases and consistent with what has been previously reported as occurring with other tacrolimus-containing products.

Fatal SAEs comprised 3 events in two subjects, which all occurred in the Prograf group: cardio-respiratory arrest, CMV infection and sepsis. There is no consistent pattern suggesting differences between LCP-Tacro and Prograf with respect to AEs leading to study drug discontinuation: the frequency was higher with LCP-Tacro (7 events in 7 of 88 patients [8.0%] vs. one event in one of 88 patient [1.1%] with Prograf), however, patients receiving LCP-Tacro were exposed for a greater length of time and had a greater opportunity to experience AEs. Overall, the combined analysis of stable, converted and *de novo* liver transplant patients revealed no significant differences in the nature and number of AEs, SAEs and clinically significant AEs between the LCP-Tacro and the Prograf groups. The types and frequencies of AEs were not unexpected in this patient population.

A re-analysis of safety data has been submitted by the applicant during the procedure, using tighter levels such as fasting plasma glucose level > 126 mg/dL, total cholesterol > 5 mmol/L; LDL cholesterol > 3 mmol/L; triglycerides > 2 mmol/L; and eGFR < 60 mL/min. Re-analyses of clinically significant laboratory measures with tighter cut-off levels performed by the applicant during the assessment showed no significant difference in the incidence of pre-defined potentially clinically significant laboratory tests between tacrolimus from either LCP-Tacro tablets q.d. or Prograf capsules b.i.d. in stable as well as in *de novo* kidney transplant patients.

The integrated safety data pool of liver transplant patients (stable and *de novo* combined) included all liver transplant recipients treated with study medication from the completed Phase 2 clinical Study LCP-Tacro 2012, its extension Study LCP-Tacro 2012E, and Study LCP-Tacro 2018. The safety analysis set comprised a total of 117 liver transplant patients, of which 88 each were treated with LCP-Tacro and Prograf, respectively. None of the liver transplant patients were exposed to Advagraf. The proportion of patients who completed study in the respective treatment groups across the pooled clinical Phase 2 studies was fairly comparable (LCP-Tacro: 79.5%, Prograf: 85.2%). The overall exposure of liver transplant patients to LCP-Tacro was substantially higher as compared to Prograf, with a cumulative exposure of 64.6 patient-years as compared to 21.2 person-years, reflecting a longer duration of exposure to LCP-Tacro in the LCP-Tacro 2012E extension study.

In study 2012, there were no safety concerns regarding LCP-Tacro tablets q.d., and no patient experienced graft loss.

The safety profile observed in study 2012E with a combined total of 52 weeks of LCP-Tacro treatment in the stable liver transplant setting was consistent with findings generally observed in such patients. In this study, most AEs were mild or moderate, did not significantly differ between the drug groups, and the incidence, type, and severity of adverse events were in the range expected in this patient population. Most of the adverse events were not related to study drug with no specific adverse event or unexpected trend of adverse events that indicated a dug related event. Overall, no new safety concerns related to LCP-Tacro were raised by the results of this study. One patient experienced mild acute rejection that responded to glucocorticoid treatment and the patient was able to continue treatment with LCP-Tacro. There were no deaths or graft losses. Headache, fatigue, back pain and diarrhoea were the most frequent adverse events. Renal and liver function parameters remained stable and there were no remarkable findings with regard to fasting blood glucose.

In study 2018 there were no significant differences in safety between LCP-Tacro (q.d.) and Prograf (b.i.d.).

In study 3001 a numerically higher serious non-fatal AEs (22.2%, n=36) was reported in the LCP-Tacro study versus Prograf (16% n=26). Two (2) patients in the LCP-Tacro group died of cardiac arrest versus 0 patients in the Prograf group.

Pooled analysis of phase 1 studies report a numerically higher TEAEs in the LCP-Tacro group (number of subjects=480; number of TEAEs=657; 48.3%) versus Prograf (number of subjects=90; number of TEAEs=23; 25.6%). In addition there has been a higher incidence of discontinuations associated to LCP-Tacro versus Prograf in across both phase I (24/485 (4.4%) vs. 3/90 (3.3%)) and phase II studies 8/88 (9.1%) for LCP-Tacro vs. 3/88 (3.4%) for Prograf. As requested by CHMP, the applicant discussed the observation that overall across all phase I studies there have been increased discontinuations in subjects exposed to LCP-Tacro vs. comparators. The pooling of Phase 1 study data showed that a higher number of subjects discontinued participation in Phase 1 clinical studies due to adverse events (21 subjects [4.4%]) in the LCP-Tacro treatment groups, versus 3 [3.3%] in the Prograf and 2 [8.7%] in the Advagraf treatment groups. The overall exposure of healthy subjects to LCP-Tacro tablets was substantially higher as compared to the comparators Prograf and Advagraf, with a cumulative exposure of 15.7 person-years as compared to 1.32 and 0.59 person-years, respectively. Adverse events reported

for healthy subjects across the combined clinical Phase 1 studies were headache, diarrhoea, constipation, nausea, dizziness, upper respiratory tract infection (URTI) and abdominal pain. The CHMP concluded that the results obtained appear not to be indicative for a potentially higher rate of AEs for tacrolimus from LCP-Tacro tablets as compared to tacrolimus from Prograf capsules or Advagraf capsules. The CHMP therefore agreed with the applicant's justification that the apparently higher discontinuation rate due to adverse events across the clinical Phase 1 studies is mostly likely due to the far greater tacrolimus exposure in patients-years from LCP-Tacro tablets as compared to Prograf and Advagraf. With respect to the overall adverse event and suspected adverse drug reaction profile, there is no meaningful difference between LCP-Tacro and the comparator Prograf, in particular when the differences in exposure are considered.

During the assessment the applicant provided the safety results from Study LCP-Tacro 3002 in *de novo* kidney transplant setting. A total of 543 patients at 70 sites were randomly assigned to study drug and 517 patients completed through the 12-month visit. The numbers of patients who experienced adverse events resulting in discontinuation from study drug and/or withdrawal from the study were similar in the treatment groups (approximately 12.3%). Adverse events leading to discontinuation of study drug or study withdrawal that occurred in more than 2 patients in any treatment group were sepsis (0 and 3 [1.1%] patients in the LCP-Tacro and Prograf groups, respectively) and kidney transplant rejection (1 [0.4%] and 3 [1.1%] patients in the LCP-Tacro and Prograf groups, respectively).

The safety results obtained in study 2017 in *de novo* kidney transplant patients (i.e. the higher risk group and the group that is most likely to discontinue treatment due to AEs) indicated that there is no imbalance between LCP-Tacro and Prograf.

The CHMP concluded that discontinuations due to adverse events in kidney transplant recipients treated with tacrolimus from either LCP-Tacro tablets q.d. or Prograf capsules b.i.d. do essentially not differ between treatments.

Altogether, the available data indicates that LCP-Tacro is considered to be not inferior to Prograf and Advagraf from a safety point of view.

2.6.2. Conclusions on the clinical safety

With respect to the overall safety of the active substance, the CHMP is of the opinion that many of the adverse drug reactions stated for tacrolimus are reversible and/or respond to dose reduction. Therapeutic drug monitoring by specialised personal (keeping target whole blood levels in relatively small window) enables safe administration of tacrolimus as described in the product information and the RMP.

The CHMP considered that there are no significant differences between LCP-Tacro and Prograf with respect to the AE profile. This information brings no new signals with tacrolimus. All SAEs listed with LCP-Tacro are known AEs for tacrolimus.

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.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version, the PRAC considers by consensus that the risk management system for tacrolimus (Envarsus) in the prevention of kidney or liver transplant rejection is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Important identified risks	• Medication errors with tacrolimus-containing medicinal
	• Interaction with other medication, herbal drugs and MMF
	• Hypertension
	• Cardiac arrhythmias
	• Prolonged QT interval
	• Torsades de Pointes
	• Neurological and visual disorders
	• Diabetogenicity
	• Electrolyte changes
	• Hepatic dysfunction
	• Renal dysfunction
	• Blood cell changes
	• Coagulopathies
	• Ventricular hypertrophy, cardiomyopathies
	• Use during pregnancy
	• Use during lactation
	• GI perforation
	• Diarrhoea
	• Neoplasms
	• EBV-associated lymphoproliferative disorders
	• Serious infections and reactivation of pre-existing
	• Pure red cell aplasia (PRCA)
	• Posterior reversible encephalopathy syndrome
Important potential risks	
	• Off-label use
Missing Information	• Use in children

- **Pharmacovigilance plans**

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures. ″

- **Risk minimisation measures**

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Medication errors with tacrolimus-containing medicinal products	Use of brand name **Envarsus** Indication of correct use in SmPC and Patient Information Leaflet Warnings in section 4.4 of the proposed SmPC: Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist	HCP (doctor and pharmacist) educational materials and patient card. Monitoring of medication errors via a targeted medication error follow-up questionnaire.
Interaction with other medication, herbal drugs and MMF	Warnings in section 4.4 and 4.5 of the proposed SmPC for Envarsus. When substances with a potential for interaction (see section 4.5), particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or inducers of CYP3A4 (such as rifampicin or rifabutin), are being combined with tacrolimus, tacrolimus blood levels should be monitored to	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. Herbal preparations containing *St. John's Wort* (Hypericum perforatum) should be avoided when taking Envarsus due to the risk of interactions that lead to a decrease in both blood concentrations and the therapeutic effect of tacrolimus. Care should be taken when administering tacrolimus to patients who have previously received other immunosuppressant like ciclosporin (see sections 4.2 and 4.5 of the SmPC)	
Hypertension	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: *blood pressure*, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Listed in section 4.8 of the proposed SmPC.	None
Cardiac arrhythmias	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, *ECG*, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Listed in section 4.8 of the proposed SmPC.	None
Prolonged QT interval, Torsade de Pointes	**Special warnings and precautions for use** Cardiac disorders Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome. Proposed text in SmPC, section 4.8: **Undesirable effects** Cardiac disorders	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	common: ischaemic coronary artery disorders, tachycardia uncommon: heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, ECG investigations abnormal, ventricular hypertrophy, palpitations, heart rate and pulse investigations abnormal rare: pericardial effusion very rare: echocardiogram abnormal	
Neurological and visual disorders	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, *neurological and visual status*, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Listed in section 4.8 of the proposed SmPC.	None
Diabetogenicity	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, *fasting blood glucose levels*, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.	None
Electrolyte changes	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, *electrolytes (particularly potassium)*, liver and renal function tests, haematology parameters, coagulation values, and plasma protein	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.	
Hepatic dysfunction	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), *liver* and renal *function tests*, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Listed in section 4.8 of the proposed SmPC.	None
Renal dysfunction	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and *renal function tests*, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Listed in section 4.8 of the proposed SmPC.	None

Blood cell changes	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, *haematology parameters*, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Listed in section 4.8 of the proposed SmPC.	
Coagulopathies	Warnings in section 4.4 of the proposed SmPC for Envarsus: During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, *coagulation values, and plasma protein determinations*. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. Listed in section 4.8 of the proposed SmPC.	None

Ventricular hypertrophy , cardiomyopathies	Warnings in section 4.4 of the proposed SmPC for Envarsus: Ventricular hypertrophy or hypertrophy of the septum reported as cardiomyopathies, have been observed in Prograf treated patients on rare occasions and may therefore also occur with Envarsus. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppressives should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 to 12 months). If abnormalities develop, dose reduction of Envarsus therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing *Torsades de Pointes*. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome. Listed in section 4.8 of the proposed SmPC.	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Diarrhoea	Warnings in section 4.4 of the proposed SmPC for Envarsus: Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea. Listed in section 4.8 of the proposed SmPC.	None
GI perforation	Proposed text in SmPC, section 4.8: **Undesirable effects** Gastrointestinal disorders Common: Gastrointestinal ulceration and perforation	None

Neoplasms	Warnings in section 4.4 of the proposed SmPC for Envarsus: As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8). As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.	None
EBV-associated lymphoproliferative disorders	Statement in section 4.4 of the proposed SmPC for Envarsus: Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. A combination of immunosuppressives such as antilymphocytic antibodies given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-viral capsid antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Envarsus. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma. Listed in section 4.8 of the proposed SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Serious infections and reactivation of pre-existing infections	Patients treated with immunosuppressants, including Envarsus are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken. Listed in section 4.8 of the proposed SmPC.	None
Pure red cell aplasia (PRCA)	Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA. Listed in section 4.8 of the proposed SmPC.	None

Posterior reversible encephalopathy syndrome (PRES)	Statement in section 4.6 of the proposed SmPC for Envarsus: PRES Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control, and immediate discontinuation of systemic tacrolimus is advised.	None

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Off-label use	With the alignment of indications for Envarsus with Advagraf the risk of off-label use for Envarsus should be low. The proposed Envarsus SmPC indicates in section 4.4 "Special warnings and precautions for use" that due to the lack of data, Envarsus should not be used for the treatment of children and not as primary therapy in heart transplant recipients. The MAH will keep off-label use as an important potential risk and considers sufficient to monitor such risk through routine pharmacovigilance measures.	None

Use in pregnancy	Statement in section 4.6 of the proposed SmPC for Envarsus: Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse events on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of in utero exposure, monitoring of the newborn for the potential adverse events of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) as well as for hyperkalaemia in the newborn.	None
Use in lactation	Statement in section 4.6 of the proposed SmPC for Envarsus: Human data demonstrate that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving Envarsus.	None

The CHMP endorsed this advice without changes.

2.9. 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

To support the application two pivotal phase III studies (3001 & 3002) and 2 phase II PK studies (2017/2011) have been submitted as well as numerous PK studies in healthy volunteers, a food interaction study and 2 PK studies in Liver transplant patients (2012 including 2012E/2018).

The activity of the clinical comparator Prograf in terms of prophylaxis of transplant rejection in adult kidney allograft recipients been demonstrated and is well characterised. The event rate for locally

read biopsy-confirmed acute rejection (BPAR) during the 360 day study was 1.2% in the LCP-Tacro group (N=162) post conversion from Prograf at a dose ratio of 0.7:1 mg and 1.2% in the group maintained on Prograf (N=162). The efficacy failure rate as measured by the composite endpoint of death, graft loss, locally read BPAR and loss to follow-up was 2.5% in both the LCP-Tacro and Prograf groups. The treatment difference (LCP-Tacro - Prograf) was 0% (95% confidence interval [-4.21%, 4.21%]). The treatment failure rate using the same composite end-point with centrally read BPAR was 1.9% in the LCP-Tacro group and 3.7% in the Prograf group (95% confidence interval [-6.51%, 2.31%]).

In *de novo* kidney patients, the percentage of patients with one or greater than one episodes of clinically-suspected and treated rejections during the 360-day study was 13.8% for the Envarsus group (N=268) and 15.6% for the Prograf group (N=275). The event rate for centrally-read, biopsy-confirmed acute rejection (BPAR) during the 360-day study was 13.1% in the Envarsus group (N=268) and 13.5% in the Prograf group (N=275). The efficacy failure rate as measured by the composite endpoint of death, graft loss, centrally read BPAR and loss to follow-up was 18.3% in the Envarsus group and 19.6% in the Prograf group. The treatment difference (Envarsus-Prograf) was -1.35% (95% confidence interval [-7.94%, 5.27%]).

The pharmacokinetics, efficacy and safety of Envarsus and tacrolimus immediate-release capsules, both in combination with corticosteroids was compared in 117 liver transplant recipients, of whom 88 received treatment with Envarsus. In the *de novo* liver transplant study, 29 subjects were treated with Envarsus. The event rate of biopsy-confirmed acute rejection within the 360 day study period was not significantly different between the Envarsus group and the tacrolimus immediate-release group. The overall incidence of fatal treatment emergent adverse events for the combined *de novo* and stable liver transplant population was not significantly different between the Envarsus group and the tacrolimus immediate-release group.

Initially, the applicant proposed a limited indication (for use in kidney transplant patients). During the assessment, the applicant has substantiated the extrapolation of the PK data available with LCP-Tacro in the *de novo* kidney patients and in the liver and transplantation setting (including rescue indication). Based on the extensive clinical knowledge with the clinical comparator Prograf and the European reference medicinal product Advagraf, the CHMP considered that the available pharmacokinetics data for LCP-Tacro from *de novo* and conversion renal and liver setting allow bridging both products with regards to the use in the treatment of acute rejection setting. This data and the extensive clinical knowledge on tacrolimus-containing products support the therapeutic indication for LCP-Tacro tablets in the: *"Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients"* in line with the European reference medicinal product Advagraf and the clinical comparator Prograf.

Uncertainty in the knowledge about the beneficial effects.

Allograft transplant patients maintained on twice daily Prograf (immediate-release) or Advagraf (once daily) dosing requiring conversion to once daily Envarsus should be converted on a 1:0.7 (mg:mg) total daily dose basis, i.e. the Envarsus maintenance dose should be 30% less than the Prograf or Advagraf dose. In stable patients converted from tacrolimus immediate-release products (twice daily) to Envarsus (once daily) on a 1:0.7 (mg:mg) total daily dose basis, the mean systemic exposure to tacrolimus (AUC_{0-24}) was similar to that of immediate-release tacrolimus. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for Envarsus

is similar to that of immediate-release tacrolimus. No studies have been conducted with conversion of patients from Advagraf to Envarsus. However, data from healthy volunteers would suggest that the same conversion rate is applicable as with the conversion from Prograf to Envarsus. When converting from tacrolimus immediate-release products (e.g. Prograf capsules) or from Advagraf prolonged-release capsules to Envarsus, trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained after the switch. The CHMP also noted that black patients may require a higher dose to achieve the targeted trough levels (as reflected in the product information).

Risks

Unfavourable effects

The most commonly reported AEs (reported for at least 5% of patients) were as follows: Diarrhoea, UTI, blood creatinine increased and nausea are the most common AEs reported for patients in Phase 2/ 3 clinical kidney transplant studies. No large differences can be observed for LCP-Tacro and Prograf groups. The majority of AEs were mild or moderate and no major differences were observed between LCP-Tacro and Prograf groups.

Uncertainty in the knowledge about the unfavourable effects

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed with tacrolimus-containing products. This has led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. The educational materials described in the RMP states that patients should be maintained on a single formulation of tacrolimus with the corresponding dosing regimen. If alterations in formulation or regimen are clinically indicated, this should only take place under the close supervision of the clinical specialist, as close monitoring of tacrolimus levels is required.

As requested by the CHMP the applicant will also ensure that, prior to launch, all health professionals who are expected to prescribe/dispense LCP-Tacro are provided with Educational materials highlighting the authorised indications, the need for prescribing and dispensing with attention to pharmaceutical form (prolonged release) and posology (once daily administration); the importance of avoiding inadvertent switching between tacrolimus containing products and the risk of under and overdosing if monitoring is inadequate; the clinical risks associated with over- and under-dosing. These risk minimisation activities are described in the RMP and the product information.

Benefit-risk balance

Importance of favourable and unfavourable effects

The benefits of Envarsus in the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients have been adequately demonstrated in the clinical programme.

The safety profile of Envarsus is in line with the other tacrolimus formulations.

The benefit risk balance in the proposed indication is considered positive.

Discussion on the benefit-risk balance

The results from pivotal study 3001 showed that in de stable kidney transplanted patients LCP-Tacro is non-inferior to the clinical comparator Prograf. The results from pivotal study 3002 showed that in *de novo* kidney transplanted patients LCP-Tacro is non-inferior to Prograf. The applicant has also substantiated the extrapolation of the PK data available with LCP-Tacro in the *de novo* kidney patients and in the liver and transplantation setting (including rescue indication) with data as well as discussion establishing efficacy of LCP-Tacro in *de novo* kidney and liver indications. Based on the outcomes of the clinical Phase 2 and 3 development programme on LCP-Tacro tablets for the prevention of kidney or liver allograft rejection, it can be concluded that LCP-Tacro tablets, as Prograf capsules b.i.d. and Advagraf capsules q.d. are also safe and efficacious in a solid organ rejection rescue medication setting. In accordance with the approved tacrolimus products Prograf capsules b.i.d. and Advagraf capsules q.d., this supports the therapeutic indication for LCP-Tacro tablets q.d. in the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients".

There are no significant differences between LCP-Tacro and Prograf with respect to the AE profile. This information brings no new essential signals with tacrolimus. All SAEs listed are known AEs for tacrolimus. The applicant has discussed the safety results observed in the Phase I trials where the number of patients who experienced adverse events resulting in discontinuation from study drug and/or withdrawal from the study were similar in the treatment groups (approximately 12.3%). Therefore the results obtained indicate that discontinuations due to adverse events in kidney transplant recipients treated with tacrolimus from either LCP-Tacro tablets q.d. or Prograf capsules b.i.d. do not differ between treatments.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Envarsus for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder should ensure that, at launch, all Healthcare Professionals who are expected to prescribe or dispense Envarsus are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals
- Patient cards to be given to patients with the product

The educational material for Healthcare Professionals should include information on the following key elements:

- The authorised indications
- The need for prescribing and dispensing with attention to pharmaceutical form (prolonged release) and posology (once daily administration).
- The importance of avoiding inadvertent switching between tacrolimus containing products and the risk of under and overdosing if monitoring is inadequate.

- The clinical risks associated with over- and under-dosing.
- The need for specialist supervision and monitoring if there is a clinical decision to switch a patient to another tacrolimus containing products.
- The role of the patient card in ensuring that patients are aware of the product they are taking and the recommendations for safe and effective use in particular once daily dose and the importance of avoiding switching between other tacrolimus containing products except under the advice and supervision of your doctor

The patient card should include information on the following key elements:

- The product name
- That the dose is once daily
- The importance of avoiding switching between other tacrolimus containing products except under the advice and supervision of physicians.

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