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RESEARCH**

APPLICATION NUMBER:

206406Orig1s000

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #	206406
SDN # / eCTD SN #	49/0046
Received Date	6/12/2015
Amendment	7/7/2015
PDUFA Date	8/12/2015
Drug	ENVARUSUS XR (tacrolimus extended-release tablets), LCP-Tacro Tablets
Indication	Prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate release preparations
Sponsor	Veloxis Pharmaceuticals (formerly LifeCycle Pharma A/S [LCP])
Document location	\\CDSESUB1\evsprod\NDA206406\206406.enx
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Background

The initial NDA submission for ENVARUSUS XR (tacrolimus extended-release tablets) for the indication of prophylaxis of organ rejection in patients receiving a kidney transplant was submitted on December 30, 2013. See statistical review dated 9/24/14 in DARRTS for details of the NDA submission. The Division agrees that the two Phase 3 Studies (3001 and 3002) are required for approval of the applicant's proposed labeling in the December 30, 2013 application, along with the results of Study 2017 that provides support for the 0.14 mg/kg/day starting dose. However, Astagraf XL, NDA 204096, approved July 19, 2013 requested and was granted 3-year marketing exclusivity as a new dosage form (NDF). Astellas, the applicant for Astagraf XL, sent a letter to the Agency on September 12, 2014, asking whether the agency agreed that Astellas' exclusivity blocked approval of Envarsus XR. An October 30, 2014 Memorandum summarizes the Exclusivity Board's findings regarding the Astagraf XL exclusivity and effect on Envarsus XR approval. The memorandum noted that based on the Exclusivity Board's determination that the conditions of approval for which Astagraf XL currently has exclusivity are shared by Envarsus XR, DTOP may only tentatively approve Envarsus XR at this time. (See also memorandum dated January 12, 2015 regarding exclusivity issues.)

Subsequently, a Tentative Approval letter was sent to the sponsor on October 30, 2014. For details, see Division Director review by Dr. Albrecht and Dr. Belen in DARRTS.

On December 5, 2014, FDA held a teleconference with the sponsor and suggested to Veloxis that one possible path forward would be to approve the Envarsus XR NDA with an indication that would cover the conversion of patients who are stable on immediate-release tacrolimus to Envarsus XR, a condition of approval that would not be blocked by Astagraf XL's exclusivity. Specifically, the Agency stated that Veloxis could submit revised draft labeling to the Envarsus XR NDA seeking approval only for patients seeking conversion from an immediate-release formulation of tacrolimus to Envarsus XR based on the clinical trials conducted by Veloxis and submitted to NDA 206406. This option would require Veloxis to submit revised draft labeling that omits references to the de novo patient population (Study 3002 and Study 2017), and only discusses the information relating to the conversion population (Study 3001). Approval of the application would be dependent upon reaching final agreement on labeling. For details of the communications between the Agency and the sponsor, see FDA General Advice letters dated December 12, 2014 and January 12, 2015 in DARRTS.

Submission Summary

This submission contains a Class 1 Resubmission for NDA 206406 for ENVARSUS XR (tacrolimus extended-release tablets) that consisted of proposed labeling for the indication of prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate release preparations, in combination with other immunosuppressants.

Compared to the content of labeling enclosed in the Tentative Approval letter dated 10/30/14, the revised labeling deleted information regarding Study 3002 and Study 2017. The remaining information regarding Study 3001 is acceptable from statistical perspective.

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/s/

HONGLING ZHOU
07/10/2015

YAN WANG
07/10/2015
I concur.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 206406
Drug Name: LCP-Tacro Tablets (Tacrolimus), Envarsus XR
Indication(s): Prophylaxis of organ rejection in patients receiving a kidney transplant
Applicant: Veloxis Pharmaceuticals (formerly LifeCycle Pharma A/S [LCP])
Date(s): Receipt Date: December 30, 2013
PDUFA Due Date : October 30, 2014
Review Priority: Standard

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Keywords: active control/non-inferiority, open-label, delta choice (active control), effect size.

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

The sponsor for this NDA submission is seeking approval for the use of a once daily extended release formulation of tacrolimus, LCP-Tacro in patients receiving a kidney transplant. The proposed trade name for LCP-Tacro is Envarsus XR. This NDA submission contains two phase 3 studies. Study 3002 is a double-blind, double-dummy, randomized study of the efficacy and safety of LCP-Tacro tablet once daily compared to Prograf® capsule twice daily conducted in *de novo* kidney transplant patients. Study 3001 is an open-label study of the efficacy and safety of conversion from Prograf® capsules twice daily to LCP-Tacro tablets once daily conducted in stable renal transplant patients. Study 3002 is considered as a pivotal study and Study 3001 is considered supportive. The focus of this review is Study 3002. Study 2017 is a phase 2 pharmacokinetic study and was not designed to show efficacy. The efficacy results for study 2017 became an interest due to the reason noted in clinical review by Dr.Velidedeoglu that the starting dose of 0.14 mg/kg/day for Study 2017 is likely to be the recommended dose in the label given the observation that the higher starting dose 0.17 mg/kg/day for the LCP-Tacro in Study 3002 resulted in higher than expected tacrolimus exposure within the first 7-10 days after transplantation in the LCP-Tacro group.

The results on efficacy failure endpoint from these three clinical trials are shown in Table 1. Compared to the sponsor's results for study 3002, one additional patient (patient ID 034154017) in the LCP-Tacro arm is included as an efficacy failure event since the patient had a rejection occurred within the 12 month study period, although the biopsy was performed 8 days later.

Table 1 Efficacy Failure Results*for Studies 3002, 3001 and 2017

	Study 3002, 12M		Study 3001, 12M		Study 2017, 6M	
	LCP-Tacro N=268	Prograf N=275	LCP-Tacro N=162	Prograf N=162	LCP-Tacro N=32	Prograf N=31
Efficacy Failure	50 (18.7)	54 (19.6)	4 (2.5)	4 (2.5)	2 (6.3)	3 (9.7)
BPAR**	36 (13.4)	37 (13.5)	2 (1.2)	2 (1.2)	1(3.1)	2 (6.5)
Death	8 (3.0)	8 (2.9)	2 (1.2)	1 (0.6)	0	0
Graft loss	9 (3.4)	11 (4.0)	0	0	0	0
LTFU	4 (1.5)	5 (1.8)	0	1 (0.6)	1 (3.1)	1 (3.2)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	-1.0% (-7.6%, 5.6%)		0% (-4.2%, 4.2%)		-3.4%(-20.7%,12.6%)	

*Efficacy failure assessed at 12 months for Studies 3002 and 3001, and at 6 months for Study 2017.

**BPAR: biopsy proven acute rejection. BPAR was based on central biopsy readings for Study 3002, and was based on local biopsy readings for Study 3001 and Study 2017.

For study 3002, the incidence rate for efficacy failure was slightly lower for the LCP-Tacro group (18.7%) than the incidence rate for the Prograf group (19.6%), with a difference between the two groups (LCP-Tacro – Prograf) of -1.0% and 95% confidence interval of (-7.6%, 5.6%).

The upper bound of this CI is smaller than the pre-specified NI margin of 10%. The sponsor's justification for the 10% NI margin is appropriate.

The efficacy results from Study 3002 in *de novo* kidney transplant patients demonstrated the noninferiority of LCP-Tacro, an extended-release formulation of tacrolimus given once daily, to Prograf twice daily based on a 10% non-inferiority margin on efficacy failure (central read biopsy proven acute rejection, death, graft loss or lost to follow-up). The incidence rates were comparable for each individual components of the efficacy failure endpoint (BPAR, death, graft loss, lost to follow-up). Treatment differences were also comparable across subgroups with no statistically significant differences by subgroup observed. The significantly higher tacrolimus exposure level for the first two weeks in the LCP-Tacro group does not appear to have an effect on efficacy results. The conclusion on efficacy outcome would stay the same using locally read BPAR results.

The efficacy results from Study 3001 in stable kidney patients were comparable between the LCP-Tacro group and the Prograf group. There were 4 efficacy failures in each treatment group based on local laboratory readings, with a 95% confidence interval of the difference of the efficacy failure rates between the two groups (-4.2%, 4.2%). The sponsor attempted to claim non-inferiority of LCP-Tacro compared with Prograf with a (b) (4) NI margin for this study. However, the (b) (4) NI margin was not justified for this study. As a result, there is no basis for a non-inferiority claim for Study 3001. There was no statistically significant difference of the efficacy failure rates between the two groups ($p=1.0000$, Fisher's exact test). The efficacy conclusion does not change with the use of central read BPAR.

Estimated GFR values over time were comparable between the two treatment groups for both Study 3002 and Study 3001. For study 3002, there were no statistically significant difference for mean change of GFR from baseline to Months 3, 6 and 12 (Month 3, 6, 12 – baseline) between the two treatment groups with and without imputations for missing GFR values. The incidences of other AEs were also comparable between the two groups for both studies.

Study 2017 was not designed to show efficacy. The efficacy results appeared to be comparable between the two groups for the small number of patients in the study. Because the size of the study is small, no definitive conclusions regarding efficacy and safety can be drawn for this study.

In the assessment of this reviewer, there is appropriate statistical evidence for establishing effectiveness of LCP-Tacro for the indication of prophylaxis of organ rejection in patients receiving a kidney transplant.

2 INTRODUCTION

2.1 Overview

The sponsor for this NDA submission is seeking approval for an extended- release formulation of tacrolimus, LCP-Tacro tablets 0.75 mg, 1.0 mg and 4.0 mg in patients receiving a kidney transplant. Tacrolimus is a macrolide immunosuppressant drug with a similar mechanism of action to that of cyclosporine. Tacrolimus, a calcineurin inhibitor (CNI) marketed as Prograf given twice daily, is FDA approved for the prophylaxis of organ rejection in allogeneic liver, kidney or heart transplant recipients and is available in 0.5, 1, and 5 mg capsules (NDA 50708) or 5 mg/ml injection (NDA 50709) for twice daily dosing.

LCP-Tacro tablets were developed by the sponsor (formerly LifeCycle Pharma) as an extended-release formulation of tacrolimus aimed to improve its bioavailability with lower water solubility. The target dosing for LCP-Tacro is once daily. The sponsor's product development rationale is to provide the convenience of q.d. dosing in conjunction with an improved pharmacokinetic (PK) profile as compared to already approved and marketed tacrolimus formulations for use in the prophylaxis of allograft rejection in recipients of (b) (4) transplants.

On May 20, 2008, an End-of-Phase 2 meeting was held during which the results from the Phase 2 studies in stable transplant patients were presented. The Agency suggested that LCP should conduct a separate pharmacokinetic study in de novo transplant patients in order to ascertain appropriate initial dosing regimen(s) prior to the initiation of the de novo Phase 3 study. On February 16, 2010, an additional End-of-Phase 2 meeting was held by teleconference with the Agency. LCP proposed and the Agency agreed that a Special Protocol Assessment (SPA) be filed for the pivotal trial, and in parallel, data could be submitted to address nonclinical program issues.

On March 31, 2010, an SPA was filed for pivotal trial protocol LCP-Tacro 3002. The Division subsequently issued an SPA Agreement letter to the sponsor on August 5, 2010. The focus of this review is Study 3002. A phase 3 conversion study (Protocol LCP-Tacro 3001) is reviewed as a supportive study. The results for phase 2 PK Study 2017 with the starting dose of 0.14 mg/kg/day for LCP-Tacro is summarized in Appendix 2. The efficacy results for study 2017 is included due to the reason that the starting dose of 0.14 mg/kg/day for Study 2017, as opposed to 0.17 mg/kg/day for study 3002, is likely to be the recommended dose in the label. Please see clinical review by Dr. Velidedeoglu for detailed discussion regarding the initial dosing aspect of the study design. These three studies are summarized in Table below.

List of studies included in this review

Study	Phase and Design	Primary endpoint and objective	LCP-Tacro	Prograf	Study Population
3002	Phase 3, double-blind, double-dummy, multi-center, prospective, randomized study of the efficacy and safety of LCP-Tacro™ once daily compared to Prograf® capsules twice daily with MMF	Death, graft failure, BPAR or lost to follow-up within 12 months after randomization. To show NI.	N= 268 LCP-Tacro tablets, 0.75 mg, 1.0 mg, and 4.0 mg once daily (QD)	N=275 Prograf capsules (tacrolimus), 0.5 mg, 1 mg, and 5 mg twice daily (BID)	Adult <i>De Novo</i> Kidney transplant recipients
3001	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	Efficacy failure defined as death, graft failure, BPAR or LTFU at 12 months after the first dose of study drug. To show NI.	N=163 LCP-Tacro 0.5-, 1-, 2-, and 5-mg tablets (QD). Initial dosing 0.7 of total daily dose of Prograf being taken for non-blacks, 0.85 multiple for blacks	N=163 Prograf 0.5-, 1-, and 5-mg capsules(BID). Only patients taking a stable total daily dose of at least 2 mg of Prograf were eligible for entry into the study.	Stable kidney transplant patients
2017	Phase 2, open-label, multi-center, randomized trial to demonstrate the PK of LCP-Tacro tablets once daily and Prograf® capsules twice daily.	Tacrolimus PK on Days 1, 7, and 14 and the proportion of patients achieving tacrolimus trough levels of 7 to 20 ng/mL on Days 1, 2, 3, 4, 7, 10, 12, and 14. Efficacy also assessed.	N=32 LCP-Tacro 0.5 mg, 1 mg, 2 mg, and 5 mg tablets once daily (QD)	N=31 Prograf 0.5 mg, 1 mg, and 5 mg capsules twice daily (BID)	Adult <i>de novo</i> kidney transplant patients

2.2 Data Sources

This NDA submission along with additional information at the request of reviewers was received electronically. The full electronic path according to the CDER EDR naming convention is as follows:

<\\CDSESUB1\evsprod\NDA206406>

The quality and integrity of the data will be discussed in Section 3.1.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Pertinent to ICH E3 Guidance for Industry: Structure and Content of Clinical Study Reports, the sponsor submitted documentation of data quality control/assurance procedures in section 9.6 of the study report 3002. The procedures described appear to be acceptable.

Study 3002 is a double blind study. Section 9.4.6 of the study report as well as the SAP Addendum 2 documented the blinding/unblinding procedures. A double-blind, double-dummy study design was used to mask the placebo and active formulations. Both the investigator and patient did not know the treatment group to which the patient was assigned.

The final version of the statistical analysis plan (SAP) was submitted on 8/28/12. Given that the study was initiated (first patient first visit) on October 13, 2010 and was completed (last patient Month 12 visit) on March 20, 2013, the relevant analysis decisions appeared to be made prior to unblinding.

This reviewer was able to reproduce the sponsor's primary and secondary efficacy results based on the data source provided by the sponsor in the submission. The efficacy datasets (ADTTE.xpt for Study 3002 and ADEFF.xpt for Study 3001) were easier to navigate than other datasets, e.g., datasets for Tacrolimus trough levels ADTAC, ADLTAC, dataset for eGFR ADEGFR and rejection analysis dataset ADREJ. The data was not presented in a standardized format (such as CDISC ADaM). In addition, the define files provided with the datasets were not well documented. Definitions for variables on the datasets were not sufficiently explicit and thereby presented many challenges for the reviewer. The comment fields for the variables were not providing much helpful information.

Note that all tables and graphs in this review were created by the reviewer unless otherwise noted in the text. Also all text copied from the applicant's study reports are notated with the source.

3.2 Evaluation of Efficacy

This NDA contains two phase 3 studies. The pivotal phase 3 study (Protocol LCP-Tacro 3002) was conducted in *de novo* kidney transplant patients. The study is titled

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

The supportive phase 3 conversion study (Protocol LCP-Tacro 3001) was conducted in stable renal transplant patients. The study is titled

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

This section presents and discusses the details of these two studies. The focus will be more on Study 3002 as this study conducted in *de novo* kidney transplant patients is considered as pivotal.

3.2.1 Study 3002

The original Protocol LCP-Tacro 3002 was submitted as an SPA on March 31, 2010. The Agency subsequently issued a No Agreement letter on May 14, 2010. The sponsor resubmitted the SPA with a revised protocol on June 24, 2010. The SPA resubmission included the sponsor's responses to the No Agreement letter, including further information to justify the 10% NI margin, approaches to deal with missing data, inclusion/exclusion criteria, duration of follow-up and dosing justification. On August 5, 2010, the Division sent an SPA Agreement letter to the sponsor. A set of statistical comments were included in the SPA Agreement letter asking for further details regarding the NI margin sensitivity analyses, and approaches to deal with missing data in the analysis of renal function. During the pre-NDA meeting held on August 7, 2013, the Agency requested that the NDA submission includes the materials previously submitted to justify the NI margin for Study 3002 as well as information to justify the NI margin for Study 3001 and also include responses to our comments in August 5, 2010 SPA Agreement letter asking for further details regarding the NI margin sensitivity analyses. The sponsor addressed these comments in this NDA submission. Please see Appendix I for details regarding the sponsor's responses as well as the NI margin justification included in the SPA request.

3.2.1.1 Study Design and Endpoints

The study objectives are

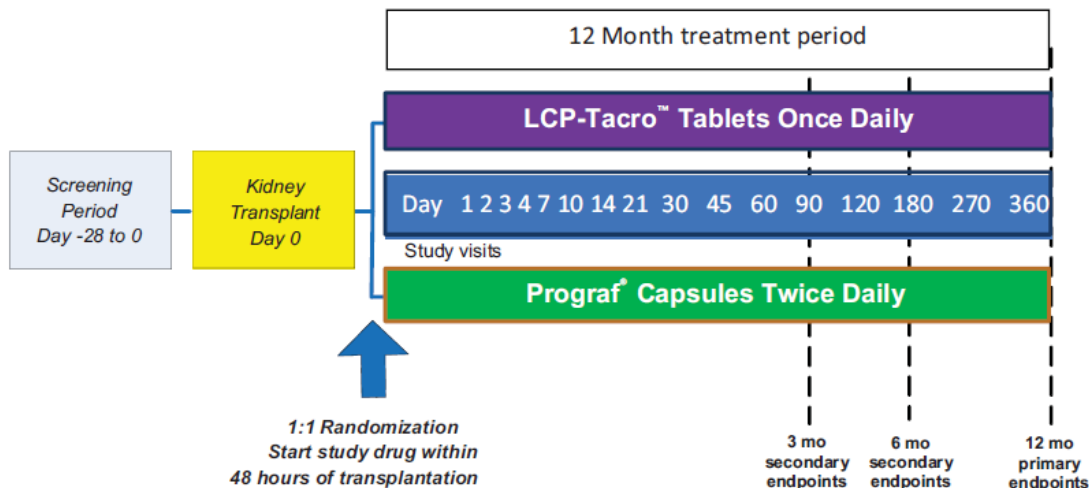
- To evaluate the efficacy and safety of LCP-Tacro (tacrolimus) tablets administered once daily compared to Prograf (tacrolimus) capsules twice daily as immunosuppression for the prevention of acute allograft rejection in *de novo* adult kidney transplant recipients treated for a 12 month treatment period followed by a 12 month, blinded treatment extension period.
- 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.

This was a prospective, randomized, 2-arm parallel group, double-blind, double-dummy, multicenter, Phase 3 clinical trial to establish the efficacy and safety of LCP-Tacro tablets once daily, in comparison to an established standard of care (Prograf capsules twice daily), for the prevention of allograft rejection in *de novo* adult male and female renal transplant recipients. Patients were randomly assigned to study treatment in a 1:1 ratio, using an interactive, automated system. Randomization was stratified by site and race (black vs nonblack).

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. The initial dosage was calculated and indicated via an interactive, automated system and subsequent doses were determined by the investigator. The administration of the first dose of study drug was to be given in the morning following transplantation or no later than 48 hours following transplantation. Patients who could not fulfill this criterion were not randomly assigned to study drug. All patients also received mycophenolate mofetil (MMF), corticosteroids, and IL-2 receptor antagonist (e.g, Simulect®, basiliximab) per the standard of care.

Following screening assessments and kidney transplantation, scheduled study visits for the 12-month treatment period were performed at Days 1, 2, 3, 4, 7, 10, 14, 21, 30, 45, 60, 90, 120, 180, 270 and 360 post transplant. A posttreatment follow-up safety interview via a telephone call (or at a study visit if needed for clinical follow-up on a safety issue) was conducted 30 days after the end of study drug treatment.

The diagram for the 12 month study design is shown below.



The primary efficacy endpoint is the incidence of treatment failures within 12 months after randomization to study drug. Treatment failure is a composite endpoint that will include occurrence in any patient of the following: death, graft failure, biopsy-proven acute rejection (BPAR, Banff Grade $\geq 1A$) or lost to follow-up. Based on the protocol, central laboratory results were used for assessment of the study outcomes.

Secondary efficacy endpoints include 6-month treatment failure rates, 6-month and 12-month all cause mortality rates, 6-month and 12-month graft failure rates, 6-month and 12-month BPAR rates, 6-month and 12-month lost to follow-up rates, 6-month and 12-month incidences of patient death or graft failure, 6-month and 12-month clinically suspected and treated acute rejections, 6-month and 12-month premature discontinuation for any reason, severity grades of the first episode of BPAR, and time to death, time to graft failure, time to first episode of BPAR, and time to lost to follow-up. Primary endpoint results and selected secondary endpoint analysis results are presented in Section 3.2.1.4.

The Intent-to-Treat (ITT) dataset consisted of all patients randomized to receive study drug. The ITT dataset was the primary dataset for assessment of efficacy and safety of the study. Patients who were randomly assigned but did not take study drug, or discontinued study treatment and switched to other therapies during the study period, were included in the treatment group to which they were randomly assigned. The protocol also defined All Treated Dataset as all randomized patients who received at least one dose of randomized study drug. This dataset was used for sensitivity analysis.

3.2.1.2 Statistical Methodologies

The null hypothesis for the primary efficacy analysis will be that LCP-Tacro is inferior to Prograf with respect to the proportion of treatment failures 12 months after randomization. The non-inferiority of LCP-Tacro with respect to treatment failure within 12 months was assessed

using a 2-sided 95% CI based on the difference in treatment failure rates between the treatment groups at 12 months, i.e., LCP-Tacro minus Prograf. The protocol states the 95% CI for the difference in treatment failure rates would be calculated using (b) (4) (b) (4)

The final version of the SAP (Version 6, submission date 8/28/2012) changed the method to Newcombe-Wilson Score method. The study report in the NDA submission presents the confidence interval constructed using Newcombe-Wilson Score method. The study report stated that Newcombe-Wilson score intervals were chosen to be consistent with the method used for sample size calculation. Based on the 95% CI, one of the following conclusions may be drawn:

- If the upper bound of the 95% CI for the difference in treatment failure rates (LCP-Tacro – Prograf) was less than 0.10, then LCP-Tacro was considered non-inferior to Prograf.
- If the upper bound of the 95% CI for the difference in treatment failure rates was less than 0, then LCP-Tacro will be considered superior to Prograf.

Regarding the justification for the 10% margin, please see Appendix 1 for detailed discussion.

Individual components of the composite efficacy variable (death, graft failure, BPAR, and lost to follow-up) were evaluated separately. Per the protocol, the BPAR determinations from the central biopsy reading were used when analyzing the primary efficacy endpoint.

This reviewer will calculate the efficacy results using the simple proportion and confidence interval with normal approximation. The results using Newcombe-Wilson score method and the exact method will also be presented in Section 3.2.1.4 of this review. There are only minor differences between the reviewer's and the sponsor's analyses results and that the interpretation of the results do not change based on the method used.

An analysis of covariance (ANCOVA) model was used as the primary method of analysis to evaluate the difference between treatment groups for eGFR (calculated using abbreviated MDRD7 [Modification of Diet in Renal Disease 7] equation) at each time point; the model will include main effects for treatment, investigator and race (Black/Non-Black), with baseline value as a covariate. The difference in least-squares means between the treatment groups and corresponding 2-sided 95% CIs will be presented. Only observed eGFR values will be used for the primary analysis without imputation of data for missing or incomplete observations. The SAP proposed a secondary analysis where missing eGFR values were set to zero for patients who experience death, graft failure, or lost to follow-up or discontinue the study due to adverse events related to renal function. However, the secondary analysis included in final study report only imputed for graft failure as zero.

The SAP proposed several sensitivity analyses to evaluate the effect of missing or incomplete data on eGFR conclusions. The proposed analyses included

- Multiple Imputation (MI) Method - the multiple imputation method was implemented with SAS® procedure PROC MI, which performs multiple imputation by replacing each missing value with a set of plausible values using the Markov Chain Monte Carlo (MCMC) method. Details of PROC MI can be found in SAS documentation. In the dataset adegrf.xpt, 10 sets of imputed data were included.

- Nonparametric Analysis of Treatment Effect on GFR - nonparametric ANOVA was proposed to test the difference between treatment groups in the change of eGFR from baseline at each time point. The data is rank-transformed prior to testing. The SAP specified SAS procedures PROC RANK, PROC REG and PROC MIXED are used to perform the test for each of the 10 data sets generated by the multiple imputation method.
- Mixed effects model analysis of treatment effect on GFR - A Repeated Measures Linear Model with random intercept and slope was proposed to fitted for each imputed complete dataset. The model included fixed effects of treatment, race group, and baseline eGFR; the effects of individual patients and time (expressed as 3, 6, 9, 12 months in the study) were included in the model as random effects. An unstructured covariance matrix between intercept and slope estimates were used. PROC MIANALYZE and PROC MIXED procedure with the RANDOM subcommand were used for this analysis.
- Twelve-month eGFR analysis by chronic kidney disease (CKD) stage definition - Based on the eGFR at baseline and Month 12, the number (%) of patients at each CKD stage were tabulated for each treatment group. Shift tables were used to show the change in stage from baseline (Day 30) to Month 12.

This reviewer will perform two imputation methods, one imputing the estimated GFR as 0 for patients who had graft loss or died, the other imputing GL/D to 0 and all other missing values as 15. The conclusions from these two imputation methods are the same as from the analysis without imputation as well as the conclusion from the sponsor's imputation methods. There were no statistically significant difference for mean GFR as well as mean change of GFR from baseline at Months 3, 6 and 12 (Month 3, 6, 12 – baseline) between the two treatment groups with and without imputations.

For sample size calculation, with the assumption that both treatment groups in this study would have a 15% 12-month treatment failure rate, the study would require 270 patients per group to have 90% power to reject the null hypothesis that LCP-Tacro is inferior to Prograf based on a 2-sided 95% CI and a 0.10 non-inferiority margin. The results are based on 10000 simulations using the Newcombe-Wilson score method to construct the confidence interval via nQuery.

The SAP (Version 4) also presented a sensitivity analysis of study power as shown in Table 2 (same as Table 14-1 of the study report and verified by this reviewer). Assuming that the investigational drug (LCP-Tacro) would have a 14% 12-month treatment failure rate and the Prograf would have a 15% 12-month treatment failure rate in this study, the study would require 216 patients per arm to have 90% power to reject the null hypothesis. Using the treatment failure rates as shown in Table 1 , the study power would range from 88% to 98% (Scenarios 4, 5 and 6) based on 270 patients per group.

Table 2 Sample Size Assessment for Study 3002 Based on Two-Group Test of Equivalence in Proportions (Using Confidence Interval)

Scenario	1	2	3	4	5	6
Confidence level, 1- α (one-sided)	0.975	0.975	0.975	0.975	0.975	0.975
Standard proportion, π_s	0.15	0.15	0.14	0.1145	0.1567	0.0825
Test expected proportion, π_T	0.15	0.14	0.14	0.1145	0.1567	0.0825
Upper limit for $\pi_T - \pi_s$	0.10	0.10	0.10	0.1000	0.1000	0.1000
Number of simulations	10000	10000	10000	10000	10000	10000
Random seed for simulations	1234	3567	2387	9876	75643	12345
Power (%)	90.26	90.00	91.54	95.33	88.46	98.54
N per group	270	216	270	270	270	270

nQuery Advisor version 7.0 (Upper confidence limit for difference in proportions (simulation)).

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Study 3002 was initiated (first patient enrolled) on October 13, 2010 and was completed (last patient completed 12-month visit) on March 20, 2013. The study was conducted in 68 centers located in the United States, Latin America, Europe and Asia. A total of 601 patients were enrolled into the study. Of these patients, 58 (9.7%) were not randomized. Out of 601 enrolled patients, 543 patients were randomized to the two treatment groups with 268 in the LCP-Tacro group and 275 in the Prograf group.

Note: Originally there were 69 sites that enrolled patients. The original investigator at site 1045 left the site without a PI. The sponsor decided to leave the patient IDs (001045-001 and 001045-002) as is. As a result, the analysis data has 69 sites with randomized patients. These two patients were included in site 1049 in the Clinical Study Report. The CSR has a typo on page 3 with 70 as the total number of study sites.

Patient disposition for the ITT population for the 12 month analysis is presented in Table 3 below (extracted from Table 10-1 in the study report). Rates for discontinuation of study medication prior to 12 months were similar for the LCP-Tacro group(22.3%) and the Prograf control group (18.9%). Overall, AEs were the major reason for discontinuation of study medication in the LCP-Tacro arm (8.6%) and the Prograf control arm (9.8%). Similar proportions of patients withdraw from the study (prior to completing Month 12) for the 2 treatment groups (4.5% for LCP-Tacro and 5.1% for Prograf). Overall, death was the key reason for study discontinuation with 8 patients (3.0%) in the LCP-Tacro group and 8 patients (2.9%) in the Prograf group.

Table 3 Patient Disposition for Study 3002 (All Randomized Patients)

	LCP-Tacro N=268 n(%)	Prograf N=275 n(%)
Patients who received at least one dose of study drug	266	271
Completed 12 month study drug treatment	206 (76.9)	219 (79.6)
Completed the 12-month study period	256 (95.5)	261 (94.9)
Discontinued study drug prior to Month 12	60 (22.4)	52 (18.9)
Reasons for early discontinuation of study drug		
Graft failure	3 (1.1)	1 (0.4)
Adverse event	23 (8.6)	27 (9.8)
Unsatisfactory therapeutic effect	1 (0.4)	2 (0.7)
Patient voluntarily discontinued	22 (8.2)	18 (6.5)
Physician decision	4 (1.5)	2 (0.7)
Noncompliance	2 (0.7)	0
other	5 (1.9)	2 (0.7)
Withdraw from study prior to Month12	12 (4.5)	14 (5.1)
Reasons for early termination from study		
Death	8 (3.0)	8 (2.9)
Adverse event	1 (0.4)	2 (0.7)
Lost to follow-up	0	2 (0.7)
Voluntarily discontinued	3 (1.1)	2 (0.7)

Recipient demographic characteristics and baseline transplant information are summarized in Table 4 below (taken from Table 11-1 and Table 11-2 of the study report and verified by this reviewer). The two groups were generally balanced with respect to demographic and background characteristics. LCP-Tacro group was on average (mean=44.8 years) slightly younger than the Prograf group (mean=46.9 years). Across groups, about 65% of patients were males, and the

Table 4 Demographic and Baseline Transplant Information – Study 3002 (ITT)

		LCP-Tacro N=268	Prograf N=275
Age (years)	Mean±SD	44.8±13.3	46.9±14.3
	Range	18-70	18-70
	Median	46	50
	<65 years	252 (94.0)	247 (89.8)
	≥65 years	16 (6.0)	28 (10.2)
Sex- n(%)	Male	174 (64.9)	181 (65.8)
	Female	94 (35.1)	94 (34.2)
Race –n(%)	White	203 (75.7)	214 (77.8)
	Black	10 (3.7)	15 (5.5)
	Asian	10 (3.7)	10 (3.6)
	American Indian or Alaska native	0	1 (0.4)
	Pacific Islander	1 (0.4)	1 (0.4)
	Other	44 (16.4)	34 (12.4)
Ethnicity	Hispanic/Latino	74 (27.6)	79 (28.7)
	Non-Hispanic/Latino	194 (72.4)	196 (71.3)
Baseline BMI (kg/m ²)	Mean±SD	25.7±4.6	26.7±4.9
	Range	16.6 - 38.2	15.6 – 42.1
	Median	25.2	26.5
Donor Type n(%)	Living	135 (50.4)	129 (46.9)
	Deceased	133 (49.6)	145 (52.7)
	missing	0	1 (0.4)
Previous Transplant n(%)	Yes	11 (4.1)	11 (4.0)
	No	257 (95.9)	263 (95.6)
	missing	0	1 (0.4)
HLA mismatches - n(%)	0	31 (11.6)	37 (13.5)
HLA-A	1	129 (48.1)	135 (49.1)
	2	91 (34.0)	83 (30.2)
	0	32 (11.9)	21 (7.6)
HLA-B	1	127 (47.4)	136 (49.5)
	2	91 (34.0)	97 (35.3)
	0	45 (16.8)	51 (18.5)
HLA-DR	1	136 (50.7)	141 (51.3)
	2	67 (25.0)	62 (22.5)

majority of patients were Caucasian (76.8%). The LCP-Tacro group had slightly higher proportion of living donor than the Prograf group (50.4% vs 46.9%). The majority of patients had not received a prior transplant (520/543=95.8%). The majority patients had 2 or less HLA mismatches. Approximately half of all patients had 1 mismatch in HLA-A, HLA-B, and HLA-DR.

Study drug doses were adjusted in order to maintain tacrolimus trough levels within predefined target ranges. By protocol, dose adjustments to maintain tacrolimus trough levels will be based on local laboratory determinations. A portion of the sample will also be collected and stored for later shipment to a central laboratory for archival storage and/or possible re-assay of tacrolimus level. The sponsor presented the Tacrolimus exposure levels using central laboratory data in the study report. Mean tacrolimus trough levels for the local laboratory data by visit window are summarized in Table 5 for the treatment arms. For the first two weeks, mean tacrolimus trough levels were significantly higher in the LCP-Tacro arm than in the Prograf control arm. The 95% CI of the mean difference for trough levels along with the p-values are presented in the Table. Starting from Week 3 through Month 12, the trough levels between the two groups were comparable. The mean trough levels were consistently higher at all visit windows, in LCP-Tacro arm compared to the mean in the Prograf control arm. The results for central laboratory trough levels over time were similar to that of the local data. Figure 1 shows tacrolimus trough level over time for both central and local laboratory readings. To explore if there is a treatment effect for the initial different trough level, the reviewer performed a subgroup analysis stratified by Day 2 trough level (median = 6.6 as cutoff) as shown in 4.2.

Figure 1 Mean Tacrolimus Trough Levels Over Time by Treatment Group – Study 3002

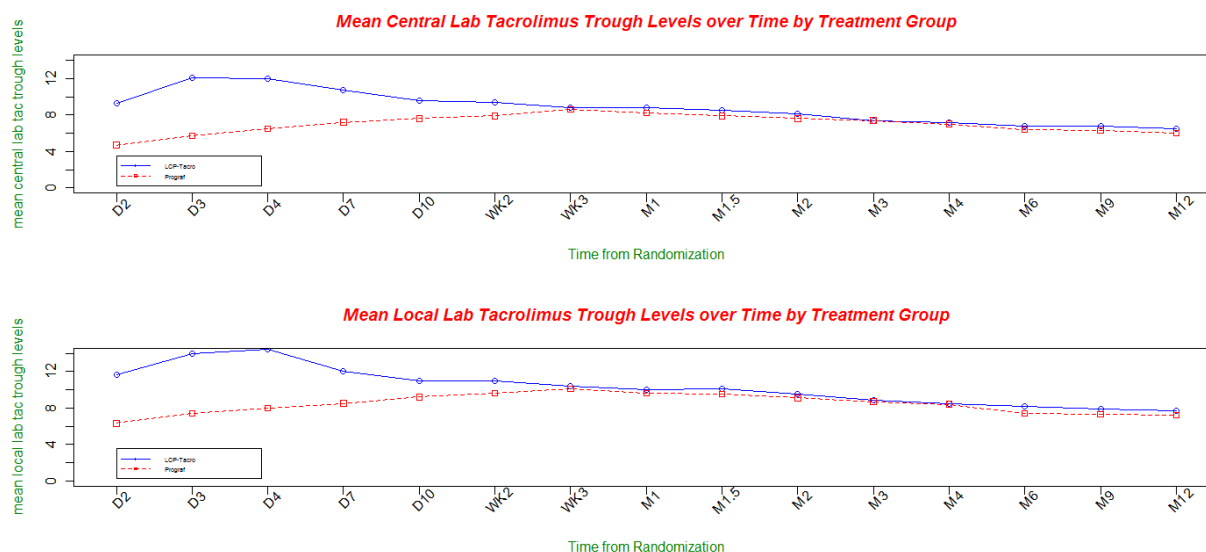


Table 5 Tacrolimus Trough Levels for Local Laboratory Data by Visit – Study 3002

Visit		LCP-Tacro	Prograf
Day 2	N Mean (SD) Median (range)	174 11.6 (8.4) 9.2 (0.4 – 54.4)	192 6.3 (4.9) 4.9 (0.8-29.3)
		95% C.I. of mean difference (3.9, 6.8), P<0.0001	
Day 3	N Mean (SD) Median (range)	239 14.0 (8.8) 11.9 (0.2 – 54.0)	236 7.4 (4.9) 6.3 (0.8 – 38.6)
		95% C.I. of mean difference (5.3, 7.9), P<0.0001	
Day 4	N Mean (SD) Median (range)	226 14.4 (7.8) 13.1 (2.0 – 57.0)	232 8.0 (4.7) 7.3 (0.6 – 29.7)
		95% C.I. of mean difference (5.2, 7.6), p<0.0001	
Day 7	N Mean (SD) Median (range)	219 12.0 (6.6) 10.8 (1.9 – 47.0)	240 8.5 (4.1) 7.7 (1.6 – 25.1)
		95% C.I. of mean difference (2.5, 4.6), p<0.0001	
Day 10	N Mean (SD) Median (range)	199 11.0 (5.6) 10.1 (1.2 – 33.6)	200 9.2 (4.0) 8.5 (2.7 – 23.6)
		95% C.I. of mean difference (0.8, 2.8), p=0.0003	
Week 2	N Mean (SD) Median (range)	250 11.0 (4.4) 10.7 (2.3 – 30.0)	256 9.6 (3.8) 9.1 (1.6 – 32.0)
		95% C.I. of mean difference (0.7, 2.1), p=0.0002	
Week 3	N Mean (SD) Median (range)	246 10.4 (4.2) 10.0 (2.6 – 32.2)	253 10.1 (3.9) 9.5 (1.6 – 37.0)
Month 1	N Mean (SD) Median (range)	243 10.0 (3.9) 9.6 (1.4 – 26.3)	251 9.6 (2.9) 9.4 (2.7 – 20.3)
Month 1.5	N Mean (SD) Median (range)	245 10.1 (3.8) 9.5 (2.1 – 25.1)	242 9.5 (3.1) 9.4 (2.9 – 28.8)
Month 2	N Mean (SD) Median (range)	243 9.5 (3.8) 8.8 (2.2 – 23.5)	240 9.1 (3.0) 8.9 (2.3 – 29.3)
Month 3	N Mean (SD) Median (range)	239 8.8 (3.1) 8.4 (2.0 – 21.8)	241 8.7 (2.8) 8.2 (2.2 – 20.5)
Month 4	N Mean (SD) Median (range)	229 8.5 (3.3) 8.1 (2.7 – 29.0)	239 8.4 (2.8) 8.0 (1.8 – 23.2)
Month 6	N Mean (SD) Median (range)	224 8.2 (3.4) 7.8 (1.5 – 30.0)	232 7.4 (2.3) 7.1 (2.3 – 14.0)
Month 9	N Mean (SD) Median (range)	216 7.9 (3.4) 7.4 (2.6 – 29.6)	223 7.3 (2.7) 7.1 (2.0 – 19.1)
Month 12	N Mean (SD) Median (range)	211 7.7 (3.2) 7.2 (1.0 – 21.5)	222 7.2 (2.9) 6.6 (2.2 – 22.3)

3.2.1.4 Results and Conclusions

Comparisons between treatment groups on efficacy failure endpoint (BPAR/Death/Graft Loss/Lost to Follow up) as well as each component of the endpoint are summarized in Table 6 and Table 7. Table 6 shows the analysis results based on efficacy analysis dataset ADTTE.xpt. The incidence rate for efficacy failure was slightly lower for the LCP-Tacro group (18.3%) than the incidence rate for the Prograf group (19.6%), with a difference between the two groups (LCP-Tacro – Prograf) of -1.3% and 95% confidence interval of (-7.9%, 5.2%). The upper bound of this CI is smaller than the pre-specified NI margin of 10%. LCP –Tacro was therefore shown to be non-inferior on efficacy failure compared to Prograf based on a 10% NI margin. The protocol states the 95% CI for the difference in treatment failure rates would be calculated using (b) (4). The final version of the SAP (Version 6, submission date 8/28/2012) changed the method to Newcombe-Wilson Score method. The study report in the NDA submission presents the confidence interval constructed using Newcombe-Wilson Score method. This reviewer calculated the efficacy results using the simple proportion and confidence interval with normal approximation. The results using Newcombe-Wilson score method and the exact method will also be presented in Section 3.2.1.4 of this review. There are only minor differences between the reviewer's and the sponsor's analyses results and that the interpretation of the results do not change based on the method used.

While a noninferiority margin for the endpoint of graft loss/death/lost to follow-up cannot be justified statistically given the lack of historical data to estimate the effect size of the active control over putative placebo, the Division continues to consider this an important endpoint. The incidence rate for the endpoint of graft loss/death/lost to follow-up was also lower for the test drug LCP-Tacro (7.1%) compared with the control Prograf (8.4%). The difference between the two groups on GL/Death/LTFU(LCP-Tacro – Prograf) is -1.3% with 95% CI of (-5.8%, 3.2%). This confidence interval was computed using a normal approximation. For the individual components of the efficacy endpoint, incidence rate of BPAR, graft loss and rate of lost to follow-up were slightly lower in the LCP-Tacro arm than the Prograf arm. There were 8 deaths occurred in each arm.

Table 6 Efficacy Results by Treatment Group at 12 Months (ITT Population) – Study 3002

Endpoints	LCP-Tacro N=268 n(%)	Prograf N=275 n(%)
Efficacy Failure Endpoint	49 (18.3)	54 (19.6)
	95% CI of LCP-Tacro - Prograf: -1.4% (-7.9%, 5.2%) ^(a)	
Biopsy Proven Acute Rejection	35 (13.1)	37 (13.5)
Death	8 (3.0)	8 (2.9)
Graft Loss	9 (3.4)	11 (4.0)
Lost to Follow-up	4 (1.5)	5 (1.8)
Graft Loss or Death or Lost to Follow-up	19 (7.1)	23 (8.4)
	95% CI of LCP-Tacro – Prograf: -1.3%(-5.8%, 3.2%)	
Graft Loss or Death	15 (5.6)	18 (6.6)
Lost to Follow-up	4 (1.5)	5 (1.8)
95% CI for difference in efficacy failure rate compared to Prograf group calculated using exact method(b)	(-8.0%, 5.3%)	
95% CI for difference in efficacy failure rate compared to Prograf group calculated using the Newcombe-Wilson score method(c)	(-8.0%, 5.2%)	

(a) CI calculated using normal approximation

(b) The method specified in the protocol

(c) The method specified in the SAP version 6.

An inspection of Rejection Analysis dataset ADREJ.xpt revealed that Patient 034154017 in the LCP-Tacro arm was randomized on March 4 2012 and had a biopsy on March 4 2013 that resulted in the confirmation of an acute rejection event. Per the SAP, The date of onset of BPAR was defined as the date when the biopsy was performed and the cut-off date for the 12 month primary analysis including incidence of BPAR is Day 365 after the randomization date (Study Day 360 plus 5-day window). Because the biopsy date was Day 366 after randomization, this acute rejection event was not included as a BPAR event and therefore was not an efficacy failure in the Efficacy Analysis dataset ADTTE.xpt. However, further inspection of the eCRF revealed that this rejection event occurred on Feb 25 2013 and the biopsy was performed 8 days later on March 4 2013 which happened to be Study Day 366, one day past the cut-off date for 12 month primary analysis. The statistical reviewer consulted the medical reviewer about this case. The statistical reviewer agreed with the medical reviewer's recommendation to include the rejection occurred for patient 034154017 as an event since the rejection occurred within the 12 month study period, although the biopsy was performed 8 days later. Table 7 below is updated with inclusion of patient 034154017 as having had an BPAR event therefore an efficacy failure for

the primary analysis. Table 7 shows 36 patients in the LCP-Tacro group had BPAR event compared with 37 patients in Prograf group had BPAR. With the addition of an efficacy failure event in the LCP-Tacro arm, the 95% confidence interval of the difference between the two groups changes slightly to (-7.6%, 5.6%), from (-7.9%, 5.2%) in Table 6. The efficacy conclusion does not change with the addition of this one event in the test arm.

Table 7 Efficacy Results by Treatment Group at 12 Months (ITT Population) (Modified) – Study 3002

Endpoints	LCP-Tacro N=268 n(%)	Prograf N=275 n(%)
Efficacy Failure Endpoint	50 (18.7)	54 (19.6)
	95% CI of LCP-Tacro - Prograf: -1.0% (-7.6%, 5.6%) ^(a)	
Biopsy Proven Acute Rejection	36 (13.4)	37 (13.5)
Death	8 (3.0)	8 (2.9)
Graft Loss	9 (3.4)	11 (4.0)
Lost to Follow-up	4 (1.5)	5 (1.8)
Graft Loss or Death or Lost to Follow-up	19 (7.1)	23 (8.4)
	95% CI of LCP-Tacro – Prograf: -1.3%(-5.8%, 3.2%)	
Graft Loss or Death	15 (5.6)	18 (6.6)
Lost to Follow-up	4 (1.5)	5 (1.8)
95% CI for difference in efficacy failure rate compared to Prograf group calculated using exact method(b)	(-7.7%, 5.7%)	
95% CI for difference in efficacy failure rate compared to Prograf group calculated using the Newcombe-Wilson score method(c)	(-7.6%, 5.6%)	

(a) CI calculated using normal approximation

(b) The method specified in the protocol

(c) The method specified in the SAP version 6.

Figure 2 displays the Kaplan-Meier survival curve for patients in the two treatment groups on the efficacy endpoint of BPAR/GL/D/LTFU over the 12 month treatment period. The LCP-Tacro group appears to have better responses compared to the Prograf group over the time during the trial. However, there are no statistically significant differences of median time to event between the two groups (p=0.7052, log-rank test).

Figure 2 Kaplan-Meier Survival Curve for Efficacy Failure (12 month analysis for ITT population) – Study 3002

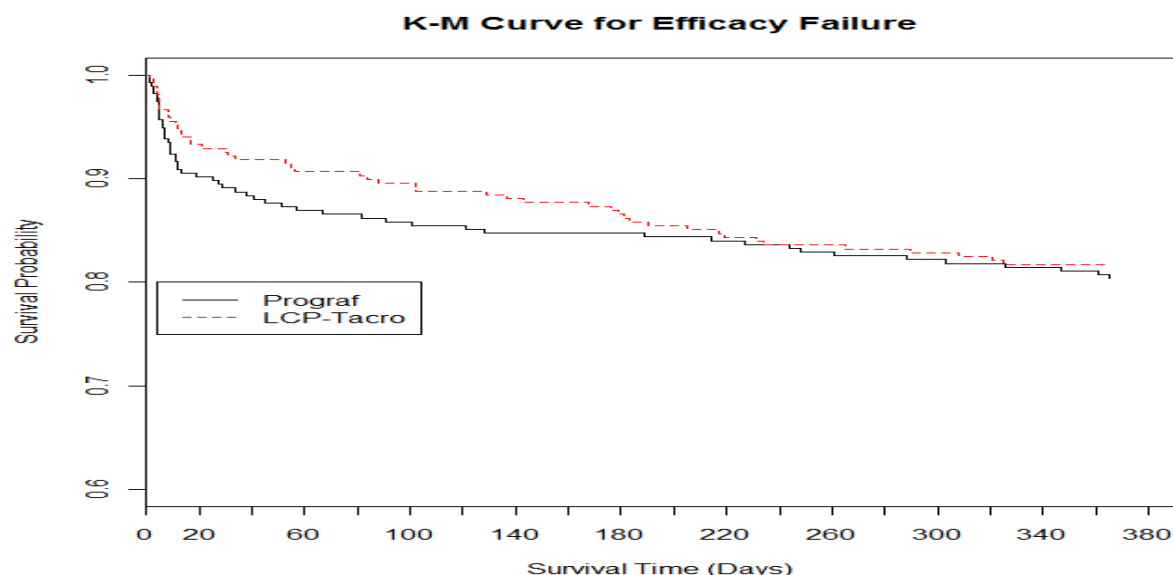
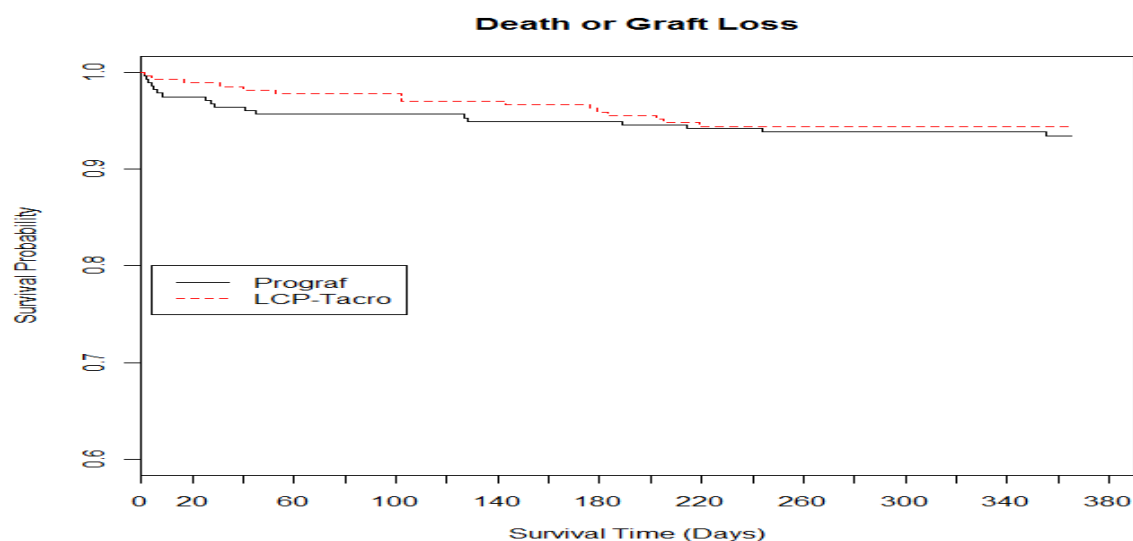


Figure 3 shows Kaplan-Meier survival curve for patients free from death or graft loss (12 month analysis for ITT population). The LCP-Tacro arm appears to have better response than the Prograf arm for the first 6 months and then the two groups are almost the same. Based on the log-rank test, there were no statistically significant differences between the two groups with respect to median time to death or graft loss event ($p=0.6251$).

Figure 3 Kaplan-Meier survival curve for patients free from death or graft loss (12 month analysis for ITT population) – Study 3002



In general, the incidence of efficacy failure is mainly driven by the events of BPAR(Biopsy Proven Acute Rejection). Efficacy failure therefore is considered as rate of BPAR with death,

graft loss and lost to follow-up imputed as failures. In this study, allograft biopsies were performed for clinical cause, such as suspected acute allograft rejection, and in the case of some investigative sites, allograft biopsies were also performed for routine surveillance. Biopsies were read locally at each site by a pathologist. Treatment decisions were based on the local interpretation. All biopsies were also read by a single, blinded central reader and the central reading was used for the primary efficacy analysis as shown in Table 5 and Table 6. The result of a biopsy is classified by Banff grades. In this trial, BPAR is defined as Banff Grade $\geq 1A$.

Results of the local biopsy readings were presented in data listings but not summarized in the study report. Table 8 below shows efficacy Results at 12 Months (ITT Population) by local BPAR readings. The local BPAR results were based on dataset ADREJ.xpt. The 95% CI of the difference in efficacy failure rate between the two groups (LCP-Tacro – Prograf) is (-5.8%, 3.2%). This confidence interval happened to be the same for the exact method, the Newcombe-Wilson score method and the normal approximation. Using locally read BPAR results, the conclusion on efficacy outcome would stay the same as using the results from central readings.

Table 8 Efficacy Results at 12 Months (ITT Population) by Local Read BPAR – Study 3002

Endpoints	LCP-Tacro N=268 n(%)	Prograf N=275 n(%)
Efficacy Failure Endpoint	42 (15.7)	45 (16.4)
	95% CI of LCP-Tacro - Prograf: -0.7%(-6.9%, 5.5%) ^(a)	
Biopsy Proven Acute Rejection	25 (9.3)	23 (8.4)
Death	8 (3.0)	8 (2.9)
Graft Loss	9 (3.4)	11 (4.0)
Lost to Follow-up	4 (1.5)	5 (1.8)
Graft Loss or Death or Lost to Follow-up	19 (7.1)	23 (8.4)
	95% CI of LCP-Tacro – Prograf: -1.3%(-5.8%, 3.2%)	
Graft Loss or Death	15 (5.6)	18 (6.6)
Lost to Follow-up	4 (1.5)	5 (1.8)
95% CI for difference in efficacy failure rate compared to Prograf group calculated using exact method(b)	(-6.9%, 5.5%)	
95% CI for difference in efficacy failure rate compared to Prograf group calculated using the Newcombe-Wilson score method(c)	(-6.9%, 5.5%)	

(a) CI calculated using normal approximation

(b) The method specified in the protocol

(c) The method specified in the SAP version 6.

Note that there were less BPAR events based on local lab results (25 in the LCP-Tacro arm and 23 in the Prograf arm) as compared to the results from central readings (36 in the LCP-Tacro arm and 37 in the Prograf arm). The difference between the local and central readings was explored with respect to the BPAR events confirmed by central readings. Table 9 shows comparison of local and central biopsy assessments for the BPAR events confirmed by central reading as treatment failures. Note that in this trial, BPAR is defined as Banff Grade $\geq 1A$. Mild severity category is defined as 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 using Banff 2007 criteria. Non-specific/borderline changes were not considered as AR event in this trial. Among the biopsies that were confirmed as AR by central reading, 19 (52.8% of 36) in LCP-Tacro arm and 22 (59.5% of 37) in Prograf arm were not considered as AR events by local readings. While the central review identified 1 severe rejection in LCP-Tacro group, the local review identified 1 severe rejection in the Prograf control arm. Overall, local lab readings appear to be more conservative compared with central readings. The statistical reviewer consulted with the medical reviewer Dr. Velidedeoglu about the founding. Dr. Velidedeoglu noted this is contrary to the results from other studies and that generally the BPAR rates in the local readings are higher compared to the central readings.

Table 9 Local Biopsy Assessments for Central BPAR Events – Study 3002

	Central Assessment		Local Assessment	
	LCP-Tacro	Prograf	LCP-Tacro	Prograf
Number of biopsies confirmed as BPAR by central reading	36	37	36	37
non-specific/borderline change	0	0	19	22
mild	29	29	10	9
moderate	6	8	5	5
severe	1	0	0	1
missing	0	0	2	0

Table 10 presents distribution of number of BPARs and the severity distribution of central biopsy assessments for first episode of BPAR occurred within 12 months after randomization. The numbers of patients with 1-4 BPAR episodes were similar between the two groups. Severity of first BPAR episode was similarly distributed between the two groups as well. Note that the results presented in Table 11-8 of the study report show that 38 patients in LCP-Tacro arm and 40 patients in Prograf arm had ≥ 1 BPAR episode, which included 5 more subjects (2 subjects in the LCP-Tacro arm and 3 subjects in the Prograf arm) who experienced BPAR between Month 12 and Study day 404. Of the 2 patients in the LCP-Tacro arm, 1 had mild first BPAR episode and 1 had moderate BPAR episode. Of the 3 patients in Prograf arm, 2 experienced mild episode and 1 had severe episode of first BPAR.

Table 10 Number of BPAR and First BPAR Episode Severity Assessment* within 12 Months by Treatment Group (ITT set) – Study 3002

	LCP-Tacro N=268	Prograf N=275
No. of Patients who had BPAR	36 (13.4)	37 (13.5)
Number of BPAR		
No. of Patients with 1 BPAR episode	27 (10.1)	29 (10.5)
No. of Patients with 2 BPAR episodes	6 (2.2)	6 (2.2)
No. of Patients with 3 BPAR episodes	2 (0.7)	2 (0.7)
No. of Patients with 4 BPAR episodes	1 (0.4)	0 (0)
Severity Assessment* of first BPAR		
Mild	29 (10.8)	29 (10.5)
Moderate	6 (2.2)	8 (2.9)
Severe	1 (0.4)	0 (0)

*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 using Banff 2007 criteria.

3.2.2 Study 3001

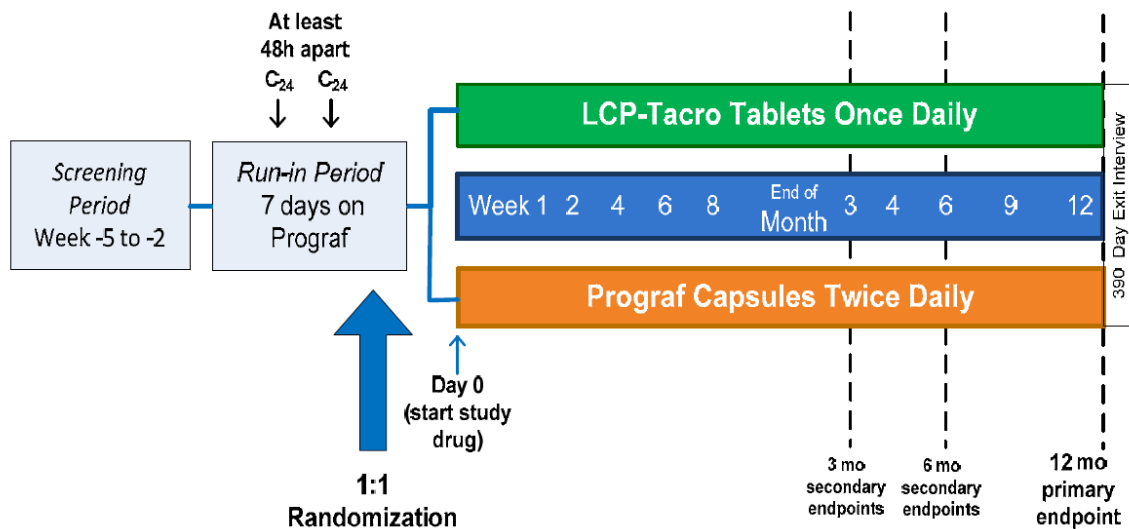
3.2.2.1 Study Design and Endpoints

The primary objective of the study is 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.

This was an open-label, parallel-group, prospective, randomized, Phase 3, multicenter study in stable kidney transplant patients. After completion of a screening visit, eligible patients entered a 7-day Run-in Period during which they were to continue on their regular dose of Prograf. At least 2 consecutive tacrolimus whole blood trough levels, measured at least 48 hours apart, were obtained during the Run-in Period. Patients with consecutive whole blood trough levels within the predefined therapeutic range of 4 to 15 ng/mL were randomly assigned at the end of the Run-in Period to either convert from Prograf capsules twice daily to a reduced dose of LCP-Tacro tablets once daily, or to continue on Prograf twice daily.

The 12 month treatment period began on Day 0 after the run-in period and included study visits scheduled at Weeks 1, 2, 4, 6, 8, and Months 3, 4, 6, 9 and 12 (as shown in Table 8-2 of the Study report). All descriptive and comparative statistics for laboratory parameters, including tacrolimus whole blood trough levels, were based on central laboratory assessments, but dosing adjustments were based on tacrolimus whole blood trough levels obtained from local laboratories.

The diagram for the study design is shown below.



Abbreviations: h, hour; mo, month.

The primary efficacy endpoint is the cumulative incidence of efficacy failure by 12 months after randomization. Efficacy failure is a composite primary endpoint and includes any patient experiencing any one of the following within 12 months (by Day 360) after randomization: death, graft failure (return to dialysis for > 30 days, allograft nephrectomy, or retransplantation), biopsy-proven acute rejection (BPAR, Banff grade $\geq 1A$), or lost to follow-up. BPAR will be graded according to the 1997 Banff criteria. The local and central pathologists will be blinded with regard to treatment assignment. The diagnosis of BPAR (Banff grade $\geq 1A$) was based on local histological grading using the Banff criteria as specified in the protocol and SAP.

Secondary efficacy endpoints include incidence of efficacy failure in the mITT and the PP analysis sets within 6 months after first dose of study drug, incidence of efficacy failure in the PP analysis set within 12 months after first dose of study drug, incidence of death or graft failure within 6 months and 12 months after first dose of study drug, incidence of BPAR within 6 months and 12 months after first dose of study drug, proportion of severity grades of the first episode of BPAR (Banff grade) occurring within 6 months and 12 months after first dose of study drug and incidence of premature discontinuation of randomized study drug for any reason within 12 months after first dose of study drug. Primary endpoint results and selected secondary endpoint analysis results are presented in Section 3.2.2.4.

The primary efficacy analysis will be performed using the mITT analysis set defined as all randomly assigned patients who receive at least one dose of study drug (LCP-Tacro tablets or Prograf capsules). The primary safety assessment and secondary endpoints will also be assessed using the mITT analysis set. Per-protocol patients (PP) are all patients who complete the study without any major deviations from the protocol procedures. If the upper bound of the 95% CI for the difference in efficacy failure rates was less than 0.09, then LCP-Tacro was to be considered non-inferior to Prograf. The 95% CI for the difference in efficacy

failure rates was calculated using an exact method that is based on the standardized statistic and inverting a 2-sided test.

3.2.2.2 Statistical Methodology

The non-inferiority of LCP-Tacro with respect to the composite primary variable was assessed using a 2-sided 95% CI based on the difference for the efficacy failure rates between the treatment groups (i.e., LCP-Tacro minus Prograf). The 95% CI for the difference in efficacy failure rates will be calculated using an exact method that is based on the standardized statistic and inverting a 2-sided test (Agresti, A., and Min, Y. On small-sample confidence intervals for parameters in discrete distributions. *Biometrics*. 2001; 57(3): 963-971.). If the upper bound of the 95% CI for the difference in efficacy failure rates was less than (b) (4), then LCP-Tacro was to be considered non-inferior to Prograf.

The final SAP (date: Nov 24, 2010) states that the non-inferiority margin (b) (4) was chosen based on the following assumptions:

(b) (4)

The draft guidance for Non-Inferiority Clinical Trials states that M1 should be based on the treatment effect estimated from the historical experience with the active control drug, which means that the justification needs to be data driven. The NI margin justification above clearly is not acceptable.

Note: In the preliminary comments to the sponsor dated 2/5/2010 for the End of Phase 2 meeting, the Division commented that based on the information provided in the EOP2 meeting briefing package, using only the acute rejection rates, we have concluded that the data referenced by the sponsor would support a margin no larger than (b) (4). During the meeting, the Division asked whether the sponsor would continue to pursue a justification for the noninferiority margin in Study 3001, LCP responded that they plan to limit enrollment to 300 patients and stated they would “agree to disagree” with the Division over the margin. The Division acknowledged some limitations with regards to the existing data which complicate justifying a margin for this study, but encouraged LCP to attempt to more rigorously justify the margin and refine their estimate. For details of the Division’s preliminary meeting comments and meeting discussion on this topic, see the EOP2 meeting minutes dated 3/12/2010 in DARRTS for IND 75250.

Sample size calculation was based on the assumptions of (b) (4) efficacy failure rate in both arms and a (b) (4) non-inferiority margin with (b) (4) power at a 1-sided (b) (4) significance level. The calculation resulted in 136 patients per group. Taking into account a (b) (4) dropout rate, the total sample size for this study was determined to be approximately 151 patients per group or approximately 302 patients overall.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 3001 was initiated (first patient enrolled) on December 23, 2008 and was completed (last patient completed 12-month visit) on February 7, 2011. The study was conducted in 47 centers located in the United States, UK, France, Poland, Germany and Spain. A total of 409 patients were enrolled into the study. Of these patients, 83 (20.3%) were not randomized. Out of 409 enrolled patients, 326 patients were randomized to the two treatment groups with 163 patients in each treatment group. One patient in each treatment group did not receive study drug. Hence, a total of 324 patients (162 in LCP-Tacro group and 162 in Prograf group) were included in mITT analysis set, which was defined as the analysis dataset for the primary efficacy analysis and safety analysis.

Patient disposition for the ITT population for the 12 month analysis is presented in Table 11 below (extracted from Table 9-1 in the study report and verified by this reviewer). Rates for discontinuation of study medication and discontinuation of the study prior to 12 months were higher for the LCP-Tacro group (12.9%) compared to the Prograf control group (5.5%). The difference of discontinuation rates of the two groups was statistically significant ($p=0.02149$, chi-square test). Discontinuation rate due to AE was also higher in the LCP-Tacro arm (7.4%) compared with the Prograf control arm (1.2%). This difference between the two groups was also statistically significant with a p-value of 0.01146 based on the Fisher's exact test.

Table 11 Patient Disposition for Study 3001 (Randomized Patients)

	LCP-Tacro N=163 n(%)	Prograf N=163 n(%)
Patients who received at least one dose of study drug	162 (99.4)	162 (99.4)
Completed 12 month study drug treatment	142 (87.1)	154 (94.5)
Completed the 12-month study period	142 (87.1)	154 (94.5)
Discontinued study drug prior to Month 12^(a)	21 (12.9)	9 (5.5)
Reasons for discontinuation of study drug		
AE ^(a)	12 (7.4)	2 (1.2)
Patient voluntarily discontinued	6 (3.7)	3 (1.8)
Physician decision	2 (1.2)	0
Sponsor decision	0	2 (1.2)
Rejection	1 (0.6)	0
Other ^(b)	0	2 (1.2)
Discontinued from study prior to Month 12	21 (12.9)	9 (5.5)
Reasons for early termination from study		
AE	10 (6.1)	3 (1.8) ^(c)
Protocol violation	0	2 (1.2)
Lost to follow-up	0	1 (0.6)
Death	2 (1.2)	0 ^(c)
Patient voluntarily discontinued	7 (4.3)	3 (1.8)
Physician decision	2 (1.2)	0

(a)Statistically significant difference between the two groups.

(b)Other includes patients that failed to complete final visit due to lost to follow-up (1 patient) and patient took commercial Prograf (1 patient).

(c)1 death reported in the Prograf group categorized as due to AE.

Recipient demographic characteristics and baseline transplant information are summarized in Table 12 below (taken from Table 10-2 of the study report and verified by this reviewer). The two groups were generally balanced with respect to demographic and background characteristics. Across groups, 67.2% (219/326) of patients were males, and the majority of patients (237/326=72.7%) were white. There were slightly more male patients in the LCP-Tacro group than in the Prograf group. Most patients had received their kidneys from deceased donors. Proportion of patients with living donor for the LCP-Tacro group was higher than the proportion for the Prograf group (38.0% vs 31.3%). The difference was not statistically significant (p=0.2005). There were more patients in the LCP-Tacro group who had 1 and 2 HLA mismatches compared with the Prograf group, and fewer number of patients in the LCP-Tacro group who had more than 3 HLA mismatches compared with the Prograf group (119 vs 129 or 73.0% vs 79.1%).

Table 12 Demographic and Other Baseline Characteristics – Study 3001 (Randomized Set)

		LCP-Tacro N=163	Prograf N=163
Age (years)	Mean±SD	50.4±11.7	50.2±13.5
	Range	18-73	18-77
	Median	51	52
	<65 years	146 (89.6)	137 (84.0)
	≥65 years	17 (10.4)	26 (16.0)
Sex- n(%)	Male	117 (71.8)	102 (62.6)
	Female	46 (28.2)	61 (37.4)
Race –n(%)	White	120 (73.6)	117 (71.8)
	Black	36 (22.1)	34 (20.9)
	Asian	3 (1.8)	3 (1.8%)
	American Indian or Alaska native	0	1 (0.6)
	Pacific Islander	0	1 (0.6)
	Other	4 (2.5)	7 (4.3)
Ethnicity	Hispanic/Latino	26 (16.0)	29 (17.8)
	Non-Hispanic/Latino	137(84.0)	134 (82.2)
Baseline BMI (kg/m ²)	Mean±SD	29.0±5.4	28.7±6.1
	Range	18.4-46.8	17.8-53.0
	Median	28.2	27.7
Donor Type n(%)	Living	62 (38.0)	51 (31.3)
	Deceased	101 (62.0)	112 (68.7)
No. of human leukocyte antigen (HLA) mismatches - n(%)	0	16 (9.8)	15 (9.2)
	1	10 (6.1)	8 (4.9)
	2	18 (11.0)	11 (6.7)
	≥3	119 (73.0)	129 (79.1)

3.2.2.4 Results and Conclusions

Comparisons between treatment groups on efficacy failure endpoint (BPAR/Death/Graft Loss/Lost to Follow up) as well as each component of the endpoint are summarized in Table 13. BPAR results in Table 12 were based on local laboratory readings as specified in the protocol and SAP. There were very few events in this conversion study of stable kidney transplant patients. There were 4 efficacy failures in each treatment group, with a 95% confidence interval of the difference of the efficacy failure rates between the two groups (-4.2%, 4.2%). This confidence interval was constructed using the exact method, same as the method specified in the protocol and the SAP. The sponsor states in the study report that as the upper limit of the confidence intervals for the difference was below (b) (4) (the predefined non-inferiority margin in the original protocol) and hence LCP-Tacro successfully demonstrated non-inferiority compared to Prograf. However, given that the (b) (4) NI margin was never justified for this study as well as for

stable kidney transplant patients in general, non-inferiority of LCP-Tacro to Prograf control cannot be claimed for Study 3001. There was no statistically significant difference of the efficacy failure rates between the two groups ($p=1.0000$, Fisher's exact test).

The incidence rate ($2/162 = 1.2\%$) for the endpoint of graft loss/death/lost to follow-up was also the same for the two treatment groups. The 95% CI of the difference between the two groups was $(-3.4\%, 3.4\%)$ for the endpoint of GL/D/LTFU. This confidence interval was also constructed using the exact method.

For the individual components of the efficacy failure endpoint, the two groups were comparable as well. The incidence rate of BPAR ($2/162=1.2\%$) was the same for the two groups. There were 2 deaths in the LCP-Tacro group and 1 death in the Prograf group. No graft losses occurred within the 12 month study period. One patient in the Prograf arm was lost to follow-up and no patients in the Prograf arm were lost to follow-up.

Table 13 Efficacy Results by Local Read BPAR at 12 Months (mITT Population) – Study 3001

Endpoints	LCP-Tacro N=162 n(%)	Prograf N=162 n(%)
Efficacy Failure Endpoint	4 (2.5)	4 (2.5)
	95% CI of LCP-Tacro - Prograf: 0% (-4.2%, 4.2%)	
Biopsy Proven Acute Rejection	2 (1.2)	2(1.2)
Death	2 (1.2)	1 (0.6)
Graft Loss	0	0
Lost to Follow-up	0	1(0.6)
Graft Loss or Death or Lost to Follow-up	2 (1.2)	2 (1.2)
	95% CI of LCP-Tacro - Prograf: 0%(-3.4%, 3.4%)	
Graft Loss or Death	2 (1.2)	1(0.6)
Lost to Follow-up	0	1(0.6)

Table 14 presents efficacy results using central laboratory readings. The confidence intervals in Table 14 were also constructed using the exact method. The incidence of efficacy failure in the LCP-Tacro arm ($3/162=1.9\%$) was slightly lower compared with the Prograf control ($6/162=3.7\%$). The difference of the efficacy failure rates between the two groups (LCP-Tacro – Prograf) was -1.9% with a 95% C.I. of $(-6.5\%, 2.3\%)$. There was no statistically significant difference of the efficacy failure rates between the two groups ($p=0.3389$, Fisher's exact test). The numbers for graft loss, death and lost to follow-up are the same as in Table 13.

Table 14 Efficacy Results by Central BPAR at 12 Months (mITT Population) – Study 3001

Endpoints	LCP-Tacro N=162 n(%)	Prograf N=162 n(%)
Efficacy Failure Endpoint	3 (1.9)	6 (3.7)
	95% CI of LCP-Tacro - Prograf: -1.9%(-6.5%, 2.3%)	
Biopsy Proven Acute Rejection	1(0.6)	4(2.5)
Death	2 (1.2)	1 (0.6)
Graft Loss	0	0
Lost to Follow-up	0	1(0.6)
Graft Loss or Death or Lost to Follow-up	2 (1.2)	2 (1.2)
	95% CI of LCP-Tacro - Prograf: 0%(-3.4%, 3.4%)	
Graft Loss or Death	2 (1.2)	1(0.6)
Lost to Follow-up	0	1(0.6)

The LCP-Tacro test arm has slightly better results using the central read BPAR as opposed to the local read BPAR results. In the proposed label, the sponsor presented the efficacy failure results of study 3001 using central read BPAR. By the protocol and the SAP, the diagnosis of BPAR (Banff grade $\geq 1A$) would be based on local histological grading using the Banff criteria for renal allograft pathology. Blinded central review of the biopsies would also be performed at the end of the study but would not be used in the primary analysis of the composite variable. Although central reading is generally considered less biased, this reviewer recommend to use the local read BPAR results in the label because the use of local read BPAR for the primary analysis was pre-specified in the protocol and the SAP.

For study 3001, 4 patients (2 in each arm) were identified as having had BPAR by local lab biopsy results that contributed to the efficacy failure events. Five (1 in LCP-Tacro arm and 4 in Prograf arm) patients were identified as BPAR by central laboratory biopsy results. Contrary to other transplant studies but same as for Study 3002, the central lab identified more BPAR events than the local labs did in Study 3001.

3.3 Evaluation of Safety

3.3.1 Estimated Glomerular Filtration Rate (eGFR)

Study 3002

Renal function measured by eGFR at 12-month post-transplantation was typically considered as a safety endpoint in transplant studies. Mean change from Baseline (Day 30) in estimated GFR as calculated using abbreviated MDRD7 formula at Months 3, 6, and 12 was specified as a secondary endpoint in the protocol LCP-Tacro 3002. Incidence of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ was one of the primary safety endpoints specified in the protocol. The sponsor's proposed imputation methods for missing eGFR is described in 3.2.1.2.

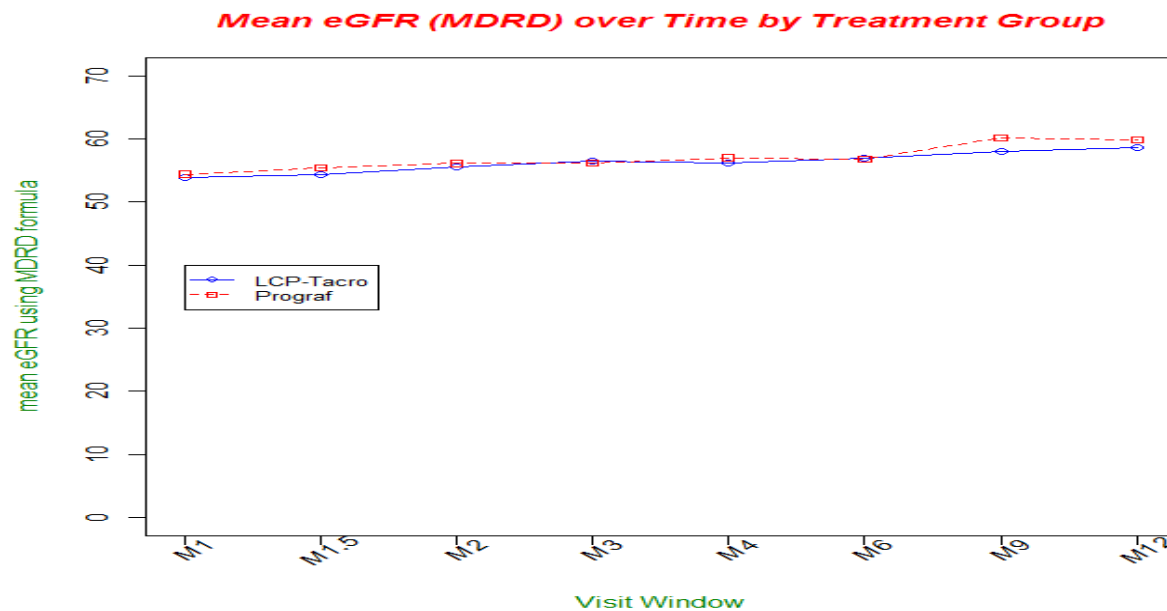
A summary of the estimated GFR at baseline, Months 3, 6 and 12 by treatment groups are provided in Table 15. The mean estimated GFR values (without imputations) over different study visit windows within 12 months by treatment groups are shown in Figure 4. Mean eGFR were similar in both treatment groups up through Month 6, and slightly greater in the Prograf group compared with the LCP-Tacro group at Months 9 and 12, but no statistically significant difference between the groups. Two imputation methods were performed by this reviewer, one imputing the estimated GFR as 0 for patients who had graft loss or died, the other imputing GL/D to 0 and all other missing values as 15. The results for these two imputation methods were also listed in Table 15. The conclusion from these two imputation methods are the same as from the analysis without imputation.

Table 15 Summary of eGFR at Baseline, Months 3, 6 and 12 by Treatment Group (ITT Population)

Visit	LCP-Tacro (N=268)	Prograf (N=275)	p-value*
No imputation			
Baseline (Day 30)			0.7733
N	241	249	
Mean (SD)	53.8 (19.7)	54.4 (20.5)	
Median (range)	52 (9-140)	54 (7 – 117)	
Month 3			0.9242
N	235	246	
Mean (SD)	56.4 (18.1)	56.2 (20.1)	
Median (range)	54 (7-147)	54 (9-164)	
Month 6			0.8855
N	225	233	
Mean (SD)	57.0 (18.4)	56.8 (19.2)	
Median (range)	55 (10-122)	56 (18-123)	
Month 12			0.3997
N	218	228	
Mean (SD)	58.2 (18.8)	59.8 (20.6)	
Median (range)	59 (7-130)	59 (9-122)	
Imputing GL/D →0			0.6358
Baseline (Day 30)			
Mean (SD)	53.2 (20.4)	52.3 (22.7)	
Median (range)	51 (0 –140)	53 (0 – 117)	
Month 3			0.4739
Mean (SD)	55.0 (20.0)	53.6 (22.9)	
Median (range)	54 (0 – 147)	53 (0 – 164)	
Month 6			0.6882
Mean (SD)	54.3 (21.7)	53.5 (22.8)	
Median (range)	54 (0 – 122)	54 (0 – 123)	
Month 12			0.8287
Mean (SD)	54.9 (22.7)	55.4 (25.2)	
Median (range)	58 (0 – 130)	56.5 (0 – 122)	
Imputing missing → 15 and GL/D →0			0.8646
Baseline (Day 30)			
Mean (SD)	49.8 (22.3)	50.1 (23.7)	
Median (range)	50.0 (0 – 140.0)	51.0 (0-117.)	
Month 3			0.8952
Mean (SD)	50.9 (22.4)	51.2 (24.1)	
Median (range)	51(0-147)	52(0 – 164)	
Month 6			0.9853
Mean (SD)	49.6 (24.0)	49.6 (24.5)	
Median (range)	51 (0 – 122)	52 (0 – 123)	
Month 12			0.4400
Mean (SD)	49.4 (25.2)	51.1 (26.9)	
Median (range)	53 (0-130)	51 (0 – 122)	

* For comparison of mean eGFR between the two groups.

Figure 4 Mean estimated GFR over time by Treatment Group – Study 3002



To assess if different values of mean GFR at Months 3, 6 and 12 were due to any baseline imbalances, change of GFR from baseline to Month 12 was assessed. Table 16 shows change of GFR from baseline at Months 3, 6 and 12 (Month 3, 6, 12 – baseline). Two imputation methods were performed by the reviewer, one imputing the estimated GFR as 0 for patients who had graft loss or died, the other imputing GL/D to 0 and all other missing values as 15. Note that when imputing GL/D to 0 and all other missing values as 15, both 6 month and 12 month mean GFR were lower than the average GFR at baseline. There were no statistically significant difference for mean change of GFR from baseline at Months 3, 6 and 12 (Month 3, 6, 12 – baseline) between the two treatment groups with and without imputations.

Table 16 Change of eGFR from Baseline at Months 3, 6 and 12 by Treatment Group (ITT Population)

Visit	LCP-Tacro (N=268)	Prograf (N=275)	p-value*
No imputation			
Month 3			0.6459
N	235	246	
Mean (SD)	2.0 (11.8)	1.5 (12.5)	
Median (range)	1.5 (-59, 37)	2.0 (-45, 47)	
Month 6			0.5711
N	225	233	
Mean (SD)	2.3 (15.1)	1.5 (12.5)	
Median (range)	3.5 (-67, 44)	2.0 (-43, 32)	
Month 12			0.2023
N	218	228	
Mean (SD)	2.7 (16.0)	4.6 (13.8)	
Median (range)	3.0 (-64, 48)	5.0 (-54, 46)	
Imputing GL/D ->0			
Month 3			0.5568
Mean (SD)	1.9 (11.7)	1.3 (12.4)	
Median (range)	1.0 (-59, 37)	1.0 (-45, 47)	
Month 6			0.9633
Mean (SD)	1.2 (16.3)	1.2 (12.4)	
Median (range)	3.0 (-67, 44)	1.0 (-43, 32)	
Month 12			0.1316
Mean (SD)	1.3 (17.5)	3.5 (14.7)	
Median (range)	2.0 (-64, 48)	4.0 (-66, 46)	
Imputing missing -> 15 and GL/D ->0			
Month 3			0.9528
Mean (SD)	1.2 (14.5)	1.1 (14.5)	
Median (range)	0 (-59, 64)	1.0 (-71, 56)	
Month 6			0.8018
Mean (SD)	-0.1 (18.5)	-0.5 (16.3)	
Median (range)	0 (-67, 64)	0 (-71, 65)	
Month 12			0.4087
Mean (SD)	-0.3 (20.6)	1.0 (18.5)	
Median (range)	0(-64, 72)	2.0 (-78, 54)	

* For comparison of mean eGFR between the two groups.

Sponsor reported that the treatment differences in the eGFR change from baseline at Month 3, 6, and 12 were not statistically significant when using nonparametric ANCOVA based on imputed eGFR values after the multiple imputation method was implemented. An exploratory analysis of

eGFR by repeated measure linear mixed model adjusting for the effects of race, group, and baseline was used to test the treatment effects in eGFR change from baseline based on imputed complete data for Months 3, 6, 9, and 12. The result of this model is shown in Table 17 below (taken from Table 14.3.7.5 of the study report). The study report also states that no significant differences for eGFR were found using other imputation methods proposed in the SAP, as described in Section 3.2.1.2.

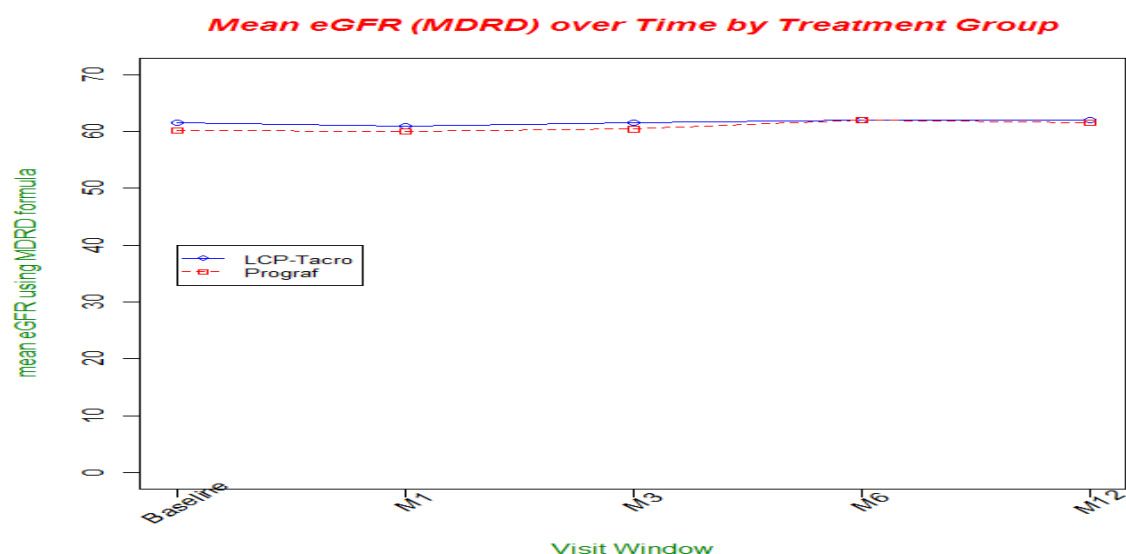
Table 17 Repeated Measures Linear Model Analysis of imputed eGFR by multiple imputation method

Effect	Estimate	95% CI	S. E.	P-value
Mean of Intercept	11.523	(7.326, 15.721)	2.132	<0.001
Treatment (LCP-Tacro – Prograf)	1.482	(-1.187, 4.152)	1.358	0.276
Race group (Black – non-black)	1.497	(-3.092, 6.086)	2.332	0.521
Baseline eGFR	-0.214	(-0.283, -0.145)	0.035	<0.001
Time	0.875	(0.384, 1.367)	0.249	<0.001
Treatment*Time	-0.240	(-0.570, 0.090)	0.167	0.153
Baseline*Time	-0.008	(-0.017, 0.000)	0.004	0.052

Study 3001

Figure 5 shows the mean observed estimated GFR values over different study visit windows within 12 months by treatment groups. The dataset ADGFR.xpt contains GFR values only at baseline (randomization), Months 1, 3, 6 and 12. There were no statistically significant differences for mean change of GFR from baseline at Month 1($p=0.4522$), Month 3($p=0.5005$), Month 6 ($p=0.3536$) and Month 12 ($p=0.7227$) between the two treatment groups. The p-values were obtained via two sample t test.

Figure 5 Mean estimated GFR over time by Treatment Group – Study 3001



3.3.2 New-Onset Diabetes Mellitus (NODM)

The onset of diabetes post transplant is a safety issue of concern after kidney transplantation. The condition is usually referred to as NODAT (New Onset Diabetes). The sponsor used NODM in the study report. NODM is defined by the composite occurrence of fasting plasma glucose (FPG) values ≥ 126 mg/dL, new onset of insulin use for ≥ 31 days, need for an oral hypoglycemic, and/or HbA_{1c} $\geq 6.5\%$ among kidney transplant patients with no medical history of diabetes. Per protocol, patients were at risk if they had no diabetes in medical history, baseline FPG < 126 mg/dL, no prior use of hypoglycemic agents or insulin for diabetes conditions, and baseline HbA_{1c} $< 6.5\%$ before the first dose. The data in Table 18 is extracted from Table 14.3.8 of Study report 3002. There are no statistically significant difference of NODM occurrence between the two groups. There are also no significant difference of each component of NODM between the two treatment groups.

Table 18 Incidence of New Onset Diabetes Mellitus (NODM) Within 12 Months After Randomization (ITT set)

	LCP-Tacro n (%) N=268	Prograf n (%) N=275
Patients at risk for NODM	88	74
Patients with NODM	18/88 (20.5)	11/74 (14.9)
Fasting Plasma Glucose Values ≥ 126 mg/dL on 2 consecutive occurrences	7/88 (8.0)	8/74 (10.8)
HbA _{1c} $\geq 6.5\%$	11/88 (12.5)	6/74 (8.1)
Insulin Use ≥ 31 days	1/88 (1.1)	3/74 (4.1)
Use of Oral Hypoglycemic Agent	6/88 (6.8)	4/74 (5.4%)

3.3.3 Other Common AEs

The following is a brief summary of adverse events reported in the study report. For overview of the safety results, please see details in the clinical review by the medical officer Dr. Velidedeoglu.

Table 19 summarizes the adverse events that occurred in $>10\%$ of LCP-Tacro patients in study 3002 through one year. The corresponding event rates in Study 3001 is also included in the Table. The information is extracted from Table 14.3.2.2 of the study report 3002 and Table 14.3.1.2 of Study report 3001. The most commonly reported AEs for LCP-Tacro patients were diarrhea, anemia, urinary tract infection, hypertension, tremor and diabetes mellitus. The event rates between the two treatment groups are comparable.

Table 19 Adverse Reactions Occurring in ≥ 10 % of LCP-Tacro-Treated Kidney Transplant Patients in Study 3002 through 1 Year of Treatment and Corresponding Event Rate in Study 3001

Adverse Reaction*	Study 3002		Study 3001	
	LCP-Tacro n (%) N=268	Prograf n (%) N=275	LCP-Tacro n (%) n=162	Prograf N(%) N=162
Diarrhea	82 (30.6)	92 (33.5)	22 (13.6%)	15 (9.3%)
Anemia	70 (26.1)	79 (28.7)	4 (2.5%)	1 (0.6%)
Urinary tract infection	66 (24.6)	67 (24.4)	14 (8.6%)	22 (13.6%)
Hypertension	62 (23.1)	62 (22.5)	7 (4.3%)	10 (6.2%)
Tremor	51 (19.0)	46 (16.7)	4 (2.5%)	2 (1.2%)
Constipation	49 (18.3)	67 (24.4)	7 (4.3%)	2 (1.2%)
Diabetes mellitus	44 (16.4)	37 (13.5)	7 (4.3%)	6 (3.7%)
Oedema peripheral	42 (15.7)	57 (20.7)	11 (6.8%)	10 (6.2%)
Hyperkalaemia	40 (14.9)	30 (10.9)	5 (3.1%)	2 (1.2%)
Headache	39 (14.6)	26 (9.5)	15 (9.3%)	11 (6.8%)
Hypophosphataemia	36 (13.4)	42 (15.3)	3 (1.9%)	0
Leukopenia	36 (13.4)	38 (13.8)	4 (2.5%)	3 (1.9%)
Insomnia	35 (13.1)	29 (10.5)	3 (1.9%)	1 (0.6%)
Blood creatinine increased	32 (11.9)	37 (13.5)	20 (12.3%)	14 (8.6%)
Hypokalaemia	32 (11.9)	33 (12.0)	3 (1.9%)	2 (1.2%)
Hypomagnesaemia	32 (11.9)	32 (11.6)	3 (1.9%)	2 (1.2%)
Hyperglycaemia	29 (10.8)	33 (12.0)	2 (1.2%)	0

*A patient reporting more than 1 adverse event within a system organ class or preferred term is counted only once at that level of summarization

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses in this section will be focused on the *De Novo* Study 3002. There were very few events in Study 3001 to allow meaningful subgroup analyses. Unless otherwise noted in this section, the confidence intervals are constructed using a normal approximation and P-values were based on a Chi-square test.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analysis of the efficacy endpoints by gender is presented in Table 20. The efficacy failure rates among males were slightly higher (21.3%) in the LCP-Tacro group than the failure rate (19.3%) in the Prograf group. Among females, the efficacy failure rate in the LCP-Tacro arm was lower (13.8%) than the failure rate in the Prograf arm (20.2%). The difference was not statistically significant ($p=0.2443$, chi-square test). The failure rate for GL/D/LTFU was also lower in the LCP- Tacro arm (7.4%) than in the Prograf arm (11.7%) among females.

Table 20 Efficacy Outcome by Gender

Number of Patients (%)	Males N=355		Females N=188	
	LCP-Tacro N=174	Prograf N=181	LCP-Tacro N=94	Prograf N=94
Efficacy Failure	37 (21.3)	35 (19.3)	13 (13.8)	19 (20.2)
GL/D/LTFU	12 (6.9)	12 (6.6)	7 (7.4)	11 (11.7)
GL/D	10 (5.7)	10 (5.5)	5 (5.3)	8 (8.5)
BPAR	27 (15.5)	25 (13.8)	9 (9.6)	12 (12.8)
Death	5 (2.9)	5 (2.8)	3 (3.2)	3 (3.2)
Graft loss	5 (2.9)	6 (3.3)	4 (4.3)	5 (5.3)
LTFU	2 (1.1)	2 (1.1)	2 (2.1)	3 (3.2)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-6.4%, 10.3%)		(-17.1%, 4.3%)	
p-value	0.6517		0.2443	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-5.0%, 5.5%)		(-12.6%, 4.1%)	
p-value	0.9203		0.3215	

Subgroup analysis of the efficacy endpoints by Age is presented in Table 21. Age is categorized by <65 and ≥ 65 . There were more younger than 65 (252 vs 247) and fewer older than 65 patients (16 vs 28) were assigned to the test drug LCP-Tacro arm than to the Prograf control arm. This distribution of the patients is to the advantage of the test group. Among patients younger than 65 years of age, the efficacy failure rates were the same (19.4%) for the two treatment groups. Among older than 65 years patients, the efficacy failure rate was lower in the LCP-Tacro test arm (1/16=6.3%) than in the Prograf control arm (6/28=21.4%). The difference was not statistically significant ($p=0.2263$, Fisher's Exact test).

Table 21 Efficacy Outcome by Age Category

Number of Patients (%)	Age (<65) N=499		Age (≥ 65) N=44	
	LCP-Tacro N=252	Prograf N=247	LCP-Tacro N=16	Prograf N=28
Efficacy Failure	49 (19.4)	48 (19.4)	1 (6.3)	6 (21.4)
GL/D/LTFU	18 (7.1)	19 (7.7)	1 (6.3)	4 (14.3)
GL/D	14 (5.6)	15 (6.1)	1 (6.3)	3 (10.7)
BPAR	35 (13.9)	34 (13.8)	1 (6.3)	3 (10.7)
Death	7 (2.8)	5 (2.0)	1 (6.3)	3 (10.7)
Graft loss	8 (3.2)	10 (4.0)	1 (6.3)	1 (3.6)
LTFU	4 (1.6)	4 (1.6)	0 (0)	1 (3.6)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-6.9%, 7.0%)		(-35.5%, 10.8%)*	
p-value	0.9975		0.2263**	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-5.1%, 4.0%)		(-27.5%, 16.6%)*	
p-value	0.8148		0.4533**	

* Confidence interval constructed using the exact method.

** P-value based on Fisher's exact test.

Subgroup analysis of the efficacy endpoints by race (White, Black and Other) is presented in Table 22. Race (black vs non-black) was one of the stratification factors at randomization. The majority of the patients in the study were white (417/543=76.8%). The results between the two treatment groups appear to be similar for white and other groups of patients. For black patients, the failure rate was lower (3/10=30%) in the LCP-Tacro arm than in the Prograf arm (6/15=40%). The difference was not statistically significant (p=0.6426).

Table 22 Efficacy Outcome by Race

Number of Patients (%)	White N=417		Black N=25		Other N=101	
	LCP-Tacro N=203	Prograf N=214	LCP-Tacro N=10	Prograf N=15	LCP-Tacro N=55	Prograf N=46
Efficacy Failure	37 (18.2)	40 (18.7)	3(30.0)	6 (40.0)	10 (18.2)	8 (17.4)
GL/D/LTFU	15 (7.4)	17 (7.9)	2 (20.0)	3 (20.0)	2 (3.6)	3 (6.5)
GL/D	11 (5.4)	14 (6.5)	2 (20.0)	1 (6.7)	2 (3.6)	3 (6.5)
BPAR	25 (12.3)	27 (12.6)	2 (20.0)	3 (20.0)	9 (16.4)	7 (15.2)
Death	6 (3.0)	6 (2.8)	2 (20.0)	0 (0)	0 (0)	2 (4.3)
Graft loss	6 (3.0)	8 (3.7)	1 (10.0)	1 (6.7)	2 (3.6)	2 (4.3)
LTFU	4 (2.0)	3 (1.4)	0 (0)	2 (13.3)	0 (0)	0 (0)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-7.9%, 7.0%)		(-46.1%, 30.0%)*		(-14.2%, 15.8%)	
p-value	0.9026		0.6426**		0.9177	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-5.7%, 4.6%)		(-31.8%, 37.8%)*		(-15.2%, 7.3%)*	
p-value	0.8315		1.000**		0.6055**	

* Confidence interval constructed using exact method.

** P-value based on Fisher's exact test.

Subgroup analysis of the efficacy endpoints by region (US vs non-US) is presented in Table 23. There were 137 US patients randomized in the study. Of the 137 US patients, 67 were assigned to the LCP-Tacro group and 70 were assigned to the Prograf control group. There were 406 non-US patients randomized in the study, of which, 201 were assigned to LCP-Tacro group and 205 were assigned to the Prograf control group. The efficacy failure rates among US patients were slightly higher (17.9%) in the LCP-Tacro group than in the Prograf group (14.3%). Among non-US patients, the failure rate for LCP-Tacro arm was lower 18.9% compared with failure rate for Prograf arm (21.5%).

Table 23 Efficacy Outcome by Region (US vs non-US)

Number of Patients (%)	US N=137		Non-US N=406	
	LCP-Tacro N=67	Prograf N=70	LCP-Tacro N=201	Prograf N=205
Efficacy Failure	12 (17.9)	10 (14.3)	38 (18.9)	44 (21.5)
GL/D/LTFU	4 (6.0)	4 (5.7)	15 (7.5)	19 (9.3)
GL/D	4 (6.0)	3 (4.3)	11 (5.5)	15 (7.3)
BPAR	9 (13.4)	7 (10.0)	27 (13.4)	30 (14.6)
Death	4 (6.0)	1 (1.4)	4 (2.0)	7 (3.4)
Graft loss	1 (1.5)	2 (2.9)	8 (4.0)	9 (4.4)
LTFU	0 (0)	1 (1.4)	4 (2.0)	4 (2.0)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-8.7%, 15.9%)		(-10.4%, 5.2%)	
p-value	0.5635		0.5210	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-9.0%, 9.6%)*		(-7.2%, 3.6%)	
p-value	0.9998**		0.5114	

*Confidence interval constructed using exact method.

** P-value based on Fisher's exact test.

The study report presented the subgroup analysis stratified by geographic region defined as US, Europe, Latin America and Asia Pacific, as shown in Table 24. Efficacy failure rate in Latin America was noticeably lower for the LCP-Tacro arm (14%) compared with the rate for the Prograf arm (28.8%). The difference though was borderline not significant (p=0.05296). In Asia Pacific region, the efficacy failure rate was higher in the LCP-Tacro arm (50%) compared with the Prograf arm (33.3%). The difference was not statistically significant (p=0.3625). The efficacy results for Europe were similar between the two treatment groups.

Table 24 Efficacy Outcome by Region (as defined in the Study Report)

No. of Patients (%)	US N=137		Europe N=261		Latin America N=116		Asia Pacific N=29	
	LCP-Tacro N=67	Prograf N=70	LCP-Tacro N=130	Prograf N=131	LCP-Tacro N=57	Prograf N=59	LCP-Tacro N=14	Prograf N= 15
Efficacy Failure	12(17.9)	10(14.3)	23(17.7)	22(16.8)	8(14.0)	17(28.8)	7(50.0)	5(33.3)
GL/D/LTFU	4(6.0)	4(5.7)	12(9.2)	12(9.2)	8(14.0)	7(11.9)	0(0)	0(0)
GL/D	4(6.0)	3(4.3)	8(6.2)	10(7.6)	3(5.3)	5(8.5)	0(0)	0(0)
BPAR	9(13.4)	7(10.0)	14(10.8)	12(9.2)	6(10.5)	13(22.0)	7(50.0)	5(33.3)
Death	4(6.0)	1(1.4)	3(2.3)	4(3.1)	1(1.8)	3(5.1)	0(0)	0(0)
Graft loss	1(1.5)	2(2.9)	6(4.6)	6(4.6)	2(3.5)	3(5.1)	0(0)	0(0)
LTFU	0(0)	1(1.4)	4(3.1)	2(1.5)	0(0)	2(3.4)	0(0)	0(0)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-8.7%, 15.9%)		(-8.3%, 10.1%)		(-29.4%,-0.1%)		(-18.8%, 52.1%)	
p-value	0.5635		0.8476		0.05296		0.3625	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-9.0%, 9.6%)*		(-6.9%, 7.1%)		(-10.1%, 14.4%)		(-21.7%,23.3%)*	
p-value	0.9998**		0.9843		0.7276		1.000**	

*Confidence interval constructed using exact method.

**P-value based on Fisher's exact test.

4.2 Other Special/Subgroup Populations

Table 25 presents efficacy analyses stratified by donor type. One patient did not have donor type information in the dataset ADTP.xpt. There were slightly more patients with a living donor(135 vs 129) and fewer patients with a deceased donor(133 vs 145) were assigned to the test drug LCP-Tacro arm than to the Prograf control arm. Note that this is to the advantage of the LCP-Tacro test arm. Among patients with a living donor, the efficacy failure rate was lower in the LCP-Tacro group (14.8%) than the failure rate in the Prograf group (19.4%). Among patients with a deceased donor, the failure rates were slightly higher in the LCP-Tacro arm (22.6% vs 20%).

Table 25 Efficacy Results by Donor Type

Number of Patients (%)	Living Donor N=264		Deceased Donor N=278	
	LCP-Tacro N=135	Prograf N=129	LCP-Tacro N=133	Prograf N=145
Efficacy Failure	20 (14.8)	25 (19.4)	30 (22.6)	29 (20.0)
GL/D/LTFU	4 (3.0)	8 (6.2)	15 (11.3)	15 (10.3)
GL/D	4 (3.0)	6 (4.7)	11 (8.3)	12 (8.3)
BPAR	17 (12.6)	19 (14.7)	19 (14.3)	18 (12.4)
Death	2 (1.5)	3 (2.3)	6 (4.5)	5 (3.5)
Graft loss	2 (1.5)	3 (2.3)	7 (5.3)	8 (5.5)
LTFU	0 (0)	2 (1.6)	4 (3.0)	3 (2.1)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-13.6%, 4.6%)		(-7.1%, 12.2%)	
p-value	0.3241		0.6026	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-8.3%, 1.8%)		(-6.4%, 8.2%)	
p-value	0.2067		0.8022	

As discussed in 3.2.1.3, for the first two weeks, mean tacrolimus trough levels were significantly higher in the LCP-Tacro arm than in the Prograf control arm. To explore if there is a treatment effect for the initial different trough level, the reviewer performed a subgroup analysis stratified by Day 2 trough level (median = 6.6 as cutoff) as shown in Table 26. Day 2 trough level was chosen since it was the earliest trough level recorded in the datasets. Note that only subjects who had Day 2 trough level recorded in dataset ADLTAC.xpt are included for this analysis. There were noticeably fewer LCP-Tacro patients who had Day 2 tacrolimus trough level <6.6 (53 or 28.3% compared with 134 or 71.7% Prograf patients). Among the patients who had Day 2 tacrolimus trough level ≤6.6, the LCP-Tacro arm had better efficacy outcome (efficacy failure rates 13.2% vs 20.1%) compared to the Prograf control. The difference was not statistically significant (P=0.2674). Among the patients who had tacrolimus trough level >6.6, the Prograf arm had better efficacy results (efficacy failure rates 13.8% vs 19.8%) compared with the LCP-Tacro arm. This difference was also not statistically significant (p=0.3235).

Table 26 Subgroup Analysis by Day 2 Local Tacrolimus Trough level

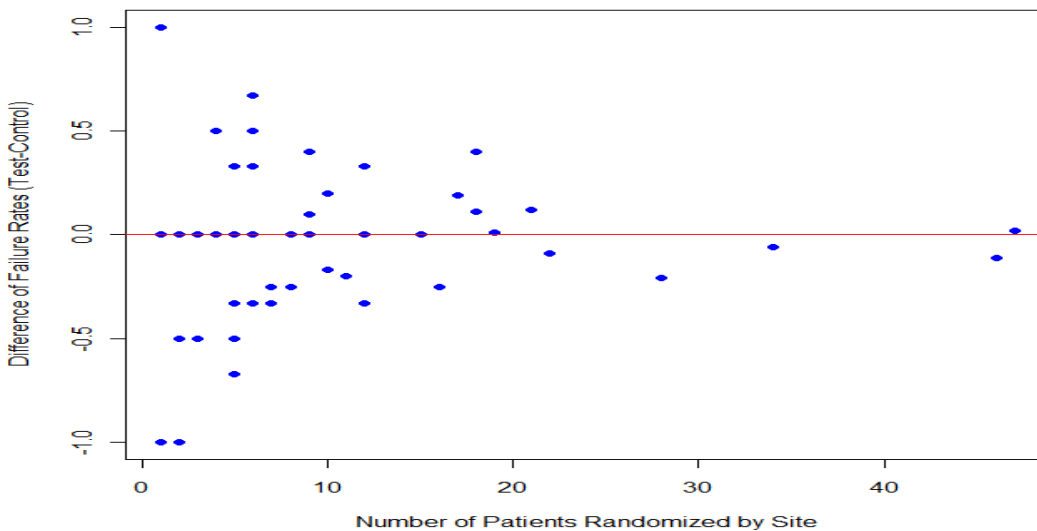
Number of Patients (%)	Day 2 Trough level ≤ 6.6 N= 187		Day 2 Trough level >6.6 N= 179	
	LCP-Tacro N=53	Prograf N=134	LCP-Tacro N=121	Prograf N=58
Efficacy Failure	7 (13.2)	27 (20.1)	24 (19.8)	8 (13.8)
GL/D/LTFU	3 (5.7)	10 (7.5)	12 (9.9)	3 (5.2)
GL/D	1 (1.9)	9 (6.7)	11 (9.1)	3 (5.2)
BPAR	5 (9.4)	20 (14.9)	15 (12.4)	6 (10.3)
Death	0(0)	4 (3.0)	7 (5.8)	2 (3.4)
Graft loss	1 (1.9)	6 (4.5)	5 (4.1)	1 (1.7)
LTFU	2 (3.8)	1 (0.7)	1 (0.8)	0 (0)
95% CI of Efficacy Failure (LCP-Tacro - Prograf)	(-18.3%, 4.4%)		(-5.3%, 17.4%)	
p-value	0.2674		0.3235	
95% CI of GL/D/LTFU (LCP-Tacro - Prograf)	(-9.0%, 9.0%)*		(-5.1%, 12.6%)*	
p-value	0.7322**		0.3093**	

*Confidence interval constructed using exact method.

**P-value based on Fisher's exact test.

In Study 3002, randomization was stratified by site and race. Subgroup analysis by race was discussed in Section 4.1. Figure 6 below shows the difference of efficacy failure rates between the two groups (LCP-Tacro – Prograf) for each site. For sites with total number of patients <15, the difference of failure rates appear to be evenly distributed by 0. For sites with close to 20 patients, the LCP-Tacro arm appears to have higher failure rate. For sites with >20 patients, the Prograf arm has higher failure rate.

Figure 6 Difference of Failure Rates by Site



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Both Studies 3001 and 3002 were designed as non-inferiority study. The original Protocol LCP-Tacro 3002 was submitted as an SPA. The SPA submissions included information to justify the 10% NI margin. In the SPA Agreement letter to the sponsor dated August 5, 2010, the Division agreed to the proposed 10% NI margin and also requested for further details regarding the NI margin sensitivity analyses. During the pre-NDA meeting held on August 7, 2013, the Agency requested that the NDA submission includes the materials previously submitted to justify the NI margin for Study 3002 as well as information to justify the NI margin for Study 3001 and also include responses to our comments in August 5, 2010 SPA Agreement letter asking for further details regarding the NI margin sensitivity analyses. The sponsor addressed these comments in this NDA submission. Please see Appendix I for details regarding the sponsor's responses as well as the NI margin justification included in the SPA request. In this reviewer's opinion, the justification for the 10% NI margin for Study 3002 is appropriate.

For Study 3001, the ^{(b) (4)} NI margin was proposed based on the following ^{(b) (4)} assumptions:

^{(b) (4)}

The draft guidance for Non-Inferiority Clinical Trials states that M1 should be based on the treatment effect estimated from the historical experience with the active control drug, which means that the justification needs to be data driven. The NI margin justification above clearly is not acceptable. Because the proposed NI margin is not justified, there is no basis for a noninferiority claim for study 3001.

5.2 Collective Evidence

This NDA submission contains two phase 3 studies. Study 3002 was conducted in de novo kidney transplant patients, which is considered as a pivotal study. Study 3001 was conducted in stable renal transplant patients, which is considered supportive. Due to the different study design and different study population, a pooled analysis would not be interpretable. Each study was evaluated separately.

For Study 3002, using the sponsor's efficacy analysis dataset, the incidence rate for efficacy failure was slightly lower for the LCP-Tacro group (18.3%) than the incidence rate for the Prograf group (19.6%), with a difference between the two groups (LCP-Tacro – Prograf) of -1.3% and 95% confidence interval of (-7.9%, 5.2%). This confidence interval was constructed using normal approximation. The upper bound of this CI is smaller than the pre-specified NI margin of 10%. The protocol states the 95% CI for the difference in treatment failure rates would be calculated using (b) (4) (b) (4)

The final version of the SAP (Version 6, submission date 8/28/2012) changed the method to Newcombe-Wilson Score method. There are only minor differences between the reviewer's and the sponsor's analyses results and that the interpretation of the results do not change based on the method used.

One additional patient (patient ID 034154017) in the LCP-Tacro arm is included as an efficacy failure event since a rejection occurred within the 12 month study period, although the biopsy was performed 8 days later. The sponsor did not include this acute rejection event as an event for primary analysis for the reason that this rejection event occurred on Feb 25, 2013 and the biopsy was performed 8 days later on March 4, 2013, which happened to be Study Day 366, one day past the cut-off date for 12 month primary analysis. With the addition of an efficacy failure event in the LCP-Tacro arm, the 95% confidence interval of the difference between the two groups changes slightly to (-7.6%, 5.6%), from (-7.9%, 5.2%). The efficacy conclusion does not change with the addition of this one event in the test arm.

The incidence rate for the endpoint of graft loss/death/lost to follow-up was also lower for the test drug LCP-Tacro (7.1%) compared with the control Prograf (8.4%). The difference between the two groups on GL/Death/LTFU (LCP-Tacro – Prograf) is -1.3% with 95% CI of (-5.8%, 3.2%). For the individual components of the efficacy endpoint, incidence rate of BPAR, graft loss and rate of lost to follow-up were slightly lower in the LCP-Tacro arm than the Prograf arm. There were 8 deaths occurred in each arm.

There were very few events in the conversion study 3001 in stable kidney transplant patients. There were 4 efficacy failures in each treatment group based on local laboratory readings, with a 95% confidence interval of the difference of the efficacy failure rates between the two groups (-4.2%, 4.2%). The sponsor states in the study report that as the upper limit of the confidence intervals for the difference was below (b) (4) (the predefined non-inferiority margin in the original protocol) and hence LCP-Tacro successfully demonstrated non-inferiority compared to Prograf. However, given that the (b) (4) NI margin was never justified for this study as well as for stable kidney transplant patients in general, non-inferiority of LCP-Tacro to Prograf control cannot be claimed for Study 3001. There was no statistically significant difference of the efficacy failure rates between the two groups ($p=1.0000$, Fisher's exact test).

When central laboratory BPAR readings were used, the incidence of efficacy failure in the LCP-Tacro arm ($3/162=1.9\%$) was slightly lower compared with the Prograf control ($6/162=3.7\%$). The difference of the efficacy failure rates between the two groups (LCP-Tacro – Prograf) was -1.9% with a 95% C.I. of (-6.5%, 2.3%). There was no statistically significant difference of the efficacy failure rates between the two groups ($p=0.3389$, Fisher's exact test).

5.3 Conclusions and Recommendations

The efficacy results from Study 3002 in *de novo* kidney transplant patients demonstrated the noninferiority of LCP-Tacro, an extended- release formulation of tacrolimus given once daily, to Prograf twice daily, based on a 10% non-inferiority margin on efficacy failure (central read biopsy proven acute rejection, death, graft loss or lost to follow up). The incidence rates were comparable for each individual components of the efficacy failure endpoint (BPAR, death, graft loss, lost to follow up). Treatment differences were also comparable across many subgroups. There were no statistically significant treatment differences by subgroups considered in this review.

The efficacy results from Study 3001 in stable kidney patients were comparable between the LCP-Tacro group and the Prograf group. The sponsor attempted to claim non-inferiority of LCP-Tacro compared with Prograf for this study. The study was designed as a non-inferiority (NI) trial, however, the NI margin was not justified for this study as well as for conversion studies in general. As a result, there is no basis for a non-inferiority claim for Study 3001.

Estimated GFR values over time were comparable between the two treatment groups in both Study 3002 and Study 3001. There were no statistically significant difference for mean change of GFR from baseline at Months 3, 6 and 12 (Month 3, 6, 12 – baseline) between the two treatment groups with and without imputations for missing GFR values. The incidences of other AEs were also comparable between the two groups.

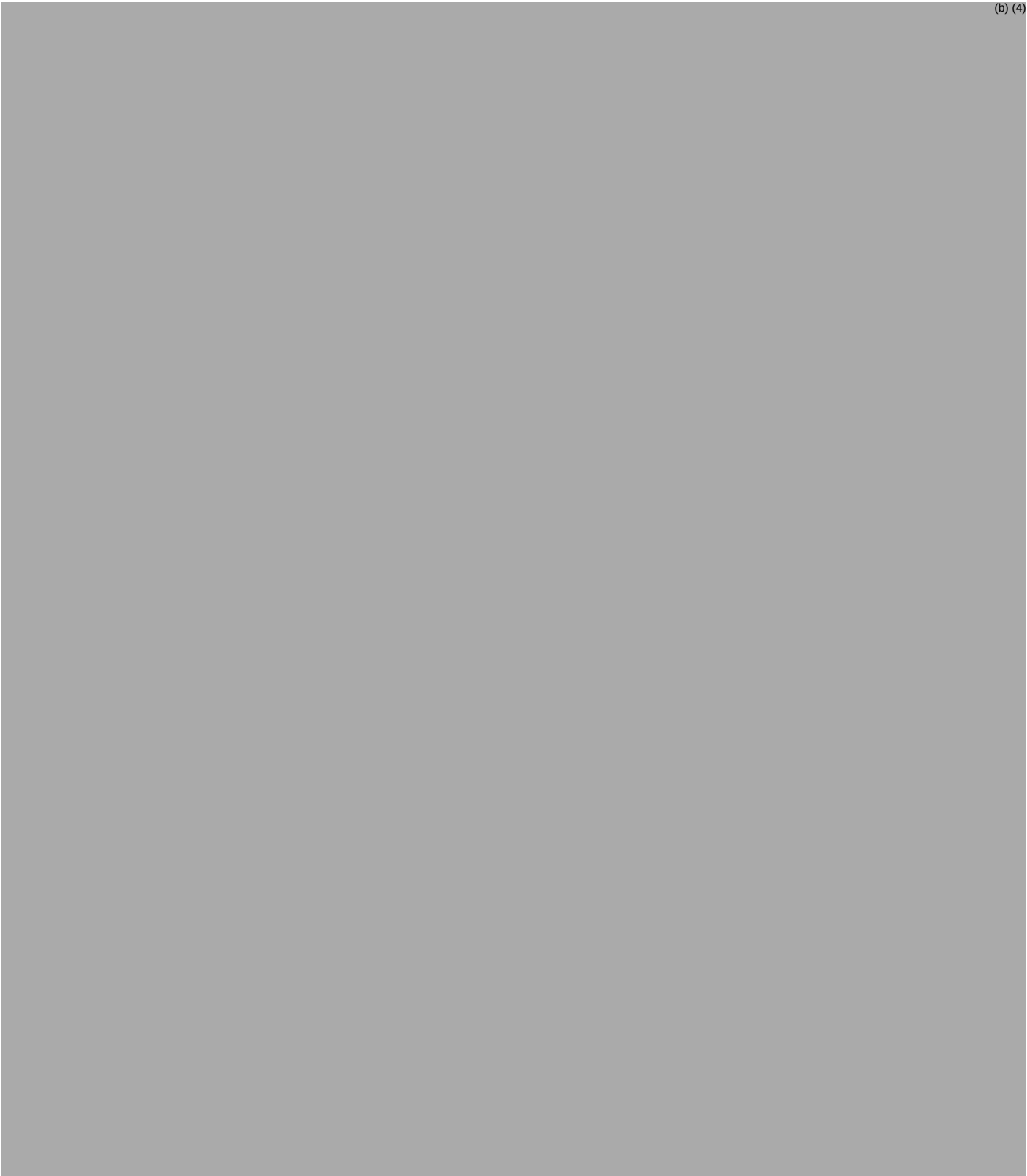
In the assessment of this reviewer, there is appropriate evidence for establishing effectiveness of LCP-Tacro for the indication of prophylaxis of organ rejection in patients receiving a kidney transplant.

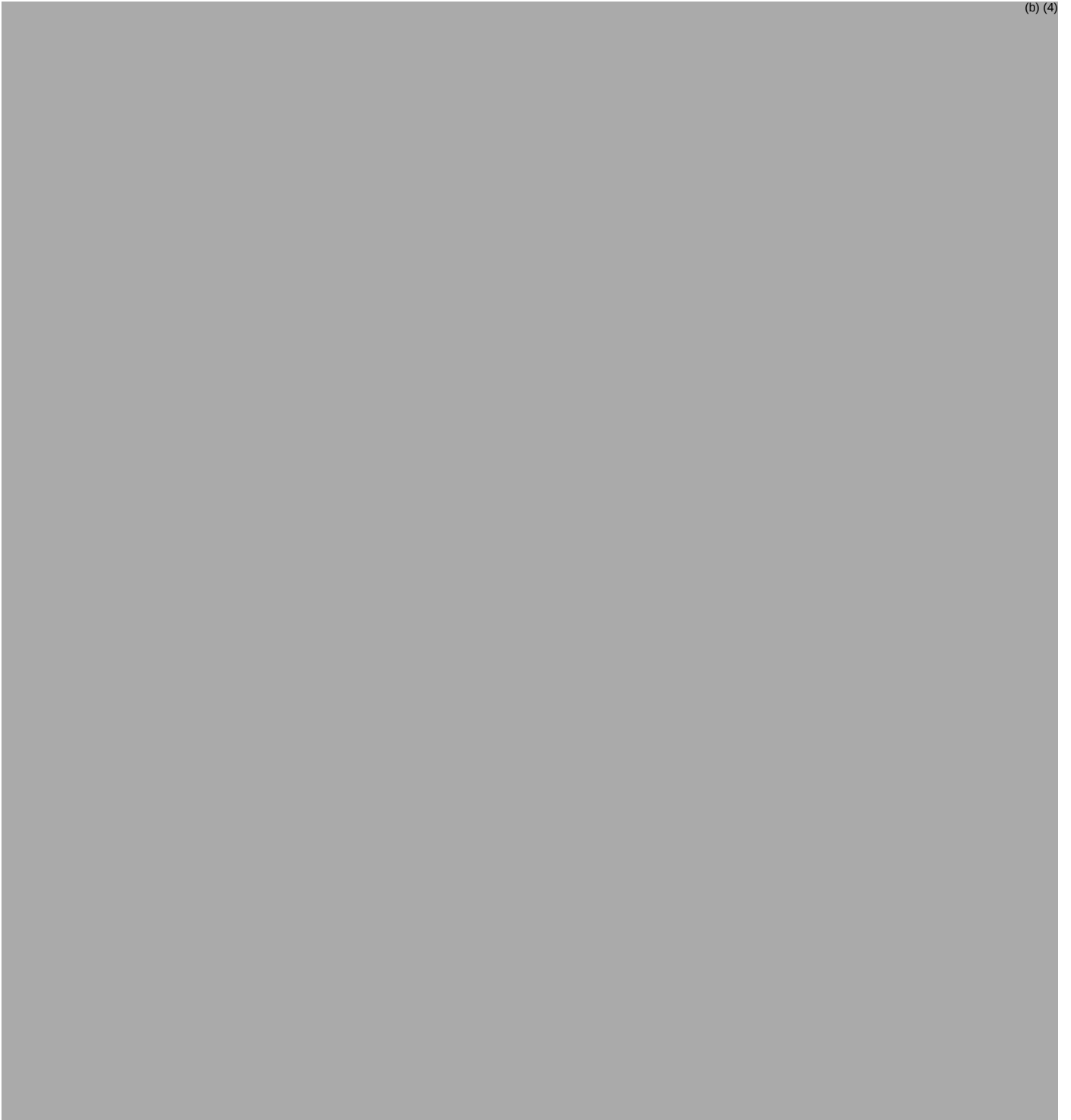
5.4 Labeling Recommendations (as applicable)

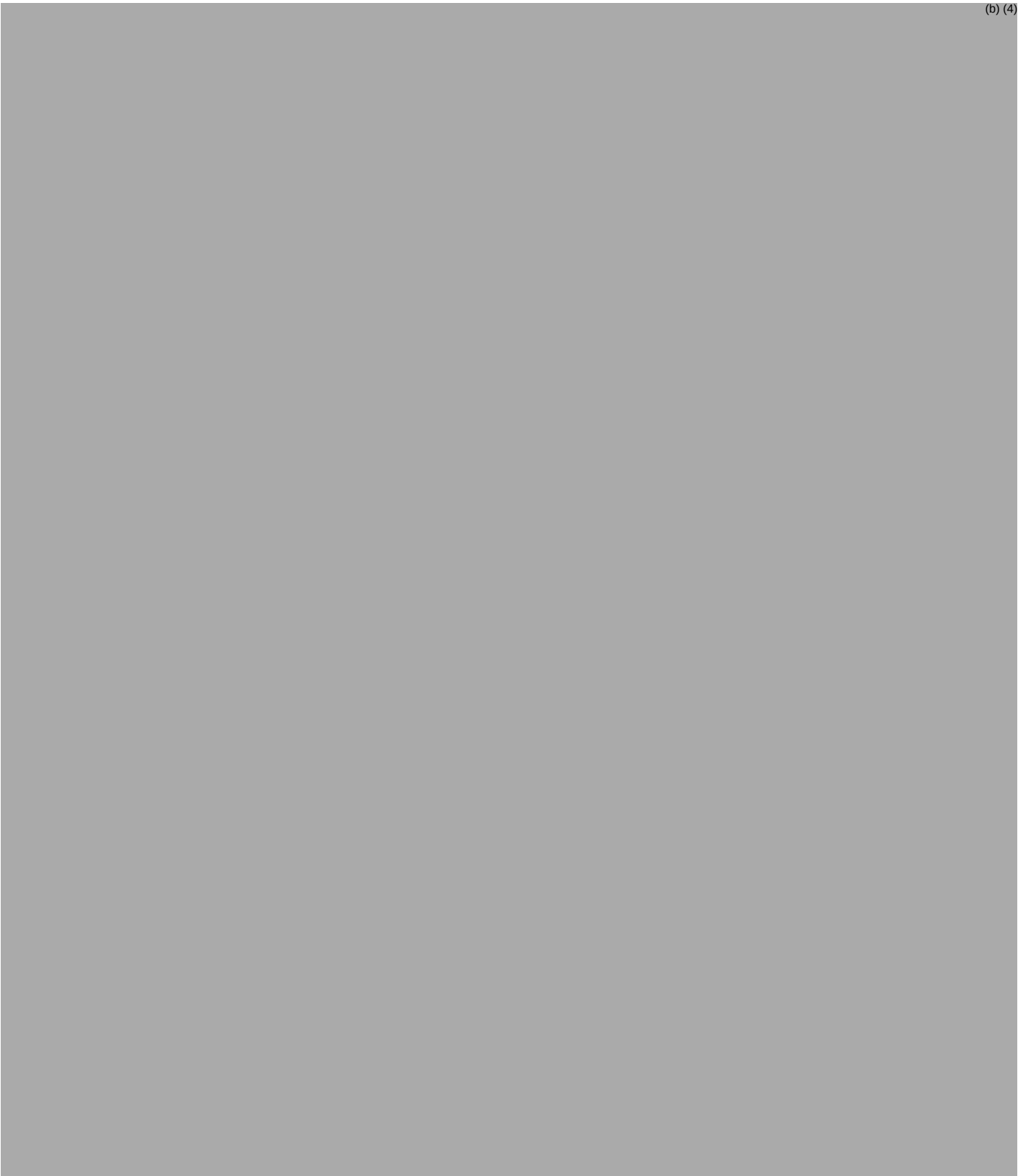
The statistical reviewer has the following labeling recommendations:

- Per DTOP convention, recommend deletion of statements (b) (4).

(b) (4)







Appendix 1 NI Margin Justification for Study 3002

The sponsor proposed a 10% NI margin for the primary efficacy endpoint of treatment failure defined as death, graft failure, BPAR, or loss to follow-up at month 12 post- transplant. The sponsor's NI margin justification was contained in the SPA request resubmission (IND 75250 SDN55). For a detailed review of the justification, please see statistical review for the NI margin justification by Dr. John Yap dated 8/11/2010 in DARRTS. Below is a summary of the key elements of the NI margin justification.

The following treatment arms were considered in the non-inferiority (NI) margin calculation:

Experimental: basiliximab (B) + MPA + corticosteroids (CS) + LCP-Tacro

Active control: basiliximab (B) + MPA + corticosteroids + Prograf

Putative placebo: basiliximab + MPA + corticosteroids

To assess the non-inferiority of LCP-Tacro compared to Prograf in Study 3002, the effect of active control compared to the putative placebo needs to be estimated using data from previously conducted clinical trials. Ten articles were chosen through a literature search that satisfied the following criteria:

1. *de novo* kidney transplantation in adult patients
2. 12-month outcome of BPAR available
3. One of the study arms identical to either the control or the putative placebo arm of current study except that induction could be either daclizumab (D) or basiliximab (B).

The sponsor also included Vincenti (2001) as recommended by the Division and the Symphony study (Ekberg, 2007). A total of 12 articles from 11 studies (there were 2 articles reported different sets of data from a single study) were used to perform the analysis.

The event rates extracted from each study are shown in Table below

ID	Article	Treatment Arm	Acute Rejection [1] Rate and 95% CI (%)	Efficacy Failure [1] Rate and 95% CI (%)
1	1 Vincenti (2001)	CS + D + MMF	53.1 (42.7, 63.2)	58.2 (47.8, 68.1)
2	30 Garcia (2007)	CS + D + MMF	48.5 (30.8, 66.5)	54.5 (36.4, 71.9)
3	34 Silva (2007)	CS + B + MMF + Tacro	7.5 (4.4, 12.0)	15.1 (10.6, 20.6)
4	3 Busque (2009)	CS + B + MMF + Tacro	9.5 (1.2, 30.4)	9.5 (1.2, 30.4)
5	77 Meulen (2004)	CS + D + MMF + Tacro	14.5 (9.8, 20.4)	NA
6	93 Ahsan (2002)	CS + D + MMF + Tacro	6.0 (1.3, 16.5)	6.0 (1.3, 16.5)
7	19 Ciancio (2008)	CS + D + MMF + Tacro	2.7 (0.3, 9.3)	2.7 (0.3, 9.3)
8	79, 80 Ciancio (2004)	CS + D + MMF + Tacro	4.0 (0.5, 13.7)	14.0 (5.8, 26.7)
9	2 Ekerg (2007)	CS + D + MMF + Tacro	12.2 (9.2, 15.8)	12.2 (9.2, 15.8)
10	24 Ciancio (2008)	CS + D + MMF + Tacro	20.0 (7.7, 38.6)	NA
11	17 Kumar (2008)	CS + B + MMF + Tacro	14.0 (5.8, 26.7)	NA

[1] 95% CI for each study was estimated using SAS procedure PROC FREQ with exact method.

Source: Table 2 in the Sponsor's NI margin justification document (page 7) in IND75250 SDN55.

The pooled event rates are shown in Table below

Event	Control ^[1] Rate and 95% CI (%)	Putative Placebo ^[1] Rate and 95% CI (%)	Difference ^[1] (Placebo – Active)	P-value for test null ^[2]
Random Effect Model				
Acute Rejection	10.43 (7.65, 14.07)	51.91 (43.37, 60.33)	26.00 (21.63, 30.91)	<0.0001
Efficacy Failure	11.45 (8.25, 15.67)	57.25 (48.64, 65.43)	30.50 (25.47, 36.05)	<0.0001
Fixed Effect Model				
Acute Rejection	11.41 (9.58, 15.55)	51.91 (43.37, 60.33)	17.85 (15.49, 20.48)	<0.0001
Efficacy Failure	12.44 (10.28, 14.99)	57.25 (48.64, 65.43)	20.99 (18.12, 24.19)	<0.0001

[1] Point estimates and corresponding 95% CIs were estimated using Comprehensive Meta-Analysis version 2.2 with random effect model; Biostat, 14 North Dean Street, Englewood, NJ 07631

[2] p-value for test null that mean effect is zero based on Z-statistics.

Source: Table 3 in the Sponsor's NI margin justification document (page 8) in IND75250 SDN 55.

Using the method described in the draft guidance on noninferiority trials for situations where information on the putative placebo and the active control arm come from separate sources is to take the difference in rates between the pooled CI in the putative placebo (lower bound of the CI) and the pooled CI in the active control groups (upper bound of the CI). Using the pooled CIs in Table above, conservative estimates of treatment effect under the random effects model are 29.30 (=43.37-14.07) and 32.97 (=48.64-15.67), for acute rejection and efficacy failure, respectively. Under the fixed effects model, the conservative estimates are 27.82 (=43.37-15.55) and 33.65 (=48.64-14.99), for acute rejection and efficacy failure, respectively. The estimated treatment effect of the active control arm over the putative placebo arm is greater than 15%, providing support for the use of a NI margin no greater than 10%.

The sponsor performed additional analyses to estimate the treatment effect of the active control over the putative placebo including a sensitivity analysis using the random effects model by removing one study at a time from the active control group to evaluate the impact of a particular study on the results of the overall pooled point estimate and 95% CI in the active control group, a sensitivity analysis excluding studies 9, 10 and 11 which were identified as different from the other studies, and a sensitivity analysis excluding Study 7 to study the impact of these studies on the estimates for acute rejection rates. An analysis by a nonlinear mixed effects model was also performed to estimate the contribution of each of the immunosuppressant drugs to the combination therapy event rate. The results of the heterogeneity test suggests that the studies are not homogeneous for acute rejection (p-value=0.0408) but the differences among the studies for efficacy failure were small enough to pass the heterogeneity test (p-value=0.1200). Table below summarizes the analysis results described above (from Dr. John Yap's statistical review dated 8/11/10). These additional analyses showed that the estimated treatment effect is larger than the proposed 10% NI margin.

<i>Approach</i>	<i>BPAR</i>	<i>Efficacy Failure</i>
<i>1. FDA*</i>		
<i>Random Effects</i>	<i>29.30</i>	<i>32.97</i>
<i>Fixed Effects</i>	<i>27.82</i>	<i>33.65</i>
<i>2. Nonlinear MEM</i>	<i>26.80</i>	<i>34.90</i>
<i>3. Sensitivity Analysis</i>		
<i>Omitting study 7 **</i>	<i>23.33</i>	<i>21.72</i>
<i>Omitting studies 9-11***</i>		
<i>Random Effects</i>	<i>30.76</i>	
<i>Fixed Effects</i>	<i>30.72</i>	
<i>*based on sponsor's results; **smallest CI lower bound; ***3 studies different from the rest; NLMEM=nonlinear mixed effects model</i>		

Source: Statistical review by Dr. John Yap dated 8/11/10 for IND 75250

In the SPA Agreement letter dated 5/14/10, the Division stated that we agree with the sponsor's justification for a 10% non-inferiority margin, but have some additional recommendations for the sponsor to further strengthen the justification. The requests for additional information regarding the non-inferiority margin are as follows:

- 1 Please include any information regarding missing data from each of the 11 studies selected for analysis and also include a discussion on how the amount of missing data in the studies may affect the estimated NI margin. The reliability of the event rates in each study and the analyses estimates may largely depend on the amount of missing data and it is important to account for this in the determination of the NI margin.
- 2 We appreciate all the sensitivity analyses that you performed. The table below (extracted from Tables 1a and 1b) shows that studies 3, 5, 6 and 9 have proportionally more white patients (range from 72% to 96%) compared to studies 4, 7, 8, 10, and 11 (range from 30% to <46%). Moreover, the sample sizes in the former studies are generally larger than those in the latter studies. The first group of studies may have more power to detect the true rates in studies with mostly white patients because of the larger sample sizes. Please include a sensitivity analysis using only studies 3, 5, 6 and 9 (exclude studies 4, 7, 8, 10, and 11) in the analysis.

Study	n	Whites (%)	Location	Tacro	BPAR
3. Silva (2007)	212	72	US, CA, Brazil	SD	7.5
5. Mullen (2004)	186	83	Netherlands	MD	14.5
6. Ahsan (2002)	50	96	US	MD	6.0
9. Ekerger (2007)	401	94	Europe	Low dose	12.2
4. Busque (2009)	21	43	US	SD	9.5
7. Ciancio (2008)	75	40	US	Reduced	2.7
8. Ciancio (2004)	50	34	US	MD	4.0
10. Ciancio (2008)	30	30	US	MD	20.0
11. Kumar (2008)	50	<46*	US	SD	14.0

*Blacks=54%; n=study size; SD=standard dose; MD=maintenance dose

The sponsor responded to these two requests in this NDA submission. Regarding recommendation #1, the sponsor responded that based on a re-review of the 11 published studies used for the meta-analysis, Veloxis found no evidence that missing or incomplete follow-up data had any significant impact on the observed event rates. The studies were determined to be adequately designed and conducted, and met quality criteria for inclusion in the meta-analysis based on a comprehensive literature review. The methods used to assess patients for acute rejection, immunosuppressive therapy, and survival over the 12-month follow-up period appeared to be thorough and well-documented in each of the studies. The sponsor noted that the incidence of acute rejection episodes is highest during the first 3-6 months after transplant, a period when surveillance for graft loss is typically most rigorous. As a result, very few, if any, rejection events or deaths would have gone undetected; even limited under-reporting would not have introduced bias in the meta-analysis or extended the lower limit of the confidence interval beyond the 10% margin. The sponsor concluded that they found no evidence that missing data had a significant impact on calculations used for estimating the putative placebo effect or justifying the non-inferiority margin selected for study 3002.

Regarding recommendation #2, the sponsor provided results for additional sensitivity analyses that include the requested analysis using only studies 3, 5, 6 and 9 (exclude studies 4, 7, 8, 10, and 11) as highlighted in the first Table below for treatment failure rates and second Table for acute rejection. Note that treatment failure rates for Studies 5, 10 and 11 were not available.

Sensitivity analysis of Treatment Failure Rates and 95% confidence intervals

		Pooled Analysis Using Random Effect Model					
Analysis		No. of Studies	Point Estimate	Lower Limit	Upper Limit	Z-Value	p-Value
1	Pooled All Studies	N=6	0.1145	0.0825	0.1567	-11.0605	<0.0001
2	Removed 3. Silva (2007)	N=5	0.0965	0.0607	0.1500	-8.7238	<0.0001
3	Removed 4. Busque (2009)	N=5	0.1137	0.0791	0.1608	-10.0243	<0.0001
4	Removed 6. Ahsan (2002)	N=5	0.1219	0.0884	0.1657	-10.7970	<0.0001
5	Removed 7. Ciancio (2008)	N=5	0.1288	0.1063	0.1553	-17.1847	<0.0001
6	Removed 8. Ciancio (2004)	N=5	0.1067	0.0714	0.1565	-9.4630	<0.0001
7	Removed 9. Ekerge (2007)	N=5	0.0983	0.0561	0.1666	-7.1651	<0.0001
8	Removed 4, 7, and 8	N=3	0.1272	0.0956	0.1673	-11.7487	<0.0001

Sensitivity analysis of Acute Rejection Rates and 95% confidence intervals

		Pooled Analysis Using Random Effect Model					
Analysis		No. of Studies	Point Estimate	Lower Limit	Upper Limit	Z-Value	p-Value
1	Pooled All Studies	N=9	0.1043	0.0765	0.1407	-12.3876	<0.0001
2	Removed 3. Silva (2007)	N=8	0.1122	0.0810	0.1535	-11.2343	<0.0001
3	Removed 4. Busque (2009)	N=8	0.1040	0.0747	0.1429	-11.6461	<0.0001
4	Removed 5. Meulen (2004)	N=8	0.0950	0.0656	0.1357	-10.9775	<0.0001
5	Removed 6. Ahsan (2002)	N=8	0.1083	0.0788	0.1472	-11.7651	<0.0001
6	Removed 7. Ciancio (2008)	N=8	0.1131	0.0864	0.1467	-13.5062	<0.0001
7	Removed 8. Ciancio (2004)	N=8	0.1099	0.0813	0.1469	-12.3302	<0.0001
8	Removed 9. Ekerge (2007)	N=8	0.0963	0.0635	0.1435	-9.7056	<0.0001
9	Removed 10. Ciancio (2008)	N=8	0.0977	0.0709	0.1331	-12.4624	<0.0001
10	Removed 11. Kumar (2008)	N=8	0.0994	0.0702	0.1389	-11.3737	<0.0001
11	Removed 4, 7, 8, 10, and 11	N=4	0.1086	0.0785	0.1482	-11.5621	<0.0001

This reviewer considers the sponsor's responses to be acceptable. The assessment for a 10% NI margin appears to be robust.

Appendix 2: Summary of Study 2017

The pivotal study which supports the sponsor's efficacy claims is study 3002, the assessment of which is the focus of this review. Both Study 2017 and the Phase 3 Study 3002 were conducted in de novo kidney transplant recipients and the results of the Phase 2 Study 2017 informed the design of Phase 3 Study 3002 but the starting doses and target trough levels both for LCP-

Tacrolimus and the comparator Prograf are different in each study. The starting dose for Prograf was decreased from 0.2 mg/kg/day to 0.1 mg/kg/day whereas the starting dose for LCP-Tacro was increased from 0.14 mg/kg/day to 0.17 mg/kg/day when moving from the Phase 2 Study 2017 to the Phase 3 Study 3002. As noted in clinical Review by Dr. Velidedeoglu, The starting dose of 0.14 mg/kg/day for Study 2017 is likely to be the recommended dose in the label due to the observation that the higher starting dose for the LCP-Tacrolimus in Study 3002 resulted in higher than expected tacrolimus exposure within the first 7-10 days after transplantation in the LCP-Tacro group. Due to concerns related to possible tacrolimus overexposure in the LCP-Tacrolimus group of the Study 3002 at least early on, it became necessary to review the Phase 2 Study 2017 which utilized a lower starting dose for LCP-Tacro (0.14 mg/kg/day instead of the 0.17 mg/kg/day) as part of the assessment of using a lower starting dose for LCP-Tacro in support of the de novo indication. The efficacy results of Study 2017 will be briefly reviewed below. The study is titled

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

A total of 63 patients were randomized. 32 received LCP-Tacro and 31 received Prograf. The demographic and baseline data were comparable between the 2 groups. Overall, 58 (92.1%) patients completed the pharmacokinetics portion of the study and 24 (75.0%) patients in LCP-Tacro arm and 25 (80.6%) patients in Prograf arm, respectively, completed the study through the Day 360 visit. Five patients withdrew their consent, 4 patients discontinued due to AEs, 2 patients were lost to follow-up, 2 were discontinued by the sponsor or regulatory authority, and 1 patient discontinued due to “other”. The following table contains information on patient disposition.

Table 6 Summary of Patient Disposition: Completion and Reasons for Early Withdrawal - mITT Patients

Patient Disposition	LCP-Tacro N=32	Prograf N=31	Overall N=63
Number of Patients who Completed the Pharmacokinetic Portion of the Study - n (%)			
Yes	29 (90.6%)	29 (93.5%)	58 (92.1%)
No	3 (9.4%)	2 (6.5%)	5 (7.9%)
Reason for Early Withdrawal - n (%)			
Withdrew consent	3 (9.4%)	1 (3.2%)	4 (6.3%)
Request for termination by sponsor or regulatory authorities	0.0%	1 (3.2%)	1 (1.6%)
Number of Patients who Completed the Study Through Day 360 - n (%)			
Yes	24 (75.0%)	25 (80.6%)	49 (77.8%)
No	8 (25.0%)	5 ^a (16.1%)	13 (20.6%)
Reason for Early Withdrawal - n (%)			
Adverse event	2 (6.3%)	2 (6.5%)	4 (6.3%)
Withdrew consent	4 (12.5%)	1 (3.2%)	5 (7.9%)
Lost to follow up	1 (3.1%)	1 (3.2%)	2 (3.2%)
Request for termination by sponsor or regulatory authorities	0 (0.0%)	2 (6.5%)	2 (3.2%)
Administrative/other reason	1 (3.1%)	0 (0.0%)	1 (1.6%)

Source: Table 6 from study report 2017.

Treatment failure at Month 6 was defined as patients who died, experienced graft loss, BPAR, or were lost to follow-up on or before Day 187. No patients died or experienced graft failure. A total of 3 patients experienced BPAR (1 LCP-Tacro, 2 Prograf) and 2 patients were lost to follow-up (1 LCP-Tacro and 1 Prograf). Treatment failure therefore included 2 patients in the LCP-Tacro treatment group and 3 patients in the Prograf group. There was no statistically significant difference between treatment groups in the cumulative incidence of freedom from BPAR and no statistically significant difference in the severity of BPAR episodes in LCP-Tacro patients compared to Prograf patients at Day 180 or Day 365. The following table gives the results of treatment failure at Month 6.

Event	LCP-Tacro N = 32	Prograf N = 31
BPAR/D/GL/LTFU	2 (6.3) 95% exact C.I. of LCP-Tacro – Prograf (-20.7%, 12.6%) P=0.7082	3 (9.7)
BPAR	1 (3.1)	2 (6.5)
Death	0 (0)	0 (0)
Graft loss	0 (0)	0 (0)
Lost to follow-up	1 (3.1)	1 (3.2)
Death/Graft Loss	0 (0)	0 (0)

Table below presents the statistics on daily dose in both groups. The mean and median daily dose remained within the recommended therapeutic range in both treatment groups.

Days	Statistic	LCP-Tacro (N=32)	Prograf (N=31)
1-7	Mean (SD)	10.29 (3.328)	10.88 (3.417)
	Median	10.39	11.57
	Min-Max	4.3-17.4	4.3-17.0
	n	32	31
8-14	Mean (SD)	10.27 (4.183)	8.47 (4.208)
	Median	9.71	7.64
	Min-Max	1.9-19.4	1.2-18.0
	n	31	30
15-30	Mean (SD)	9.80 (4.454)	8.12 (3.980)
	Median	9.97	7.91
	Min-Max	1.0-19.8	2.00-16.3
	n	28	30
31-90	Mean (SD)	8.55 (5.031)	7.62 (3.901)
	Median	8.89	7.78
	Min-Max	2.2-22.0	1.1-15.2
	n	28	30
181-360	Mean (SD)	5.84 (3.336)	5.88 (4.114)
	Median	6.21	4.84
	Min-Max	1.2-14.0	1.5-16.7
	n	23	25

Source: Table 18 of the Study report 2017.

Table below shows an overall summary of AEs. Except for 1 patient in the Prograf group, all patients in this study experienced at least 1 AE. There were no deaths. Thirty-six patients overall

(15 LCP-Tacro, 21 Prograf) experienced SAEs. Most AEs were either mild or moderate and did not lead to discontinuation from the study. Twelve patients overall experienced severe AEs (7 LCP-Tacro, 5 Prograf) and 4 patients overall discontinued due to AEs (2 patients in each group).

Table 19 Brief Summary of Adverse Events (n [%]) - mITT Population

Proportion of Patients	LCP-Tacro (N=32)	Prograf (N=31)
Adverse Events	32 (100%)	30 (96.8%)
Deaths	0 (0%)	0 (0%)
Serious Adverse Events	15 (46.9%)	21 (67.7%)
Discontinued Due to Adverse Events	2 (6.3%)	2 (6.5%)
Severe Adverse Events	7 (21.9%)	5 (16.1%)
Related (Suspected) Adverse Events	15 (46.9%)	15 (48.4%)

Source: Table 19 of the Study report 2017.

Conclusion

The study was mainly designed as a PK study. It was not powered to show efficacy. The 95% exact C.I. of difference of efficacy failure rates between LCP-Tacro and Prograf is (-20.7%, 12.6%) with a p-value of 0.7082. There were lower rates of serious AEs in the LCP-Tacro group (15/32=46.9%) compared with the Prograf group (21/31=67.7%), but higher rates of severe AEs in LCP-Tacro group (7/32=21.9%) compared with the Prograf group (5/31=16.1%). Because the size of the study is small, no definitive conclusions regarding efficacy and safety can be drawn.

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/s/

HONGLING ZHOU
09/24/2014

YAN WANG
09/24/2014
Concur with overall conclusion.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

?

NDA Number: 206406

Applicant: Veloxis

Stamp Date: 12/30/2013

Drug Name: LCP-Tacro

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____x____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			NI margin justification may not be appropriate for Study 3001
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	No interim analyses prior to 12 months proposed
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

An information request with the following comments was sent to the sponsor on February 12, 2014:

1. We were not able to find in the Study 3001 analysis datasets the variable that identifies the country where the patients were enrolled in the study. This variable is needed for us to perform the subgroup analysis regarding geographic regions. If the variable is included in the analysis datasets, please inform where the data is located. Otherwise please resubmit the efficacy analysis dataset (ADTTE.xpt) that includes this variable.
2. On the last page of the define files for Study 3002 and Study 3001, the codelist for PARAMCD/PARAM does not match with the variable PARAMCD/PARAM in the efficacy analysis datasets for respective studies (ADEFF.xpt for Study 3001 and ADTTE.xpt for Study 3002). Please clarify.
3. The efficacy analysis datasets were set up differently for Study 3002 and Study 3001. The analysis dataset for Study 3001 (ADEFF.xpt) identifies whether the central biopsy reading or local reading was used to determine the outcome for primary endpoint BPAR/D/GL/LTFU. However, we are not able to identify this information in the analysis dataset for Study 3002 (ADTTE.xpt).
4. We found discrepancies regarding number of study sites in the Study report and efficacy analysis dataset ADTTE.xpt for Study 3002. In the dataset, there are 69 study sites that randomized patients for Study 3002. However, your study report states 68 sites enrolled patients (page 2). The study report also states patients at 70 sites were randomized (page 3). Please clarify the discrepancies.
5. Please submit all SAS (or R) programs for Study 3002 and Study 3001 that were used to create analysis variables as well as programs that were used to produce analysis results.

Hongling Zhou

2/12/2014

Reviewing Statistician

Date

Supervisor/Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HONGLING ZHOU
02/14/2014

YAN WANG
02/14/2014