CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204096Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **204096** SUPPL # **N/A** HFD # **590**

Trade Name **Astagraf XL**

Generic Name **tacrolimus extended-release capsules**

Applicant Name **Astellas**

Approval Date, If Known **July 19, 2013**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES X NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

NOTE: Please see Attachments 1 and 2 (submitted by applicant on July 20, 2012, and July 2, 2013, respectively)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ **NO X**

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ **NO X**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES X NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA# **50708** **Prograf (tacrolimus)**

NDA# **50709** **Prograf (tacrolimus)**

NDA# **50777** **Protopic (tacrolimus)**

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ **NO X**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES X NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES X NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ **NO X**

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ **NO X**

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 02-0-158 "A Phase III, Randomized, Open-Label, Comparative, Multi-Center Study to Assess the Safety and Efficacy of Prograf® (tacrolimus)/MMF, Modified Release (MR) Tacrolimus/MMF and Neoral® (cyclosporine)/MMF in De Novo Kidney Transplant Recipients"

Study FG-506E-12-03 "A Multicenter, 1:1 Randomized, Double Blind, Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506E (MR4) Versus Tacrolimus FK506 in Combination with MMF (Cellcept®) and Steroids in Patients Undergoing Kidney Transplantation"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

NOTE: Study 02-0-158, Investigation #1 below, has three arms. One of the arms was used to support approval of another NDA.

Investigation #1 **02-0-158** YES ☐ NO ☐

Investigation #2 **FG-506E-12-03** YES ☐ **NO X**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 02-0-158 YES ☐ **NO X**

Investigation #2 FG-506E-12-03 YES ☐ **NO X**

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 02-0-158 **Investigation #2 FG-506E-12-03**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # **64148** **YES X** ! NO ☐

! Explain:

Investigation #2

IND # YES ☐ ! **NO X**
! Explain: **Study #2 (12-03) was not conducted under an IND, but conducted by the applicant.**

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ **NO X**

If yes, explain:

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Name of person completing form: **Jacquelyn Smith**
Title: **Senior Regulatory Project Manager**
Date: **July 19, 2013**

Name of Office/Division Director signing form: **Renata Albrecht, M.D.**
Title: **Division Director**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

Enclosure:
Attachments

Advagraf (FK506E, MR4)

NDA 204096

Kidney and Liver Transplant

Exclusivity Request

Astellas

Including, but not limited to, Astellas Pharma Global Development, Inc,
Astellas Pharma Europe BV and Astellas Pharma Inc.

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1 INTRODUCTION

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and the implementing regulation 21 CFR 314.50 *Content and format of an application*, Astellas is submitting a New Drug Application (NDA 204096) for Advagraf (tacrolimus extended-release capsules, 0.5 mg, 1 mg and 5 mg strengths) for the indications of the prophylaxis of organ rejection in kidney transplant patients and the prophylaxis of organ rejection in male liver transplant patients.

Astellas is requesting a three-year period of exclusivity for each of the above mentioned indications for a new condition of use of tacrolimus (as Advagraf capsules) upon approval of the NDA. This Module 1.3.5.3 *Exclusivity Request* provides the background and rationale for the three year exclusivity request.

2 BACKGROUND

In 1994, Astellas received approval for Prograf (tacrolimus) Capsules and Injection as described in NDAs 50-708 and 50-709 under Section 507 of the Food, Drug, and Cosmetic Act (FDCA) for the indication of prophylaxis of organ rejection in patients receiving allogeneic liver transplants. The indication was expanded to include kidney and heart transplants in 1997 and 2006, respectively. In addition, a topical formulation of tacrolimus (Protopic® (tacrolimus) Ointment, 0.03% and 0.1%) as described in NDA 50-777 was approved in December 2000 and is now indicated for second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.

Astellas is now seeking approval for Advagraf (tacrolimus extended-release capsules) through a New Drug Application (NDA) under Section 505(b)(1). Unlike Prograf capsules, which are administered twice a day, Advagraf capsules are intended to be dosed once daily.

Prior to 1997, antibiotic drugs, such as Prograf, were approved under section 507 of the FDCA rather than section 505. The 1984 Hatch-Waxman amendments to the FDCA established a statutory pathway for approval of generic versions of drugs approved under section 505. The amendments, however, did not establish a statutory pathway for approval of generic versions of antibiotic drugs approved under section 507. In 1997, as part of the Food and Drug Administration Modernization Act (FDAMA), Congress repealed section 507 of the FDCA. Section 125 of FDAMA provided that, going forward, all NDAs for antibiotic drugs would be submitted under section 505. Such drugs were therefore within the Hatch-Waxman generic drug approval scheme and therefore entitled to exclusivity, subject to patent

listing, subject to abbreviated new drug applications (ANDAs), and entitled to 30-month stays.

Section 125(d)(1) of FDAMA declared that an antibiotic application approved under section 507 before enactment of FDAMA would be considered an application submitted and filed under section 505(b) and approved under section 505(c). Under FDAMA section 125(d)(2), certain Hatch-Waxman provisions would not apply to an "application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of an application for marketing receiving by the Secretary of Health and Human Services under section 507" prior to FDAMA. These Hatch-Waxman provisions included the patent listing, patent certification, and marketing exclusivity provisions of section 505.

In 2008, Congress added section 505(v) to the FDCA to amend FDA's rules regarding "old antibiotics" and to incentivize the development of antibiotics. Section 505(v)(1) governs any NDA submitted after enactment of section 505(v), if the drug that is the subject of the NDA contains an antibiotic drug that was the subject of an application approved by FDA under section 507. Under section 505(v), such an antibiotic is eligible for three-year exclusivity under section 505(c) or section 505(j). This rule, however, does not apply to an NDA for a condition of use for which the relevant drug was approved prior to enactment of section 505(v).

Because Advagraf contains tacrolimus, an antibiotic drug that was the subject of an approved application under section 507 before enactment of section 505(v), Advagraf is subject to section 505(v)(1). This means that so long as:

(1) Astellas is seeking approval of Advagraf for a condition of use different from any condition of use for which Prograf was approved, and
(2) Advagraf's NDA satisfies the requirements set forth in section 505(c)(3)(E)(iii), Advagraf will be entitled to three-year exclusivity.

In addition, if Advagraf is subject to section 505(v), then the Hatch-Waxman amendments (including the patent-listing requirements) would also apply to the drug.

3 NEW CONDITION OF USE

FDA has not specifically defined the phrase "condition of use" for purposes of determining whether a particular change to an already approved drug product would qualify for three-year exclusivity. The FDA has, however, identified certain types of product changes that would normally warrant three-year exclusivity, including "changes in dosing regimen." See 59 Fed. Reg. at 50357. Further, FDA has stated that conditions of use "include, among other things, indications and dosage instructions…." 54 Fed. Reg. at 28881 (describing the information

that an ANDA must include to show that the conditions of use for which the applicant is seeking approval have been previously approved for the reference listed drug). FDA has referred to the phrase "conditions of use" similarly in the animal-drug context. See 77 Fed. Reg. 735, 741 (Jan. 6, 2012) and 71 Fed. Reg. 48840, 48843 (Aug. 22, 2006).

Since Advagraf's once-daily dosing is a new dosing regimen for tacrolimus, it qualifies as a new condition of use. Therefore, Advagraf's proposed dosing regimen should qualify as the type of change that warrants three-year exclusivity.

4 SECTION 505 (C) (3) (E) (III) REQUIREMENTS FOR EXCLUSIVITY

4.1 Section 505 (c) (3) (E) (iii) Requirements for Exclusivity – De Novo Kidney Transplant Recipients

In addition to showing that Advagraf is seeking approval for a novel condition of use, Astellas must also ensure that the NDA satisfies the exclusivity requirements in section 505(c)(3)(E)(iii) before FDA will grant it three-year exclusivity for Advagraf. Section 505(c)(3)(E)(iii) sets forth the requirements for obtaining three-year exclusivity for a drug that includes an active pharmaceutical ingredient that has already been approved under section 505(b). In the case of a change to a drug containing an already approved active pharmaceutical ingredient, such as approval for a new indication, the law provides for three-years of exclusivity under section 505(c)(3)(E)(iii) if the NDA contains (1) reports of "new clinical investigations (other than bioavailability studies) [(2) that are] essential to the approval of the application and [(3) that are] conducted or sponsored by the applicant." All three of these criteria must be met before three-year exclusivity under section 505(c)(3)(E)(iii) will be granted.

FDA has defined "new clinical investigation" to mean an "investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of a previously approved drug product for any indication…." 21 CFR § 314.108(a). The FDA has defined "essential to approval" to mean "with regard to an investigation, that there are no other data available that could support approval of the application." In addition, FDA has defined "conducted or sponsored by the applicant" to mean that "the applicant was named as the sponsor of the investigational new drug application under which the investigation was conducted."

In this case, Advagraf contains tacrolimus, which is an already approved active pharmaceutical ingredient under NDAs 50-708 (Prograf Capsules), 50-709 (Prograf Injection) and 50-777 (Protopic Ointment). Thus, for Astellas to obtain three-year exclusivity under section 505(c)(3)(E)(iii) for Advagraf, Advagraf's NDA must contain one or more new

clinical investigations conducted in humans, other than bioavailability studies, that are both essential to approval and sponsored or conducted by Astellas.

Clinical study 02-0-158 (hereafter referred to as the "158 study") is a "new clinical investigation" that would qualify for three years of Hatch-Waxman exclusivity under the FDCA section 505(c)(3)(E)(iii). The 158 study is the pivotal efficacy study essential to the approval of Advagraf for the indication of the prophylaxis of organ rejection in kidney transplant patients. It was a phase 3, randomized, open-label, comparative, multi-center study in de novo kidney transplant recipients. The 158 study had three arms:

i. Once-daily Advagraf (tacrolimus extended-release capsules),
ii. Twice-daily Prograf (tacrolimus capsules), and
iii. Twice-daily Neoral (cyclosporine capsules).

The Neoral arm was the control arm. As described in the 158 Clinical Study Report, the primary objective of the 158 study was:

1. to compare the safety and efficacy of Prograf and Neoral in de novo kidney transplant recipients and
2. to compare the safety and efficacy of Advagraf and Neoral in de novo kidney transplant recipients.

The two comparisons above were two independent analyses. The clinical study report for the 158 study (which included data from all three arms of the 158 study) was included in an NDA submission for Advagraf in 2005 that was eventually withdrawn. The same clinical study report for the 158 study was also included in a 2006 supplemental NDA ("NDA/S-027") for Prograf. This Prograf supplement was approved on May 19, 2009 and the Prograf label was updated to include this Prograf data in kidney patients. The Prograf label includes 158 study efficacy and safety data, but only for the Prograf and Neoral arms (objective number 1 above). FDA did not include data from the Advagraf versus Neoral analysis (objective number 2 above) of the 158 study in the Prograf label. Further, it is assumed FDA would not have needed to directly rely on the Advagraf arm data to demonstrate the effectiveness of Prograf for use in kidney transplant patients.

Although the Advagraf versus Neoral data contained in the 158 study was not specifically described as a separate investigation in the clinical study report, the data could be viewed in that manner and the results are being relied on for the first time in the new Advagraf NDA and are essential to the approval of the NDA. Thus the Advagraf arm was a separate investigation as the efficacy and safety data were not pooled with the Prograf data nor reviewed as part of the prior application. The legislative history makes clear that the three-year exclusivity provisions were primarily intended for efficacy studies and to reward

"significant innovations" that require "considerable time and expense in FDA required clinical testing." The Advagraf arm of the 158 study meets these requirements.

Astellas believes that Advagraf's modified dosing regimen is a new condition of use that constitutes a significant innovation, that the Advagraf data can be viewed independently from the Prograf data and was not considered in the Prograf application, that including the Advagraf arm in the 158 study required considerable time and expense, and that the arm is necessary for Advagraf's approval.

4.2 Section 505 (c) (3) (E) (iii) Requirements for Exclusivity – De Novo Male Liver Transplant Recipients

Section 505(c)(3)(E)(iii) sets forth the requirements for obtaining three-year exclusivity for a drug that includes an active pharmaceutical ingredient that has already been approved under section 505(b). In the case of a change to a drug containing an already approved active pharmaceutical ingredient, such as approval for a new indication, the law provides for three-years of exclusivity under section 505(c)(3)(E)(iii) if the NDA contains (1) reports of "new clinical investigations (other than bioavailability studies) [(2) that are] essential to the approval of the application and [(3) that are] conducted or sponsored by the applicant." All three of these criteria must be met before three-year exclusivity under section 505(c)(3)(E)(iii) will be granted.

For the de novo male liver transplant indication, (b) (4)

5 CONCLUSION

Astellas believes that Advagraf's new dosing regimen is a new condition of use that constitutes a significant innovation in transplant therapy. In this NDA, Astellas is providing two new clinical investigations (one for the de novo kidney transplant indication and one for the de novo male liver transplant indication) and each one is essential to the approval of the application. Both of the new clinical investigations were conducted by Astellas. Therefore, the three criteria mentioned above have been met and three-year exclusivity under section

505(c)(3)(E)(iii) can be obtained for the de novo kidney and the de novo male liver transplant indication.

Astagraf XL (FK506E, MR4)

NDA 204096

Kidney Transplant

Update to the Exclusivity Request for NDA 204096

Astellas

Including, but not limited to, Astellas Pharma Global Development, Inc,
Astellas Pharma Europe BV and Astellas Pharma Inc.

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UPDATE TO THE EXCLUSIVITY REQUEST FOR NDA 204096

Please refer to New Drug Application (NDA) 204096 dated September 21, 2012 and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for tacrolimus 0.5 mg, 1 mg, and 5 mg extended-release capsules[1] as well as our formal Exclusivity Request dated August 2012.[2]

Astellas Pharma Global Development, Inc., Astellas Pharma Europe BV, and Astellas Pharma Inc. (collectively "Astellas") is augmenting our existing request for three-year Hatch-Waxman exclusivity for NDA 204096 under sections 505(v)(1) and 505(c)(3)(E)(iii) of the FDCA and FDA's implementing regulations at 21 CFR 314.50(j), 314.108(a), and 314.108(b)(4).

Astellas' intent with this update is to make the indications content consistent with the revision to remove use in liver transplant recipients and to clarify that in addition to clinical study 02-0-158 (the "158 study"), which was discussed in our original Exclusivity Request, NDA 204096 also contains data (other than bioavailability data) from another new clinical investigation that Astellas sponsored and which we believe is essential to approval of the NDA and the labeling for tacrolimus extended-release capsules for kidney transplant recipients. We continue to conclude that the NDA qualifies for exclusivity per the FDCA and implementing regulations citations above. The information contained in this update further supports our request for three years of exclusivity as described in our August 2012 Exclusivity Request. The clinical trial and analyses of the data referenced in this update to our Exclusivity Request was previously submitted to the FDA as part of the original submission of NDA 204096.

1 BACKGROUND

As detailed in the Background section of the original Exclusivity Request in the NDA, Astellas is seeking approval for tacrolimus extended-release capsules through an NDA under FDCA section 505(b)(1). Tacrolimus is an already approved active pharmaceutical ingredient under NDAs 50-708 (Prograf capsules), 50-709 (Prograf injection), and 50-777 (Protopic ointment). Unlike Prograf capsules which are administered twice a day, tacrolimus extended-release capsules are intended to be dosed once daily. As discussed in our original Exclusivity Request, this new dosing regimen constitutes a "new condition of use."

[1] The NDA submission and clinical studies refer to the proprietary name Advagraf; Astellas acknowledges that the FDA has deemed this name as unacceptable but will use it in this document for consistency.

[2] A copy of the original Exclusivity Request is attached as Exhibit A.

2 SAFETY AND EFFICACY STUDY ESSENTIAL TO THE APPROVAL OF TACROLIMUS EXTENDED-RELEASE CAPSULES IN KIDNEY TRANSPLANT RECIPIENTS

In addition to the 158 study, discussed in detail in the original Exclusivity Request, Protocol FG-506E-12-03 *A Multicenter, 1:1 Randomized, Double Blind, Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506E (MR4) Versus Tacrolimus FK506 in Combination with MMF (CellCept®) and Steroids in Patients Undergoing Kidney Transplantation* ("12-03 study") provides safety and efficacy data -- beyond bioavailability data[3] - essential to approval of tacrolimus extended-release capsules in kidney transplant recipients. From prior communications with FDA, most notably in the FDA Approvable Action Letter dated March 13, 2008 for an Astellas NDA[4] for tacrolimus extended-release capsules, they state that the approval of the application for use in kidney transplant patients would be contingent on our submission and FDA review of the full study report and complete datasets for study 12-03. Similar to the comments in the same Approvable Action letter, during a meeting held in September 2009 between Astellas and FDA to discuss submission of a new application, FDA reiterated the importance of including study 12-03 in any future application seeking approval in kidney transplantation. During the more recently held pre-NDA meeting (January 31, 2012) for the current NDA the FDA stated that dosing information for inclusion in the product labeling would be determined after completing their review of clinical studies 158 and 12-03. A pre-NDA meeting for NDA 204096 was held on January 31, 2012. At the meeting, the FDA noted that the dosing information to be included in the product labeling would be determined after completing their review of the clinical studies 02-0-158 and FG-506E-12-03. In summary, Astellas believes that the 12-03 study is essential to the approval of NDA 204096 based upon the information presented above, as well as the content of the draft product labeling which includes data in the Clinical Studies section and language under Indications and Usage which references use of the product, as investigated in study 12-03, without induction therapy,

Astellas also references the foreign Clinical Site Inspections conducted in 2013 by FDA in support of the application[5]. Two investigators who participated in study 12-03 conducted in Germany and Sweden were each subject to a site inspection. An investigator in Brazil who participated in both study 12-03 and 158, was subject to an FDA inspection at the site for study

[3] Bioavailability and tolerability data was based on Protocols: 99-0-060, 00-0-076, 00-0-077, 00-0-078, FG-506E-04-31, FG-506-04-21, FG-506-04-25, 01-0-123, 02-0-153, 02-0-148, FJ-506E-0001, and FJ-506E-0002.

[4] Astellas previously submitted NDA 50-811 for tacrolimus extended-release capsules indicated for kidney transplant patients in December 2005. The approvable letter related to NDA 50-811, but the NDA was subsequently withdrawn. The letter is attached as Exhibit B.

[5] Compliance Program Guidance Manual 7348.811 for Bioresearch Monitoring for Clinical Investigators and Sponsor-Investigators Part IIB.2.a.ii.

158. FDA's interest in inspecting clinical sites for studies 12-03, as well as study 158, supports the importance of the data generated from these trials to the review and approval of the application.

3 CLAIM FOR THREE-YEAR EXCLUSIVITY

In accordance with sections 505(v)(1) and 505(c)(3)(E)(iii) of the FDCA; FDA's regulations at 314.50(j), 314.108(a), and 314.108(b)(4); and the facts and circumstances summarized above, Astellas requests three years of marketing exclusivity on the basis of the information in our August 2012 Exclusivity Request as well as the supplemental information in this letter.

3.1 "NEW CLINICAL INVESTIGATIONS"

Astellas certifies that to the best of its knowledge NDA 204096 includes clinical investigations that meet the definition of "new clinical investigation" set forth in 21 CFR 314.108(a). Specifically, the NDA included new clinical data on the safety and efficacy of tacrolimus extended-release capsules from study 12-03. Further, as discussed in the original Exclusivity Request in the NDA, Astellas believes the 158 study should also qualify as a new clinical investigation because the tacrolimus extended-release arm of the study was not previously relied on by the FDA. As FDA stated when promulgating its regulations on three-year exclusivity, clinical studies that are not bioavailability studies and that establish the efficacy or the safety of a drug may qualify for exclusivity.

3.2 "ESSENTIAL TO APPROVAL"

Astellas provided with NDA 204096 a list of all published studies or publicly available reports of clinical investigations known to it through a literature search that are relevant to the conditions for which Astellas has sought approval (see Module 2.7.4 Kidney, Section 6.2 *Safety in Literature* of the electronic Common Technical Document submission). Astellas certifies that it has thoroughly searched the scientific literature and, to the best of Astellas' knowledge, the list is complete and accurate. In Astellas' opinion, such published studies or publicly available reports did not provide a sufficient basis for the approval of the condition for which Astellas seeks approval without reference to the new clinical investigations in the application. To the best of our knowledge, studies 158 and 12-03 are essential to approval of NDA 204096 and its product labeling content.

3.3 "CONDUCTED OR SPONSORED BY"

Astellas was the sponsor named in the Form FDA 1571 for Investigational New Drug application 64148 under which new clinical investigation 158 was conducted. Astellas was the sponsor of the other new clinical investigation 12-03 although the investigation was a non-IND study conducted ex-US.

4 CONCLUSION

In summary, tacrolimus 0.5 mg, 1 mg, and 5 mg extended-release capsules are for a new condition of use of tacrolimus -- once daily dosing. The studies discussed above are new clinical investigations which resulted in data that is essential to the approval of NDA 204096. Thus, tacrolimus extended-release capsules qualify for three years of marketing exclusivity under the Hatch-Waxman provisions.

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/s/

DIANA M WILLARD
07/19/2013
Diana Willard for Jacquelyn Smith

RENATA ALBRECHT
07/19/2013

1.3.3 DEBARMENT CERTIFICATION

On behalf of Astellas Pharma US, Inc., Astellas Pharma Global Development, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Marcia Marconi

August 20, 2012

Marcia Marconi
Vice President
Regulatory Affairs and Quality Assurance
Astellas Pharma Global Development, Inc.

Date

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF TELECONFERENCE

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: June 26, 2013; 11:00 AM-12:00 PM
Meeting Location: Teleconference

Application Number: NDA 204096
Product Name: Astagraf XL (tacrolimus extended-release capsules)
Indication: Prophylaxis of organ rejection in adult patients receiving kidney transplants
Sponsor/Applicant Name: Astellas Pharma US, Inc.

Meeting Chair: Renata Albrecht, M.D.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Renata Albrecht, MD, Director, DTOP
Joette Meyer. PharmD, Clinical Team Leader
Marc Cavaillé-Coll, MD, Clinical Reviewer
Mark Seggel, PhD, ONDQA
Ozlem Belen, MD, Deputy Director of Safety
Jamie Wilkins Parker, PharmD, DMEPA
Jacquelyn Smith, M.A. Senior Regulatory Project Manager

SPONSOR ATTENDEES

Bill Fitzsimmons, PharmD, MS, Divisional Executive VP, Global Regulatory Affairs, Global Clinical and Research Quality Assurance
Marcia Marconi, VP, Regulatory Affairs and Quality Assurance
Ahsan Arozullah, MD, MPH, Medical Director, Product Safety and Pharmacovigilance
Reena Patil, PhD, Assistant Director, Pharmaceutical Technology Management
Jay Erdman, MS, Project Management
Christine Slover, Project Management
Mary Jo Pritza, PharmD, Regulatory Affairs
Glen Spears, PhD, Regulatory Affairs

BACKGROUND

The discussion topic during the June 26, 2013 teleconference is color schemes of the capsules, the bottles and the bottle caps and labels for Astagraf (all strengths). In addition, there was discussion of the color schemes of Prograf (all strengths). This teleconference was scheduled by FDA to discuss with Astellas the capsule and bottle presentations, share with Astellas the current status of the FDA review of this topic and hear from Astellas their rationale for the selections of the color schemes for their products.

Meeting Discussion

During the June 26, 2013 teleconference with between Astellas and FDA, FDA noted that the proposed (b) (4) .
Astellas acknowledged FDA's concern and stated that they would address and follow-up.

Post Meeting:

- In a July 3, 2013 submission, Astellas requested withdrawal of the (b) (4) (b) (4) .

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/s/

RENATA ALBRECHT
08/09/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204096 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Astagraf XL Established/Proper Name: tacrolimus Dosage Form: extended release capsules		Applicant: Astellas Pharma US, Inc. Agent for Applicant (if applicable):
RPM: Jacquelyn Smith		Division: Division of Transplant and Ophthalmology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 7/19/13	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	7/24/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 7/19/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	6/14/13
• Original applicant-proposed labeling	9/21/13
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	6/18/13
• Original applicant-proposed labeling	9/21/13
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	7/3/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	4/4/13 11/19/12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 12/4/12 ☒ DMEPA 6/17/13 ☒ DMPP/PLT (DRISK) 6/6/13 ☒ ODPD (DDMAC) 6/7/13 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	11/16/12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/22/13 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	7/9/13; 6/6/13
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 7/19/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7/11/13
PMR/PMC Development Templates *(indicate total number)*	☐ None 6
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	7/12/13
• Clinical review(s) *(indicate date for each review)*	7/19/13; 6/19/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	clinical Rv./6/19/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	5/13/13 ☐ None 5/23/13
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	----------☐ None requested 5/30/13 (5)

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 7/17/13; 5/10/13
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 7/17/13; 6/4/13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/13/13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/15/13; 6/12/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7/12/13; 6/14/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 12/7/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	6/14/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 5/29/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

JACQUELYN E SMITH
07/24/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: July 17, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096/ Astagraf XL (tacrolimus extended-release capsules)

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 204096
Astagraf XL (tacrolimus extended-release capsules)

Dear Dr. Spears,

Please refer to your NDA 204906/ Astagraf XL (tacrolimus extended-release capsules).

We are proposing a few more revisions to the package insert. We think we have identified all revisions needed, but we will let you know if we find anything else. If you would like to discuss these edits with us in further detail, please contact me to set up a brief teleconference.

If you have any questions regarding this communication, please contact me at 301-796-1002.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

32 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

JACQUELYN E SMITH
07/17/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Tuesday, July 16, 2013 6:45 PM
To: Spears, Glen
Subject: FW: Gastroenteritis rates in NDA 204096

Hi Glen,

The reviewers looked at the information you provided July 16, 2013 for gastroenteritis. Based on the tables your provided, they determined that the gastroenteritis totals (subtracting the gastritis only events) are 6 Prograf and 17 Astagraf XL in study 158 and 8 Prograf and 17 Astagraf XL patients in study 12-03. Therefore, your Table 3 should be revised as shown below. Please calculate the correct percentages to go with the respective numbers and include them in the table.

In addition, please provide a listing of individual patient ID numbers (unique patient identifiers) by study and treatment arm

Study 1: 17 Astagraf XL and 6 Prograf patients
Study 2: 17 Astagraf XL and 8 Prograf patients

(b) (4)

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.
Thank you.

PS: Please submit through the gateway the information from the July 16, 2013 email as well as the response to the above email. We need to have this information documented officially.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
07/16/2013

Smith, Jacquelyn

From Spears, Glen [Glen.Spears@astellas.com]
Sent Tuesday, July 16, 2013 12:15 PM
To Smith, Jacquelyn
Subject RE: Gastroenteritis rates in NDA 204096

Hi Jackie,

Here is the Astellas response to the question in your July 15, 2013 email.

The data presented in Table 3 from the draft package insert ("PI Table 3") are derived from clusters as defined in the ISS SAP, Appendix 2 (Clustered Safety Events), not any individual MedDRA term. The data presented in PI Table 3 were pulled from Labeling Tables 4 and 5 in Module 1.11.3 in the June 28, 2013 NDA amendment. The "gastroenteritis" in PI Table 3 includes the terms found below in ISS Tables K5.1.2.1 (for the 158 study) and K5.1.4.1 (for the 12-03 study).

Please note that PI Table 3 is based on Study FAS data while the ISS tables are based on the integrated safety analysis set. The data from the -158 study ISS Table K5.1.2.1 exactly matches the data in PI Table 3 because the integrated safety analysis set and the FAS for the 158 study ("Study 1") are identical. However, for the 12-03 study, the integrated safety analysis set and FAS are similar but not identical, as described in the SAP, and therefore the data in ISS Table K5.1.4.1 do not match PI Table 3 ("Study 2") exactly. This is the rationale for providing the Labeling Tables 4 and 5 (both based on the FAS) in the June 28, 2013 NDA amendment.

PROGRAM: /SAS/STUDYDBS/MR4/MR4_IS/PROGS/PROD/TABLES/ALC_.SAS PAGE 14 OF 37
OUTPUT: ALC_IND_158.LST 30MAY2012 16:26
MR4 -FINAL-

TABLE K5.1.2.1
Incidence Of Treatment (All Groups) Emergent Clustered Safety Events
Integrated Safety Analysis Set - Adult De Novo Kidney Transplant Patients
02-0-158 - Primary Study Database

CLUSTER=GASTROENTERITIS SUMMARY=INCIDENCE

CRITERIA	TREATMENT GROUP PROGRAF (N=212)	MR4 (N=214)	NEORAL (N=212)
ANY AE	9 (4.2%)	23 (10.7%)	7 (3.3%)
GASTRITIS	2 (0.9%)	2 (0.9%)	2 (0.9%)
GASTRITIS EROSIVE	0 (0.0%)	4 (1.9%)	0 (0.0%)
GASTRITIS HAEMORRHAGIC	1 (0.5%)	0 (0.0%)	0 (0.0%)
GASTROENTERITIS	1 (0.5%)	14 (6.5%)	4 (1.9%)
GASTROENTERITIS SALMONELLA	0 (0.0%)	1 (0.5%)	0 (0.0%)
GASTROENTERITIS STAPHYLOCOCCAL	0 (0.0%)	1 (0.5%)	0 (0.0%)
GASTROENTERITIS VIRAL	5 (2.4%)	1 (0.5%)	1 (0.5%)
HELICOBACTER GASTRITIS	0 (0.0%)	1 (0.5%)	0 (0.0%)

PROGRAM: /SAS/STUDYDBS/MR4/MR4_IS/PROGS/PROD/TABLES/ALC_.SAS PAGE 13 OF 37
OUTPUT: ALC_IND_1203.LST 30MAY2012 16:33
MR4 -FINAL-

TABLE K5.1.4.1
Incidence Of Treatment (All Groups) Emergent Clustered Safety Events
Integrated Safety Analysis Set - Adult De Novo Kidney Transplant Patients
FG-506E-12-03 - Primary Study Database

CLUSTER=GASTROENTERITIS SUMMARY=INCIDENCE

CRITERIA	TREATMENT GROUP PROGRAF (N=352)	MR4 (N=345)
ANY AE	26 (7.4%)	27 (7.8%)
GASTRITIS	17 (4.8%)	10 (2.9%)
GASTRITIS EROSIVE	3 (0.9%)	1 (0.3%)
GASTROENTERITIS	3 (0.9%)	11 (3.2%)
GASTROENTERITIS BACTERIAL	1 (0.3%)	1 (0.3%)
GASTROENTERITIS CLOSTRIDIAL	0 (0.0%)	1 (0.3%)
GASTROENTERITIS CRYPTOSPORIDIAL	1 (0.3%)	0 (0.0%)
GASTROENTERITIS VIRAL	3 (0.9%)	4 (1.2%)
HELICOBACTER GASTRITIS	0 (0.0%)	1 (0.3%)

The tables from the Clinical Study Reports included in the attachment to the July 15, 2013 email display the specific individual MedDRA term gastroenteritis (not the cluster) and therefore would not be expected to match the cluster data displayed in Table 3 of the PI.

Please let us know if you have any additional questions or concerns.

Best regards,

Glen

****
Glen W Spears, Ph D
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc
Ph: (224) 205-5935
****

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Monday, July 15, 2013 8:52 PM
To: Spears, Glen
Subject: FW: Gastroenteritis rates in NDA 204096

Hi Glen,

The reviewers are trying to reconcile the different numbers reported in the row, "Gastroenteritis" in Table 3 of the proposed package, with the information presented in the Study reports for 158 (legacy and current) and Study 12-03.

(b) (4)

Attached is a PDF document that contains pages with Tables from the studies that report rates of "Gastroenteritis"

- The 158 legacy report - four pages – Tables 36, 39, 42, 49
- 158 current report – two pages – Tables 15 and 19
- 12-03 report – two pages – Table 23 and 30

Please clarity why the numbers in the Tables from the study reports are different from the numbers in proposed Table 3.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.
Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
07/16/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Monday, July 15, 2013 9:41 PM
To: 'Spears, Glen'
Subject: FW: NDA 204096, Section 6 Adverse Reactions
Attachments: ASTAGRAF XL_Section 6 ADVERSE REACTIONS 15JUL2013.jm.docx

Hi Glen,

As a follow up to today's discussion, please see the attached FDA comments.

Regards,
Jacquelyn

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/s/

JACQUELYN E SMITH
07/15/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Monday, July 15, 2013 9:52 PM
To: 'Spears, Glen'
Subject: FW: Gastroenteritis rates in NDA 204096
Attachments: gastroenteritis NDA 204096.pdf

Hi Glen,

The reviewers are trying to reconcile the different numbers reported in the row, “Gastroenteritis” in Table 3 of the proposed package, with the information presented in the Study reports for 158 (legacy and current) and Study 12-03.

(b) (4)

Attached is a PDF document that contains pages with Tables from the studies that report rates of “Gastroenteritis”

- The 158 legacy report - four pages – Tables 36, 39, 42, 49
- 158 current report – two pages – Tables 15 and 19
- 12-03 report – two pages – Table 23 and 30

Please clarity why the numbers in the Tables from the study reports are different from the numbers in proposed Table 3.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.
Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
07/15/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: July 11, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096/ Astagraf XL (tacrolimus extended-release capsules)
Dear HCP, Pharmacist, and Professional Society

Document to be mailed: ☐ YES ☑ NO

NDA 204096
Astagraf XL (tacrolimus extended-release capsules)

Dear Dr. Spears,

Please refer to your NDA 204906/ Astagraf XL (tacrolimus extended-release capsules).

Please find attached the Dear Health Care Provider (DHCP) letter containing our proposed edits. Please note that we only edited the DHCP letter, but the comments pertain to all 3 letters, unless otherwise noted. If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JACQUELYN E SMITH
07/11/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: July 11, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600
Subject: NDA 204096/ Astagraf XL (tacrolimus extended-release capsules)	

Document to be mailed: ☐ YES ☑ NO

NDA 204096
Astagraf XL (tacrolimus extended-release capsules)

Dear Dr. Spears,

Please refer to your NDA 204906/ Astagraf XL (tacrolimus extended-release capsules).

Please find attached the package insert for Astagraf XL containing our proposed edits. We would like to discuss the text boxes in Section 6 (Adverse Reactions) in more detail. If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JACQUELYN E SMITH
07/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

MEETING MINUTES

Astellas Pharma US, Inc.
Attention: Glen Spears, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 21, 2012, received September 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Astagraf XL (tacrolimus extended-release capsules).

We also refer to the teleconference between representatives of your firm and the FDA on June 20, 2013. The purpose of the meeting was to discuss the lost-to-follow-up data in Study FG-506E-12-03.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, M.A., Senior Regulatory Project Manager at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: June 20, 2013; 10:00 AM-10:30 AM
Meeting Location: Teleconference

Application Number: NDA 204096
Product Name: Astagraf XL (tacrolimus extended-release capsules)
Indication: Prophylaxis of organ rejection in adult patients receiving kidney transplants
Sponsor/Applicant Name: Astellas Pharma US, Inc.

Meeting Chair: Joy Mele, M.S.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES
Karen Higgins, Sc.D., Statistics Team Leader
Joy Mele, M.S., Statistics Reviewer
Jacquelyn Smith, M.A. Senior Regulatory Project Manager

SPONSOR ATTENDEES
Rick Croy, MA Statistician
Yili Pritchett, PhD, Statistician
Chunzhang Wu, PhD, Statistician
Xuegong Wang, MD, PhD, Medical
Beth Cywin, MBA, Clinical
Jay Erdman, MS, Project Management
Christine Slover, Project Management
Mary Jo Pritza, PharmD, Regulatory Affairs
Glen Spears, PhD, Regulatory Affairs

BACKGROUND

Between May 24, 2013 and June 18, 2013 numerous correspondences took place between FDA and Astellas regarding the analysis of the results presented in Table 21, Summary of Efficacy Failures (12 months) included in Astellas original NDA dated September 21, 2012 for Study FG-506E-12-03. FDA was unable to replicate the results using the data and the information stated in the define file. Specifically, FDA obtained different numbers of subjects who were lost-to-follow-up (also referred to as unknown outcome) and with an LBCAR event.

Astellas responded regarding the number of subjects with an LBCAR event. There was an additional patient considered by Astellas as having an event, but not reported in the data set. FDA responded to Astellas, in an information request dated May 31, 2013, that it was important to have submitted data that support Table 21 for Study FG-506E-12-03 in their NDA submission. Astellas submitted an updated data set on June 4, 2013.

Despite multiple correspondences regarding the number of subjects who were lost-to-follow-up, it was still unclear how Astellas arrived at the numbers presented in Table 21. To come to a common understanding of those lost-to-follow in FG-506E-12-03, FDA agreed with Astellas that a teleconference was necessary, so the June 20, 2013 meeting was scheduled.

Meeting Discussion

The following points were discussed at the June 20, 2013 teleconference between FDA and Astellas regarding data for Study FG-506E-12-03:

- It was agreed that the definition of a lost to follow-up (LTFU) was a patient with a last day less than Day 351 and with no efficacy failures within 12 months.
- It was noted that the last dose day variable (LDOSEDAY) was needed in order to identify those patients on study less than 351 days. Astellas acknowledged that the define file did not include this variable in the definition of LTFU.
- Astellas explained that the variables ENDSLDAY and ENDSDAY used to identify LTFUs have different values in the EFF dataset for the 12 month study and the EFF dataset for the full dataset. The full dataset includes data from both the 12 month period and the extension period. It was agreed that individual patients should not have different values for the same variable without clear explanation in the define file.
- Astellas agreed to provide more information regarding the location of information explaining the differences between the two datasets named EFF submitted under Study FG-506E-12-03.

Action Items:

- Astellas to provide to the FDA information regarding the location of information in the NDA explaining the differences between the two datasets named EFF submitted under Study FG-506E-12-03.

- Astellas submitted the requested information via email on June 21, 2013 and acknowledged that the description of the EFF datasets was not clear in the NDA submission.

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/s/

JACQUELYN E SMITH
07/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

GENERAL ADVICE

Astellas
Attention: Glen W. Spears
Associate Director of Regulatory Affairs
1 Astellas Way
Northbrook, Il 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Astagraf XL® (tacrolimus) Extended-Release Capsules.

We also refer to your New Drug Application dated September 20, 2012, and received September 21, 2013.

We have reviewed the referenced material and have the following comments:

A: Dissolution Testing

The following regulatory dissolution test and acceptance criteria will be in effect until data generated during fulfillment of the post-marketing commitments described below become available to support establishment of an alternative dissolution test method and/or acceptance criteria:

Table 1. Regulatory Dissolution Test Method and Acceptance Criteria

Procedure	USP <711> Dissolution
Apparatus	Apparatus 2, Paddle
Speed	50 rpm
Volume	900 mL
Medium	0.10 % sodium lauryl sulfate and 0.005 % hydroxypropyl cellulose (MW 100,000) solution whose pH is adjusted to pH 4.5 with diluted phosphoric acid (3 in 50); degas by stirring under reduced pressure for 10 minutes or equivalent
Temperature	37°C
Acceptance Criteria	The percentages of dissolved FK506 to the labeled amount at specified time points conform to the acceptance criteria indicated the Acceptance Table 2 under <711>

Time (hours)	Capsules	Ranges of Dissolved FK506 to the Labeled Amount
0.5	0.5 mg capsules	Between (b) (4) %
	1.0 mg capsules	Between (b) (4) %
	3.0 mg capsules	*Between (b) (4) %*
	5.0 mg capsules	Between (b) (4) %
1.5	all	Between (b) (4) %
7	all	NLT (b) (4) % *
24	all	Not less than (b) (4) %

*Note that an acceptance criterion of NLT (b) (4) % at 7 hours was used for release of clinical lots.

B: Post-Marketing Commitments (PMC)

PMC No. 1 - Optimize the dissolution method with respect to detection of [(b) (4)] content, by evaluating the dissolution profiles[a,b] of 0.5 mg and 5 mg capsules containing [(b) (4)] under different test conditions (medium with 0.0%, 0.05% and 0.1% added sodium lauryl sulfate (SLS), at paddle speeds of 50, 75 and 100 rpm).

Table 2. Dissolution Test Conditions Matrix

	50 rpm	75 rpm	100 rpm
0% SLS	x	x	x
0.05% SLS	x	x	x
0.1% SLS	x*	x	x

*This is the proposed regulatory test condition.

After a discriminating[c] dissolution method is developed and it is evaluated and accepted by FDA, conduct a complete assessment[d] of the dissolution method on capsules containing [(b) (4)], and [(b) (4)] content.

Conduct the following assessments using the selected discriminatory dissolution method:

1. The dissolution profiles of aged capsules (0.5 mg and 5 mg), 25°C/60% RH at 36 months;

2. The dissolution profiles of stressed capsules (0.5 mg and 5 mg), 25°C/75% RH open dish, >3 months.

Comment: *Propose timelines for the submission of the study design, interim report, study completion, and final report.*

ADVISE COMMENTS:

a. Dissolution profiles should be generated using frequent sampling (e.g., two-hour intervals) in order to establish the shape of curve and select the sampling time points for regulatory testing and setting of the acceptance criteria three to four sampling time points.

b. Data for the 1 mg [(b) (4)] capsules will also need to be collected in order to establish the acceptance criteria for the early time point, if this will vary across strengths (as is currently proposed).

c. Include the testing and criteria that will be used to evaluate the discriminating capability of the method.

d. Include the details of the complete assessment in the study design

PMC No. 2 - Optimize the acceptance criteria for the regulatory dissolution test method by analyzing the dissolution profile data of all the strength of your product at release and on stability, obtained by collecting data at two-hour intervals until a minimum of [(b) (4)] of tacrolimus is released, as well as at

the 24 hour time point. Based on these results, propose the revised acceptance criteria for the dissolution test of your product.

Comments:

- *Propose timelines for the submission of the study design, interim report, study completion, and final report.*
- *The study design should include the number of batches to be evaluated.*

PMC No. 3 - Evaluate the relationship between [redacted] (b) (4), and dissolution rate under stressed conditions and under long term stability.

Comments:

- *Propose timelines for the submission of the study design, interim report, study completion, and final report.*
- *Include the details in the study design.*

PMC No. 4 - Characterize the [redacted] (b) (4), in order to confirm the proposed shelf life of the [redacted] (b) (4) using a validated and appropriately discriminating direct measurement (e.g., ss-NMR, NIR) of [redacted] (b) (4) content and using the optimized discriminating dissolution test. Evaluate stressed and aged samples. Compare the [redacted] (b) (4) content of [redacted] (b) (4) prior to introduction into manufacture of capsules, to the [redacted] (b) (4) content of the resulting capsules.

Comment: *Propose timelines for the submission of the study design, interim report, study completion, and final report.*

ADDITIONAL COMMENTS:

1. As you develop the regulatory dissolution method, please consider the following approaches.
    a. Adjustment of the volume of the dissolution medium used for lowest strength(s) of Astagraf XL capsules, in order to enhance the sensitivity of the test method.
    b. Developing a two stage dissolution test where sodium lauryl sulfate is added after some intermediate sampling time point (e.g., 12 hours).
    c. Consider using other nonionic, cationic or anionic surfactants.

2. Consider the use of a two tier dissolution test for [redacted] (b) (4) content determination. When the regulatory dissolution test method results in a value below some pre-specified limit, a second dissolution test that can discriminate [redacted] (b) (4) content could be used (e.g. without added SLS).

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
07/03/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Wednesday, July 03, 2013 2:38 PM
To: 'Spears, Glen'
Subject: NDA 204096/tacrolimus XL

Hi Glen,

We received your 7/2/13 submission. The (b) (4) is not acceptable because the protocol does not include proposed labeling and it does not address concerns about potential medication errors. We recommend that this (b) (4) be withdrawn from the current application.

Regards,
Jacquelyn

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/s/

JACQUELYN E SMITH
07/03/2013

Smith, Jacquelyn

From	Spears, Glen [Glen.Spears@astellas.com]
Sent	Friday, June 21, 2013 12:07 PM
To	Smith, Jacquelyn; Spears, Glen
Subject	RE: NDA-204096 Information Request
Attachments	1-2-reviewers-guide.pdf

Jackie,

The follow up item for Astellas from the June 20, 2013 teleconference was to provide to the FDA a description of where in the original NDA submission the information on the two records per patient in the EFF dataset was located.

Astellas acknowledges that the description of the EFF dataset was not clear in the NDA submission.

The location in the NDA where general information about the extension data can be found is in Table 4 of the NDA Reviewer's Guide (Module 1.2) and in the text in Section 8 of the Reviewer's Guide, especially the second paragraph in Section 8.1. Here Astellas explained the 14-02 extension study and indicated that 12-03 has 2 databases (primary and full) included in the Integrated Safety Data. The NDA Reviewer's Guide is attached to this email.

Details on how the extension data were handled can be found in the first comment under the list of datasets in the Define File. For ease of review, the relevant text from the Define file is pasted below. This text describes how the protocol numbers in the datasets are specified for both primary and extension data.

Note, as also explained in the text, a notation in the define file such as FG-506E-11-03/b is an abbreviation to indicate that there are two protocols, one for the primary (FG-506E-11-03) and one for the full database (FG-506E-11-03b).

The comment for dataset EFF lists the protocols as FG-506E-12-03/b indicating that there are two protocols as described in the previous sentence.

Specification Comment

MR4 DEFINE.pdf: NOTES FOR THE NEW NDA SUBMISSION:
(including contents of subsets for datasets larger than 1GB)

1. Protocol numbers for this MR4 ISD include items such as 02-0-131 and 02-0-131e where 02-0-131 identifies the protocol database for the primary phase only and 02-0-131e identifies the full database including extension phase data along with the primary phase data. When the extension data is combined with the primary data various changes may be made to the primary data; for example, change from baseline values may be calculated from a different baseline value. Many such changes are detailed throughout this document but the primary plus extension database for the European transplant protocols deserve additional attention here.

   Extension data for the European transplant protocols, FG-506-11-01, FG-506E-12-01, FG-506E-12-02, FG-506E-11-03, FG-506E-12-03, and FG-506-15-02 were collected

Tacrolimus Extended-Release ISD Define.pdf Page 2 of 2457

in another protocol, FG-506-14-02. For this ISD a patient's extension data were pulled from the extension protocol and joined with the patient's primary data. The combined or full database has a protocol number as already explained; for example, FG-506-11-01c. All relative study days for dates in the full database which come from the extension database have been recalculated relative to the primary begin date. This recalculation is not noted over and over again for the many relative study days defined in this specification. Data for FG-506-14-02 are not included in this ISD except as combined with the data for a corresponding primary protocol.

Very few extension data were collected in FG-506-14-02 for PMR-EC-1210 (OSAKA) so a combined database was not produced for this protocol.

In order to facilitate use of this ISD database, variables are included in the first ISD data set, ACCT, which can be used to subset for groups of protocols used for the ISS tables. These variables are ISSGRFCD, ISSPEDCD, ISSTYPCD, MR4CD, NEORALCD, and PROGRFCD. ISSTYPCD (and the associated decode variable ISSTYP) identify protocols as DE NOVO, CONVERSION, or HEALTHY VOLUNTEER. In the variable descriptions of this define document, derivation logic frequently differs for DE NOVO and CONVERSION protocols. Sometimes all protocols of a type are listed in the description; other times just the terms DE NOVO and CONVERSION are used without listing the protocols of a given type. Note also that an abbreviated notation is sometimes used to indicate that a statement applies to the primary and full database for a protocol; for example, FG-506E-11-03/b is an abbreviation for FG-506E-11-03 and FG-506E-11-03b.

Please let us know if you have any questions.

Best regards,

Glen

****
Glen W Spears, Ph D
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc
Ph: (224) 205-5935
****

From: Spears, Glen
Sent: Thursday, June 20, 2013 3:45 PM
To: 'Smith, Jacquelyn'
Subject: RE: NDA-204096 Information Request

Jackie,

The Astellas attendees for today's teleconference were:

1. Rick Croy, Statistician
2. Yili Pritchett, Statistician
3. Chunzhang Wu, Statistician
4. Xuegong Wang, Medical
5. Beth Cywin, Clinical
6. Jay Erdman, Project Management
7. Christine Slover, Project Management
8. Mary Jo Pritza, Regulatory Affairs
9. Glen Spears, Regulatory Affairs

Thanks again!

Glen

****
Glen W Spears, Ph D
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc
Ph: (224) 205-5935
****

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/s/

JACQUELYN E SMITH
06/26/2013

Smith, Jacquelyn

From: Spears, Glen [Glen.Spears@astellas.com]
Sent: Wednesday, May 29, 2013 4:36 PM
To: Smith, Jacquelyn
Cc: Willard, Diana M
Subject: RE: NDA 204096/tacrolimus extended-release - comments in preparation for May 30, 2013, teleconference
Attachments: H8204-CRF.pdf; Astellas response to May 24, 2013 FDA questions.pdf

Jackie,

Here's the Astellas response! Thanks for your help! We're still planning to meet with you by teleconference on Thursday to discuss unless we hear otherwise.

Best regards,

Glen

****
Glen W. Spears, Ph.D.
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc.
Ph: (224) 205-5935
****

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Wednesday, May 29, 2013 9:41 AM
To: Spears, Glen
Cc: Willard, Diana M
Subject: RE: NDA 204096/tacrolimus extended-release - comments in preparation for May 30, 2013, teleconference

Hi Glen,

Thanks for the update. Upon receipt of your response, I will forward to the statisticians.

Regards,
Jackie

From: Spears, Glen [mailto:Glen.Spears@astellas.com]
Sent: Wednesday, May 29, 2013 10:23 AM
To: Smith, Jacquelyn
Cc: Willard, Diana M
Subject: RE: NDA 204096/tacrolimus extended-release - comments in preparation for May 30, 2013, teleconference

Hi Jackie! I just wanted to let you know that our team is working to provide some background on the questions provided last Friday and we will provide to you sometime today. When you receive

it, could you please forward to your statisticians? Thanks!

Glen

****
Glen W. Spears, Ph.D.
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc.
Ph: (224) 205-5935
****

From: Willard, Diana M [mailto:Diana.Willard@fda.hhs.gov]
Sent: Friday, May 24, 2013 10:14 AM
To: Spears, Glen
Cc: Smith, Jacquelyn
Subject: NDA 204096/tacrolimus extended-release - comments in preparation for May 30, 2013, teleconference

Hi! Dr. Spears – enclosed please find comments in preparation for the May 30, 2013, teleconference with the Division regarding NDA 204096.

Please contact Ms. Jacquelyn Smith is you have any questions.

Regards,
Diana

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
Telephone: 301-796-0833

FG-506E-12-03

8204 (Prod: BE003)

A MULTICENTRE, 1:1 RANDOMISED, DOUBLE BLIND, TWO ARM PARALLEL GROUP STUDY TO EVALUATE AND COMPARE THE EFFICACY AND SAFETY OF MODIFIED RELEASE TACROLIMUS FK506E (MR4) VERSUS TACROLIMUS FK506 IN COMBINATION WITH MMF (CELLCEPT®) AND STEROIDS IN PATIENTS UNDERGOING KIDNEY TRANSPLANTATION

Short Title: FK506E (MR4) vs FK506 in de novo KTx

Generated By: Pinar Caca_pdf

Generated On: 26 Jul 2007 05:38:13

All times stamps listed in this document are displayed in GMT

Reference is made the May 24, 2013 FDA information request concerning the in-text Table 21 of the FG-506E-12-03 Clinical Study Report.

The Astellas response follows.

General Comments:

Astellas would like to provide the following general comments. The major differences between the two datasets used for this study, OUTCOME and EFF are as follows:

1. The OUTCOME dataset was created first to support the Clinical Study Report (CSR). It was designed with multiple records per patient for each efficacy parameter because the study SAP specified events reported by time point (e.g., 24 weeks, 12 months).
2. In contrast, the EFF dataset was created later to support the ISE analysis for the NDA. It was designed with one record per patient for each efficacy parameter.

The major difference between the two datasets is the use of cutoff days to capture efficacy events. The table below summarizes the differences between the efficacy parameters related to Table 21 in each dataset.

Table 1 Summary of Differences Between Select Efficacy Parameters in the OUTCOME and EFF Datasets

Parameter	OUTCOME dataset	EFF dataset	Comment
DEATH	Captured all events through the end of the 1-year window, as defined in the study SAP (i.e., death day<=379)	Captured all events throughout the study without any data cutoff date being specified	2 FAS patients with event day > 379 were in EFF but not OUTCOME
GRLOSS (Graft loss)	Captured all events through the end of the 1-year window, as defined in the study SAP (i.e., graft loss day<=379)	Captured all events throughout the study without any data cutoff date being specified	4 FAS patients with event day > 379 were in EFF but not OUTCOME
LBCAR (BCAR via local pathologist)	Captured all events through the last dose day of study drug during the 1-year study period	Captured all events throughout the study without any data cutoff date being specified	OUTCOME reflects the protocol-planned primary analysis of this endpoint

Parameter	OUTCOME dataset	EFF dataset	Comment
LTFU (Lost to follow-up)	Recorded for all patients that did not die and whose last assessment day was prior to 1 year as defined in the study SAP (i.e., last assessment day<351)	Recorded for all patients that did not die and whose last assessment day was prior to 1 year as defined in the ISE SAP (i.e., last assessment day<335)	Last assessment day was calculated using max (ENDSDAY or ENDSLDAY or LDOSEDAY) for both datasets. The choice of 335 for the 1 year cutoff in the ISE was to be consistent with the pivotal study, 02-0-158
EFFL (Efficacy failure)	Based on any event (death, graft loss, or LBCAR) through the 1-year window, as defined in the study SAP (i.e., event day<=379). Patients that did not have death, graft loss, or LBCAR and whose outcome was unknown at 1-year (i.e., last assessment day <351; see LTFU, below) were also considered to have the event	Based on any event (death, graft loss, or LBCAR) during the study without any data cutoff date being specified. Patients that did not have death, graft loss, or LBCAR and whose outcome was unknown at 1-year (i.e., last assessment day <335; see LTFU, below) were also considered to have the event	4 FAS patients with event day <=379 were in OUTCOME and not EFFL because their last assessment day was between 335 and 351 (see LTFU above) (Note: none of the 4 from OUTCOME had death, graft loss, or LBCAR). 2 FAS patients with event day > 379 were in EFFL and not OUTCOME.

In addition to the subsetting criteria that the Reviewer specified, Astellas would like to add the following:

1. The primary database should be used (i.e., use PROTOCOL="FG-506E-12-03") because the records from the full database (i.e., PROTOCOL="FG-506E-12-03b") included data from the extension protocol, FG-506E-14-02.
2. The parameter values, EFFL and LTFU should be used rather than LBCARI and UNKOUT, because the latter parameters are specific to the full database.
3. Use the maximum cut day observation (i.e. use OMAX="YES") to ensure all events through the maximum cut day on the dataset are available. More details on the variable, OMAX, are provided in the data definition file provided in the NDA submission.

FDA Question 1. Efficacy Failures

> Using the EFF dataset, we count 74 failures on Prograf based on PARMCD LBCARI. If we use the OUTCOME dataset, we obtain the number of 78 shown in the table. The additional 4 patients (H6313, H8211, H8804 and H8805) are all recorded as lost-to-follow-ups in OUTCOME. Why don't the results for the two datasets match? Is the number of 78 from the OUTCOME dataset correct?

Astellas response: The count of efficacy failure on Table 21 can be obtained from OUTCOME using OPARMCD="EFFL". The 4 patients identified by the Reviewer as being efficacy failures on OUTCOME but not on EFF is because of the difference in dataset construction as described above. These 4 patients were considered to be LTFU in OUTCOME but not in EFF given the difference in data cutoff dates for 1 year.

Subsetting the OUTCOME dataset as described in the General Comments above (i.e., PROTOCOL="FG-506E-12-03" and OMAX="YES", etc.) provides consistent results to those described by the Reviewer. That is, 78 Prograf patients with efficacy failure, including the 4 that are not in the EFF dataset.

FDA Question 2. LBCAR

> We count 67 events for Tac-XL not 68 as recorded in the table. We believe the discrepancy is based on Patient H1807 who is counted in EFF as having an LBCAR on Day 556 but is not counted as an LBCAR event or as an efficacy failure in OUTCOME. Note that there are 12 patients (8 Tac-Xl and 4 Prograf) who are recorded as LBCAR events in EFF but not in OUTCOME; however, these same 12 are counted as having an efficacy failure in OUTCOME but without the component event recorded in the dataset.

Astellas response: There are 67 Tac-XL patients with LBCAR in the EFF dataset, all of which were counted on Table 21. However, the additional patient counted on Table 21 was not H1807 since the LBCAR event for this patient was found only from the full database (i.e. where PROTOCOL="FG-506E-12-03b"), indicating that the event was from the FG-506E-14-02 protocol (see General Comments above). The additional patient counted on Table 21 was patient H8204; the patient was not captured on either dataset since these datasets were derived using the Rejection and Biopsy Case Report Forms (CRFs), which indicated that no diagnostic biopsy was performed during the study for this patient. However, on the Graft Status CRF it was recorded that the patient had a biopsy confirmation approximately 50 days after the last dose of randomized treatment, which was contrary to the record on the Rejection and Biopsy CRF. A decision was made at the time of data analysis to include this patient as LBCAR in Table 21. Given the

inconsistency, Astellas has attached the CRF forms for patient H8204; the CRF pages referred to herein are pages 90, 149, and 154.

Each of the 12 patients referred to by the Reviewer as having a LBCAR event in EFF but not in OUTCOME was because the LBCAR events occurred after each patient's respective last dose of randomized study drug. As explained above, the OUTCOME dataset was designed to only capture LBCAR events through the last dose day of randomized treatment; therefore these 12 patients were not identified as having LBCAR in the OUTCOME dataset. However, these 12 patients did have a LBCAR event within 1-year (albeit after last dose of randomized treatment) and therefore they qualified as an efficacy failure and were denoted as such in OUTCOME.

FDA Question 3. We are able to replicate your numbers for Graft Loss and Patient Death using either EFF or OUTCOME.

No Astellas comment.

FDA Question 4. Unknown outcome

> Using the EFF dataset or the OUTCOME dataset, we are not able to replicate your numbers of 7 and 4. If we use PARMCD of UNKOUT in dataset EFF, we obtain 4 events for Tac-XL and 8 events for Prograf. If we count patients who did not have an event within the 12 month period and who did not complete the study based on their end date (ENDSLDAY or ENDTDAY <351), we obtain 6 Tac-XL patients and 18 Prograf patients. We noticed that 13 of these patients have last dose days beyond Day 365 so apparently these patients did complete the study; however, the data in EFF or OUTCOME does not allow one to indentify these patients as Month 12 completers. What programming steps did you follow to identify patients you count as unknown outcome?

Astellas response: Astellas agrees that the OUTCOME dataset alone cannot be used to replicate the numbers for "Unknown outcome" on Table 21; therefore, Astellas describes below how these numbers may be ascertained. The definition of "Unknown outcome" on Table 21 refers to patients whose last assessment day was <351 and who did not die, have graft loss, or have a biopsy confirmed acute rejection at any time during the study. Since LBCAR in OUTCOME only captured the events that occurred while patients were on therapy, the OUTCOME dataset alone is not sufficient to identify the 11 patients counted on the table.

Astellas suggests using the following two steps to identify the 11 patients with Unknown Outcome on Table 21:

1. Identify the patients in OUTCOME whose last assessment day was prior to the 1 year window (OPARMCD="LTFU" and OEV="YES") and did not die (OPARMCD="DEATH" and OEV="NO") and did not have graft loss (OPARMCD="GRLOSS" and OEVCD="NO")
2. From the patients identified in step 1, remove patients with LBCAR at any time during the study. Since OUTCOME only identified the LBCAR events through the last dose day of randomized treatment, it is most straight forward to use the EFF dataset to identify patients that had a LBCAR at any time during the study (i.e. PARMCD="LBCAR" and EVENT="YES")

The following 11 patients are those counted under *Unknown outcome* on Table 21:

- Prograf = H2908, H6313, H7902, H8211, H8302, H8804, H8805;
- Tac-XL = H6303, H8501, H8603, H8605.

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/s/

JACQUELYN E SMITH
06/26/2013

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

Memorandum to NDA File

NDA/BLA Serial #:	204,096/Original 1
Drug Name:	Tacrolimus extended release capsules (Astagraf XL)
Indication(s):	Prophylaxis of organ rejection in adult patients receiving kidney transplants.
Applicant:	Astellas
Statistical Reviewer:	Joy Mele, M.S. DBIV
Subject of Memo	Information requests to applicant

Information requests were sent to the applicant regarding Table 21 on page 84 of the study report for Study FG-506E-12-03 submitted under NDA 204096. A summary of those requests (IR) and the applicant's responses (AR) is provided here:

4/26/13 IR Discrepancy between datasets EFF and OUTCOME for the number of LBCARs
5/20/13 AR EFF includes follow-up past Month 12 while OUTCOME does not

5/24/13 IR FDA could not replicate the numbers in Table 21; details are in the IR in DARRTS
5/29/13 AR Astellas stated that one patient who had a LBCAR was not included in the datasets provided in the NDA.

5/31/13 IR FDA acknowledged that 3 of 4 enquiries from 5/24 were adequately addressed. FDA requested a new dataset to support the numbers in Table 21 and further details regarding the patients lost to follow-up (LTFU) where LTFU is defined as patients who did not complete the 12 months on Study 1203 and did not have an efficacy failure
6/5/13 AR Astellas amended the NDA with the requested dataset **CSRT21** and a corresponding DEFINE file.

6/18/13 IR The new dataset did not address concerns regarding the LTFU count for Study 1203. FDA provided Astellas with a listing of LTFU identified from dataset EFF and asked for further clarification. FDA suggested to have a teleconference.
6/19/13 AR Astellas provided additional details regarding the LTFU in Study 1203 and agreed that a teleconference was necessary.

Following the communications outlined above, there was a teleconference on June 20,2013 between Astellas staff (3 statisticians plus additional personnel) and FDA (Karen Higgins, Joy Mele and Jackie Smith). The following points were discussed:

- It was agreed that the definition of a LTFU was a patient with a last day less than Day 351 and with no efficacy failures within 12 months.

- It was noted that the last dose day variable (LDOSEDAY) was needed in order to identify those patients on study less than 351 days.
- Astellas explained that the variables ENDSLDAY and ENDSDAY used to identify LTFUs have different values in the EFF dataset for the 12 month study and the EFF dataset for the full dataset. The full dataset includes data from both the 12 month period and the extension period. It was agreed that individual patients should not have different values for the same variable without clear explanation in the define file.
- Astellas agreed to provide more information regarding the location of information explaining the differences between the two datasets named EFF submitted under Study 1203.

Astellas followed up with a communication on June 24, 2013 that provided clarifying information regarding the two datasets named EFF submitted under Study 1203 and the use of 12-03b in defining the protocol for records in the full database. The full database contains all data collected on patients randomized to Study 1203 including both the Month 12 data and the extension data (12-03b).

There are no additional outstanding issues regarding the data for Study 1203.

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/s/

JOY D MELE
06/25/2013

KAREN M HIGGINS
06/25/2013
I concur.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: June 21, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096/ Astagraf XL (tacrolimus extended-release capsules)

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES ☑ NO

NDA 204096
Astagraf XL (tacrolimus extended-release capsules)

Dear Dr. Spears,

Please refer to your NDA 204906/ Astagraf XL (tacrolimus extended-release capsules).

Please find attached comments regarding the carton and container labels and Dear Healthcare Provider Letter for the Astagraf XL product. If you would like to discuss our comments with us in further detail, after receiving them, please contact me to set up a teleconference.

Comments

1. Revise the presentation of the proprietary name from all upper case letters to title case to improve readability. For example, "ASTAGRAF" should be revised to read "Astagraf."

2. Although the established name is at least half the size of the proprietary name, the active ingredient "Tacrolimus" is more prominent than the words "extended-release capsules." Ensure the entire established name is displayed with equal prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

3. Revise the highlighted box that encases the strength and the "Once-Daily" statements so that only the strength statement is highlighted on the container labels, carton, and blister pouch labeling. The "Once-Daily" statement should appear outside the highlighted box.

4. Blister Carton Label (All Strengths)
    - Revise the strength statement on the blister carton to read XX mg per Capsule.
    - Revise the net quantity statement on the blister carton to read similar to "50 capsules (5 Blister cards containing 10 capsules each)."

5. Bottle Container Labels (All Strengths)
    - Relocate the "Once-Daily" statement to appear below the strength similar to the proposed presentation on the carton labeling.
    - Relocate the net quantity statement "30 capsules" to appear outside of the highlighted box and place below the statement "Swallow capsule whole. Do not cut, crush, or chew capsule."
    - Decrease the prominence of the statement "Swallow capsule whole. Do not cut, crush, or chew capsule" by presenting this in a smaller font size.

6. Individual Bottle Carton Labels (All Strengths)
    - The strength statement is missing from the top panel which includes the lot number and expiration date. Since it is common practice in a clinical setting to display the box upright, we recommend switching the top panel with the bottom panel to ensure the strength statement is visible when viewed from the top.

7. Accumulated Bottle Carton Labels (All Strengths)
    - The strength statement is missing from the side panel which includes the lot number and expiration date. In order to provide additional differentiation between the different strengths of Astagraf XL, include the strength statement on the panel with the lot number and expiration date.

8. Dear Healthcare Provider Letter
    - In the Dear Pharmacist Letter, the section titled (b) (4) However, this information is omitted from the Dear Healthcare Provider Letter. We recommend including this same information in the Dear Healthcare Provider Letter as post marketing data identified wrong drug errors involving wrong prescribing with Astagraf XL and this information is also important for warning prescribers of the potential medication errors.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JACQUELYN E SMITH
06/21/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Tuesday, June 18, 2013 2:36 PM
To: glen.spears@astellas.com
Subject: FW: NDA-204096 Information Request

Hi Glen,

Please see the following information request

In your communication of June 4, 2013, you state that you identified 16 Tac-XL patients "who did not have an event within the 12 month period and who did not complete the study based on their end date (ENDSLDAY or ENDTDAY <351)." Based on the definition of LTFU for the efficacy failure endpoint, these 16 patients should be included as lost-to-follow-ups in your Table 21 and also 12 additional failure events should be ascribed to Tac-XL. If you believe the number 16 is correct, please explain why these subjects are not considered events for this endpoint?

As you noted, we identified 6 Tac-XL patients (not 16) using your definition above of no event within the 12 month period and patients who did not complete the study based on their end date (ENDSLDAY or ENDTDAY < 351); 4 of the 6 are listed in your Table 21 which contain the breakdown of the results for efficacy failure. We also identified 18 Prograf patients; 7 are included in your Table 21. We have listed these 24 patients below, highlighting those patients that are included in Table 21 as lost to follow-ups. As we mentioned in our earlier communications, we also noted that the last dose days for the patients not highlighted below are beyond Day 351. In your dataset submitted June 5th (dataset CSRT21), you include a variable LASTDAY that is defined as max(ENDSDAY, ENDSLDAY, LDOSEDAY). Is the definition of a 12 month completer based on all three variables, including the last dose day, not just the end day?

To come to a common understanding of the lost-to-follow-ups in 1203, we agree that a teleconference is necessary.

FDA table of 24 patients who did not have an event within 12 months and who did not complete the study based on their end day (ENDSLDAY or ENDTDAY <351) using dataset EFF. Highlighted patients are counted as lost-to-follow-ups (i.e. unknown outcomes) in Table 21 of the Study 1203 study report.

Obs	TRTGP	PATIENT	FAS	ENDSDAY	ENDSLDAY	ENDTDAY	LDOSEDAY	UNBLNDAY
1	MR4+MMF	H8603	YES	1	1	0	0	343
2	MR4+MMF	H8605	YES	1	1	1	1	273
3	MR4+MMF	H8501	YES	27	27	8	8	415
4	MR4+MMF	H6303	YES	11	183	11	11	550
5	MR4+MMF	H2907	YES	332	332	332	482	427
6	MR4+MMF	H5901	YES	336	336	336	557	529
7	PROGRAF+MMF	H8302	YES	0	0	0	0	429
8	PROGRAF+MMF	H8211	YES	150	350	150	150	374
9	PROGRAF+MMF	H2908	YES	268	268	268	268	412
10	PROGRAF+MMF	H7902	YES	280	280	278	278	483
11	PROGRAF+MMF	H8805	YES	342	342	342	342	332
12	PROGRAF+MMF	H8804	YES	344	344	344	344	332
13	PROGRAF+MMF	H6313	YES	350	350	350	350	424
14	PROGRAF+MMF	H4905	YES	349	349	349	423	412
15	PROGRAF+MMF	H6711	YES	348	348	348	435	407
16	PROGRAF+MMF	H6608	YES	349	349	349	464	423
17	PROGRAF+MMF	H5910	YES	338	338	338	466	405
18	PROGRAF+MMF	H6706	YES	350	350	350	468	436
19	PROGRAF+MMF	H3511	YES	346	346	346	528	468
20	PROGRAF+MMF	H6603	YES	345	345	345	542	493
21	PROGRAF+MMF	H5906	YES	335	335	335	570	500
22	PROGRAF+MMF	H2421	YES	333	333	333	579	488
23	PROGRAF+MMF	H3901	YES	330	330	330	586	554
24	PROGRAF+MMF	H2902	YES	342	343	342	646	598

The statistical team would like to have a 30 minute teleconference Thursday . I will follow up with you tomorrow morning on a specific time.

Regards,
Jackie

From: Spears, Glen [mailto:Glen.Spears@astellas.com]
Sent: Tuesday, June 04, 2013 10:05 PM
To: Smith, Jacquelyn
Subject: RE: NDA-204096 Information Request

Jackie,

With the new dataset submitted today, Astellas can verify all the data in Table 21. However, further to your email communication below in regards to question 4, Astellas re-verified the patient numbers and cannot match the FDA's numbers in the May 24, 2013 communication. Astellas obtains 16 Tac-XL patients (not 6) who did not have an event within the 12 month period and who did not complete the study based on their end date (ENDSLDAY or ENDTDAY <351). Would it be possible to schedule a short teleconference (with WebEx if necessary) with the statistician to quickly resolve this question?

Best regards,

Glen

****
Glen W. Spears, Ph.D.
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc.

Ph: (224) 205-5935
****

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Tuesday, June 04, 2013 11:36 AM
To: Spears, Glen
Subject: RE: NDA-204096 Information Request

Hi Glen.

Please see statistician response:

Please refer to the following comment in our first correspondence. We identified a total of 24 patients satisfying the criteria for LTFU based on the OUTCOME dataset - the details are below in the comment. 11 of those patients are the ones they identified as unknown outcomes. We assume that the 13 other patients actually completed the study although their last day is less than 351 according to ACCT and OUTCOME datasets. Please confirm that for us.

4.Unknown outcome

Using the EFF dataset or the OUTCOME dataset, we are not able to replicate your numbers of 7 and 4. If we use PARMCD of UNKOUT in dataset EFF, we obtain 4 events for Tac-XL and 8 events for Prograf. If we count patients who did not have an event within the 12 month period and who did not complete the study based on their end date (ENDSLDAY or ENDTDAY <351), we obtain 6 Tac-XL patients and 18 Prograf patients. We noticed that 13 of these patients have last dose days beyond Day 365 so apparently these patients did complete the study; however, the data in EFF or OUTCOME does not allow one to indentify these patients as Month 12 completers. What programming steps did you follow to identify patients you count as unknown outcome?

Thanks,
Jackie

From: Spears, Glen [mailto:Glen.Spears@astellas.com]
Sent: Tuesday, June 04, 2013 11:56 AM
To: Smith, Jacquelyn
Subject: RE: NDA-204096 Information Request

Jackie,

Astellas has a question on the May 31, 2013 information request, “question 4”. Astellas can confirm the count of 11 patients but we cannot confirm the 13 patients noted in the information request. Could you please help us understand how these 13 patients were obtained, either by email or teleconference?

Astellas is planning to submit the requested dataset either tonight or Wednesday.

Best regards,

Glen

****
Glen W. Spears, Ph.D.

Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc.
Ph: (224) 205-5935
****

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Friday, May 31, 2013 2:14 PM
To: Spears, Glen
Subject: NDA-204096 Information Request

Hi Glen,

After the stat team reviewed your response to their questions, they provided the attached response and are requesting a reply. Please also note that the stat team is cancelling Monday's teleconference and if after the stat team reviews Astellas' reply, a teleconference is need, it will be rescheduled.

Regards,
Jacquelyn

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/s/

JACQUELYN E SMITH
06/19/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: June 18, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096/ Astagraf XL (tacrolimus extended-release capsules)

Total no. of pages including cover: 9

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 204096
Astagraf XL (tacrolimus extended-release capsules)

Dear Dr. Spears,

Please refer to your NDA 204906/ Astagraf XL (tacrolimus extended-release capsules).

Please find attached a clean version of the Medication Guide for Astagraf XL containing our proposed edits. If you would like to discuss our proposed edits with us in further detail, after receiving them, please contact me to set up a teleconference.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

6 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

JACQUELYN E SMITH
06/18/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Tuesday, June 18, 2013 7:16 AM
To: glen.spears@astellas.com
Cc: MaryJo.Pritza@astellas.com
Subject: RE: NDA 204096/ tacrolimus extended-release capsules (Astagraf XL)-Astellas

Hi Glen,

We acknowledge that various sections of the proposed Astagraf XL package insert (PI) that was sent to you on Friday, June 14th are not consistent with the approved Prograf (PI). This working draft of the Astagraf XL PI has been modified to follow the various labeling Guidances.

Kind Regards,

Jackie

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6114
Silver Spring, Maryland 20993
Telephone: 301-796-1002
Fax: 301-796--9881
Email: jacquelyn.smith@fda.hhs.gov

From: Almoza, Lois
Sent: Friday, June 14, 2013 1:23 PM
To: glen.spears@astellas.com
Cc: MaryJo.Pritza@astellas.com; Smith, Jacquelyn
Subject: NDA 204096/ tacrolimus extended-release capsules (Astagraf XL)-Astellas

Good Afternoon Dr. Spears,

Attached please find proposed edits to the package insert submitted on March 13, 2013. This was sent on Jacquelyn Smith's behalf who is off today. If you have any questions that cannot wait until Monday when Jacquelyn will be back in the office, you can send them to me. However, Jacquelyn is still your point of contact for NDA 204096 and will return on Monday for any questions you may have at that time.

Thank you,

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue

Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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/s/

JACQUELYN E SMITH
06/18/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: June 14, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096/ Astagraf XL (tacrolimus extended-release capsules)

Total no. of pages including cover: 32

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 204096
Astagraf XL (tacrolimus extended-release capsules)

Dear Dr. Spears,

Please refer to your NDA 204906 for Astagraf XL (tacrolimus extended-release capsules).

Please find attached a clean version of the package insert (PI) for Astagraf XL containing our proposed edits to the version you submitted March 13, 2013, noting that our version still includes "TRADENAME XL" instead of "ASTAGRAF XL." Our edits to the Medication Guide will be sent separately within the next few days.

Within the next 2 weeks, please resubmit the PI which addresses our comments and requests for information. Also, within the next 2 weeks, please submit the revised Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society letters that are consistent with the labeling as revised. These letters will be reviewed by the Division and consulted to the Office of Prescription Drug Promotion (OPDP). After review, we will provide you with our comments on these letters.

Finally, we plan to send you comments regarding the carton and container labels and other related issues next week.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
06/14/2013
signed on behalf of Jacquelyn Smith

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

MEETING MINUTES

Astellas Pharma US, Inc.
Attention: Glen Spears, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 20, 2012, received September 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for tacrolimus extended-release capsules.

We also refer to May 20, 2013, teleconference, scheduled to discuss your tacrolimus product prior to the May 22, 2013 PeRC (Pediatric Review Committee) meeting.

If you have any questions, call Jacquelyn Smith, M.A., Senior Regulatory Project Manager at 301 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures: Meeting Minutes

MEMORANDUM OF TELECONFERENCE

Meeting Date: May 20, 2013

Meeting Type: Informational

Application: NDA 204096

Drug: Tacrolimus extended-release capsules

Sponsor: Astellas Pharma US, Inc.

Indication: Prophylaxis of Organ Rejection in Kidney Transplant

FDA Participants:

Renata Albrecht, MD	Director, DTOP
Joette Meyer, PharmD	Clinical Team Leader, DTOP
Ozlem Belen, MD	Deputy Director of Safety, DTOP
Jacquelyn Smith, MA	Senior Regulatory Project Manager, DTOP

Astellas Pharma US, Inc.

Bill Fitzsimmons, PharmD	Executive VP, Regulatory Affairs, Drug Safety and Pharmacovigilance
M. Roy First, MD	VP, Global Therapeutic Area Leader, Transplant
James Keirns, PhD	Vice President, Clinical Pharmacology
Xuegong Wang, MD, PhD	Medical Director Global Medical Science Transplantation and Immunology/Inflammation
Jay Erdman, MS	Senior Director, Global Development Project Leader
Mary Jo Pritza, PharmD	Director, Regulatory Affairs
Glen W. Spears, PhD	Associate Director, Regulatory Affairs

Purpose of the meeting:

On May 20, 2013 representatives from Astellas and the FDA Division of Transplant and Ophthalmology Products (DTOP) held a teleconference to discuss the proposed pediatric studies for tacrolimus extended-release (XL) capsules, and the tacrolimus immediate release products including a granule formulation marketed in Europe, in preparation for the May 22, 2013, Pediatric Review Committee (PeRC) meeting.

Background:

Astellas requested a partial waiver for the pediatric kidney transplant recipients from 0 to < 5 years of age for tacrolimus XL because studies are impossible or highly impractical. There are only about 500 children between 1 and 5 years that were transplanted between 2009 and 2011 (three year period) and are dispersed among approximately 200 transplant centers in the US; and only about 5

patients between 0-1 year of age. Tacrolimus XL is an extended release version of tacrolimus (marketed as Prograf) that may not be suitable for administration to children below 5 years of age who are unable to swallow the capsule. In addition, pediatric patients generally need higher doses and more frequent dosing than older children and adults because of higher clearance, and often the regimen is individualized to the patient. Tacrolimus XL is intended for once-daily administration in adults; more frequent dosing in children and/or doses requiring multiple capsules may not be feasible with the tacrolimus XL product given not only its quite large size but also because it may not be possible to attain the same pharmacokinetic profile as in adults and conducting controlled pediatric efficacy and safety studies is not feasible because of the small number of pediatric transplant recipients.

Astellas also requested a deferral for the pediatric kidney transplant recipients from 5 to 16 years of age for tacrolimus XL. Astellas proposed to obtain PK data in 24 recipients of kidney transplants converted to tacrolimus XL capsules from Prograf (tacrolimus immediate release capsules) after at least 6 months post-transplant. This sample size is considered to be adequate to compare the PK parameters between children and adults and to establish a dosing regimen in children.

Based on information found on the EMA web site,[1] Astellas Pharma Europe developed a granule formulation of immediate release tacrolimus, as 0.2 mg and 1 mg sachets. The product was first marketed in Japan in 2001 as Prograf granules and received marketing authorization from the European Medicines Agency (EMA) as Modigraf® in 2009 for the "prophylaxis of transplant rejection in adult and pediatric kidney, liver, or heart allograft recipients." According to the EMA Assessment Report for Modigraf, "for children and for seriously ill adults with difficulties to swallow capsules, there has been a widespread off-label clinical practice to break the Prograf capsules and use the granules." The document also states that the oral granule formulation was developed "to provide a dosing formulation suitable for paediatric transplant recipients, and to provide a formulation that allows fine dose adjustments."

Meeting Discussion

The meeting discussion began with introductions, followed by introductory comments from FDA about the information provided to PeRC and the purpose for the May 20, 2013 teleconference. FDA was interested in additional details on Astellas' rationale for requesting the waiver of patients 0 to < 5 years and deferral of patients 5 to 16 years, as well as further background on pediatric development of the immediate release product. Following discussion, Astellas confirmed that the information FDA plans to present at the PeRC meeting accurately reflects their proposal.

FDA asked why the Modigraf product approved for marketing in Europe is not being marketed in the United States (US). Astellas responded [redacted] (b) (4)

[1] EMA Assessment Report for Modigraf: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000954/WC500030473.pdf

FDA further inquired about whether Astellas had ever attempted to formulate an oral liquid formulation of Prograf. Astellas responded that (b) (4) .

Finally, FDA asked whether Astellas was aware of published data on the pharmacokinetics and efficacy of immediate release tacrolimus in the literature and whether they would be willing to submit the information to support pediatric labeling for Prograf in kidney transplantation. Astellas (b) (4) .

Minutes Preparer: Jacquelyn Smith, M.A., Senior Regulatory Project Manager, DTOP
Chair Concurrence: Renata Albrecht, M.D., Director, DTOP

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/s/

RENATA ALBRECHT
06/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

INFORMATION REQUEST

Astellas Pharma US, Inc.
Attention: Glen W. Spears, PhD
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted September 21, 2013 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules.

We also refer to your April 19, 2013, submission, containing a response to our February 14, 2013 information request.

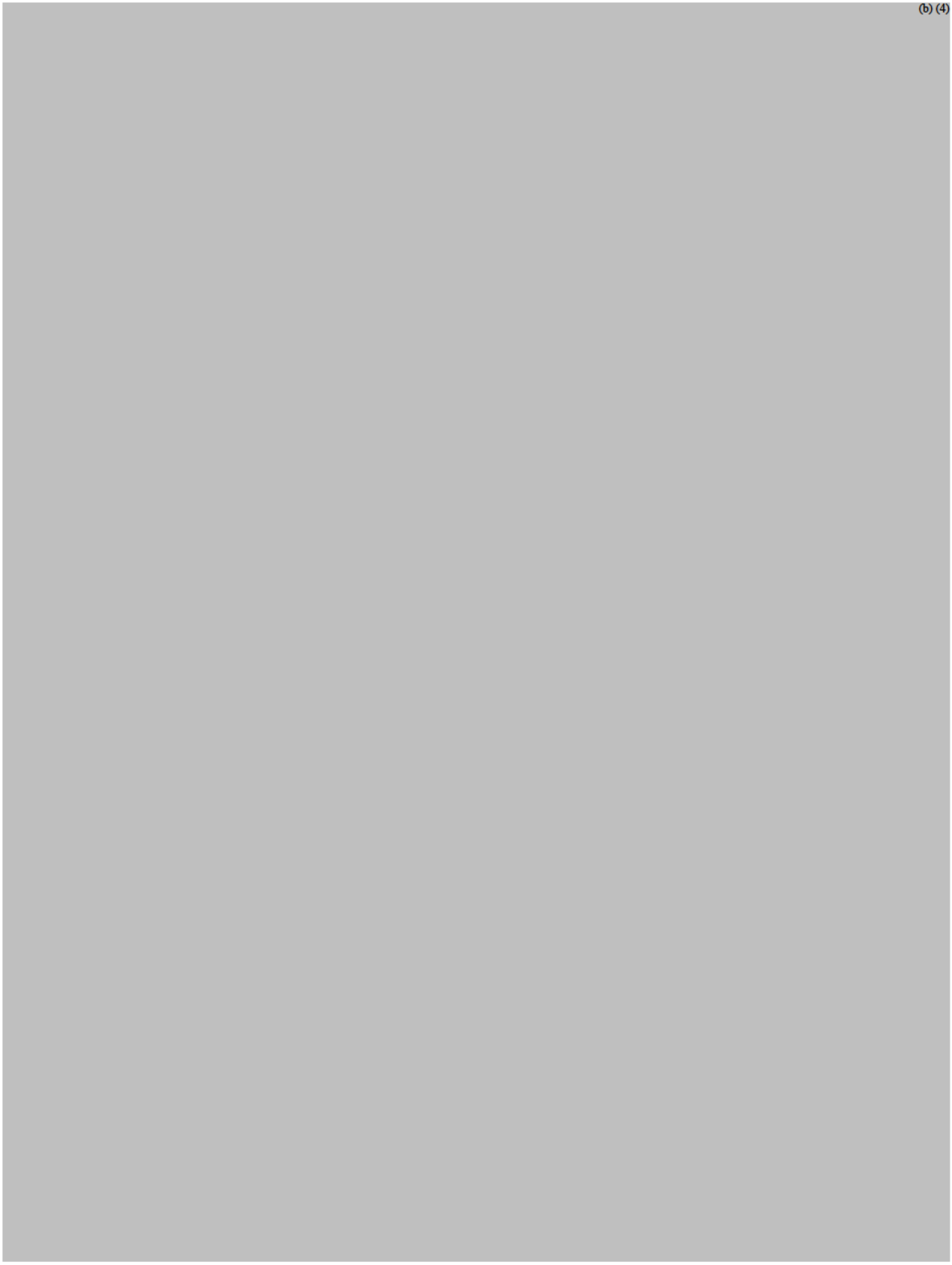
We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by June 9, 2013, in order to continue our evaluation of your NDA.

1. The proposed dissolution test method and acceptance criteria for tacrolimus extended-release capsules are:

(b) (4)

Test Items	Specifications	Methods
Dissolution	(b) (4)	USP <711> Dissolution

(b) (4)



2. (b) (4)

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
06/04/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204096

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Astellas Pharma US, Inc.
1 Astellas Way
Northbrook, IL 60062

ATTENTION: Glen W. Spears, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 20, 2012, and received September 21, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Extended- release Capsules, 0.5 mg, 1 mg, and 5 mg.

We also refer to your April 9, 2013, correspondence, received April 10, 2013, requesting review of your proposed proprietary name, Astagraf XL. We have completed our review of this proposed proprietary name, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your April 10, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact Jacquelyn Smith, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-1002.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/31/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: May 31, 2013

To: Glen Spears, Ph.D. Associate Director, Regulatory Affairs	**From:** Jacquelyn Smith, M.A. Senior Regulatory Project Manager
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** jacquelyn.smith@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096 tacrolimus extended-release

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES ☑ NO

NDA 204096
tacrolimus extended-release

Dear Dr. Spears,

Please refer to your NDA 204906/tacrolimus extended-release.

We have received your response to our questions and comments from May 24, 2013 regarding Study FG-506E-12-03 submitted under NDA 204096.

It is necessary to have submitted data that support Table 21 in your NDA submission. As it does not appear that Table 21 can be created from submitted data, we will need you to submit an additional dataset. This dataset should contain the efficacy failure data and the events that support that outcome for Month 12. Please provide this dataset with a define file made specifically for this dataset. This define file should describe how lost-to-follow-ups were defined in detail. It should also describe how this dataset differs from the other two datasets you have provided (EFF and OUTCOME). You should describe the one patient with an LBCAR that is counted in your table but not in the previously submitted datasets.

Your reply to our Question 4 is not sufficient. Your programming steps include subsetting on patients defined as LTFU in OUTCOME. We were able to obtain a count of 11 patients (the same ones you list) by the steps we stated (no event and an end date<351) and also by noting that 13 patients had a dosing date after their end date. Please confirm that this is correct. You should include last dose day or a study completer variable in your new dataset.

We are canceling the teleconference planned for Monday June 3rd at 9:30 AM EST. We will determine after receiving the new dataset and additional information whether a new meeting is necessary.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JACQUELYN E SMITH
05/31/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: May 24, 2013

To: Glen Spears, Ph.D.	**From:** Diana Willard Chief, Project Management Staff
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** diana.willard@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096/tacrolimus extended-release – material in preparation for May 30, 2013, teleconference

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES ☑ NO

Dear Dr. Spears:

Please refer to your NDA 204096/tacrolimus extended-release.

The following comments are for use in preparation for the May 30, 2013, teleconference.

Table 21: Summary of Efficacy Failures (12 Months)

Per Protocol Set		
	FK506 (N=291)	**MR4 (N=280)**
Number of efficacy failures	55 (18.9)	63 (22.5)
Local biopsy-confirmed acute rejection	49 (16.8)	59 (21.1)
Graft loss	7 (2.4)	9 (3.2)
Patient Death	3 (1.0)	3 (1.1)
Unknown outcome or latest assessment before Day 351	5 (1.7)	0
Full Analysis Set		
	FK506 (N=336)	**MR4 (N=331)**
Number of efficacy failures	78 (23.2)	93 (28.1)
Local biopsy-confirmed acute rejection	54 (16.1)	68 (20.5)
Graft loss	24 (7.1)	28 (8.5)
Patient Death	8 (2.4)	10 (3.0)
Unknown outcome	7 (2.1)	4 (1.2)

Patients (%) (more than one event per patient was possible).

Efficacy failure was defined as a biopsy-confirmed acute rejection (local biopsy, incl. the follow-up period until 12 month for withdrawals), graft loss, death or unknown outcome at the end of the 12-month period.

We were not able to replicate your numbers in Table 21 shown above. We defined our Month 12 dataset based on FAS="YES" and using a cutoff day (max of ENDSDAY or ENDSLDAY) of 379. We used Day 379 based on the SAP (page 15) which states that the window for analysis for DAY 365 is Day 351 to Day 379. We analyzed both datasets EFF and OUTCOME.

We have the following comments regarding the events displayed in the above table for the Full Analysis Population in Study 1203.

1. Efficacy Failures
   Using the EFF dataset, we count 74 failures on Prograf based on PARMCD LBCARI. If we use the OUTCOME dataset, we obtain the number of 78 shown in the table. The additional 4 patients (H6313, H8211, H8804 and H8805) are all recorded as lost-to-follow-ups in OUTCOME. Why don't the results for the two datasets match? Is the number of 78 from the OUTCOME dataset correct?

2. LBCAR
   We count 67 events for Tac-XL not 68 as recorded in the table. We believe the discrepancy is based on Patient H1807 who is counted in EFF as having an LBCAR on

Day 556 but is not counted as an LBCAR event or as an efficacy failure in OUTCOME. Note that there are 12 patients (8 Tac-Xl and 4 Prograf) who are recorded as LBCAR events in EFF but not in OUTCOME; however, these same 12 are counted as having an efficacy failure in OUTCOME but without the component event recorded in the dataset.

3. We are able to replicate your numbers for Graft Loss and Patient Death using either EFF or OUTCOME.

4. Unknown outcome
   Using the EFF dataset or the OUTCOME dataset, we are not able to replicate your numbers of 7 and 4. If we use PARMCD of UNKOUT in dataset EFF, we obtain 4 events for Tac-XL and 8 events for Prograf. If we count patients who did not have an event within the 12 month period and who did not complete the study based on their end date (ENDSLDAY or ENDTDAY <351), we obtain 6 Tac-XL patients and 18 Prograf patients. We noticed that 13 of these patients have last dose days beyond Day 365, so apparently these patients did complete the study; however, the data in EFF or OUTCOME does not allow one to identify these patients as Month 12 completers. What programming steps did you follow to identify patients you count as unknown outcome?

If you have any questions regarding this communication, please contact Ms. Jacquelyn Smith at (301) 796-1600.

Sincerely,

Diana Willard
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
05/24/2013

PeRC PREA Subcommittee Meeting Minutes
May 22, 2013

PeRC Members Attending:
Lynne Yao
Robert "Skip" Nelson
Karen Davis-Bruno (Tacrolimus Review Only)
Rosemary Addy
Patricia Dinndorf
Peter Starke
Hari Cheryl Sachs
Wiley Chambers
Lily Mulugeta
Kevin Krudys
Susan McCune (Tacrolimus Review Only)
Dianne Murphy
George Greeley
Courtney Suggs
Andrew Mosholder
Martha Nguyen
Daiva Shetty (Did not review (b) (4)
Julia Pinto
William Rodriguez
Gregory Reaman
Rachel Witten
Maura O'Leary

Guests Attending:

Dionna Green (OCP)
Donna Snyder (PMHS)
Jeremiah Momper (OCP)
Gil Burckart (OCP)
Terrie Crescenzi (OPT)
Nichella Simms (PMHS)
Stacey Min (DAVP)
Jagjit Grewal (DGIEP)
Erica Wynn (PMHS)
Meredith Libeg (DOP2)
Ethan Hausman (PMHS)
Patricia Keegan (DOP2)
Robert Levin (DPP)
Ozlem Benen (DTOP)
Gerlie Gieser (OCP)
Renata Albrecht (DTOP)
Phil Colangelo (DTOP)
Huixia Zhang (OCP)
Reiling Yang (OB)
Famoth Sohrabi (DGIEP)
Erica Radden (PMHS)
Dionna Green (OCP)
Amy Taylor (PMHS)
Alyson Karesh (PMHS)
Jeanine Best (PMHS)
Lori Gorski (PMHS)
Denise Cook (DDDP)
Michelle Roth-Cline (OPT)
Sandra Casar (DOP2)
Jane Inglese (ORP)
Diko Kazandiion (DOP2)
Juliette Toure (DPP)
Violette Kh'mek (DPP)
Joette Meyer (DTOP)
Jacquelyn Smith (DTOP)
Ergun Velidelegolin (DTOP)
Lucas Kempt (DPP)
Hao Zhn (OCP)
Robert Ferentino (DGIEP)
Matthew Scherer (DGIEP)

Agenda

NDA 204-096 Tacrolimus XL Partial Waiver/Deferral/Plan

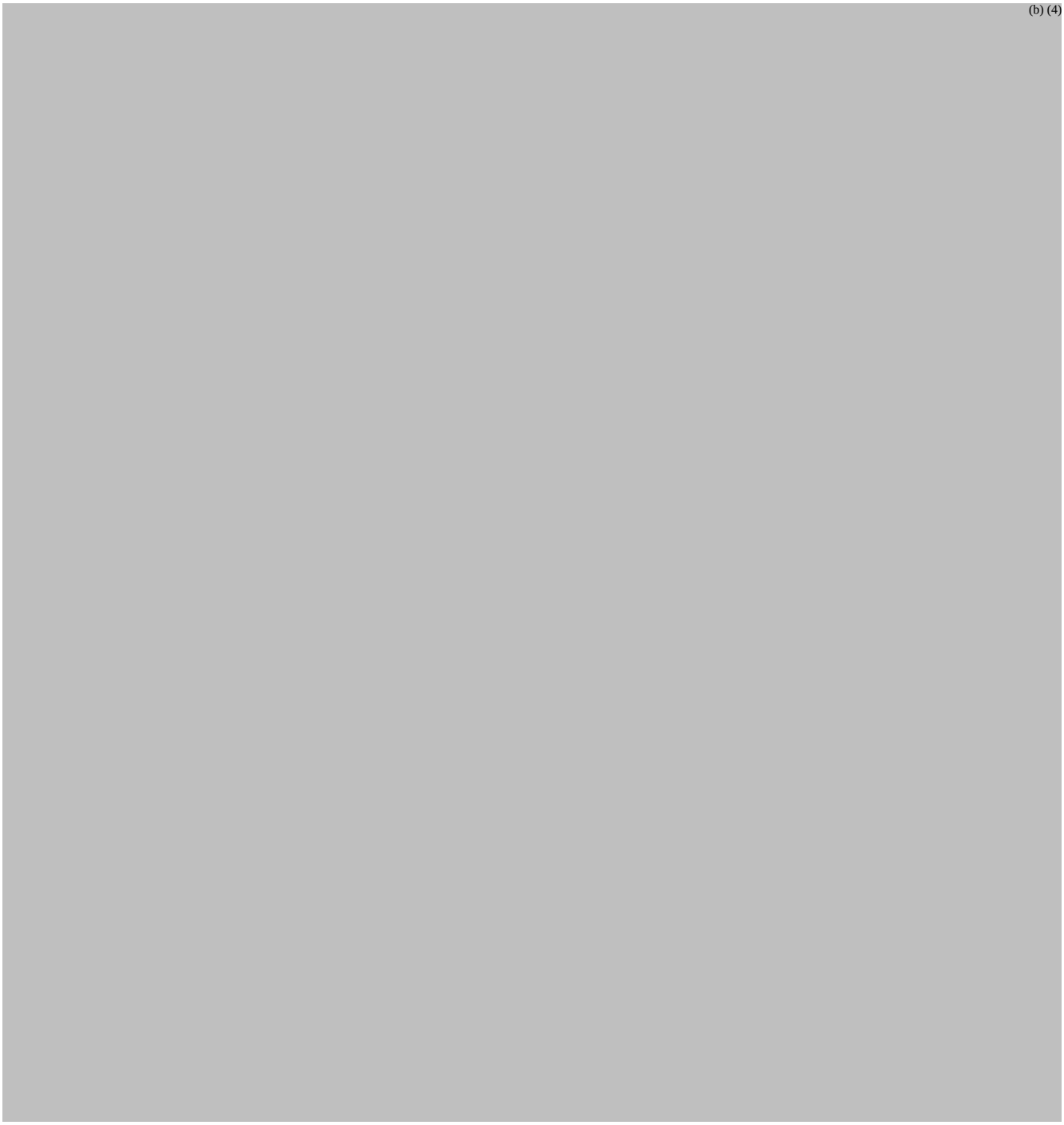
NDA [redacted] (b) (4)

Tacrolimus XL Partial Waiver/Deferral/Plan

- NDA 204-286, Tacrolimus XL, capsules were studied for the prophylaxis of organ rejection in adult patients receiving kidney transplants.
- The application was submitted September 21, 2012 and has a PDUFA date of July 21, 2013.
- This product triggers PREA as a new dosage form and new dosing regimen.
- The Division is requesting a partial waiver in pediatric patients ages birth to < 5 years of age because studies are impossible or highly impractical and a deferral in patients 5-16 years of age because adult studies are completed and the product is ready for approval.
- *Division justification for waiver*:
- Based on the 2010 annual data report of the Scientific Registry of Transplant Recipients (SRTR), over the three year period from 2007 to 2009, there were only seven (7) pediatric kidney transplant patients ages younger than one (1) year and only 478 pediatric kidney transplant patients ages between one (1) to five (5) years old in the United States for the two year period. By contrast, there were 2,050 kidney transplant recipients between six (6) to 17 years of age in the United States. More recent data from 2011 shows the number of pediatric kidney transplant recipients continues to be approximately 500 pediatric kidney recipients 1-5 years of age in the three year period 2009 to 2011.
- The Division states that this is an extended release formulation of Tacrolimus XL and the capsule is too large for young children to swallow resulting in a request for a waiver in the youngest population. It is unlikely that a pediatric extended release formulation could be formulated.
- The IR formulation was approved in the early 1990's and the company has a capsule formulation. (b) (4) [redacted]. It was also noted that a sache was developed and marketed for use in Europe and is being used as an alternate IR formulation.
- Committee members questioned whether the Agency could require a sponsor to develop an age-appropriate formulation for both the IR and ER dosage forms.
- According to what was found on the public database, the current indication under review is not exempt from PREA.

- The PeRC recommends that the Division not waive patients below the age of five years in order to allow for the development of an age-appropriate formulation.
- The PeRC agreed with the Division to grant a partial waiver in patients birth to <1 year because studies are impossible or highly impractical and agreed to deferral in patients ages 1 to <5 years to develop a pediatric formulation. The PeRC also agreed to defer pediatric studies in patients 5 to 16 years because the product is ready for approval in adults.

(b) (4)



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/s/

GEORGE E GREELEY
01/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096 [Original 1-Kidney]
NDA 204096 [Original 2- Liver (Males)]

WITHDRAWAL OF ORIGINAL 2 AND REMS

Astellas Pharma US, Inc.
Attention: Glen W. Spears, PhD
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 21, 2012 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for tacrolimus extended-release capsules.

We acknowledge your February 6, 2013 submission requesting that NDA 204096 Original 2-Liver (males) for tacrolimus extended–release capsules be withdrawn without prejudice to refilling.

We also acknowledge your submission dated April 18, 2013 requesting withdrawal of the REMS.

If you have any questions, call Ms. June Germain, Acting Safety Regulatory Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

OZLEM A BELEN
05/14/2013

Memo to File
NDA 204096, Tacrolimus XL capsules
Ozlem Belen, MD, MPH

Memorandum to NDA 204096

NDA:	**204096 administratively split [Original 1 – Kidney] and [Original 2 – Liver (males)]**
Supporting Document Number(s):	11 and 30
Dates Received:	February 6, 2013 and April 19, 2013
Subject:	Withdrawal of the Liver Indication and REMS
Sponsor:	Astellas
Product:	Tacrolimus extended-release (XL) capsules
Deputy Director for Safety:	Ozlem Belen, MD, MPH
Team Leader:	Joette Meyer, Pharm. D.
Date:	May 13, 2013, 2013

Astellas Pharma submitted NDA 204096 for tacrolimus extended-release (XL) capsules (Advagraf®)[1] on September 21, 2012 for the following proposed indications:

- Prophylaxis of organ rejection in adult patients receiving kidney transplants.
- Prophylaxis of organ rejection in adult male patients receiving liver transplants

Astellas also proposed a Risk Evaluation and Mitigation Strategy (REMS) that consisted of a communication program to inform healthcare providers and patients about the following potential risks of tacrolimus XL:

1. Increased mortality in female liver transplant recipients treated with tacrolimus XL compared to Prograf (tacrolimus XL is not recommended in female patients receiving *de novo* liver transplants).
2. Risk of medication errors with tacrolimus XL due to unintentional conversion or substitution between approved tacrolimus formulations (once-daily extended-release and twice-daily immediate-release versions).

On February 6, 2013 Astellas requested that NDA 204096 [Original 2 – Liver (Males)] for tacrolimus XL capsules be withdrawn without prejudice to refiling.

The Review Division (Division of Transplant and Ophthalmology Products – DTOP), in consultation with the Office of Surveillance and Epidemiology (OSE) / Division of Risk Management (DRISK) and the Division of Medication Error Prevention and Analysis (DMEPA), determined that the medication error issue should be handled outside of a REMS. Astellas was notified of that the medication error issue should be handled outside of a REMS on January 30th, 2013. On February 19, 2013, Astellas re-submitted the medication error information to the NDA as a separate document (*Medication Error Minimization Strategy*). This amendment and other additional information pertaining to medication error issue requested by DMEPA are currently under review.

[1] The trade name Advagraf was not found acceptable by DMEPA

On April 18, 2013 Astellas requested that the REMS for NDA 204096 be withdrawn.

Since the liver indication has been withdrawn and the medication errors are being managed independent of a REMS, both of the proposed goals of the REMS are no longer relevant and the Review Division agrees that the REMS for NDA 204096 can be withdrawn. A letter acknowledging the withdrawal of the liver indication and REMS will be issued.

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/s/

OZLEM A BELEN
05/13/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Friday, May 10, 2013 12:59 PM
To: 'Spears, Glen'
Cc: Smith, Jacquelyn
Subject: NDA 204096-TAC-XL Information Request re alcohol induced dose dumping

Hi Glen,

Please respond to the below information request:

In light of your finding that there was significant acceleration of the in vitro dissolution of tacrolimus extended release (TAC XL) capsules in 40% alcohol at pH 1.2 (i.e., “dose dumping”), we recommend that you propose labeling language that would warn against the concomitant administration of TAC-XL capsules with alcoholic beverages. In addition, please propose how you will address whether there is a time window later in the day when it would be safe for patients taking TAC-XL capsules to consume alcohol. Please provide your responses within 2 weeks of receiving this information request.

If there are any questions regarding this request, a brief teleconference can be scheduled to discuss.

Kind Regards,
Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6141
Silver Spring, Maryland 20993
Telephone: 301-796-1002
Fax: 301-796--9881
Email: jacquelyn.smith@fda.hhs.gov

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/s/

JACQUELYN E SMITH
05/10/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: April 26, 2013

To: Glen Spears, Ph.D.	**From:** Diana Willard Chief, Project Management Staff
Company: Astellas Pharma US, Inc.	Division of Transplant and Ophthalmology Products
Email: glen.spears@astellas.com	**Email:** diana.willard@fda.hhs.gov
Telephone Number: 224-205-5935	**Phone number:** 301-796-1600

Subject: NDA 204096 tacrolimus extended-release

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES ☑ NO

NDA 204096
tacrolimus extended-release

Dear Dr. Spears,

Please refer to your NDA 204906/tacrolimus extended-release.

We have the following comment regarding your September 20, 2012, submission:

> Your Table 21 on page 84 of your study report for Study FG-506E-12-03 shows 54 LBCARs for Prograf and 68 for Tac-XL for the full analysis set. Dataset OUTCOME yields 50 LBCARs for Prograf and 59 for Tac-XL, a discrepancy of 13 LBCARs. We found that the LBCAR count in dataset EFF yielded a number matching your Table 21. Of these 13 patients with a recorded LBCAR in dataset EFF but not in dataset OUTCOME, one patient had an event day of 556 while the rest had event days within the 12 month follow-up period. Eleven of these 13 patients were recorded as having an efficacy failure in dataset OUTCOME with no record of the type of failure. For most of these patients the event day recorded for outcome EFFL in the OUTCOME dataset- equaled the event day recorded for LBCAR in dataset EFF.
>
> We did not find any discrepancies with the other outcome variables in the OUTCOME dataset.
>
> Please explain these data problems. If there are indeed errors in the OUTCOME dataset, please submit an updated OUTCOME dataset for Study FG-506E-12-03 with a define file specifically written for this dataset.
>
> Please submit the requested information by May 7, 2013.

In addition, we have the following comment regarding your April 24, 2013, response to our April 17, 2013, information request:

> In light of the small number of kidney transplant patients who received tacrolimus as a compounded suspension via the nasogastric tube in Studies 158 (N = 1) and 12-03 (N=11), we are no longer interested in receiving the previously requested SAS datasets.

If you have any questions regarding this communication, please contact Ms. Jacquelyn Smith at (301) 796-1600.

Sincerely,

Diana Willard
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
04/26/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Wednesday, April 17, 2013 3:44 PM
To: 'Spears, Glen'
Subject: NDA 204096--TAC-XL Information Request: nasogastric administration of tacrolimus suspension from capsule contents

Hi Glen,

Please respond to the below information request:

Please provide information regarding the number of kidney transplant patients in Studies 12-03 and 158 who received their initial tacrolimus XL (TAC XL) doses as a suspension via a nasogastric tube, and the detailed procedure for preparation and administration of the suspension. Please submit the supporting .xpt datasets, including the time of the preparation of the suspension and the time of actual administration. If available, please also provide data regarding the stability of the compounded suspension preparation of TAC XL.

Kind Regards,
Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6141
Silver Spring, Maryland 20993
Telephone: 301-796-1002
Fax: 301-796--9881
Email: jacquelyn.smith@fda.hhs.gov

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/s/

JACQUELYN E SMITH
04/18/2013

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Tuesday, April 09, 2013 3:04 PM
To: 'Spears, Glen'
Subject: NDA 204096 tac-XL: response to Study 11-01-3/6/13 submission

Hi Glen,

A mistake was made when referring to the relevant figures in the tables below. All the figure numbers were 1.1 now they are 1.1, 1.2 and 1.3 as they should be so please replace the previous email with this email.

Thanks,
Jacquelyn

For All patients:

Day 1	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	10.88	< 10
Prograf Female	21.78	< 20
Tac XL Male	10.49	< 10
Prograf Male	19.84	< 17.5

Day 14	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	22.18	≈ 22 (no discrepancy)
Prograf Female	23.12	< 20
Tac XL Male	26.78	< 35
Prograf Male	24.92	≈ 22.5

Day 42	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	33.43	≈ 27.5
Prograf Female	23.33	≈ 20
Tac XL Male	27.84	< 25
Prograf Male	28.81	≈ 25

For Recipients of Female Donors:

Day 1	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.2
Tac XL Female	7.90	7.90 (no discrepancy)
Prograf Female	23.01	< 20
Tac XL Male	9.28	< 8
Prograf Male	20.42	< 17.5

Day 14	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.2
Tac XL Female	25.52	< 25
Prograf Female	23.48	< 20
Tac XL Male	31.85	< 30
Prograf Male	24.12	< 22.5

Day 42	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.2
Tac XL Female	35.16	≈ 27.5
Prograf Female	25.37	≈ 22.5
Tac XL Male	26.69	≈ 25
Prograf Male	30.02	≈ 27.5

For Recipients of Male Donors:

Day 1	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.3
Tac XL Female	13.86	< 10
Prograf Female	19.06	< 20
Tac XL Male	11.25	< 10

Prograf Male	19.57	< 17.5

Day 14	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.3
Tac XL Female	19.40	≈ 22.5
Prograf Female	22.33	≈ 22.5 (no discrepancy)
Tac XL Male	23.63	≈ 22.5 (no discrepancy)
Prograf Male	25.20	≈ 22.5

Day 42	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.3
Tac XL Female	31.98	< 30
Prograf Female	18.57	≈ 17.5
Tac XL Male	28.55	≈ 25
Prograf Male	28.41	≈ 25

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Tuesday, April 09, 2013 11:41 AM
To: 'Spears, Glen'
Subject: NDA 204096 tac-XL: response to Study 11-01-March 6, 2013 submission

Hi Glen,

In spot checking the data plotted in Figure 1.1 on Days 1, 14, and 42 we noticed that the mean Cmax values do not match the mean Cmax values listed in Table 1.1 on the corresponding days. Examples are listed below. Please provide an explanation for the discrepancies or let us know if there was an error in the tables or the figures.

For All patients:

Day 1	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	10.88	< 10
Prograf Female	21.78	< 20
Tac XL Male	10.49	< 10
Prograf Male	19.84	< 17.5

Day 14	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	22.18	≈ 22 (no discrepancy)
Prograf Female	23.12	< 20
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Prograf Male	24.92	≈ 22.5

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Tac XL Male	27.84	< 25
Prograf Male	28.81	≈ 25

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Day 1	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	7.90	7.90 (no discrepancy)
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Tac XL Male	9.28	< 8
Prograf Male	20.42	< 17.5

Day 14	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
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Tac XL Male	31.85	< 30
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Day 1	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	13.86	< 10
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Day 42	Mean Cmax from Table 1.1	Estimated mean Cmax from Figure 1.1
Tac XL Female	31.98	< 30
Prograf Female	18.57	≈ 17.5
Tac XL Male	28.55	≈ 25
Prograf Male	28.41	≈ 25

We would like to follow up with you in a tcon in the next few days to find out more about where the problem lies.

Regards,
Jackie

Jacquelyn Smith, M.A.

Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6141
Silver Spring, Maryland 20993
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/s/

JACQUELYN E SMITH
04/09/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204096

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Astellas Pharma US, Inc.
1 Astellas Way
Northbrook, IL 60062

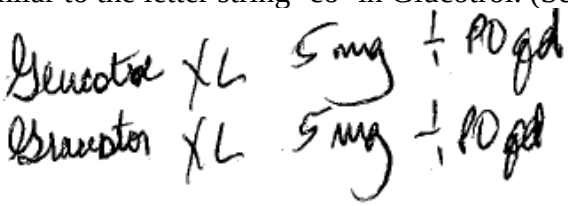
ATTENTION: Glen W. Spears, PhD
Associate Director, Regulatory Affairs

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 20, 2012, and received September 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended- release capsules, 0.5 mg, 1 mg, and 5 mg.

We also refer to your January 3, 2013, correspondence, received January 4, 2013, requesting review of your proposed proprietary name, Graceptor XL. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, Graceptor XL, is orthographically similar to and has overlapping product characteristics with the currently marketed product, Glucotrol XL (Glipizide Extended-release) Tablets. Both names contain the same number of letters (9), begin with the letter 'G,' contain the letter 'c' in the 4th position, contain a cross-stroke 't' in a similar position which is closely followed by the letter 'o,' and both names have the same modifier 'XL.' Moreover, if both letters 'l' in Glucotrol are scripted without a prominent upstroke, the letters 'l' in Glucotrol may look similar to the letters 'r' in Graceptor. This similarity was confirmed by the Agency's prescription studies. Additionally, if the letter 'p' in Graceptor is scripted without a prominent downstroke, the infix letter string 'cep' in Graceptor may look similar to the letter string 'co' in Glucotrol. (See example below.)



In addition to the orthographic similarity of this name pair, the products have overlapping product characteristics such as strength (5 mg), dosage (2.5 mg, 5 mg, 10 mg), both are a solid oral dosage form, route of administration (oral), and frequency of administration (once daily). These overlapping product characteristics in conjunction with the orthographic similarity make the name pair vulnerable to confusion which can lead to wrong drug errors.

We acknowledge that our conclusion on the acceptability of the name differs from the conclusions reached by the (b) (4) However, the name Glucotrol XL was not identified or evaluated in the external name review. There is no information provided in the submission that account for why the external consultants did not identify the name.

We note that you have proposed an alternate proprietary name in your submission dated January 4, 2013. In order to initiate the review of the alternate proprietary name, Astagraf XL, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hyun Son, at 301-796-1939.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
04/04/2013

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: March 8, 2013

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939
Subject: NDA 204096 tacrolimus extended-release: request for information Studies 158 and 12-03	
Total no. of pages including cover: 5	

Document to be mailed: YES ☑ NO

Dear Dr. Spears,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules, NDA 204096. We are reviewing your submission and have the following information requests for Studies 02-0-158 and FG-506E-12-03 (kidney transplant).

We request that you submit the responses **within 2 weeks**. Please let us know if you will not be able to meet this timeline.

As discussed below, we have created table templates to show how we would like the data presented. However, as some of our requests are complex, please consider preparing your own mock tables/figures once you have considered our requests, if you believe they are more appropriate. We can review your proposal and provide comments, before you submit the final version with complete data.

If you have any questions about these requests, please contact me (Hyun Son) to obtain clarification or schedule a brief conference with the Division. If you have previously submitted data in the same format as requested below, please assist us in locating the information within the NDA submission.

Please use the FAS population for all analyses.

New Onset Diabetes After Transplantation (NODAT):

1. We refer you to the Adverse Reactions section of the Prograf® package insert. Table 9 "Incidence of New Onset Diabetes After Transplant at 1 year in Kidney Transplant Recipients in a Phase 3 Trial (Study 2)" presents the data from Study 02-0-158 for the Prograf and Neoral® arms of the study. Please create a similar table including data from the tacrolimus XL arm, in addition to the other two arms. As in Table 9, please define NODAT as a composite of any of the following occurring in a subject without diabetes mellitus at baseline: fasting plasma glucose values of 126 mg/dL or more; HbA1C $\geq$ 6%, insulin use $\geq$ 30 days or oral hypoglycemic use. For each cell provide the numbers and % as the proportion of the patients at risk without pre-transplant history of diabetes mellitus. See mock table below with the columns containing the information from Table 9.

Incidence of New Onset Diabetes After Transplant at 1 year in Kidney Transplant Recipients without Pre-Existing Diabetes Mellitus* in Study 02-0-158

Parameter	Treatment Group		
	Prograf/MMF (n = 212)	Tacrolimus XL/MMF (n=214)	Neoral/MMF (n = 212)
NODAT**	112/150 (75%)		93/152 (61%)
Fasting Plasma Glucose ≥ 126 mg/dL	96/150 (64%)		80/152 (53%)
HbA1C ≥ 6%	59/150 (39%)		28/152 (18%)
Insulin Use ≥ 30 consecutive days	9/150 (6%)		4/152 (18%)
Oral Hypoglycemic Use	15/150 (10%)		5/152 (3%)

* Incidence is calculated based upon the number of patients in the FAS population who did not have diabetes mellitus at randomization (pre-transplant)
** Patients with NODAT were defined as those experiencing one or more or the criteria listed individually in the table.

2. Using the same composite definition of NODAT, please create a similar table using data from FG-506E-12-03. Again, in each cell please provide the numbers and % as the proportion of the patients without pre-transplant history of diabetes mellitus.

Diarrhea and Loose Stools:

3. Diarrhea and loose stools are recognized hazards associated with the use of mycophenolate mofetil (MMF) in combination with tacrolimus. In our earlier review of Study 02-0-158 in kidney transplantation, the following tables were generated by the FDA reviewer. Please verify that the tables are accurate. If your analysis produces different results, please provide revised tables for our review.

Diarrhea	Prograf N=212	MR4 N=214	Neoral N=212
Patients	94	97	54
Events	134	134	72
Duration of diarrhea Mean no. of days	31.25	31.08	21.5

Source: ADV. Dataset
Mean duration was calculated using the ADUR listed.
For events listed as "continuing" the duration was calculating the following:
If the subject completed the study, duration was calculated as (365 – first day of adverse event).
If the subject crossed over to another arm, duration was calculated as (last day in the randomized arm – first day of adverse event + 10 days).

Severity of Diarrhea	Prograf N=212	MR4 N=214	Neoral N=212
Mild	90	90	44
Moderate	39	41	25
Severe	5	3	3

Source: ADV dataset

Loose Stools	Prograf N=212	MR4 N=214	Neoral N=212
Patients	15	11	3
Events	15	12	3
Duration of loose stools Mean no. of days	31.2	47.75	8.3

Source: ADV. Dataset
Mean duration was calculated using the ADUR listed.
For events listed as "continuing" the duration was calculating the following:
If the subject completed the study, duration was calculated as (365 – first day of adverse event).
If the subject crossed over to another arm, duration was calculated as (last day in the randomized arm – first day of adverse event + 10 days).

Severity of Loose Stools	Prograf N=212	MR4 N=214	Neoral N=212
Mild	13	10	3
Moderate	2	2	0
Severe	0	0	0

Source: ADV. Dataset

4. Please conduct similar analyses using data from FG-506E-12-03 and populate the tables below:

Diarrhea	MR4 N=331	FK506 N=336
Patients (%)		
Events		
Duration of diarrhea Mean no. of days		

Severity of Diarrhea	MR4 N=331	FK506 N=336
Mild		
Moderate		
Severe		

Loose Stools	**MR4 N=331**	**FK506 N=336**
Patients		
Events		
Duration of loose stools Mean no. of days		

Severity of Loose Stools	**MR4 N=331**	**FK506 N=336**
Mild		
Moderate		
Severe		

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/s/

HYUN J SON
03/08/2013

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: February 21, 2013

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939

Subject: NDA 204096 tacrolimus extended-release: request for information Study 11-03

Total no. of pages including cover: 4

Document to be mailed: YES ☑ NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

Dear Dr. Spears,
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules, NDA 204096. We are reviewing your submission and have the following information requests for Study FG-506E-11-03 (liver transplant).

We request that you submit the responses **within 4 weeks**. Please let us know if you will not be able to meet this timeline.

If you have any questions about these requests, please contact me (Hyun Son) to obtain clarification or schedule a brief conference with the Division. If you have previously submitted data in the same format as requested below, please assist us in locating the information within the NDA submission.

Once we have had the opportunity to understand these analyses of Study 11-03, we may have additional requests in the future.

1. Recreate the following tables and figures from the 12 month study report showing results by gender and treatment. Use the Full Analysis Set (FAS) population for all analyses.

   a. Tables 2 through 5; 7, 8, 10; 16 through 19; and 22 through 31; and 33. See Appendix for the corresponding table titles.

      All the tables should be formatted as follows:

	FEMALES		MALES	
	TAC-XL N=76	Prograf N=64	TAC-XL N=161	Prograf N=170

   b. Figures 2 and 3: Display all 4 subgroups (TAC-XL females, Prograf females, TAC-XL males and Prograf males) on the same graph for ease of comparison. See Appendix for the corresponding figure titles.

Appendix

List of Tables from Study 11-03 12M Report:

List of Figures from Study 11-03 12M Report:

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/s/

HYUN J SON
02/21/2013

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: February 20, 2013

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939

Subject: NDA 204096 tacrolimus extended-release: request for information

Total no. of pages including cover: 9

Document to be mailed: YES ☑ NO

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Dear Dr. Spears,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules, NDA 204096. We are reviewing your submission and have the following information requests for Study FG-506E-11-01 (liver transplant).

We request that you submit the responses for questions 1 through 11 **within 2 weeks** and the remainder of the questions **within 4 weeks**. Please let us know if you will not be able to meet this timeline.

As discussed below, we have created table templates to show how we would like the data presented. However, as some of our requests are complex, please consider preparing your own mock tables/figures once you have considered our requests, if you believe they are more appropriate. We can review your proposal and provide comments, before you submit the final version with complete data.

If you have any questions about these requests, please contact me (Hyun Son) to obtain clarification or schedule a brief conference with the Division. If you have previously submitted data in the same format as requested below, please assist us in locating the information within the NDA submission.

Once we have had the opportunity to understand these analyses of Study 11-01, we may have additional requests for similar analyses for Study FG-506E-11-03 sent separately.

Background Information:

We acknowledge that you included gender specific pharmacokinetic (PK) analyses by treatment for both *de novo* liver studies (11-01 and 11-03) in the current NDA submission (2-7-2-summary-clin-pharm-studies.pdf), and previously in response to the FDA request dated February 27, 2008. We are requesting additional PK analyses of Study 11-01 for the 6 week study period using the full analysis set (FAS) population by treatment and gender subgroups, including donor and recipient gender.

PK Parameters

1. Create three tables (one for each day) of the following parameters (mean ± SD) by treatment arm and gender on Days 1, 14 and 42:
    a. AUC
    b. C_{max}
    c. C_{min}
    d. AUC/C_{min} ratio
    e. TAC-XL:Prograf ratio of the AUC means and C_{min} means and the corresponding 90% CI.

Use the following table template and format to present these analyses.

Category	**Females**		**Males**	
DAY #	Tac XL	Prograf	Tac XL	Prograf
All Donors				
number	N= xx	N= xx	N= xx	N= xx
AUC				
AUC/C_{min}				
C_{max},				
Etc.				
Female Donor				
number	N= xx	N= xx	N= xx	N= xx
AUC				
AUC/C_{min}				
C_{max}				
Etc.				
Male Donor				
Number	N= xx	N= xx	N= xx	N= xx
AUC				
AUC/C_{min}				
C_{max}				
Etc.				

2. Create three tables (one for each day) for the dose-normalized parameters (mean ± SD) by treatment arm and gender on Days 1, 14 and 42, similar to #1 above:
    a. AUC
    b. C_{max}
    c. C_{min}
    d. AUC/C_{min} ratio
    e. TAC-XL:Prograf ratio of the AUC means and C_{min} means and the corresponding 90% CI.

Concentration time profiles

3. Create three figures of whole blood tacrolimus concentration-time profiles (one for each day = Day 1, Day 14, and Day 42) by treatment arm and gender <u>for all recipients</u> (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups superimposed.

4. Create three figures of whole blood tacrolimus concentration-time profiles (one for each day = Day 1, Day 14, and Day 42) by treatment arm and gender only for recipients of female livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups superimposed.

5. Create three figures of whole blood tacrolimus concentration-time profiles (one for each day = Day 1, Day 14, and Day 42) by treatment arm and gender only for recipients of male livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups superimposed.

AUC to Cmin correlation

6. Create three figures comparing AUC on the y-axis to C_{min} on the x-axis (one for each day = Day 1, Day 14, and Day 42) by treatment arm and gender for all recipients (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups superimposed.

7. Create three figures comparing AUC on the y-axis to C_{min} on the x-axis (one for each day = Day 1, Day 14, and Day 42) by treatment arm and gender only for recipients of female livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups superimposed.

8. Create three figures comparing AUC on the y-axis to C_{min} on the x-axis (one for each day = Day 1, Day 14, and Day 42) by treatment arm and gender only for recipients of male livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups superimposed.

Daily doses over time (= 42 days)

9. Create one figure of tacrolimus daily dose (mg/kg/day) over time in days showing the mean values with standard deviation for all recipients (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males),, with the 4 subgroups on the same graph for ease of comparison.

10. Create one figure of tacrolimus daily dose (mg/kg/day) over time in days showing the mean values with standard deviation only for recipients of female livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups on the same graph for ease of comparison.

11. Create one figure of tacrolimus daily dose (mg/kg/day) over time in days showing the mean values with standard deviation only for recipients of male livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups on the same graph for ease of comparison.

C_{min} over time (= 42 days)

12. Create figures of tacrolimus C_{min} (ng/mL) over time in days showing the mean values with standard deviation for all recipients (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups on the same graph for ease of comparison.

13. Create figures of tacrolimus C_{min} (ng/mL) over time in days showing the mean values with standard deviation only for recipients of female livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups on the same graph for ease of comparison.

14. Create figures of tacrolimus C_{min} (ng/mL) over time in days showing the mean values with standard deviation only for recipients of male livers (four subgroups = TAC-XL females, Prograf females, TAC-XL males and Prograf males), with the 4 subgroups on the same graph for ease of comparison.

Tacrolimus concentrations greater than 20 ng/mL

15. Create three tables with the number and percentage of patients with at least one tacrolimus trough concentrations above 20 ng/mL (include patient ID numbers):
    a. during the initial 15 days,
    b. between Day 16 and Day 42, and
    c. during the entire 6 week study period by treatment and gender.

16. Create a second series of tables, as above, for tacrolimus trough concentrations above 25 ng/mL.

Please use the following table format for items #15 and #16 for each specified time period.

	FEMALES		MALES	
	TAC-XL N=17	Prograf N=16	TAC-XL N=49	Prograf N=45
Had at least one event [n, %]				
Events per patient [n,%] 0 1 2 3 4 5 >5				
Total number of events				
Events for all patients Mean (sd) Median Min Max				

Safety Tables

17. Create tables and figures using data for all patients from Study 11-01 by treatment and gender subgroups. Use the following table template to present these analyses.

FEMALES		MALES	
TAC-XL N=17	Prograf N=16	TAC-XL N=49	Prograf N=45

Format the tables as in Study 11-03: the following table/figure numbers correspond to the numbering used in the Study 11-03 report. In creating these tables/figures please use the same criteria and methods that you utilized in creating the tables in Study 11-03. For example, Table 18 (Adverse Events) it is stated that "Most frequently reported defined as incidence rate of at least 12% in either treatment group and those with a difference in incidence between FK506 and MR4 associated with $p < 0.05$." Please use the same criteria when creating a similar table for Study 11-01.

a. Study 11-03 Tables 4, 5, 7, 8, 17, 18, 22, and 24 through 29. See Appendix for the corresponding table titles.

b. Study 11-03 Figures 2, 3 and 7: Display all 4 subgroups (TAC-XL females, Prograf females, TAC-XL males and Prograf males) on the same graph for ease of comparison. See Appendix for the corresponding figure titles.

18. Create three new tables for each of the 5 safety categories (a. through e.) below using the same table template as in request #13 above. There should be one table each for (i) all recipients of liver transplants, (ii) recipients of female livers, and (iii) recipients of male livers:

    a. All cardiac AEs

    b. All cardiac SAEs

    c. AEs related to ascites, (similar to Table 30 in the Integrated Summary of Safety in Liver Transplantation located in Module 5).

    d. Mean/SD/median/min/max total daily IV and oral corticosteroid doses, by time period

    e. Glucose Metabolism Disorders: (similar to Table 28, but also including "composite NODAT and NODAT components" as found in Table 39 in the Integrated Summary of Safety in Liver Transplantation located in Module 5).

19. Please create three new figures showing mean creatinine clearance over time. These figures should be formatted by gender and treatment, one figure each for (i) all recipients of liver transplants, (ii) recipients of female livers, and (iii) recipients of male livers. The 4 subgroups (TAC-XL females, Prograf females, TAC-XL males and Prograf males) should be superimposed on each figure.

Appendix

List of Tables from Study 11-03:

Table 4: Summary of Patient Demographics and Viral Status

Table 5: Summary of Donor Characteristics and Donor/Recipient Mismatch

Table 7: Tacrolimus Daily Dose (mg/kg)

Table 8: Tacrolimus Trough Levels (ng/mL)

Table 17: Summary of Adverse Events

Table 18: Incidence of Most Frequently Reported Adverse Events Regardless of Relationship to Study Medication (defined as incidence rate of at least 12% in either treatment group and those with a difference in incidence between FK506 and MR4 associated with $p < 0.05$)

Table 22: Incidence of Most Frequently Reported Serious Adverse Events Regardless of Relationship to Study Medication

Table 24: Incidence of Most Frequently Reported Adverse Events Leading to Discontinuation, Regardless of Relationship to Study Medication

Table 25: Overall Summary of Infection

Table 26: Incidence of Infections

Table 27: Incidence of Adverse Events of Renal Function

Table 28: Incidence of Glucose Metabolism Disorder

Table 29: Incidence of Neurological Adverse Events

List of Figures from Study 11-03:

Figure 2: Mean Tacrolimus Daily Dose (mg/kg)

Figure 3: Mean Tacrolimus Trough Levels (ng/mL) by Period

Figure 7: Median Creatinine Clearance (Cockcroft-Gault)

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/s/

HYUN J SON
02/20/2013

From: Son, Hyun
To: Spears, Glen
Cc: Son, Hyun
Subject: NDA 204096 Tac-XL: Dissolution (b) (4)
Date: Thursday, February 14, 2013 2:19:00 PM

Hi Glen,

I have some request from our chemistry folks.

1. In vitro dissolution profiles of tacrolimus extended-release capsules were obtained in pH 4.5 dissolution medium containing 20% ethanol (section 3.2.P.2.2.3.2.5). Additional data are needed to fully evaluate the potential for *in vitro* alcohol induced dose dumping of tacrolimus extended-release capsules. Please provide dissolution profiles of the drug product in the physiologically relevant pH 1.2 medium with a range of alcohol concentrations (i.e., 0 %, 5 %, 10 %, 20 %, and 40 %).

    - Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
    - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first few hours.
    - The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
    - The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

2. (b) (4)

3. On 20-OCT-2011, the EMA reported that Advagraf 0.5 mg capsules batches were recalled following the observation that, "during the first 1.5 hours of dissolution testing, an average of (b) (4) of the tacrolimus in the capsules was released. This was above the permitted range of (b) (4) Please describe the root cause of the out-of-specification results, and describe any changes implemented as a result.

We would like a response to #3 along with timelines for completing #1 and #2 in one week.

Thanks
Hyun

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/s/

HYUN J SON
02/19/2013

From: Son, Hyun
To: "Spears, Glen"
Subject: NDA 204096 Tac XL: information request
Date: Wednesday, February 06, 2013 4:45:00 PM

Hi Glen,
Here is another information request from our review team.
Please submit these as soon as possible (expedite please).

In reviewing the reported mean total daily corticosteroid doses (by time period) for the three treatment arms of Study 02-0-158 (as summarized in Table 13.3.3 of the clinical study report), we noted that in the MEDS.xpt dataset, there are multiple dose entries for the same time period for some patients (e.g., Patient 01161001). Please submit the .xpt analysis datasets that would allow us to calculate the intravenous methylprednisolone and oral prednisone doses administered by time period in Studies 02-0-158, 12-03, PMR-EC-1210, as well as Studies 11-03 and 11-01.

Thanks
Hyun

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HYUN J SON
02/06/2013

From: Son, Hyun
To: "Spears, Glen"
Subject: NDA 204096 tacrolimus XL: Request for subject level data listings by site
Date: Monday, February 04, 2013 3:35:00 PM
Importance: High

Hi Glen,

Please provide Subject Level Data Listings by Site (as described below) for the following clinical investigators listed:

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
CZ002 Trunecka, Pavel IKEM,Dept of Hepatogastroenterology,Videnska 1958/9 Praha 4, 140 21 EZ Eastern Europe phone:420 2 6136 2620 fax: email:	FG-506E-11-03	42	A phase III, 1:1 randomized, double blind study to evaluate and compare the efficacy and safety of MR4 (extended release tacrolimus) vs. FK506 (immediate release tacrolimus) in combination with steroids in patients undergoing primary liver transplantation
	FG-506E-12-03	5	A phase III, 1:1 randomized, double blind study to evaluate and compare the efficacy and safety of MR4 (extended release tacrolimus) vs. FK506 (immediate release tacrolimus) in combination with mycophenolate mofetil (MMF) and steroids in patients undergoing kidney transplantation
DE052 Kraemer, Bernhard Klinik und Poliklinik fuer Innere Medizin II - Nephrologie,Franz-Josef-Strauß-Allee 11 Regensburg, 93042 GM Western Europe phone:49 941 944-7301 fax: email:	FG-506E-12-03	34	A phase III, 1:1 randomized, double blind study to evaluate and compare the efficacy and safety of MR4 (extended release tacrolimus) vs. FK506 (immediate release tacrolimus) in combination with mycophenolate mofetil (MMF) and steroids in patients undergoing kidney transplantation
			A phase III, 1:1 randomized,

SE002 BAckman, Lars SU/Sahlgrenska University Hospital,Dept of Transplantation and Liversurgery Gothenburg, 41345 SW Western Europe phone:46 313421000 fax: email:	FG-506E-11-03	7	double blind study to evaluate and compare the efficacy and safety of MR4 (extended release tacrolimus) vs. FK506 (immediate release tacrolimus) in combination with steroids in patients undergoing primary liver transplantation
	FG-506E-12-03	22	A phase III, 1:1 randomized, double blind study to evaluate and compare the efficacy and safety of MR4 (extended release tacrolimus) vs. FK506 (immediate release tacrolimus) in combination with mycophenolate mofetil (MMF) and steroids in patients undergoing kidney transplantation
1093 Yang, Harold Pinnacle Health at Harrisburg,205 South Front Street,Brady 8 Harrisburg, PA 17105-8700 US United States phone:717-231-8810/717-576-7070 (m) fax:717-231-8443 email:hyang@pinnaclehealth.org	02-0-158	36	A phase III, randomized, open-label, multi-center study to assess the safety and efficacy of Prograf® (immediate release tacrolimus)/mycophenolate mofetil (MMF), MR4 (extended release tacrolimus)/MMF, and Neoral® (cyclosporine)/MMF in de novo kidney transplant recipients
1020 Silva, Jr, Helio Tedesco Hospital do Rim E Hipertensa Fundacao,Oswaldo Ramos,Rua Borges Lagoa, 960, 11o. andar Villa Clementino São Paulo, SP 04038-002 BR Latin America phone:55-11-5087-8113 fax:55-11-5087-8145 email:heliotedesco@hrim.com.br	02-0-158	42	A phase III, randomized, open-label, multi-center study to assess the safety and efficacy of Prograf® (immediate release tacrolimus)/mycophenolate mofetil (MMF), MR4 (extended release tacrolimus)/MMF, and Neoral® (cyclosporine)/MMF in de novo kidney transplant recipients

Please provide site-specific individual subject data ("line") listings for each investigator listed above. The data listings should contain:

- Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
- Subject listing for treatment assignment (randomization)
- Subject listing of drop-outs and subjects that discontinued with date and reason
- Evaluable subjects/ non-evaluable subjects and reason not evaluable
- By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
- By subject listing, of AEs, SAEs, deaths and dates
- By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- By subject listing of the primary efficacy parameters.
- By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
- By subject listing, of laboratory tests performed for safety monitoring

Please submit this information as soon as possible.

Thanks
Hyun

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/s/

HYUN J SON
02/04/2013

From: Son, Hyun
To: Spears, Glen
Subject: NDA 204096 tacrolimus extended-release: medication errors
Date: Friday, February 01, 2013 5:11:00 PM

Hi Glen,

We have additional requests from our DMEPA team.

1. All PSUR's with cases written in English for all time periods since the launch of the product through the latest produced PSUR. Please provide this information in an Excel Spreadsheet with the country of origin available as a column along with all other information. Please also provide a high-level overview/summary of the cases contained in each PSUR with regard to medication errors.

2. All versions of the labels for the product, from first launch through present. Please present in a tabular format, per product, in color.

3. All packaging configurations for the product from first launch through present. Please provide color pictures with labeling if possible.

4. All risk mitigation efforts that surround the product worldwide. Please describe each program, its respective elements, and the date of implementation. Please also note if the mitigation efforts were in place at the time of the launch of the product in the respective country or if the mitigation efforts were put into place after launch of the product.

5. All medication errors seen in the clinical trials which support the current submission to the Agency. Please provide in an Excel Spreadsheet.

We are asking if you could provide this information as soon as possible.

Thanks
Have a great weekend.

Hyun

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/s/

HYUN J SON
02/01/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 28, 2013

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939

Subject: NDA 204096 tacrolimus extended-release: AC backgrounder outline

Total no. of pages including cover: 10

Document to be mailed: ☐ **YES** ☑ **NO**

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules.

We received your email communication dated January 25, 2013 consisting of a draft outline of the Astellas Executive Summary that reflects the outline of the entire backgrounder for the April 16, 2013 advisory committee meeting. Attached is DTOP's draft outline for the backgrounder in preparation of our teleconference on January 30, 2013.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Hyun Son, Pharm.D.

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/s/

HYUN J SON
01/28/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2013

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939

Subject: NDA 204096 tacrolimus extended-release: request for information Study 158

Total no. of pages including cover: 3

Document to be mailed: **YES** ☑ **NO**

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules.

We are reviewing your submission and have the following comments and information requests.

Regarding the DOSE.xpt analysis dataset of Study 02-0-158:

1. We note that only 153/221 (69%) TAC-XL and 163/274 (59%) Prograf patients included in the dataset have data for tacrolimus total daily dose on Day 1 and/or Day 0. Please explain how you arrived at the actual mean dose on day 1 for TAC-XL and Prograf, as described in Section 4.1 of Module 2.7.3 Summary of Clinical Efficacy in Kidney Transplant Patients. If possible, submit a revised dataset that provides the missing start dates/days and stop dates/days for each tacrolimus dose entry in the dataset.

2. We note that the stop dates/days for each MMF dose entry in the same dataset were not provided. Please explain how you arrived at the mean MMF dose for each treatment arm, as shown in Table 12.2.1.3.1 of the Study 02-0-158 clinical study report. If possible, revise the dataset to include the stop dates/days and add a column for "duration" (defined as stop day minus start day) for each MMF dose entry.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Hyun Son, Pharm.D.

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/s/

HYUN J SON
01/25/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 18, 2013

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939

Subject: NDA 204096 tacrolimus extended-release: response to questions regarding AC

Total no. of pages including cover: 7

Document to be mailed: ☐ **YES** ☑ **NO**

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules.

We also refer to your email communication dated January 14, 2013 which consisted of questions regarding the scheduled advisory committee (AC) meeting on April 16, 2013. We have provided comments to the questions below. Your questions are in **bold** font and our responses are in normal font.

1. (b) (4)

2.

3.

4.

(b) (4)

5.

6.

7.

8.

9.

10.

11.

Please see a very rough draft of the AC agenda attached.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Hyun Son, Pharm.D.,
Safety Regulatory Project Manager

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC)

FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD

April 16, 2013

AGENDA

(b) (4)

[redacted]

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC)

FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD

April 16, 2013

AGENDA (cont.)

(b) (4)

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/s/

HYUN J SON
01/18/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: December 18, 2012

To: Glen Spears, Ph.D.	**From:** Hyun Son, Pharm.D.
Company: Astellas Pharma US	Division of Transplant and Ophthalmology Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number: 224-205-5935	**Phone number:** 301-796-1939

Subject: NDA 204096 tacrolimus extended-release: request for information

Total no. of pages including cover: 3

Document to be mailed: YES ☑ NO

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Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules.

We are reviewing your submission and have the following comments and information requests. We request a written response by January 7, 2013 in order to continue our evaluation of your NDA.

A table containing baseline conditions of liver recipients is provided in the Liver ISS in Module 5 (Table 10: Patient Demographics for Male Adult De Novo Liver Transplant Recipients). In this table the results for Studies FG-506E-11-03 and FG-506-11-01 are pooled together. We note from the Case Report Forms and datasets for these studies that pre-transplant MELD scores do not appear to have been recorded.

1. Please comment on whether MELD scores were collected in Studies 11-03 and 11-01 or whether it would be possible to calculate MELD scores using available data. Any additional information about the scoring system for prioritizing liver transplant candidates used at the time the study was conducted in the centers that participated that may be the equivalent of the currently utilized MELD scoring system, such as Child-Pugh-Turcotte (CPT) score or UNOS status, would be helpful.

2. Please provide the information contained in Table 10 for males only, females only, and both genders combined for Studies FG-506E-11-03 and FG-506-11-01 separately. In addition to the information already reported in Table 10, please include the following additional baseline information reported as mean ($\pm$ SD) values:
    a) Recipient age
    b) Donor age
    c) MELD score at the time of listing for transplant (if available)
    d) MELD score at the time of transplant (study baseline) (if available)
    e) Child-Pugh-Turcotte (CPT) score at the time of transplant (if available)
    f) Serum creatinine at the time of transplant (mg/dL)
    g) Serum total biluribin at the time of transplant (mg/dL)
    h) INR at the time of transplant
    i) Prothrombin time at the time of transplant
    j) Serum albumin at the time of transplant (g/dL)
    k) Platelet count at the time of transplant
    l) Hepatic encephalopathy grade at the time of transplant (if available)
    m) Ascites grade at the time of transplant (if available)

n) also include Hepatitis C status for the recipient only (regardless of the donor HCV status).

3. Submit electronic datasets containing the information from the existing Table 10 and that requested in #2 above to support the tables provided. Please also include subject ID, site ID, and study number.

Pleas submit this information to NDA 204096 Original 2 by January 7, 2013. If this date is not feasible, please propose a new date of when this information can be submitted.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Hyun Son, Pharm.D.,
Safety Regulatory Project Manager

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/s/

HYUN J SON
12/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096/Original 1
NDA 204096/Original 2

ADVICE

Astellas Pharma US, Inc.
Attention: Glen Spears, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tacrolimus extended-release capsules, 0.5 mg, 1 mg, and 5 mg.

NDA 204096 provides for the use of tacrolimus extended-release capsules for the following indications which, for administrative purposes, we have designated as follows:

- NDA 204096/Original 1 - Prophylaxis of organ rejection in adult patients receiving kidney transplants.

- NDA 204096/Original 2 - Prophylaxis of organ rejection in adult male patients receiving liver transplants.

All future submissions to your NDA should specify the NDA number and all Original number(s) to which each submission pertains.

If you have any questions, call me, at (301) 796-1939.

Sincerely,

{See appended electronic signature page}

Hyun Son, Pharm.D.
Safety Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

HYUN J SON
12/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

FILING COMMUNICATION

Astellas Pharma US, Inc.
Attention: Glen Spears, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

Please refer to your New Drug Application (NDA) dated September 20, 2012, received September 21, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for tacrolimus extended-release capsules.

We also refer to your amendments dated October 2, 2012, October 26, 2012, November 15, 2012, and November 20, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 21, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 24, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Please provide a pdf file with a table which lists primary system organ class (SOC) term, MedDRA preferred term, and the specific adverse event(s), as reported by the investigator, mapped to the SOC/preferred term. Below is a portion of what such a table would look like with a mock example included.

Primary System Organ Class	**MedDRA Preferred Term**	**Reported Adverse Event**
Renal and Urinary Disorders	Renal impairment	renal dysfunction decreased renal function worsening renal function progressive renal deterioration
	…	…

2. [redacted] (b) (4)

3. Please submit a summary of the observed tacrolimus C_{min} ranges in the PMR-EC-1210 (OSAKA) trial in *de novo* kidney transplant recipients, similar to those submitted for Studies 02-0-158 and FG-506E-12-03, as summarized in Table 30 of the Clinical Efficacy Summary document, or direct us to the location of the information in the NDA submission.

4. We note that in the PK substudies of Phase 3 trials for tacrolimus extended-release capsules you have excluded female transplant patients taking hormonal contraceptives. We also note that the European labeling section entitled “Effect of Tacrolimus on the

Metabolism of Other Medicinal Products" mentions about the potential of tacrolimus to increase exposures to steroid-based contraceptives and phenytoin. In light of these potential drug-drug interactions, please provide literature regarding the potential for tacrolimus to interact with drugs that are also CYP3A substrates. See also #6 in Labeling below.

The following is being provided for your information:

5. Although we do not require that datasets be in a CDISC standardized form at this time, we do expect that analysis datasets will be formatted taking our guidances into consideration (see our guidance page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm). You have submitted datasets that do not conform to some basic parameters described in our guidances. For example, you have not included a unique subject ID on each dataset and the dataset with the primary efficacy data is not clearly labeled. You have provided a define file for each dataset but links within the define file do not provide information specific only for the study, making the file more cumbersome to use. For this application, we are not requesting that you fix these problems but wish to advise you that as we move closer to accepting only standardized datasets that these types of issues are more likely to result in a request for a new submission.

LABELING

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL) General Format

1. White space must be present before each major heading in HL.
2. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Contents: Table of Contents (TOC)

3. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
4. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Boxed Warning

5. All text must be **bolded**.

Drug Interactions

6. Include a subsection describing the potential for tacrolimus to interact with other drugs that are also CYP3A4 substrates (see also #4 in information requests above).

Patient Counseling Information

7. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
   - "See FDA-approved patient labeling (Medication Guide)"

We request that you resubmit labeling that addresses these issues by January 14, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies in kidney transplant patients 0 to < 5 years and in pediatric liver transplant patients 0 to < 5 years for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies in pediatric kidney transplant patients 5 to 16 years for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1939.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

OZLEM A BELEN
12/04/2012
Signing for Dr. Renata Albrecht

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 064148
NDA 204096

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Astellas Pharma US, Inc.
1 Astellas Way
Northbrook, IL 60062

ATTENTION: Glen W. Spears, PhD
Associate Director, Regulatory Affairs

Dear Dr. Spears:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and your New Drug Application (NDA) dated September 20, 2012 and received, September 21, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Extended-release Capsules, 0.5 mg, 1 mg, and 5 mg.

We also refer to:

- Your May 22, 2012, correspondence, received May 23, 2012, requesting review of your proposed proprietary name, Advagraf, under the IND; and

- Your correspondence, dated and received, October 26, 2012, requesting review of your proposed proprietary name, Advagraf, under the NDA.

We have completed our review of the proposed proprietary name, Advagraf, and have concluded that the name is unacceptable for the following reasons:

1. The data provided in support of the proposed proprietary name did not persuade the Agency to change their opinion about the misleading nature of the proprietary name. You state that "although Advagraf and "advantage" both start with the same four letters, the pronunciation of each is clearly differentiated (AD-va-graf versus ad-VAN-tage) with the accent on the first syllable for Advagraf and on the second syllable for advantage. However, you did not provide data that demonstrates people will not associate "Advagraf" with "advantage". Additionally, you provided examples of other marketed drugs that begin with the 3-letter triad "Adv": Advair, Advicor, and Advil". However, the concern stems from the four-letter prefix "Adva", which in the Agency's opinion, evokes "advantage", not the three-letter prefix "Adv". DMEPA notes the name Advair contains the four-letter prefix "Adva",

however, when the proprietary name Advair was first approved in August 2000, the Office of Prescription Drug Promotion (OPDP) did not review the name.

Therefore the Agency maintains the promotional objection to the proposed proprietary name "Advagraf" because it overstates the efficacy of the drug product and it implies superiority. The prefix "Adva" in the proposed proprietary name evokes the word "advantage," which is defined as "the quality or state of being superior: a more favorable or improved position or condition" ((http://unabridged.merriam-webster.com/cgi-bin/unabridged accessed 5/31/12). Thus, the proposed proprietary name misleadingly suggests that this extended-release tacrolimus product has an "advantage" and is somehow superior to other drugs approved for the same indication(s), including other tacrolimus products, such as Prograf.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

2. We acknowledge that the Division of Transplant and Ophthalmology Products (DTOP) previously requested you use the name Advagraf as the proprietary name for tacrolimus extended-release capsules to harmonize the name for this product internationally and to help reduce confusion and accidental interchange of the medications (Advagraf and Prograf). At that time, Advagraf was the only proprietary name approved anywhere in the world for this product. You cited 13 out of 34 tacrolimus once-daily abstracts presented at the American Transplant Congress (ATC) reference the once-daily tacrolimus as Advagraf, to demonstrate the product is known globally as Advagraf. However, 21 (or the majority of these abstracts) make no reference to the name Advagraf. Moreover, it is unclear as to how the use of the name Advagraf in some of the published literature will help to reduce the risk of additional medication errors. Furthermore, since receiving approval of Advagraf in Europe in 2007, tacrolimus extended-release capsules have also been approved in many other countries under several different proprietary names. Therefore, global harmonization is impossible.

3. Based on the information provided in your submission, the mix-ups between Advagraf and Prograf are primarily due to confusion between the different formulations and dosing regimens. Because Advagraf and the currently marketed Prograf products are dosed with a different frequency of administration and inadvertent substitution could lead to significant safety issues, we recommend a modifier be appended to the proprietary name that highlights the extended release properties of the proposed product. Therefore, we recommend you submit a new unique proprietary name (not Advagraf or Prograf) with a modifier, such as 'Proprietary name XL', to further reduce the potential for confusion with the immediate-release tacrolimus products.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hyun Son at (301) 796-1939.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
11/19/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

Date: November 2, 2012

To: Karen Townsend, Pharm.D.
Safety Regulatory Project Manager
Division of Medication Error Prevention & Analysis (DMEPA)

Through: Bryant Godfrey, JD, MHA
Senior Lead Regulatory Counsel
Office of Prescription Drug Promotion (OPDP)

Marci Kiester, PharmD
Associate Director
OPDP

Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
OPDP

Amie O'Donoghue, PhD
Social Science Analyst
OPDP

Quynh-Van Tran, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

From: Jessica N. Cleck Derenick, PhD
Regulatory Review Officer
OPDP

Subject: **Proprietary Name Rebuttal Response**
NDA 204096; Advagraf (tacrolimus) extended-release capsules
Astellas

****Pre-decisional Agency Information****

The Office of Prescription Drug Promotion (OPDP) reviewed the proposed proprietary name, "Advagraf," on April 5, 2007, October 4, 2007, and, most recently, May 31, 2012, and did not recommend the use of the name from a promotional perspective.

Specifically, the May 31, 2012, objection stated:

> OPDP objects to the proposed proprietary name "Advagraf" because it overstates the efficacy of the drug product and it implies superiority. The prefix "Adva" in the proposed trade name evokes the word "advantage," which is defined as "the quality or state of being superior: a more favorable or improved position or condition" ((http://unabridged.merriam-webster.com/cgi-bin/unabridged accessed 5/31/12). Therefore, the proposed trade name misleadingly suggests that this extended-release tacrolimus product has an "advantage" and is somehow superior to other drugs approved for the same indication(s), including other tacrolimus products, such as Prograf. Without substantial evidence to support that this extended-release tacrolimus product is safer or more effective than other drugs approved for the same indication(s), including other tacrolimus products, the proposed proprietary name is misleading.
>
> Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

On Wednesday, September 12, 2012, a teleconference was held between FDA, which included representatives from DMEPA, OPDP, and the Division of Transplant and Ophthalmological Products (DTOP), and Astellas to discuss Astellas' request for a proprietary name review for the proposed proprietary name, "Advagraf." During this teleconference, OPDP communicated our promotional concerns with "Advagraf" to the sponsor and DMEPA asked the sponsor to explain the role "Advagraf" plays in preventing medication errors. Following the teleconference, Astellas stated that they would be submitting a formal response to FDA regarding the concerns discussed during the September 12, 2012, teleconference.

OPDP has reviewed the rebuttal submitted by Astellas on October 2, 2012, and offers the following comments.

Review

Based on our review, OPDP continues to maintain our objection to the proposed trade name "Advagraf" for the reasons noted in our April 5, 2007, October 4, 2007, and May 31, 2012, responses. Specifically, OPDP objects to the proposed proprietary name "Advagraf" because it overstates the efficacy of the drug

product and implies superiority to other drugs approved for the same indication, including other tacrolimus products (e.g. Prograf).

OPDP seeks to reiterate our objection to the proposed trade name "Advagraf" as misleading. As discussed in our April 5, 2007, October 4, 2007, and May 31, 2012, EPD responses, the prefix "Adva" in the proposed proprietary name evokes the word "advantage". Definitions for "advantage" per the Merriam-Webster Unabridged Online Dictionary (http://unabridged.merriam-webster.com/cgi-bin/unabridged; accessed October 31, 2012) include the following:

- The quality of state of being superior : a more favorable or improved position or condition (n)
- Benefit, profit, or gain of any kind (n)

Astella is seeking approval for tacrolimus extended-release capsules for prophylaxis of organ rejection in patients receiving allogeneic kidney transplantation and in male patients receiving allogeneic liver transplantation. Currently, there are a number of other FDA-approved drug products with the same indication(s), including Prograf (tacrolimus) capsules. Either of the above definitions creates a representation that tacrolimus extended-release capsules has an "advantage," and is therefore, superior to other drugs approved for the same indication(s).

We note that Astella states that "although Advagraf and 'advantage' both start with the same four letters, the pronunciation of each is clearly differentiated (AD-va-graf versus ad-VAN-tage) . . ." OPDP has reviewed the information provided in the rebuttal, and in the absence of behavioral data that shows that people will not associate "Advagraf" with "advantage", we are not persuaded. Furthermore, Astellus has provided examples of FDA-approved drugs which include the "ADV-" prefix, such as Advair, Advicor, and Advil; however, as indicated above, OPDP's concern stems from the four-letter prefix "Adva," which, in our opinion, evokes "advantage," not the three-letter prefix "Adv".

We also note that Astellas states that "none of the claims for Advagraf are superiority claims; the only claims are non-inferiority claims to current therapies." OPDP has reviewed the information provided in the rebuttal, and given the definition of "advantage" and the lack of behavioral data to suggest that consumers will not associate "Advagraft" with "advantage," we are not persuaded.

Lastly, OPDP acknowledges that Astellas selected "Advagraf" to harmonize the name internationally and reduce confusion and accidental interchange of immediate-release and extended-release tacrolimus. We agree that safety is an important consideration in the proprietary name evaluation process; however, OPDP primarily reviews proposed proprietary names from a promotional

perspective. Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

For the reasons described in detail above, OPDP maintains our objection to the proposed proprietary name “Advagraf” because it overstates the efficacy of the drug product and misleadingly implies superiority over other drug products with the same indication(s).

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/s/

JESSICA N CLECK DERENICK
11/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204096

NDA ACKNOWLEDGMENT

Astellas Pharma US, Inc.
Attention: Glen Spears, Ph.D.
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Spears:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Advagraf (tacrolimus extended-release) Capsules

Date of Application: September 20, 2012

Date of Receipt: September 21, 2012

Our Reference Number: NDA 204096

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 20, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Hyun J. Son, Pharm.D.
Safety Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

HYUN J SON
10/01/2012