APPLICATION NUMBER:

210115Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
IND 064148

MEETING REQUEST-
WRITTEN RESPONSES

Astellas Pharma Global Development, Inc.
Attention: Mary Jo Pritza, MPH, PharmD,
Sr. Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Pritza:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Granules for Oral Suspension.

We also refer to your submission dated February 8, 2017, containing a type B meeting request. The purpose of the requested meeting was to provide additional information on the following topics:

1. Dissolution specification time point

2. Discrimination \( \text{(b)(4)} \) in drug product utilizing dissolution test method

3. Dissolution test sample preparation for the 0.2 mg tacrolimus granules

Further reference is made to our Meeting Granted letter dated March 3, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 8, 2017, background package.

If you have any questions, call me, Kristine Leahy at (240) 402-5834.

Sincerely,

\{See appended electronic signature page\}

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Written Responses
WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA CMC- Guidance

Application Number: IND 064148
Product Name: Tacrolimus granules
Indication: For the prevention of rejection in pediatric recipients of a kidney, liver or heart transplant

Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Astellas references the final minutes from the Type B pre-NDA CMC meeting held on November 14, 2016, to discuss the planned content for submission of an NDA to support approval of the tacrolimus 0.2 and 1 mg granules for oral suspension drug product. As discussed and reported in the meeting minutes [provided in Attachment 1], topics specific to the dissolution method were identified for which the Office of Pharmaceutical Quality requested additional information and subsequent review in order to provide additional feedback ahead of Astellas' submission of the NDA [Question 3, Attachment 1]. Astellas has provided additional information on the following topics:

1. Dissolution specification time point
2. Discrimination (b)(4) in drug product utilizing dissolution test method
3. Dissolution test sample preparation for the 0.2 mg tacrolimus granules

As detailed below, Astellas provides excerpts from the minutes in italics, and corresponding discussion with accompanying data following the excerpts. Full meeting minutes are included in Attachment 1. Astellas provides summary comments and seeks feedback from the Agency on their plans for submission, posed as questions.

2.0 QUESTIONS AND RESPONSES

Question 1:
Does FDA agree with Astellas' proposal to maintain the (b)(4) minute time point for the dissolution test method?

FDA Response:

No, the final determination of the acceptability of the proposed dissolution criterion for your drug product will be made during the NDA review. It should be noted that the dissolution acceptance criterion will be utilized to maintain the discriminating ability of the method. Additionally, the complete profile data should be submitted in the NDA for the primary-
registration batches throughout stability (i.e., 15 min, 30 min, 45 min, etc., n=12) to assist in the setting of the dissolution acceptance criterion of your drug product.

**Question 2:**
Does FDA agree that these additional data support the discriminating ability of the dissolution method as being adequate for the proposed drug product?

**FDA Response:**

Per the previous meeting minutes dated 12/14/2016, the discriminating ability of the dissolution method should be investigated towards the critical material attributes and critical process parameters. The information you have submitted investigates only the discriminating ability of the proposed dissolution method towards the impact of (b)(4). In your complete detailed dissolution method development report, include all information noted in the additional comment of the previous meeting minutes dated 12/14/2016.

**Question 3:**
Does FDA agree with Astellas’ proposal to continue to use (b)(4) of the 0.2 mg product to prepare the sample for the dissolution test method analysis?

**FDA Response:**

No, we do not agree. Based on the provided dissolution data, the FDA recommendation of using 1 package of 0.2 mg as stated in the previous meeting minutes dated 12/14/2016 remains. Dissolution testing should be conducted on one dosage unit per vessel. Based on the provided dissolution data, the dissolution of 1 package of 0.2 mg in 500 mL exhibits an acceptable variability.

**Additional comment:**

Provide 3 samples of the drug product in the commercial configuration.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTINE F LEAHY
03/20/2017
IND 64148

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Mary Jo Pritza, MPH, PharmD,
Sr. Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Pritza:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Granules for Oral Suspension.

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2016. The purpose of the meeting was to discuss CMC aspects of the development program for Tacrolimus Granules for Oral Suspension.

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

If you have any questions, call me at (240) 402-7765.

Sincerely,

{See appended electronic signature page}

CDR Grafton G Adams R.N., M.S.
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 14, 2016, 2:00 PM – 3:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: 64148
Product Name: Tacrolimus Granules for Oral Suspension
Indication: For the prevention of rejection in pediatric recipients of a kidney, liver or heart transplant
Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.

Meeting Chair: Balajee Shanmugam, Ph.D.
Meeting Recorder: CDR Grafton Adams, RN, MSc

FDA ATTENDEES
CDR Grafton Adams, RN, MSc
Balajee Shanmugam, Ph.D.
Chunchun Zhang, Ph.D.
Yushi Feng, Ph.D.
Gerlie Gieser, Ph.D.
Ozlem Belen, M.D.
Ergun Velidedeoglu, M.D.

Regulatory Business Process Manager OPQ
Acting Branch Chief, OPQ/ONDP
Acting CMC Lead, OPQ/ONDP
Drug Product Reviewer, OPQ/ONDP
Biopharmaceutics Reviewer, OPQ/ONDP
Deputy Director, DTOP
Clinical Reviewer, DTOP

SPONSOR ATTENDEES
Mary Jo Pritza, MPH, PharmD.
Marina Miletic
Samantha Turzynski
David Smethurst
Patrick J. Sand MSc.
Tomoko Fukushima
Junichi Matsushita

Sr. Director Regulatory Affairs, Astellas
Associate Regulatory Affairs Director CMC, Astellas
Associate Regulatory Affairs Director CMC, Astellas
Executive Director, Regulatory Affairs, Astellas
Associate Director Project and Product Management Group, Astellas
CMC Regulatory Affairs, Global Regulatory Affairs, Astellas
CMC Regulatory Affairs, Global Regulatory Affairs, Astellas, Regulatory Affairs-Japan
1.0 BACKGROUND

On August 20, 2014, the sponsor (Astellas) obtained written advice from the Agency on the proposed content for an NDA for tacrolimus granules which included comments on the Chemistry, Manufacturing and Controls (CMC) section. Specifically, the Agency recommended that Astellas submit a more detailed pre-NDA background package covering manufacturing, packaging and package components, controls, stability (including solid state form), dissolution testing, and characterization of in-use stability and dissolution on the granule formulation.

CMC Questions

**Question 1:**

As the primary packaging of the product is an impermeable aluminum foil packet, Astellas concludes that the proposed secondary packaging

(b) (4)

provides no additional function

(b) (4).

Does FDA agree with Astellas’ proposal that the secondary packaging is non-functional and therefore not subject to additional stability testing?

**FDA Response to Question 1:**

Your proposal seems reasonable.

**Discussion:**

The sponsor accepted FDA’s response, no discussion occurred.

**Question 2:**

The proposed test items of the drug product specifications are summarized in Table 1. These items were evaluated in the primary stability studies which supports the marketed version of tacrolimus granules (Modigraf®) in EU. For reference, details of the test methods, proposed specifications and brief summary of the validation of test methods can be found in the meeting package [Attachment 1, Quality Overall Summary, Section 5].

Does the FDA agree with Astellas’ proposal to use the above test items and methods to evaluate the drug product quality to support the NDA?
FDA Response to Question 2:

The proposed drug product release and stability specifications are reasonable. The proposed acceptance values for all quality attributes will be evaluated at the time of NDA review. Details of all analytical methods, specifically those which are non-compendial and the respective methods validation should be submitted to the NDA. As your development proceeds, we recommend you to include water content, particle size distribution and XRPD test in the drug product specification.

Discussion:
The sponsor, while acknowledging the agencies recommendation to include water content, particle size distribution and XRPD testing in the drug product specification indicated that based on historical data water content and particle size distribution is not being proposed to be included. Astellas mentioned the challenges in developing an XRPD method to detect the crystallinity. The Agency recommended that the sponsor provide a justification with supportive data on the above referenced issues in the NDA submission. The Agency indicated that internal discussions will be needed to address the issue and additional comments will be provided as post-meeting comments to the meeting minutes. As agreed upon at the meeting, the Agency has provided additional comments in this minutes. Additionally, information on formulation differences between the proposed drug product and the currently marketed product was recommended to be submitted.

Question 3:
The composition of the tacrolimus 0.2 mg and 1 mg granules formulation is based on the composition of the intermediate granule formulation which is used in the manufacture of the established immediate release capsules formulation of Prograf® capsules 0.5 mg, 1 mg, and 5 mg (NDA 50-708). The difference between tacrolimus granules and the finished granules in the Prograf® capsules is the content of lactose monohydrate and the presence of magnesium stearate as shown in Table 2.

Astellas intends to utilize the existing stability data to support the US NDA for the granule formulation. The dissolution test method utilized for the granule formulation registered in the EU Marketing Authorization of Modigraf® (identified as the ‘Proposed tacrolimus granules Method’ in Table 3) differs only by sampling time from the US dissolution test method for the Prograf® capsules. The dissolution test methods are summarized in Table 3.

Astellas proposes to align the dissolution test acceptance criteria for tacrolimus granules with that of the Prograf® capsules contained in the approved US NDA, see Table 4. As described in Table 5 and Table 6, the dissolution profiles of tacrolimus granules 0.2 mg and 1 mg have met the criteria of not less than % at the minutes sampling time.

Does FDA agree with the Astellas proposal to maintain the currently utilized dissolution test method sampling time and proposed acceptance criteria to support the submission and approval of the NDA for tacrolimus granules?

FDA Response to Question 3:
Although we recognize your intention to keep the same dissolution method for tacrolimus granules as that approved for Prograf® capsules, there are differences in the formulation between Prograf® capsules and the proposed tacrolimus granules. Therefore, the selection of the proposed dissolution method for the proposed drug product should be justified. The proposed dissolution acceptance criterion for the tacrolimus granules is less than appropriate. The final determination of the dissolution acceptance criterion for your product will be made during the NDA review based on the totality of the provided dissolution data. Refer to the additional comment section regarding the dissolution information that should be provided in the NDA submission.

Your approach to use of tacrolimus 0.2 mg granules instead of one packet in the dissolution test for the 0.2 mg strength is not acceptable. You may use a lower volume of dissolution medium for the 0.2 mg granules to overcome the detection limit issue.

**Discussion:**

The Sponsor is inclined to propose minutes’ as the dissolution specification time point for the Tacrolimus Powder for Oral Suspension. The FDA clarified that based on the dissolution data provided in the meeting package, it appears that an earlier (e.g., 45-minute) specification time point for a Q of % may be adequate for the Powder. It was agreed that the Sponsor will provide the necessary justification, including historical dissolution profile data for the clinical trial lots and the drug product batches released for commercial distribution worldwide.

The Sponsor intends to propose the same dissolution method as already approved by the FDA for the routine QC testing of Prograf® capsules. The Sponsor wishes to explore this approach first because they are worried that any additional dissolution method development studies will delay the NDA submission for this pediatric oral formulation of tacrolimus (an unmet medical need). The Sponsor acknowledged the need to demonstrate the discriminating ability of the dissolution method for the proposed drug product. If necessary, the Sponsor is offering to conduct any additional required investigations as part of a Post-Marketing Commitment. The FDA recommended that they submit the justification package during the Pre-NDA stage; the cover letter should specifically state that FDA feedback is requested without the need for a formal meeting.

The Sponsor reiterated their desire to use for the dissolution testing of the 0.2 mg strength of the Powder for Oral Suspension. They stated that a study was conducted to compare the vs the 1-packet dissolution testing of the 0.2 mg strength of the Powder. The FDA indicated that single-unit dissolution testing is preferred to allow for the evaluation of inter-unit variability, and reminded the Sponsor to include the results of the 1-packet dissolution study in the incoming submission so that the study findings may be considered.

**Question 4:**

In support of the EU approved product, stability studies have been carried out to evaluate both strengths of tacrolimus 0.2 mg and 1 mg granules and establish the shelf life and storage conditions. Stability results for tacrolimus granules from three batches of each strength tested in the primary packaging material, which is identical to that to be used for US commercial granules for oral suspension, are included in [Attachment 1, Quality Overall Summary,
Section 8, Stability. The proposed shelf-life of 3 years for tacrolimus 0.2 mg and 1 mg granules is considered to be supported.

Does FDA agree with the Astellas proposal to request a 3-year shelf life for tacrolimus granules?

**FDA Response to Question 4:**

The shelf life for the drug product will be determined based on the assessment of the stability information submitted in the NDA.

**Discussion:**
The sponsor accepted FDA’s response, no discussion occurred.

**Question 5:**
Common intermediate granules and final granule are used for both 0.2 mg and 1 mg drug product configurations. Therefore, Astellas proposes to submit the following Executed Batch Records (English translated version) in support of the NDA:

- one batch of intermediate granule manufacturing process
- one batch of tacrolimus granules 0.2 mg final granule manufacturing process
- one batch of tacrolimus granules 0.2 mg primary packaging process

Does FDA agree with Astellas’ proposal for submission of the batch records?

**FDA Response to Question 5:**

Your proposal regarding the submission of executed batch records is reasonable. Upon review of the submitted records in the NDA, if needed, additional executed batch records may be requested.

**Discussion:**
The sponsor accepted FDA’s response, no discussion occurred.

**Additional Comments**

**Dissolution Method:** Include the following information in the dissolution method development report supporting the selection of the proposed dissolution test:

a. Solubility data for the drug substance over the physiologic pH range.

b. Detailed description of the dissolution test being proposed for the evaluation of the product and the developmental parameters (e.g., selection of the
equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for the product. Include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions used for each test. The dissolution profile should be complete and cover at least 80% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. FDA recommends use of at least twelve samples per testing variable and sampling time points of 10, 15, 20, 30, 45, 60, 90 min etc.

c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the product. Report the dissolution data as the cumulative percentage of drug dissolved with time (the percentage is based on the product’s label claim).

d. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables).

e. Provide supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

f. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution.

Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion (a) of the product, consider the following points:

g. FDA recommends use of the dissolution profile data (i.e., 15, 20, 30, 45, 60, 90 min etc.) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) for setting the dissolution acceptance criterion (a).

h. The in vitro dissolution profile should encompass the timeframe over which at least 80% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution occurs.

i. The dissolution acceptance criterion should be based on average in vitro dissolution data (n = 12).

j. The selection of the specification time point should be where Q = 80% dissolution occurs.
k. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the CTD.

**Discussion:** In regards to comments d and f, the Agency encouraged the sponsor to submit the historical data and any additional data to support in the NDA submission.

**Post-meeting comments from the Agency:**
Following the meeting on November 14, 2016, we had further internal discussion regarding in your proposed Tacrolimus 0.2 mg and 1 mg granules products. We recommend you conduct additional studies to understand the impact to the quality and performance of the products. The studies should include stress studies (mechanical and environmental including elevated temperatures and humidities) using analytical methods capable of detecting . Additional studies on the impact on the product performance would also be helpful in assessing the product quality. We would like to examine the study results prior to the initial NDA submission.
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/s/

GRAFTON G ADAMS
12/14/2016
IND 64148

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
       Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Pritza:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)
of the Federal Food, Drug, and Cosmetic Act for Astagraf XL (tacrolimus extended release capsules).

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2016. The purpose of the meeting was to discuss the content and format of a planned NDA submission for a new formulation of tacrolimus.

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

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 17, 2016, 12:00-1:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 64148
Product Name: Tacrolimus granules for oral suspension
Indication: Treatment of pediatric liver, kidney or heart transplant recipients
Sponsor Name: Astellas Pharma Global Development, Inc.

Meeting Chair: Renata Albrecht, MD
Meeting Recorder: Judit Milstein

FDA ATTENDEES
Renata Albrecht, Director, Division of Transplant and Ophthalmology Products (DTOP)
Ozlem Belen, Deputy Director for Safety, DTOP
Ergun Velidedeoglu, Clinical Reviewer, DTOP
Marc Cavaille-Coll, Clinical Reviewer, DTOP
Jane Filie, Associate Director for Labeling (acting), DTOP
Aaron Ruhland, Pharmacology/Toxicology Reviewer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Hongling Zhou, Biostatistics Reviewer, Division of Biometrics IV (DBIV)
Yan Wang, Biostatistics Team Leader, DBIV
Shukal Bala, Immunologist, Division of Anti-Infective Products
Yongheng Zhang, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCPIV)
Amit Somani, Clinical Pharmacology Reviewer, DCPIV
Philip Colangelo, Clinical Pharmacology Team Leader, DCPIV
Roy Blay, Reviewer, Office of Scientific Investigations
Madhuri Patel, Safety Evaluator, Division of Medication Errors and Prevention Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Mishale Mistry, Team Leader, DMEPA, OSE
Judit Milstein, Chief, Project Management Staff, DTOP

Reference ID: 4014934
SPONSOR ATTENDEES
Salim Mujais, Senior Vice President, Therapeutic Area Head
Xuegong Wang, Medical Director, Immunology and Transplant
James Keirns, Vice President, Senior Clinical Pharmacology Fellow
Jay Erdman, Senior Director, Global Development Project Leader, Immunology and Transplant
Richard Croy, Associate Director, Immunology and Transplant
David Smethurst, Executive Director, Immunology and Transplant
Mary Jo Pritza, Senior Director, Immunology and Transplant
Carol Soo, Associate Director, Immunology and Transplant
Beth Cywin, Associate Director, Immunology and Transplant
Nashrah Maryum, Post-Doctoral PharmD Fellow, Regulatory Affairs

BACKGROUND
At the time of approval of NDA 204096 (Astagraf XL), Astellas committed under a Post Marketing Requirement, to develop an age-appropriate formulation to allow for dosing of tacrolimus in patients ages 1 to < 5 years. The Sponsor plans to submit an NDA for the use of tacrolimus granules for oral suspension (0.2 mg and 1 mg packets) in the treatment of pediatric liver, kidney and heart transplant patients and requested a meeting to discuss the content and format of the upcoming NDA submission, as well as the acceptability of the planned components of the application, including study data generated, planned analyses and draft labeling.

Preliminary responses to the questions posted in the briefing document dated September 15, 2016, were sent to the Sponsor on October 11, 2016.

DISCUSSION
For the purposes of these minutes, the questions posted by the Sponsor in their briefing document are in bold format, the preliminary responses are in italics and the meeting discussions are in normal font.

Nonclinical

Question 1: Nonclinical Data in Support of Tacrolimus Granules for Suspension

Nonclinical testing of tacrolimus was conducted to support approval of Prograf capsules. Astellas intends to cross-reference nonclinical data contained in previously submitted NDAs 50-708 Prograf capsules, 50-709 Prograf injection and 204096 Astagraf XL. Astellas will submit a table of contents with cross-referencing to the other applications in Module 1.4.4 [Attachment 2]. Module 2.4 will contain an overview of nonclinical development with tacrolimus. Astellas does not plan to submit content to Module 2.6, nonclinical written and tabulated summaries or data to Module 4.

Does the Agency concur with Astellas’ approach to address the existing nonclinical data previously submitted to approved NDAs in Modules 2.4 and 1.4.4 of the planned NDA?

FDA Comments: We agree.
Meeting Discussion: The Sponsor acknowledged the Division’s comments.

Clinical

Question 2: Clinical Results in Support of Tacrolimus Granules for Suspension (Modigraf) in Pediatric Patients

Studies conducted with tacrolimus granules to be included in the NDA for the new formulation are:

A phase 1, relative bioavailability study (Study 95-0-001) to compare tacrolimus immediate-release capsules (Prograf) and tacrolimus granules in 32 healthy adult subjects.

A phase 2, noncomparative pilot 12-month study (Study FG-506-01-08) to assess the safety, efficacy and pharmacokinetics of tacrolimus granules in 28 pediatric patients ≤ 15 years of age (18 were < 5 years of age) undergoing liver allograft transplantation.

A phase 3, 12-month, randomized, open-label parallel-group study (Study FG-506-01-13) to investigate the safety and efficacy of a tacrolimus granules-based regimen compared to a cyclosporine microemulsion (ME)-based regimen in 181 pediatric primary liver transplant recipients ≤ 16 years of age. In the respective tacrolimus granules and cyclosporine treatment groups, 70 (76.9%) and 70 (77.8%) patients were < 5 years of age. The primary efficacy endpoint was defined as incidence of and time to first acute rejection.

A phase 4, 2-week, multicenter, open-label, pharmacokinetic study of tacrolimus granules in de novo kidney, liver and heart allograft recipients (Study F506-CL-0403 [OPTION]) in 52 pediatric patients ≤ 12 years. Overall, 36 (69.2%) patients were < 5 years of age.

Pediatric patients who elected to could roll over into the long-term PROGRESSION study (Study F506-CL-0404). Study F506-CL-0404 is a phase 4, open-label study to evaluate the safety and efficacy of tacrolimus granules in 47 pediatric transplant recipients who participated in Study F506-CL-0403. Overall, 33 (70.2%) patients were < 5 years of age.

Clinical safety and efficacy of tacrolimus granules in a pediatric liver transplant population were demonstrated in Study FG-506-01-13. Supportive pharmacokinetic data in liver transplant patients was obtained from Study FG-506-01-08, and in heart, liver and kidney transplant patients in the OPTION study (Study F506-CL-0403). Study F506-CL-0404 is divided into 2 parts: part A to monitor the safety and efficacy of tacrolimus granules in stable pediatric allograft recipients for up to 1 year and part B to monitor dose changes and tacrolimus whole blood concentrations after conversion from tacrolimus granules to Prograf capsules.

Astellas references the Agency’s written comments in the official meeting minutes dated 20 Aug 2014 [Attachment 1]. On the basis of the minutes, Astellas anticipates the clinical study reports (CSRs) from Studies 95-0-001, F506-CL-0403, FG-506-01-08 and FG-506-01-13 will be adequate to support the application along with the datasets for dose and tacrolimus trough concentration from Studies F506-CL-0403, FG-506-01-08 and FG-506-01-13.
a) As described in the Type C meeting minutes, Astellas intends to submit analysis datasets for dose and tacrolimus trough concentrations in Studies FG-506-01-08 and FG-506-01-13. Analysis datasets for pharmacokinetic samples and parameters from Study FG-506-01-08 will also be provided, as these data pertain to drug exposure. In addition, key information regarding patient characteristics and disposition will be provided in patient-level analysis datasets. All analysis datasets for these studies will follow Clinical Data Interchange Standards Consortium (CDISC) conventions as Analysis Data Model (ADaM) datasets. The table below provides a summary of the analysis data being submitted in this NDA for Studies FG-506-01-08 and FG-506-01-13; standard data tabulation model datasets and documentation (i.e., annotated case report forms [CRFs] and defined files) that support these analysis datasets will also be provided. No other datasets will be submitted for Studies 95-0-001, FG-506-01-08, and FG-506-01-13. No integrated analysis datasets are planned for safety or efficacy. Does the Agency concur with Astellas’ approach to content and format of the datasets for inclusion in the NDA as described in the table below?

<table>
<thead>
<tr>
<th>Legacy Study</th>
<th>ADaM Dataset Name</th>
<th>Description Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG-506-01-13</td>
<td>ADSL</td>
<td><em>Patient-level Analysis Data:</em> Age, race, gender, primary diagnosis, reason for discontinuation, treatment group, reference days (skin closure, first/last dose), reference dates.</td>
</tr>
<tr>
<td></td>
<td>ADEX</td>
<td><em>Exposure:</em> Dosing intervals, dose levels, treatment group, and age.</td>
</tr>
<tr>
<td></td>
<td>ADEXIMP</td>
<td><em>Exposure Information by Day:</em> For each patient, dataset contains total daily dose (mg and mg/kg) as 1 record per day per route (iv or po). Also contains mean value over select time intervals for each patient. Treatment group and age are also included.</td>
</tr>
<tr>
<td>FG-506-01-08</td>
<td>ADPC</td>
<td><em>Drug Concentration Levels:</em> Tacrolimus and cyclosporine trough concentrations. Treatment group and age are also included.</td>
</tr>
<tr>
<td></td>
<td>ADSL</td>
<td><em>Patient-level Analysis Data:</em> Age, race, gender, primary diagnosis, reason for discontinuation, reference days (skin closure, first/last dose), reference dates.</td>
</tr>
<tr>
<td></td>
<td>ADEX</td>
<td><em>Exposure:</em> Dosing intervals, dose levels, and age.</td>
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<td><em>Exposure Information by Day:</em></td>
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</tbody>
</table>
### Legacy Study

<table>
<thead>
<tr>
<th>ADaM Dataset Name</th>
<th>Description Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADPP</strong></td>
<td><strong>Pharmacokinetic Parameters:</strong> Tacrolimus pharmacokinetic parameters. Patient’s age is also included.</td>
</tr>
<tr>
<td><strong>ADPC</strong></td>
<td><strong>Drug Concentration Levels:</strong> Tacrolimus and cyclosporine trough concentrations as well as tacrolimus pharmacokinetic sample concentrations. Patient’s age is also included.</td>
</tr>
<tr>
<td></td>
<td>For each patient, dataset contains total daily dose (mg and mg/kg) as 1 record per day per route (iv or po). Also contains mean value over select time intervals for each patient. Patient’s age is also included.</td>
</tr>
</tbody>
</table>

**FDA Comments:**
We did not find efficacy outcome variables such as BPAR, graft survival, and patient survival as well as important safety outcome variables such as infections, malignancies and eGFR in the Description Content. Please specify which analysis dataset contains these variables. We expect you to submit all the analysis datasets (including efficacy and safety datasets) used to generate the efficacy and safety results for your study reports. Since we will use these datasets to reproduce some of your study results and perform additional analysis if needed when reviewing your submission, we expect that your define file for the datasets be clearly written to expedite our review.

**Meeting Discussion:**
The Sponsor acknowledged the Division’s comments and asked if any additional analyses were needed. The Division indicated that no additional analyses are needed at this time, but they might request additional information once the NDA is submitted and under review. The Division clarified that the analysis datasets are expected to be accompanied by a “Define” file in pdf. format describing all the variables used in the datasets. The Division also repeated their additional comment at the end of the preliminary responses that the NDA (both the datasets and the clinical study reports) should include a non-adjudicated version of the safety events regardless of the study drug relatedness as assessed by the investigators.

b) For Studies F506-CL-0403 and F506-CL-0404 part A which have been completed more recently, Astellas will submit all study datasets (patient-level analysis data, safety, efficacy, dose, and tacrolimus trough concentration) in CDISC format. A Study Data Reviewer’s Guide and an Analysis Data Reviewer’s Guide along with the annotated CRF and defined files will also be provided. Does the Agency concur with the format and approach for these studies?
c) A draft statistical analysis plan (SAP) describing the planned approach to analyze the data from pediatric patients < 5 years of age in Studies FG-506-01-13 and FG-506-01-08 is included in the submission [Attachment 3]; no other analyses are planned. Note, analyses of exposure data in patients under 5 years of age are already presented in the CSRs for Studies F506-CL-0403 and F506-CL-0404 part A and are therefore not addressed in the SAP included in the submission. Does the Agency agree with Astellas’ proposed SAP and approach to the other analyses?

FDA Comments:
We agree with your proposed plan for data submission for the studies F506-CL-0403 and F506-CL-0404.

Meeting Discussion: None

d) Narratives for patients who died or discontinued the study are included in the existing CSRs and CRFs for Studies FG-506-01-13 and FG-506-01-08 which were completed in 2000 and 1998, respectively. Astellas plans to update these patient narratives to comply with internal standards. In addition, the updated narratives will address patients with graft loss. The updated patient narratives will be based on data listings from the CSRs and/or patient CRFs. Does the Agency have any specific comments on Astellas’ approach to submitting the patient narratives as described?

FDA Comments:
We agree with the plan to include analysis for patients < 5 years of age in Studies FG 506-01-13 and FG-506-01-08.

Meeting Discussion: None

FDA Comments:
We agree with your approach for submitting the patient narratives for studies FG-506-01-13 and FG-506-01-08. However, in addition to deaths, graft losses and study discontinuations, we request you to provide the narratives for malignancies, infectious and cardiovascular SAEs, CMV and BK virus infections, study medication discontinuations and losses to follow-up, grouped separately for each category. In each narrative, please provide the postoperative day instead of the calendar date when describing the course of events. For example, instead of “the patient was rehospitalized on 10/4/2000” use “the patient was rehospitalized on postoperative day 46 (or POD 46).”
**Meeting Discussion:**

The Division requested that if a patient experienced more than one major safety event such as acute rejection followed by graft loss and subsequent death, the narrative for that patient should be provided under the most important safety event category which is death without any duplicate narratives provided under the less severe safety event categories of acute rejection and graft loss. The Sponsor agreed with this request.

e) Does the Agency concur with Astellas’ plan to include CSRs from Studies FG-506-01-13, FG-506-01-08, 95-0-001, F506-CL-0403, and F506-CL-0404 part A in the application along with supportive datasets for dose and tacrolimus trough concentration from Studies FG-506-01-13, FG-506-01-08, F506-CL-0403, and F506-CL-0404 part A to be sufficient to support the filing of the NDA?

**FDA Comments:**

*We concur with all of your proposals, provided that the proposed to-be-marketed product is the same as that used in the relevant clinical studies. Please also clarify if Modigraf (tacrolimus granules) is the proposed to-be-marketed product that you intend to market in the US, or if you intend to market a different formulation of tacrolimus granules for oral administration.*

**Meeting Discussion:**

The Sponsor confirmed that they have used Modigraf in all of their studies which is the same commercial product currently approved in Europe and Japan.

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**Data Integrity Review and Inspection Planning**

**Question 3:** Data Integrity Review and Inspection Planning

Astellas anticipates that the Office of Scientific Investigations (OSI) may conduct a site inspection. To that end, we plan to develop the content of the background packages sent to the FDA field investigators with the following for the recently completed F506-CL-0403 OPTION study (1) a summary level clinical site dataset (CLINSITE) and (2) patient-level data listings by site. The structure and content of the CLINSITE dataset will be prepared using the dataset specifications referenced in the FDA Guidance for Industry dated 07 Nov 2012.

a) A separate Bioresearch Monitoring Program (BIMO) Reviewer’s Guide will be included in the NDA submission to detail the location of the CLINSITE dataset and define file, patient-level data listings, relevant clinical trial materials, sample CRFs and the original protocol and amendments. The BIMO Reviewer’s Guide will be included in Module 5.3.5.4. Do representative(s) from OSI or other members of the Agency
have any comments regarding Astellas’ plan for submission of the BIMO Reviewer’s Guide?

**FDA Comments:**

**Meeting Discussion:**
The Sponsor inquired as to whether an inspection will be scheduled for the site of the PK study. The Division indicated that they will discuss internally and a response will be provided in these minutes.

**Post Meeting Note:**
The Division confirmed that the PK bioanalytical site for Study F506-CL-0403 will likely be subjected to an FDA inspection. Please provide the complete Clinical Study Report (CSR), including the individual patient PK data listings, and the complete bioanalytical report by the time of the NDA submission. In addition, following the meeting, the Division requested information on what types of source documentation/records (CRFs, etc.) are still available for studies FG-506-08 and FG-506-13 conducted more than 15 years ago, and in whose possession, if available (Investigators or Astellas) are those records. The Sponsor responded that Astellas has on site the CRFs and TMFOs for both studies, and that they are following up with the European study sites to confirm what they have on site. As of the date of issuance of these minutes, the Sponsor indicated that study sites in Spain and the UK (Study FG-506-13) have study patient files available either at the site or at the hospital storage. The Sponsor further stated that they are still trying to obtain such information for sites in Italy, France and Denmark. Once this information is available, the Division will provide a more specific response.

b) For each of the studies in the CLINSITE dataset, separate patient-level data listings will be provided by site and sorted by patient number. The patient-level listings will include data on discontinuation reasons, reasons for non-evaluable, adverse events (AEs), serious AEs, deaths, protocol deviations, biopsy-proven acute rejection (BPAR), death and graft loss, concomitant medications and laboratory test results. Does the Agency concur with Astellas’ plans for the proposed CSR listings?

**FDA Comments:**
We concur with the plan for the proposed CSR listings.

**Meeting Discussion:** None
Regulatory

Question 4: Labeling

a) Astellas intends to submit an evaluation for the proposed proprietary name. The planned name is Prograf Granules (tacrolimus granules) for oral suspension. Does Office of Surveillance and Epidemiology have any comments on the acceptability of the proposed tradename?

FDA Comments:
The acceptability of the proposed proprietary name, Prograf Granules, will be a review issue.
We note that you have included the dosage form ‘granules’ as part of the proprietary name. Since the established name of this product will include this dosage form, it will be prominently displayed on the labels and labeling. We therefore, discourage the use of dosage form in the proprietary name as including it in the proprietary name would be duplicative. Please see the FDA Draft Guidance, “Best Practices in Developing Proprietary Names for Drugs” (May 2014), for more information regarding the inclusion of dosage forms as part of the proposed proprietary name. This draft guidance can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM398997.pdf

Meeting Discussion:
The Division clarified that the Sponsor will need to submit a proposed proprietary name for FDA evaluation as part of NDA submission.

b) Astellas has relied on FDA’s draft Guidance for Industry from February 2013 for including Pediatric Information into prescription labeling. A draft version of the labeling is included in the briefing document [Attachment 4].

o Does the Agency concur with Astellas’ approach in adding pediatric data for the new formulation to the Prograf label?

o Does the Agency have any comments on the planned approach to revising the labeling?
  o In addition Astellas will submit a supplemental application to the Prograf NDA (letter cross-referencing to the new NDA) for the new formulation. Does the Agency concur with this approach?

FDA Comments:
According to 21 CFR 201.57(c)(9)(iv)(B), (C), and (D), pediatric use information must be placed in relevant sections of the labeling, as applicable. Upon a cursory review of your proposed labeling, the sections you intend to revise to include pediatric information seem
adequate however, the acceptability of the labeling itself is a review issue and it is premature to make any specific comments at this time. We note however, that your draft labeling does not include changes addressing the Pregnancy and Lactation Labeling Requirements. See additional labeling comments at the end of the document with information to assist you in complying with the labeling requirements (see additional Division comments at end of document).

With regard to the submission of the new NDA, your approach is acceptable.

Meeting Discussion:
The Division indicated that they have consulted the Pediatric Review Committee (PeRC) regarding the need to submit an initial Pediatric Study Plan (iPSP), considering that the proposed NDA submission will respond to a Pediatric Research Equity Act (PREA) requirement and that a response will be included in the minutes of the meeting. The Sponsor also clarified that they have received Orphan Designation for the pediatric formulation and that they will submit copy of this designation to the file.

Post Meeting notes:
On October 18, 2016, the Sponsor provided via e-mail a copy of the Orphan Designation letter, which designated tacrolimus granules as an orphan product for the indication of “prevention of rejection in kidney, liver or heart transplant in pediatric patients.” The Division confirms that as the product has Orphan Designation, submission of an iPSP is not required as PREA does not apply to this product.

During the review of NDA 204096 for Astagraf XL® (tacrolimus extended-release capsules), the Division of Transplant and Ophthalmology Products and Astellas held a teleconference (May 2013) to discuss pediatric planning for Astagraf XL and the tacrolimus immediate-release products (including granules) in preparation for an upcoming Pediatric Review Committee meeting. During the meeting, Astellas was asked if we were aware of any published data on the pharmacokinetics and efficacy of the tacrolimus immediate-release formulation product in pediatric kidney transplantation.

At the Agency’s request, Astellas conducted a review of published data on the pharmacokinetics and efficacy of tacrolimus immediate-release capsules in the pediatric kidney transplant population, which was included in the briefing package to support the Type C meeting held in 2014. As described in the final minutes (August 2014), Astellas requested an opportunity to dialogue further with the Agency on whether additional labeling would be warranted. In response, the Agency cited that a final determination would be made after a formal review. In addition, the Agency requested that, at the time of the pediatric application, Astellas provide the location of the CSRs and supporting analysis datasets in the Prograf NDA for all pediatric pharmacokinetic studies in the current United State Product Insert for Prograf.
In order to assist the Agency, Astellas references the following submissions for the requested data and location:

- **Pediatric Liver Pharmacokinetic Data:** NDA 50-708, Prograf labeling supplement submitted 16 Aug 1996 (vol. 14, pages 06134 to 06174)
- **Pediatric Kidney Pharmacokinetic Data:** NDA 50-708/S-036 (sequence 0004) submitted 03 Dec 2009 in response to FDA RFI dated 27 Oct 2009

c) Does the Agency have any comments at this time related to the literature review of tacrolimus in pediatric kidney transplant patients? Does the Agency have any comments related to the reports and pharmacokinetic datasets previously submitted to the Prograf NDA and currently reported in the package insert?

**FDA Comments:**
*We do not have any comments at this time, but may have additional requests during the review of the NDA for tacrolimus granules for oral suspension.*

**Meeting Discussion:**
The Sponsor indicated that some of this information on pediatric kidney transplant patients was previously submitted to the Agency and asked if this data can be submitted by reference or if it would be preferable to resubmit in the context of this new NDA. The Division indicated that a response will be provided as a post-meeting comment.

**Post Meeting Comment:**
Considering that the above referenced information was submitted to IND 64148, and it is to be reviewed under the new NDA for tacrolimus granules, the Division’s preference would be that this information be summarized in Module 2 (e.g., 2.5, 2.7.1, 2.7.2, 2.7.4, etc.) and the study reports need to be included in Module 5, as appropriate.

**Question 5: eCTD**
Astellas is providing an eCTD table of contents (working eCTD TOC) as [Attachment 5]. Does the Agency have any comments at this time regarding the planned content of the submission?

**FDA Comments**
*We agree with your proposed content of the eCTD submission.*

**Meeting Discussion:** None
Question 6: NDA

Does the Agency concur that subject to review, the submission of the NDA for the new formulation and data as described would address the postmarketing requirement under PREA associated with the approval of NDA 204096 (Astagraf XL)?

FDA Comments

We concur that subject to review, the submission of the NDA for the new formulation and data as described would address the postmarketing requirement 2061-1 (Develop an age appropriate formulation to allow for dosing for ages 1 to <5 years.) under PREA associated with the approval of NDA 204096 (Astagraf XL). We will make our final decision after completing the review of your NDA.

Meeting Discussion: None

Additional Division Comments:

1. Prescribing Information -

Labeling

In your application, please submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56 and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015.) As you develop your proposed PI, we encourage you to review the labeling review resources:

- PLR Requirements for Prescribing Information available at:

- Pregnancy and Lactation Labeling (Drugs) Final Rule available at:

When converting to the PLLR format, you should include in the application a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format available at:
Meeting Discussion:

The Sponsor acknowledged the Division’s comments regarding the PLLR requirements and stated that appropriate language will be included in the NDA submission.

2. Adjudication of the safety events:

In the datasets and safety evaluation sections of the study reports please provide adverse event data regardless of the investigator assessment of the study drug attributability or adjudication of the events.

Meeting discussion: None

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

The Sponsor will provide information on the location of the references in support of the pediatric labeling, and the Division will provide guidance, as post meeting notes, as to whether the is information can be referenced or preferred to be included in the NDA.

The Division will provide information regarding the need of an iPSP as post-meeting notes

The Division will issue the minutes of the meeting within 30 days

ATTACHMENTS AND HANDOUTS

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
11/16/2016
NDA 204096
Astellas Pharma US, Inc.
Attention: Mary Jo Pritza, MPII, PharmD
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Dr. Pritza:

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 the submission dated May 14, 2014 requesting a Type C meeting with the Division. The meeting was scheduled on July 21, 2014 and the purpose of the meeting was “to discuss the formulation of tacrolimus 0.2 mg and 1 mg granules for oral suspension, and to obtain advice as to whether the current formulation may be appropriate to allow for dosing in pediatric patients 1 to < 5 years of age.” You further stated that you will “present information related to the formulation and clinical study data generated using this formulation to understand if these data may be adequate for submission in a future application and, pending review, may be sufficient to fulfill PMR 2061-1 of the PREA requirement.”

We sent preliminary responses dated July 17, 2014 to the questions posed in your briefing package dated May 14, 2014; the text of those responses is provided in Appendix A.

After receipt of FDA’s July 17, 2014 preliminary comments, you requested, in an email dated July 18, 2014, to cancel the face-to-face July 21, 2014 meeting, but sought written clarification on two questions located under Clinical Question #3.

Our written responses to the clarifying questions in your email dated July 21, 2014 were sent to you on July 24, 2014; the text of those responses is provided in Appendix B.

You requested further clarification via email on July 28, 2014. The text of the additional responses sent to you on August 5, 2014, is provided in Appendix C.
We acknowledge your August 12, 2014 email stating that there were no further questions or requests for clarification on the basis of the August 5, 2014 response.

In summary, the information provided in Appendix A, Appendix B and Appendix C contain the written responses to your questions in your briefing package dated May 14, 2014, and constitute the meeting minutes for this Type C 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 New Drugs
Office of Antimicrobial Products
Center for Drug Evaluation and Research
APPENDIX A

PRELIMINARY COMMENTS PRIOR TO MEETING
Division of Transplant and Ophthalmology Drug Products

Meeting Date: July 21, 2014
Meeting Location: CDER W2/22/RM 1315
Meeting Type: C
Application: NDA 204096
Drug: Astagraf XL® (tacrolimus extended-release capsules)
Indication: Prophylaxis of organ rejection in kidney transplant patients
Sponsor: Astellas Pharma Global Development

 Dear Dr. Pritza:

The following are the Division’s preliminary responses to the questions posed in your briefing package dated May 14, 2014. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. You also have the option of converting the face-to-face meeting to a teleconference.

Please note that if there are any major changes to your development plan, to the purpose of the meeting, or to the questions you submitted in your meeting package based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting.

The minutes of the July 21, 2014, meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

The questions outlined in your meeting package are presented in bold font and our responses are in italicized font.
Preliminary Comments:

Quality (Chemistry, Manufacturing and Controls)

Question 1: Description of the Tacrolimus 0.2 mg and 1 mg Granules for Suspension

Formulation Tacrolimus 0.2 mg and 1 mg granules for oral suspension are single-dose preparations presented in [ ] containing 0.2 mg or 1 mg tacrolimus as active ingredient. The granules are composed of aluminum foil, [ ] packed into cartons together with a patient information leaflet.

Tacrolimus 0.2 mg and 1 mg granules consist of the following components: tacrolimus (active ingredient), hypromellose, [ ] croscarmellose sodium, [ ] lactose monohydrate. This formulation is commercially available as “Modigraf” in Europe and "Prograf granules" in Japan and has been used in all the clinical studies listed in this document.

The compositions of tacrolimus 0.2 mg and 1 mg granules and the intermediate granules (also named Solid Dispersion Formulation, abbreviated as SDF) are described in further detail in [Section 5 of briefing document].

Does the Agency have any comments on the adequacy of the CMC data presented for tacrolimus 0.2 mg and 1 mg granules for oral suspension as described above and in [Section 5]?

Agency Response:

The CMC information provided is rather limited. To avoid overlooking any relevant issues, we recommend that Astellas submit a more detailed pre-NDA CMC background package covering manufacturing, packaging and packaging components, controls, stability (including solid state form), dissolution testing, and characterization of in-use stability and dissolution.

Nonclinical

Question 2: Nonclinical Data in Support of Tacrolimus Granules for Suspension (Modigraf)

Nonclinical testing of tacrolimus was conducted to support approval of Prograf and was summarized in support of the NDA for Astagraf XL. Astellas does not anticipate conducting new nonclinical evaluations in addition to the data package that supported the approval of Prograf to support a future application for tacrolimus granules.

Does the Agency concur that, on the basis of the known nonclinical profile for tacrolimus, no additional nonclinical work is necessary for tacrolimus granules?

Agency Response:
We concur.

Clinical

Question 3: Clinical Data in Support of Tacrolimus Granules for Suspension (Modigraf) in Pediatric Patients (1 to <5 Years of Age)

Studies conducted with Modigraf include the following:

- A single phase 1 relative bioavailability study (95-0-001) to compare tacrolimus immediate-release capsules (Prograf) and tacrolimus granules in 32 adult healthy subjects.
- A phase 2 study (FG-506-01-08) to assess the safety, efficacy and pharmacokinetics of tacrolimus granules in 28 pediatric patients < 1 to 13 years of age undergoing liver allograft transplantation.
- A phase 3 study (FG-506-01-13) to investigate the safety and efficacy of a tacrolimus granules-based regimen compared to a cyclosporine ME-based regimen in 181 pediatric primary liver transplant recipients ≤ 16 years of age.
- Postmarketing commitment to EMA included a multicenter, open-label, pharmacokinetic study in de novo kidney, liver and heart allograft recipients (F506-CL-0403; OPTION). The OPTION study is currently ongoing.

A summary of the results of the 95-0-001, FG-506-01-08 and FG-506-01-13 studies are provided in [Sections 7.1.1, 7.1.2 and 7.1.3 of the briefing document]. A summary of the key design features of Study F506-CL-0403 is provided in [Section 7.1.4 of the briefing document]. The number of patients enrolled in the studies, the range of patient ages and the number of patients < 5 years of age in each study are presented in Table 1 of the briefing document.

Astellas proposes that Modigraf results from pharmacokinetic Study 95-0-001 in adult healthy volunteers, efficacy and safety results from pediatric liver transplant recipients 1 to < 5 years of age in Studies FG-506-11-08 and FG-506-01-13, and results from Study F506-CL-0403 in pediatric de novo allograft transplant recipients may be sufficient for submission, and pending review, may fulfill the formulation requirement under PREA.

Following review of the summary of data provided in Section 7, would the Agency provide comment on the adequacy of the proposed data package to address the deferred requirement for development of an age-appropriate formulation, particularly in patients 1 to < 5 years of age?

Agency Response:

The PK data for Modigraf® (tacrolimus granules for oral suspension) appear adequate in pediatric liver transplant patients < 5 years (n=35). The adequacy of the PK data in pediatric kidney...
transplant patients < 5 years (n=9) and pediatric heart transplant patients < 5 years (n=7) will be determined upon review of the clinical study report and supporting datasets of the ongoing study F506-CL-0403 (OPTION study). Thus, the results from the pharmacokinetic Study 95-0-001 in adult healthy volunteers, efficacy and safety results from pediatric liver transplant recipients 1 to < 5 years of age in Studies FG-506-11-08 and FG-506-01-13, and results from Study F506-CL-0403 in pediatric de novo allograft transplant recipients appear sufficient for submission. Pending review, your development of tacrolimus granules for oral suspension could fulfill the formulation requirement under PREA, for an age-appropriate formulation in patients 1 to < 5 years of age.

Literature Review

Question 4: Published Data with Immediate-release Tacrolimus [Prograf®] in Pediatric Patients

During the review of NDA 204096, the Division of Transplant and Ophthalmology Products (DTOP) and Astellas held a teleconference (May 2013) to discuss pediatric planning for Astagraf XL and the tacrolimus immediate release products (including granules) in preparation for an upcoming Pediatric Review Committee (PeRC) meeting. During the meeting, Astellas was asked if we were aware of any published data on the pharmacokinetics and efficacy of the tacrolimus immediate-release formulation product in pediatric kidney transplantation. In response, Astellas conducted a review of the literature and the summary can be found in [Section 7.3 of the briefing document]. The pharmacokinetic data in pediatric renal transplantation from the literature is consistent with the AUC and Cmax information currently in the Prograf package insert [Prograf Package Insert, September 2013, Section 12.3] for renal pediatric patients. The efficacy data described in the pediatric renal transplantation literature are supportive of efficacy.

However, the standard of care for pediatric renal transplantation has changed over time such that the 2 earlier studies cited from the literature do not align with current treatment practices in the US, while the latter 2 used a previously marketed induction agent with an immunosuppressive regimen similar to that which is the current standard of care in the US (daclizumab, an IL-2 receptor antagonist is no longer available nor marketed in the US).

On the basis of the current literature, Astellas requests an opportunity for further dialogue with the Division to reach agreement on whether additional labeling changes are warranted.

Agency Response:

It may not be necessary to add in the Prograf® USPI the PK data obtained for Prograf® from the literature studies, particularly if the PK data in the literature are consistent with information that is already included in the current labeling, and if there will be no corresponding description of the
literature study(ies) in the Clinical Studies section. A final determination will be made after a formal FDA review of the cited literature studies.

At the time of the submission of the pediatric NDA supplement, we request that you resubmit electronic versions of the clinical study reports and supporting analysis datasets for all the pediatric PK studies described in the current Prograf® USPI. Alternatively, direct us to the location of the previous NDA submissions containing the requested information.

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
APPENDIX B

After receiving the preliminary comments on July 17, 2014, Astellas sent an email July 21, 2014, requesting clarification of the responses to two questions located under Clinical Question #3, and the Division provided the following response on July 24, 2014:

Dear Dr. Pritza:

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

We also refer to the preliminary comments our Division sent to you on July 17, 2014 in response to your questions contained in your meeting package dated May 14, 2014, received May 15, 2014. We further refer to your email, dated July 18, 2014, requesting clarification from the Division on our response to your Clinical question 3.

We have provided our clarification below.

CLINICAL QUESTION 3, paragraph 1:
Following on from my email on Friday, Astellas would like clarification from the Division on your response to our Clinical question 3. In your response, we note that the Division will require data from the ongoing OPTION study (0403) to be included in a data package to address our PREA commitment. We highlight that the protocol specified number of evaluable patients (ages 1 to <5 years) per organ group is stated as 12 +/- 2 (range 10-14). We anticipate that the final PK data based on this range of patient-numbers per organ group will be considered acceptable to the Division at time of submission. Would the Division please confirm whether our understanding is correct, that the described range of final data between age 1 to <5 years per group will be acceptable?”

FDA Response:
Yes, the range of 10 to 14 evaluable pediatric transplant recipients per organ group, from ages 1 to <5 years, for the OPTION Study (F506-CL-0403) is acceptable.

CLINICAL QUESTION 3, paragraph 2:
Also, we note the Division describes the overall data package to address the PREA commitment to include: “...results from the pharmacokinetic study 95-0-001 in adult healthy volunteers, efficacy and safety results from pediatric liver transplant recipients 1 to <5 years of age in studies FG-506-11-08 and FG-506-01-13, and results from Study F506-CL-0403 in pediatric de novo allograft transplant recipients...”. With regard to this statement, will the Division consider the final study reports with specific reference to completed studies 11-08, and 01-13 to be sufficient to support the final data package at time of submission?
FDA Response:
No, submission of the final Clinical Study Reports (CSR) for Studies FG-506-11-08 and FG-506-01-13 only will not be sufficient at the time of NDA submission. We request that the final CSR for completed Study 95-0-001 (bioequivalence study of Modigraf granules vs Prograf capsules in healthy adult subjects) also be submitted as part of the original NDA submission. With respect to data that would be needed to support an age-appropriate formulation in patients 1 to <5 years of age, we also need to receive the final CSR for Study F506-CL-0403, and would ideally like it to be submitted as part of the original NDA submission. However, if that would significantly delay the NDA submission and potential availability of an age-appropriate formulation, we would agree that the final CSR for the OPTION Study (F506-CL-0403) could be submitted for FDA review as soon as it becomes available.

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
APPENDIX C

After receiving the Division's July 24, 2014 responses, Astellas sent an email July 28, 2014, requesting further clarification on CLINICAL QUESTION 3, paragraph 2. FDA provided the following responses on August 5, 2014.

In addition, Astellas corrected a content error in CLINICAL QUESTION 3, paragraph 1:

For study F506-CL-0403, in the statement “...protocol specified number of evaluable patients (age 1 to <5 years) per organ group is stated as 12 +/- 2 (range 10-14)” the bolded text is incorrect.

The corrected statement is “...protocol specified number of evaluable patients (ages <12 years) per organ group is stated as 12 +/- 2 (range 10-14).”

Dear Dr. Pritza:

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

We also refer to the preliminary comments our Division sent to you on July 17, 2014 in response to your questions contained in your meeting package dated May 14, 2014, received May 15, 2014. We further refer to your email, dated July 18, 2014, requesting clarification from the Division on our response to your clinical question #3. We responded to your request for clarification on July 24, 2014. Finally, we refer to your email, dated July 28, 2014, rephrasing question #2, better describing the clarification that you are seeking and, correcting a content error made in your email dated July 18, 2014.

We are providing the responses below, addressing both items.

Question:
Will the Agency expect patient datasets (i.e., SAS transport files) for study 01-08 and 01-13, completed in 1998 and 2000, respectively, to accompany the clinical study reports in the submission? Please note, the CSRs include transplant recipients 1 to <5 years old as noted in the briefing document; however, the CSRs include analyses for the overall patient population as designated in the protocols, respectively < 13 years old for FG-506-01-08 and < 16 years old for FG-506-01-13 and do not contain specific analyses for the age group of 1 to < 5 years old.

Agency Response:
We are expecting the analysis datasets for dose and tacrolimus trough concentrations to be submitted (in SAS transport file format) with the clinical study reports (CSRs) of Studies 01-08 and...
01-13. If feasible, the CSRs should also provide separate analyses for pediatric patients 1 to < 5 years.

Question:
We highlight that the protocol specified number of evaluable patients (ages 1-to-<5-years < 12 years) per organ group is stated as 12 +/- 2 (range 10-14). We anticipate that the final PK data based on this range of patient-numbers per organ group will be considered acceptable to the Division at time of submission. Would the Division please confirm whether our understanding is correct, that the described range of final data between age 1-to-<5-years < 12 years per group will be acceptable?

Agency Response:
We consider at least 12 pediatric patients < 12 years with evaluable PK data to be an acceptable sample size for each organ group.

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

CLINICAL QUESTION 3, paragraph 2:
Also, we note the Division describes the overall data package to address the PREA commitment to include: “…results from the pharmacokinetic study 95-0-001 in adult healthy volunteers, efficacy and safety results from pediatric liver transplant recipients 1 to <5 years of age in studies FG-506-11-08 and FG-506-01-13, and results from Study F506-CL-0403 in pediatric de novo allograft transplant recipients…”. With regard to this statement, will the Division consider the final study reports with specific reference to completed studies 11-08, and 01-13 to be sufficient to support the final data package at time of submission?

FDA Response:
No, submission of the final Clinical Study Reports (CSR) for Studies FG-506-11-08 and FG-506-01-13 only will not be sufficient at the time of NDA submission. We request that the final CSR for completed Study 95-0-001 (bioequivalence study of Modigraf granules vs Prograf capsules in
healthy adult subjects) also be submitted as part of the original NDA submission. With respect
to data that would be needed to support an age-appropriate formulation in patients 1 to <5
years of age, we also need to receive the final CSR for Study F506-CL-0403, and would ideally
like it to be submitted as part of the original NDA submission. However, if that would
significantly delay the NDA submission and potential availability of an age-appropriate
formulation, we would agree that the final CSR for the OPTION Study (F506-CL-0403) could be
submitted for FDA review as soon as it becomes available.

Astellas' July 28, 2014 email provided a response, rephrasing question 2, better describing the
clarification they are seeking and also correcting a content error made in Astellas' July 18, 2014
date. FDA provided the following clarification, on August 5, 2014.

**Question:**
Will the Agency expect patient datasets (i.e., SAS transport files) for study 01-08 and 01-13,
completed in 1998 and 2000, respectively, to accompany the clinical study reports in the
submission? Please note, the CSRs include transplant recipients 1 to <5 years old as noted
in the briefing document; however, the CSRs include analyses for the overall patient
population as designated in the protocols, respectively < 13 years old for FG-506-01-08 and
< 16 years old for FG-506-01-13 and do not contain specific analyses for the age group of 1
to < 5 years old.

**Agency Response:**
We are expecting the analysis datasets for dose and tacrolimus trough concentrations to be
submitted (in SAS transport file format) with the clinical study reports (CSRs) of Studies 01-08
and 01-13. If feasible, the CSRs should also provide separate analyses for pediatric patients 1 to
< 5 years.

**Question:**
We highlight that the protocol specified number of evaluable patients (ages 1 to <5 years ≤
12 years) per organ group is stated as 12 +/- 2 (range 10-14). We anticipate that the final
PK data based on this range of patient-numbers per organ group will be considered
acceptable to the Division at time of submission. Would the Division please confirm
whether our understanding is correct, that the described range of final data between age 1
to <5 years ≤ 12 years per group will be acceptable?

**Agency Response:**
We consider at least 12 pediatric patients < 12 years with evaluable PK data to be an acceptable
sample size for each organ group.
In an August 12, 2014 email Astellas responded stating that there were no further questions or requests for clarification on the basis of the August 5, 2014 response.

Minutes Preparer: Jacquelyn Smith, M.A., Senior Regulatory Project Manager, DTOP
Chair Concurrence: Renata Albrecht, M.D., Director, DTOP
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENAATA ALBRECHT
08/20/2014