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APPLICATION NUMBER:

206406Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 206406
Related IND	IND 75250
Applicant Name	Veloxis Pharmaceuticals, Inc.
Date of Submission	December 28, 2013
Date of Receipt	December 30, 2013
Tentative Approval	October 30, 2014
Type 1 Resubmission/Labeling	June 12, 2015
PDUFA Goal Date	August 12, 2015
Proprietary Name / Established (USAN) Name	Envarsus XR tacrolimus extended-release tablets
Formulation Strength	Oral tablets 0.75, 1, and 4 mg
Proposed Indication(s)	Prophylaxis of organ rejection in kidney transplant patients converted from immediate-release tacrolimus formulations
Action for Application	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
Labeling Reviews	
Medical Officer Review of Labeling	Huseyin E Velidedeoglu, Ozlem Belen, Renata Albrecht 7/10/2015
Statistical Review of Labeling	Hongling Zhou, Yan Wang 7/1/2015
Pharmacology/Toxicology Review of Labeling	Aaron Ruhland, Lori Kotch 6/30/2015
Immunology Review of Labeling	Shukal Bala, Renata Albrecht 7/24/2014
Clinical Pharmacology Review of Labeling	Phil Colangelo 6/25/2015 Jeffrey Florian, Phil Colangelo 7/9/2015
Product Quality Manufacturing Review, PMCs	Anamitro Banerjee 7/1/2015
Biopharmaceutics Review	Banu Zolnik, Elsbeth Chikhale 6/30/2015
Project Management	Lois Almoza, Diana Willard
505(b)(2) Committee	Cleared 6/30/2015

PMCs = post-marketing commitments

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1. Summary and Recommendations

Tacrolimus is a calcineurin inhibitor. It was first approved in 1994 under the trade name Prograf (tacrolimus capsules), and is currently indicated for prophylaxis of organ rejection in liver, kidney and heart transplant recipients. Prograf is an immediate release formulation and is given twice daily. Generic versions of Prograf are now approved. Tacrolimus as an extended release capsule formulation dosed once-daily was approved in 2013 under the name Astagraf XL (tacrolimus extended-release capsules) for the indication of prophylaxis of organ rejection in kidney transplant recipients, and granted 3-year marketing exclusivity. Prograf and Astagraf XL are manufactured by Astellas.

Veloxis has developed an extended release tablet formulation which is dosed once-daily, and will be marketed under the trade name Envarsus XR; the trade name has been found to be acceptable by DMEPA.

Veloxis is a 505(b)(2) application that relies on Prograf NDA 50708 for nonclinical information. For clinical and pharmacokinetic data, Veloxis submitted results of multiple Phase 1, Phase 2 and Phase 3 studies conducted using Envarsus XR (known as LCP-tacro during development). The results of Study 2017 and Study 3002 in de novo kidney transplant recipients and the results of Study 3001 in kidney transplant recipients converted from Prograf to Envarsus XR provide evidence of safety and effectiveness of the product.

Astagraf XL has 3-year marketing exclusivity until July 19, 2016, (listed in the Orange book) based on the clinical trials in de novo kidney transplant patients conducted with Astagraf XL. It was determined that approval of Envarsus XR for the de novo use was blocked. Based on additional internal discussions including at the Center Director's briefing on December 3 and 5, 2014, it was determined that the conversion use represented a different condition of use for Envarsus XR that was not blocked by the exclusivity of Astagraf XL. Following advice provided to Veloxis on December 5 (teleconference) and December 12, 2014 (letter) as well as January 12, 2015 (advice letters), on June 12, 2015, Veloxis submitted labeling requesting approval for the following use:

1 INDICATIONS AND USAGE:

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants.

Limitations of Use

ENVARSUS XR extended-release tablets are not interchangeable or substitutable with other tacrolimus extended-release or immediate-release products [*see Warnings and Precautions (5.3)*].

2.2 Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer an ENVARSUS XR once daily dose that is 80% of the total daily dose of

the tacrolimus immediate-release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL.

Three strengths of Envarsus XR tablets will be marketed: of 0.75 mg, 1 mg and 4 mg. The overall safety profile for Envarsus XR was not significantly different from Prograf in the clinical studies. Adverse reactions seen after conversion use are included in product labeling Section 6 Adverse Reactions, and clinical outcomes results in Section 14 Clinical Studies of the package insert (See Section 8 and Section 7 of this document, respectively, for a summary of this information and see the MOR for detailed labeling).

All review disciplines have recommended that the application be approved. Facilities inspections are acceptable, clinical site inspections recommend the data are considered reliable. Labeling has been finalized, and five PMCs from chemistry have been agreed-to by the applicant, and will be included in the approval letter.

Several issues were raised by this application:

1.1 Deficiencies

None

1.2 Post-Marketing Studies

Veloxis has agreed in their letters of July 1 and 6, 2015, to a number of post-marketing commitments summarized in Section 13.3.

1.3 Other Issues

Approval of Envarsus XR use in de novo kidney transplant patients is blocked by Astagraf XL exclusivity.

2. Background and Regulatory Issues

Kidney transplantation is the generally-preferred treatment for end-stage kidney disease. The other available management is dialysis, however, studies have shown that survival after kidney transplantation is improved compared to survival while on dialysis. Because the transplanted kidney is an allograft, patients need to receive chronic immunosuppressive treatment (drugs or biologics) to prevent the recipient's immune system from rejecting the kidney. At present, there is no treatment that can reliably induce a recipient's tolerance for the allograft; therefore, patients with kidney transplants need chronic immunosuppression.

There are a number of approved immunosuppressants available, including calcineurin inhibitors (cyclosporine or tacrolimus), mammalian target-of-rapamycin inhibitors (sirolimus or everolimus), azathioprine, mycophenolate mofetil, mycophenolic acid, therapeutic proteins, antibodies, and corticosteroids. An extended-release formulation of tacrolimus was approved in 2013 as Astagraf XL (tacrolimus extended-release capsules) for once-daily dosing.

2.1 Regulatory History

Envarsus XR, developed under the name LCP-Tacro, was submitted under IND 75250 on May 30, 2006 and a pre-IND meeting was held on August 2, 2006 to discuss the development of this extended release formulation of tacrolimus, including the plan to submit this as a 505(b)(2) application.

The end of Phase 2 meeting was held May 20, 2008, during which results from Study 2011 in stable kidney patients were summarized and further development discussed. FDA requested information on de novo transplant patients, therefore a protocol for Phase 2 Study 2017 in de novo kidney transplant patients was submitted August 13, 2008 (b) (4)

Over the subsequent months, the Phase 3 protocols for Studies 3002 (de novo) and 3001 (conversion) were discussed. The main topics included blinding, the choice of a control regimen, and justification of the non-inferiority margin. FDA approved the use of Prograf with MMF on May 19, 2009; the sponsor chose to use this regimen in the control arm.

A second end-of-phase 2 meeting was held February 16, 2010 during which various new dosage strengths of LCP-Tacro were proposed for evaluation as a strategy to avoid medication errors, and the NI margins were discussed. For Study 3001, the applicant proposed a (b) (4) NI margin but FDA did not accept this. FDA noted that the information provided in the briefing package, using only the acute rejection rates, would support a margin no larger than (b) (4). For Study 3002, there was discussion that a 10% NI margin may be acceptable, if a justification using the appropriate putative placebo were provided. The initial starting dose of 0.14 mg/kg/day studied in Study 2017 was proposed for Phase 3 Study 3002.

Protocol 3002 was submitted for a Special Protocol Assessment (SPA) on March 31, 2010, and after revisions, SPA agreement was reached August 5, 2010.

A protocol for Study 3003 to evaluate tremors after switching from Prograf to LCP-tacro was submitted September 19, 2011; however, the revisions proposed by the Division were not included in the protocol for this one-way crossover study of 2-week duration.

On December 30, 2011, the applicant requested a Type C meeting to discuss (b) (4)

The applicant submitted the protocol for Study 2019 to evaluate PK of LCP-Tacro and Prograf in de novo kidney patients; this separate protocol was submitted in lieu of conducting a PK sub-study in Study 3002.

At the pre-NDA meeting held on August 7, 2013, the Division discussed the proposed content and format of the NDA, the sponsor's plan to mitigate potential medication errors related to

inadvertent switching with other tacrolimus products, by providing information in labeling, MedGuide and other strategies (e.g., (b) (4))

The NDA was submitted as a 505(b)(2) application on December 28, 2013, for the indication of prophylaxis of organ rejection in kidney transplant patients.

On September 12, 2014, Astellas submitted a letter to FDA requesting that the Agency clarify the scope of Astagraf XL's exclusivity. DTOP met with the Exclusivity Board on September 24 and October 14, 2014, during which time the scope of the Astagraf XL exclusivity was discussed.

On October 17, 2014, the Exclusivity Board sent a letter to Astellas requesting an analysis of how Astagraf XL (NDA 204096) qualifies for 3-year exclusivity under the Agency's interpretation of section 505(v) of the Federal Food, Drug, and Cosmetic (FD&C) Act as set forth in the Agency's April 9, 2012 letter from Janet Woodcock, Director, CDER, to Thomas Doyle, Docket No. FDA-2006- P-0007.¹ A copy of that letter summarizing the Agency decision on Vancocin was attached to the request sent to Astellas (and archived under NDA 204096).

Astellas responded with a letter from Covington & Burling, LLC dated October 27, 2014, (received on October 30, 2014) asserting, among other things, that the Agency had properly determined that Astagraf XL was eligible for exclusivity under the relevant sections of the statute.

On October 27, 2014, an information request was sent to Veloxis for NDA 206406 asking Veloxis for its position on whether approval of the Envarsus XR 505(b)(2) NDA would be affected by Astagraf XL's exclusivity.

In a letter dated October 29, 2014, Veloxis responded that they relied on Prograf for their 505(b)(2) application and did not rely on Astagraf XL. They further noted their product has a different dosage form and different proposed conditions of use.

An October 30, 2014, Memorandum summarizes the Exclusivity Board's findings regarding the Astagraf XL exclusivity and effect on Envarsus XR approval:

This memorandum addresses the decision by the Food and Drug Administration (FDA or the Agency) to tentatively approve Veloxis's new drug application (NDA) 206406 for Envarsus XR (tacrolimus extended-release tablets), in light of the existing 3-year exclusivity for Astagraf XL, a previously approved extended-release tacrolimus product. That exclusivity expires on July 19, 2016. Upon approving Astagraf XL, DTOP determined that it was eligible for exclusivity for new clinical investigations

¹ The Agency's interpretation was subsequently upheld in *ViroPharma, Inc. v. Hamburg*, 898 F.Supp.2d 1 (D.D.C.2012).

that were essential to its approval. In addition, after consulting with the Exclusivity Board within the Center for Drug Evaluation and Research (CDER), and based on the Exclusivity Board's determination that the conditions of approval for which Astagraf XL currently has exclusivity are shared by Envarsus XR, DTOP may only tentatively approve Envarsus XR at this time.

On October 30, 2014, the application was issued a *Tentative Approval* letter.

Veloxis met with FDA November 6, 2014 and requested approval, and considered the Tentative Approval an error. The Division had a Center Director Briefing to discuss the "new use" of conversion in stable patients from immediate release tacrolimus to Envarsus XR and noted that such use needed to be based on comparative clinical study(ies) showing that switching from one drug to another did not result in unacceptable safety or efficacy. During meetings on December 3, and December 5, 2014, the recommendation by the senior management was that "conversion use" represented a new condition of use of Envarsus XR that was not blocked by Astagraf XL, which had only been studied in de novo use. In addition, the Division noted that (b) (4)

(b) (4) Myfortic had conducted a controlled study to support conversion use. Thus controlled clinical studies had been the basis for approving conversion use. A General Advice letter issued December 12, 2014 summarizing the FDA's December 5, 2014 advice regarding conversion use, and on January 12, 2015, two General Advice letters were sent to Veloxis summarizing the Agency's analysis and conclusions regarding: whether Astellas appropriately received 3-year exclusivity for Astagraf XL, the scope of that exclusivity, and whether that exclusivity blocked approval of Envarsus XR. A second letter provided advice on the path to approval of the conversion use. This option would require Veloxis to submit revised draft labeling that omits references to the de novo patient population (Study 3002 and Study 2017), and only discusses the information relating to the conversion population (Study 3001). Approval of the application would be dependent upon reaching final agreement on labeling.

A meeting was held March 11, 2015 during which Veloxis and FDA discussed potential labeling that omitted reference to the de novo studies and use. On June 12, 2015, Judge Walton issued his decision regarding the Veloxis lawsuit. On the same day Veloxis submitted labeling for conversion use with Envarsus XR, which was accepted for review as a Class I resubmission with a 60-day PDUFA goal date of August 12, 2015.

2.2 (b) (4)

Veloxis conducted two Phase 3 Studies (3001 and 3002) for approval of NDA 206406. However, Astagraf XL, NDA 204096, approved July 19, 2013² has 3-year marketing exclusivity. As summarized under Section 2.1, above, the exclusivity blocks the approval of

² Drugs@FDA

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Envarsus XR for the use in de novo kidney transplant population but not the conversion use of Envarsus XR.³ The applicant (b) (4).

Comment: A Determination Regarding (b) (4)

2.3 Orphan designation, request for orphan exclusivity

The Office of Orphan Products Development (OOPD) granted orphan designation to Envarsus XR for the indication of prophylaxis of organ rejection in patients receiving allogeneic kidney transplant on December 20, 2013. The applicant is requesting Orphan Drug Exclusivity.

Comment: A Determination Regarding Orphan Exclusivity is pending.

3. CMC/Product Quality

For complete details, see the reviews by the product quality reviewers that resulted in recommendations to approve the product in the previous cycle. During this review cycle, the labeling was reviewed and found to be acceptable from the CMC perspective, and five PMCs (agreed to by the company) will be included in the approval letter (See section 13.3).

Envarsus XR (tacrolimus extended-release tablets) 0.75, 1 and 4 mg is a once-daily formulation of the calcineurin-inhibitor, tacrolimus. Approved formulations of tacrolimus include tacrolimus injection, tacrolimus capsules (e.g., Prograf and generic versions), and tacrolimus extended-release capsules, Astagraf XL, 0.5, 1, and 5 mg.

When protected from heat, light and moisture, tacrolimus exhibits good chemical stability as demonstrated by little increase in related substances on stability. Originally, the applicant intended (b) (4)

However, the final approved shelf-life of 24 months will begin at the time of (b) (4)

Inactive ingredients include hypromellose, lactose monohydrate, polyethylene glycol, poloxamer, magnesium stearate, tartaric acid, butylated hydroxytoluene, and dimethicone. All excipients meet USP/NF compendial requirements.

The CMC review notes that labeling (b) (4)
(b) (4) Envarsus XR is manufactured by Rottendorf Pharma GmbH. Veloxis Pharmaceuticals A/S is (b) (4) responsible for regulatory oversight of the release of the finished product. In addition, the reviewer recommends any references to (b) (4)
(b) (4) be removed from the labeling. The mention is considered promotional in nature and does not provide information that is useful for the safe prescribing of the product by healthcare provider or use by the patient.

³ Press release that in December 2013 Veloxis Pharmaceuticals submitted a New Drug Application FDA to market Envarsus for kidney transplant recipients.
<http://www.thepharmaletter.com/article/veloxis-pharma-submits-nda-for-envarsus-in-kidney-transplant-recipients>
<http://www.pharmabiz.com/NewsDetails.aspx?aid=79577&sid=2>

Environmental Assessment

Veloxis Pharmaceuticals request for categorical exclusion from the requirement to submit an Environmental Assessment (EA) according to 21 CFR 25.31(b) was considered acceptable.

Post Marketing Studies

Veloxis agreed to five post-marketing commitments which are listed in Section 13.3.

Comment: The revised labeling for the conversion use does not impact the CMC information in labeling. The information in Sections 3, 11, and 16 is acceptable, as are carton and container labels. The application can be approved from the CMC perspective.

4. Nonclinical Pharmacology/Toxicology

For detailed information, see Pharmacology /Toxicology (P/T) Reviews.

The applicant has submitted a 505(b)(2) NDA application for an extended release formulation of tacrolimus, Envarsus XR, and relies on the approval of Prograf capsules (NDA 050708) to support nonclinical safety of Envarsus XR. Revisions to the nonclinical sections of the product labeling predominantly reflect changes in the safety margins resulting from comparing the dose based on body surface area (mg/m^2) or exposure (AUC) following oral administration, based on the dose of 0.14 mg/kg/day. These revisions have been incorporated in the package insert.

The reviewer notes that in its current version, no changes were made to Sections 8.1, 13.1 or other sections that required further review from a nonclinical pharmacology/toxicology perspective. The current version of the labeling is acceptable.

Comment: The application can be approved from the Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

For complete information, see the Clinical Pharmacology review.

Based on the reviewer's analyses of tacrolimus PK, concentration and dose data from two Phase 2 studies and two Phase 3 studies in de novo kidney transplant patients and stable kidney transplant patients switched from tacrolimus immediate release capsules (Prograf®), as well as Phase 1 PK studies in healthy subjects, the reviewer's recommendations regarding the dosage and administration of Envarsus XR in conversion use are as follows:

- *Stable kidney transplant patients*
When switching from tacrolimus immediate release (e.g., Prograf) to ENVARSUS® XR, use a daily dose conversion ratio of 1:0.80 (i.e., upon conversion, the daily dose of Envarsus XR should be 80% of the daily dose of Prograf prior to conversion)
If needed, adjust Envarsus XR dosage to achieve tacrolimus trough concentrations within a 4 to 11 ng/mL range, and preferably similar to the pre-conversion level.

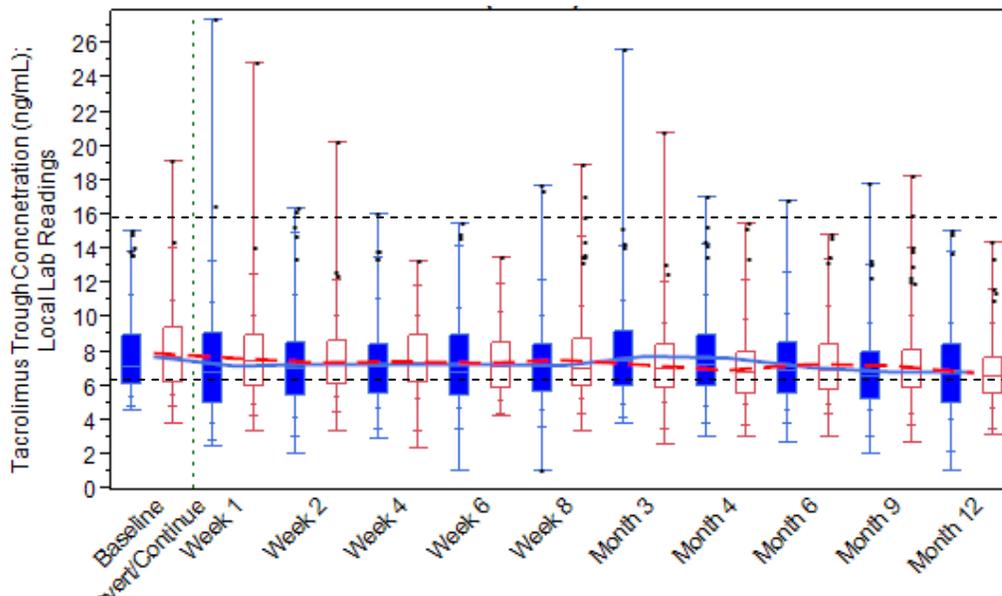
Studies in Stable Kidney Transplant Patients

In Study 2011, the steady state AUC-C_{trough} correlation lines of Envarsus XR and Prograf were superimposable (i.e., the slopes of the lines were comparable, and the data points comprising each line overlapped substantially); the AUC-C_{trough} correlation coefficients ($r \geq 0.79$) were satisfactory. This observation suggests that targeting the same tacrolimus trough concentration range as Prograf would be appropriate for stable kidney transplant patients switched from Prograf to Envarsus XR (at a daily dose conversion ratio of 1:0.8).

In Study 3001, stable kidney transplant patients (30 African Americans/Blacks and 120 non-African Americans/non-Blacks) receiving stable doses of Prograf twice daily and with tacrolimus trough concentration within 4-15 ng/mL at the end of the 7-day run-in period were randomized (1:1) at baseline to either continue treatment with Prograf twice daily at the current dose, or switch to Envarsus XR once daily. The Prograf-to-Envarsus XR daily dose conversion ratio was 1:0.85 for Blacks/African Americans, or 1:0.7 for non-African Americans/non-Blacks (slightly different from that used in Phase 2 Study 2011).

The reviewer stated that the baseline-to-Week 1 ratio of mean tacrolimus daily doses administered in Study 3001 were 0.8 for Envarsus XR conversion patients and 1.0 for Prograf continuation patients. This observation provided support for the reviewer's proposal to recommend a Prograf-to- Envarsus XR daily dose conversion ratio of 1:0.8 (regardless of race). After the first month, the target trough concentrations should be 4-11 ng/mL, similar to the pre-conversion level. Figure 3 presents the results of the tacrolimus trough concentrations in stable kidney transplant patients from Study 3001.

Figure 3. Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by Treatment



Legend: ENVARUSUS® XR (blue solid boxes with blue solid line); PROGRAF (red open boxes with red broken line); protocol defined target tacrolimus trough concentrations (black horizontal broken lines)
Source: Clinical Pharmacology Review, page 10

During review of labeling, it was noted that section **2.1 Administration Instructions** recommended

- If a dose is missed, take it as soon as possible within (b) (4) hours after (b) (4); beyond the (b) (4)-hour time frame, wait until the usual scheduled time to take the next regular daily dose.

It was noted upon further examination that Veloxis had submitted modeling of data from Study 2011 which supported a 15 hour window for a missed dose to be taken after the scheduled time, and therefore the labeling was revised to reflect information derived from Envarsus XR, as clarified in the Clinical Pharmacology addendum of July 9, 2015. In addition, the labeling submitted June 12, 2015 included a statement in section (b) (4); this statement was removed, as summarized in the June 25, 2015 review.

Section 12 includes PK results from Envarsus XR studies, and provides information on tacrolimus concentrations achieved with doses of 0.14 and 0.17 mg/kg/day.

Comment: The application can be approved from a Clinical Pharmacology perspective.

6. Immunology

For detailed information, see Immunology Review.

Based on the review of multiple published studies, the Immunology reviewer recommended that revisions be made to the labeling in **Section 12.1 Mechanism of Action**:

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

Comment: The application can be approved from a Immunology perspective.

7. Clinical/Statistical-Efficacy

7.1 Clinical Trials Supporting Approval

For complete details regarding the study design and outcome of the clinical studies, see Clinical and Statistical Reviews. The summary below is excerpted from these reviews.

This NDA contains two Phase 3 studies, 12-months in duration: Study 3002 was conducted in de novo kidney transplant patients and Study 3001 was conducted in stable renal transplant patients, 3 months to 5 years post-transplant. The table below provides an overview of Study 3001.

Study	Phase and Design	Primary endpoint and objective	LCP-Tacro	Prograf	Study Population
3001	Phase 3, open-label, multicenter, randomized study of the efficacy and safety of conversion from Prograf capsules twice daily to LCP-Tacro tablets once daily	Efficacy failure defined as death, graft failure, BPAR or LTFU at 12 months after the first dose of study drug. To show NI.	N=163 LCP-Tacro 0.5, 1, 2, and 5 mg tablets (QD). Initial dosing 0.7 of total daily dose of Prograf being taken for non-blacks, 0.85 multiple for blacks	N=163 Prograf 0.5-, 1-, and 5-mg capsules (BID). Only patients taking a stable total daily dose of at least 2 mg of Prograf were eligible for entry into the study.	Stable kidney transplant patients

Source: Adapted from Statistical Review, page 8.

The conversion study 3001 was a randomized, open-label, multinational study evaluating once daily ENVARSUS XR when used to replace tacrolimus immediate-release administered twice daily for maintenance immunosuppression to prevent acute allograft rejection in stable adult kidney transplant patients. Patients who received a kidney transplant 3 months to 5 years before study entry and on a stable dose of tacrolimus immediate-release of at least 2 mg per day and tacrolimus whole blood trough concentrations between 4 and 15 ng/mL were randomized to 1) switch from twice daily tacrolimus immediate-release to once daily ENVARSUS XR (N=163) or 2) continue tacrolimus immediate-release twice daily (N=163). MMF or mycophenolate sodium (MPS), or azathioprine (AZA) and/or corticosteroids were allowed as concomitant immunosuppressants during the study period according to the standard of care at the participating site.

The mean age of study population was 50 years; 67% were male; 73% were Caucasian, 22% were African-American, 2% were Asian and 3% were categorized as other races. Living donors provided 35% of the organs; 65% of patients received a kidney transplant from a deceased donor. Premature discontinuation from treatment at the end of one year occurred in 13% of ENVARSUS XR patients and 6% of tacrolimus immediate-release patients.

Study Drug: Tacrolimus

In the conversion study, stable kidney transplant patients converted to ENVARSUS XR at an average daily dose that was 80% of their tacrolimus immediate-release daily dose prior to conversion. Mean tacrolimus whole blood trough concentrations were maintained within a relatively narrow range throughout the duration of the study for both the ENVARSUS XR conversion group and the tacrolimus immediate-release continuation group. At Week 1 (after 7 days of stable dosing), the mean \pm SD tacrolimus trough concentrations were 7.2 ± 3.1 ng/mL for the ENVARSUS XR conversion group and 7.7 ± 2.5 for the tacrolimus immediate-release continuation group; the baseline values were 7.8 ± 2.3 , and 8.0 ± 2.3 , respectively.

Study Drug: MMF

In the conversion study, the average daily mycophenolate equivalent doses were comparable between the ENVARSUS XR and tacrolimus immediate-release treatment groups.

Efficacy Results

The efficacy failure rates including patients who developed BPAR, graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, are shown by treatment group in the table below for the modified intent-to-treat population.

Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Stable Kidney Transplant Patients

	ENVARSUS XR \pm Steroids \pm MMF, MPS, or AZA N=162	Prograf \pm Steroids \pm MMF, MPS, or AZA N=162
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI) ^a	0% (-4.2%, 4.2%)	
Treatment Failure	4 (2.5%)	4 (2.5%)
Biopsy Proven Acute Rejection	2 (1.2%)	2 (1.2%)
Graft Failure	0%	0%
Death	2 (1.2%)	1 (0.6%)
Lost to Follow-up	0%	1 (0.6%)

^a 95% CI was calculated using an exact method that is based on the standardized statistic and inverting a 2-sided test

Glomerular Filtration Rates

The mean estimated glomerular filtration rates (eGFR), using the Modification of Diet in Renal Disease 7 (MDRD7) formula, were 61.5 ml/min/1.73 m² and 60.0 ml/min/1.73 m² at baseline (Day 0) and 62.0 ml/min/1.73 m² and 61.4 ml/min/1.73 m² at 12 months in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

7.2 Non-Inferiority Margin

Regarding the non-inferiority margin for Study 3001, the meeting minutes from the end-of-phase 2 meeting for IND 75250 on February 16, 2010, the Division commented that based on the information provided in the briefing package, using only the acute rejection rates, the data referenced by the sponsor would support a margin no larger than (b) (4) (See DARRTS entry IND 75250 dated 03/12/2010.)

The non-inferiority of LCP-Tacro with respect to treatment failure within 12 months was assessed using a 2-sided 95% CI based on the difference in treatment failure rates between the treatment groups at 12 months, i.e., LCP Tacro minus Prograf.

8. Safety

The details of the safety evaluation are included in the Clinical and Statistical reviews.

Studies 3002, 3001 and 2017 were also reviewed for safety. Overall, there were 463 LCP-Tacro and 469 Prograf patients enrolled in these trials and treated for up to 12 months.

In an open label, randomized, multinational conversion study (3001), stable kidney transplant patients on a tacrolimus immediate-release product and concomitant immunosuppressants were randomized to treatment with ENVARSUS XR (N=162) or to continued treatment on the tacrolimus immediate-release product (N=162) and treated for a duration of 12 months, and demographic information is provided in the efficacy summary. The following information is from conversion study 3001.

Deaths & Graft Losses

A total of four patients died in Study 3001, three in the LCP-Tacro group and one in the Prograf group. One of the three deaths in the LCP-Tacro group occurred outside the 12 month study period. In the Clinical Reviewer's assessment none of the four deaths seem to be attributable to the study drugs. No graft losses were reported during the study period in Study 3001.

Other Serious Treatment Emergent events

SAEs were reported for 36 (22.2%) patients in the LCP-Tacro group and 26 (16.0%) patients in the Prograf group. The most frequently reported SAE was UTI (2.2% overall), and this event occurred in both treatment groups in Study 3001. Since Study 3001 is a study conducted in stable transplant patients the rates of SAEs in both groups are much lower compared to Study 3002 conducted in de novo transplant recipients. Overall SAEs are balanced across the two treatment groups.

Discontinuations

The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group was cardiac arrest (2 events).

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in stable kidney transplant recipients treated with ENVARSUS XR or tacrolimus immediate-release product are shown below.

Percentage of Stable Patients with Infections through One Year Post- Treatment in the Conversion Study^a

	ENVARSUS XR ± steroids, MMF/MPS or AZA N=162	Prograf ± steroids, MMF/MPS or AZA N=162
All infections	46%	48%
Respiratory Infections	26%	28%
Urinary Tract Infections	10%	14%
Bacterial Infections	7%	5%
Fungal Infections	4%	4%
Gastrointestinal Infections	4%	5%
BK virus ^b	2%	2%
Cytomegalovirus Infections	2%	1%
Serious Infections	8%	9%

^a The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

^b BK virus associated nephropathy (BKVAN) occurred in 1.2% (2/162) and 0.6% (1/162) in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

New Onset Diabetes after Transplantation (NODAT)

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥ 126 mg/dL, 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post baseline, insulin requirement for ≥ 31 days, an oral hypoglycemic agent use ≥ 31 days, or HbA_{1c} $\geq 6.5\%$ (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for the stable kidney transplant study through one year post-transplant is summarized in the table below in the Adverse Reactions section 6, and included in the Warnings and Precautions section 5 of labeling.

Percentage of Stable Patients with NODAT through 1 Year Post- Treatment in the Conversion Study^a

	ENVARUSUS XR ± steroids , MMF/MPS or AZA (N=90)	Prograf ± steroids, MMF/MPS or AZA (N=95)
Composite NODAT ^b	10%	11%
HbA _{1c} ≥6.5%	3%	7%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	6%
Oral hypoglycemic use	1%	1%
Insulin Use ≥31 days	1%	0%

^a The stable kidney transplant study was not designed to support comparative claims of ENVARUSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

^b Analyses restricted to patients at risk for NODAT

Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥5% of ENVARUSUS XR-treated patients compared to tacrolimus immediate-release product through one year of treatment in the conversion study is shown by treatment group in the table below.

Adverse Reactions (≥ 5%) in Stable Kidney Transplant Patients through 1 Year Post-Treatment in the Conversion Study^a

Adverse Reaction	ENVARUSUS XR N=162	Prograf N=162
Diarrhea	14%	9%
Blood Creatinine Increased	12%	9%
Urinary Tract Infection	9%	14%
Nasopharyngitis	9%	11%
Headache	9%	7%
Upper Respiratory Tract Infection	7%	9%
Peripheral Edema	7%	6%
Hypertension	4%	6%

^aThe stable kidney transplant study was not designed to support comparative claims of ENVARUSUS XR compared to tacrolimus immediate-release for the adverse reactions reported in this table.

Subgroup Analysis

There were very few events in Study 3001 to allow meaningful subgroup analyses.

Elevated Tacrolimus Trough Concentrations

As summarized in the medical officer review, there were 26 LCP-Tacro patients reported to have tacrolimus overdosing or tacrolimus toxicity, compared to 3 Prograf patients in Study 3002. This coding was used for patients whose tacrolimus trough concentrations were noticeably higher than the target concentrations. In the LCP-Tacro arm, values up to 52 ng/mL were reported. A similar imbalance was not observed in either Study 3001 or Study 2017. The PK data related to the tacrolimus toxicity will be included in the labeling.

Medication Errors

Medication Errors were reported during dispensing and administration between immediate-release formulation and extended-release formulation. For details, the Division Director Review dated October 30, 2014 should be consulted. Of note, information on this topic is found in the publically available medical literature and news reports, although it was first identified when the Astellas tacrolimus extended-release formulation (Astagraf XL) was marketed under the name Advagraf in Europe since 2007 and as Graceptor in Japan.

Comment: The clinical and the statistical reviewers concluded that benefits outweigh the risk and recommend approval of this application.

9. Advisory Committee Meeting

The review of this NDA submission for the indication of the kidney transplant indication did not raise scientific issues that needed input from the Advisory Committee.

10. Pediatrics

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.

PREA requirements do not apply to the current NDA submission since it has been granted orphan designation by the Office of Orphan Products, FDA.

11. Other Relevant Regulatory Issues

11.1 Office of Compliance Facility Inspections

The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities.

11.2 Office of Scientific Investigation (OSI) Audits

Inspections were performed at one domestic site (UCLA Medical Center) and two international sites (Poland and Germany) by the Office of Scientific Investigations (OSI). No issues were identified in any of these three sites and NAI letters will be issued.

11.3 Debarment certification

Veloxis Pharmaceuticals certified 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.

11.4 Financial Disclosure

As part of the NDA submission the Applicant included the FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and FDA Form 3455 (Disclosure Statement). Sixty-eight investigators participated in Study 3002, forty-seven participated in Study 3001, and nine in Study 2017; 2 of these 124 investigators had disclosable financial arrangements. The reviewer determined that these arrangements did not affect the reliability on the study results because these were only 2 investigators, the Phase 3 trials were blinded, and the primary and secondary endpoints were objective leaving no room for investigator bias.

11.5 Other Regulatory Issues

This is a 505(b)(2) application – the 505(b)(2) assessment committee has cleared this application from their perspective. Veloxis is relying on Prograf for non-clinical safety data. Clinical trials to support approval were conducted by Veloxis and are required for approval of this application.

The applicant (b) (4) (see Section 2.2).

The application received orphan designation on December 20, 2013 and the applicant is requesting orphan exclusivity (see Section 2.3).

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPP and OBP. OMP/DMPP and labeling recommendations were discussed. Final labeling was submitted as follows:

- Container Labels – eCTD Sequence No. 0026 submitted 9/26/2014
 - (b) (4) (overwrap) – eCTD Sequence No. 0027 submitted 10/9/2014
 - Carton – eCTD Sequence No. 0032 submitted 10/16/2014
 - Medication Guide – eCTD Sequence No. 0052 submitted 7/2/2015
 - Package Insert – eCTD Sequence No. 0054 submitted 7/7/2015
-
- **Package insert (PI):** The PI is written in PLR format. Labeling recommendations from reviewers have been incorporated; information on conversion use is retained, information specific to de novo use has been omitted. The final labeling is included in the MOR July 10, 2015
 - **Medication Guide:** Revisions recommended from various reviewers including OMP and OPDP have been incorporated. The final labeling is included in the MOR July 10, 2015.

- **Carton and Container Labels:** The labels have been reviewed by the Division, CMC and DMEPA and agreement was reached.
- **Proprietary Name:** The trade name Envarsus XR was considered acceptable from a promotional and safety perspective on April, 15 2014 and a letter to Veloxis accepting the name Envarsus XR was signed by Todd D Bridges on behalf of Kellie A Taylor on April 18, 2014 and did not need additional reviews after the Tentative Approval action.



13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA will be approved for use in stable kidney transplant patients converted from immediate-release tacrolimus to Envarsus XR, given that approval of the de novo population is currently blocked by Astagraf XL exclusivity until July 19, 2016.

13.2 Risk Benefit Assessment

End-stage kidney disease is a life-threatening condition with limited treatment options: dialysis or kidney transplantation. Long-term outcome and survival has been shown to be greater after transplantation than dialysis. The recipients of the kidney allograft need to receive immunosuppressants to prevent the recipient's immune system from rejecting the allograft.

There are a number of immunosuppressants available. Because transplant recipients are generally on multiple drugs including immunosuppressants and drugs for managing other medical conditions, Astellas developed a once-daily formulation of tacrolimus as an extended release capsule. Veloxis has developed an extended release tablet formulation.

Managing transplant patients is a balance in terms of providing sufficient immunosuppression to keep the recipient from rejecting the organ, but adjusting doses and immunosuppressants to minimize toxicity. The increased survival, reduced graft loss and reduced rates of acute rejection achieved with these products, is weighed against the toxicity associated with their use. The goal of management is achieve adequate immunosuppression and to minimize the toxicity through dose reduction, changing drugs, or treating the toxicity (e.g., infection, hypertension, NODAT, etc.).

The efficacy of the extended release tablet was evaluated in two Phase 3 studies: Study 3002 evaluated Envarsus XR in de novo kidney transplant patients and Study 3001 evaluated patients converted from Prograf to Envarsus XR. In addition, Study 2017 was relevant in the identifying the initial Envarsus XR starting dose.

The finding of elevated levels is included in the PK section of labeling. The dose of 0.17 mg/kg/day used in Study 3002 resulted in patients having levels above the target trough concentrations; troughs up to 52 ng/mL were reported for the first 2 weeks post transplantation, whereas in Study 2017, the dose of 0.14 mg/kg/day was not associated with trough concentrations significantly outside the target range. In addition, a caution is identified in the medical officer review related to protocol-specified cardiac exclusion criteria; only low cardiac risk patients were enrolled into Study 3002. Patients with electrocardiograms (ECG) demonstrating clinically relevant abnormalities (including QTc prolongation, reversible ischemia), clinically symptomatic congestive heart failure or documented ejection fraction of less than 45% were excluded from the trial. Therefore it is not known whether or not patients with high cardiac risk factors exposed to such high tacrolimus levels early on in the study would have experienced serious adverse reactions.

In the evaluation of adverse events in the Phase 3 studies, there were no significant differences reported between LCP-Tacro and Prograf. Specifically, the difference in tremors reported in the 2-week, one-way crossover Study 3003 was not reproduced in the Phase 3 trials, where tremors were reported in a small number of patients and there was no significant difference between the treatment arms.

Dosing of Envarsus XR, as well as Astagraf XL, Prograf and several other immunosuppressants, is based on therapeutic drug monitoring (TDM) and target trough concentrations. For the use of Envarsus XR in stable patients, labeling provides the conversion factor when converting patients from tacrolimus immediate-release formulation to Envarsus XR, and the target trough concentrations.

Overall, the benefits of Envarsus XR for this use outweigh its risk, and the labeling provides adequate instructions for the conversion use of Envarsus XR. The NDA will be approved.

13.3 Recommendation for other Postmarketing Requirements and Commitments

Veloxis agreed to the following PMC's.

PMC#1: Develop and validate a regulatory X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4) for determination of crystalline tacrolimus content in tacrolimus extended-release tablets. Revise 3.2.P.5 Drug Product Specification accordingly. Submit a supplemental NDA to add the XRPD testing facility.

Add XRPD testing to the on-going drug product stability protocol (first three commercial batches of each strength or next three consecutive commercial batches of each strength and annual stability commitment batches).

Final Protocol Submission:	09/2015
Study/Trial Completion:	04/2016
Final Report Submission:	07/2016
Interim Report:	01/2016

PMC#2: Develop and validate an X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4)

Add XRPD testing to tacrolimus (b) (4) stability protocol.

Final Protocol Submission:	09/2015
Study/Trial Completion:	04/2016
Final Report Submission:	07/2016
Interim Report:	01/2016

PMC#3: Evaluate the crystalline content of available legacy batches of tacrolimus (b) (4) and of drug product stability batches by XRPD.

Final Protocol Submission:	09/2015
Study/Trial Completion:	04/2016
Final Report Submission:	07/2016
Interim Report:	01/2016

PMC#4: Evaluate conditions that might be expected to promote crystallization of tacrolimus in (b) (4) tablets, including:

1. Any relationship between (b) (4) and crystalline tacrolimus content in tacrolimus extended-release tablets.
2. The (b) (4) stability of tacrolimus in (b) (4) tablets under accelerated and stress conditions.

Final Protocol Submission:	10/2015
Study/Trial Completion:	10/2016
Final Report Submission:	01/2017
Interim Report:	04/2016

PMC#5: Evaluate the effect of MeltDose manufacturing process parameters on crystalline content of (b) (4) tablets.

Final Protocol Submission:	10/2015
Study/Trial Completion:	10/2016
Final Report Submission:	01/2017
Interim Report:	04/2016

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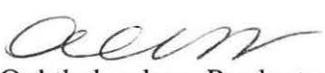
RENATA ALBRECHT
07/10/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 12, 2015

TO: NDA 206406/Envarsus XR (tacrolimus extended-release tablets)

THROUGH: Renata Albrecht, M.D., Dir., Division of Transplant and Ophthalmology Products,
Center for Drug Evaluation and Research (CDER)  1/12/15

FROM: Jay Sitlani, J.D., Office of Regulatory Policy, CDER  1/12/15

SUBJECT: Envarsus XR; Request for Final Approval

This memorandum documents the Food and Drug Administration's (FDA's or the Agency's) analysis and conclusions regarding the following issues: whether Astellas Pharma US, Inc. (Astellas) appropriately received 3-year exclusivity for the new drug application (NDA) for Astagraf XL (tacrolimus extended-release (ER) capsules) (NDA 204096), the scope of that exclusivity, and whether that exclusivity blocks approval of Veloxis Pharmaceuticals Inc.'s (Veloxis') NDA for Envarsus XR (NDA 206406).

FDA's consideration of the matter included evaluation of the arguments raised by Astellas and Veloxis; reexamination of the studies conducted to support both the Astagraf XL and Envarsus XR NDAs; review of the documents from NDAs for products cited as precedent regarding FDA's past treatment of the scope of 3-year exclusivity; and reevaluation of the Agency's prior determinations that Astagraf XL is entitled to 3-year exclusivity, that such exclusivity is not circumscribed by the limitations described in section 505(v) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(v)), and that this exclusivity blocks approval of the Envarsus XR NDA.

In summary, FDA confirms that 3-year exclusivity for Astagraf XL is proper under section 505(c)(3)(E)(iii) and 505(v) of the FD&C Act. This exclusivity is based on the new clinical investigations essential to the approval of the once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. In addition, FDA concludes that the Envarsus XR NDA is a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection that is blocked from approval for *de novo* kidney transplant patients by Astagraf XL's exclusivity until that exclusivity expires on July 19, 2016. FDA also concludes, however, that the Envarsus XR NDA can be approved now for conversion of stable kidney transplant patients from tacrolimus immediate-release (IR) products to Envarsus XR (the

conversion use), pending Veloxis' submission and FDA approval of an appropriate labeling amendment deleting reference to the *de novo* population and seeking approval for the conversion use only.

This decision has involved the intersection of complex legal, regulatory, policy, scientific, and technical issues. This decision was made with input from the Agency's scientific experts and policymakers from the Center for Drug Evaluation and Research (CDER), including personnel from the Office of the Center Director, Office of New Drugs (including scientific experts in the Office of Antimicrobial Products (OAP), Division of Transplant and Ophthalmology Products (DTOP)), Office of Clinical Pharmacology (OCP), CDER's Exclusivity Board, and other policy experts in the Office of Regulatory Policy (ORP) and the Office of Medical Policy, among others. Accordingly, this letter has been prepared in consultation with several components of the Agency.

I. BACKGROUND

A. Immunosuppression in Kidney Transplant Patients¹

The immune system distinguishes *self* from *non-self*. When a kidney (or other organ) is transplanted from one person into another person, the immune system recognizes the transplanted organ as *non-self* and will try to attack and to reject the transplanted *non-self* organ. To prevent any rejection, drugs that suppress the immune system need to be given to organ transplant recipients. The drugs must be started at the time the organ is transplanted and continue to be taken as long as the transplanted organ (graft) is viable.

Kidney transplant patients are referred to as *de novo* patients at the time of transplant surgery. Because relying solely on one immunosuppressant drug has not been shown to be sufficient to provide adequate immunosuppression to these patients, multiple drugs are now included in the patient's immunosuppressive regimen. *Induction* generally refers to the intensive level of immunosuppression administered to *de novo* kidney transplant patients from the commencement of the transplant surgery until early after the surgery. In all kidney transplant patients, induction

¹ This section has been derived from a compilation of sources. See, e.g., Morris, PJ and SJ Knechtle, 2014, *Kidney Transplantation: Principles and Practice*, 7th edition, Saunders; Kirk, AD, SJ Knechtle, CP Larsen, et al., 2014, *Textbook of Organ Transplantation*; HU Meier-Kriesche, S Li, RW Gruessner, et al., 2006, *Immunosuppression: Evolution in Practice and Trends, 1994-2004*, *Am J Transplant*, 6 (5 Pt 2):1111-1131; Hardinger, KL, DC Brennan, and CL Klein, July 2013, *Selection of Induction Therapy in Kidney Transplantation*, *Transpl Int*, 26(7):662-672; WH Lim, J Eris, J Kanellis, et al., Sept. 2014, *A Systematic Review of Conversion from Calcineurin Inhibitor to Mammalian Target of Rapamycin Inhibitors for Maintenance Immunosuppression in Kidney Transplant Recipients*, *Am J Transplant*, 14(9):2106-2119; Holdaas, H, L Rostaing, D Serón, et al., Aug. 27, 2011, *Conversion of Long-Term Kidney Transplant Recipients from Calcineurin Inhibitor Therapy to Everolimus: A Randomized, Multicenter, 24-Month Study*, *Transplantation*, 92(4):410-418; Budde, K, J Curtis, G Knoll, et al., Feb. 2004, *Enteric-Coated Mycophenolate Sodium Can Be Safely Administered in Maintenance Renal Transplant Patients: Results of a 1-Year Study*, *Am J Transplant*; 4(2):237-243.

involves, at a minimum, the use of a *triple combination* of a calcineurin inhibitor (CNI) (e.g., tacrolimus or cyclosporine) at a high initial dose; a mycophenolate preparation (which includes mycophenolate mofetil (MMF) or mycophenolate-sodium); and a higher dose of corticosteroids than regularly used for maintenance immunosuppression. In approximately 85% of *de novo* kidney transplant patients, induction involves the use of a four-drug (quadruple) combination, which includes one to six doses of an antibody preparation (antibody induction) in addition to the triple combination.²

During the early post-transplant period, the patient's regimen of these immunosuppressants is carefully and frequently monitored, which may include measuring drug trough (predose) concentrations in blood³ and may be adjusted to minimize the development of adverse reactions while keeping the immune system from rejecting the kidney. The immunosuppressive regimen is adjusted according to the patient's individual course, including the occurrence of rejection episodes (signifying increased risk for rejection), and according to adverse events (signifying poor tolerance of the regimen). The goal is to customize the regimen to find the optimum balance between the efficacy and toxicity of the immunosuppressive regimen.

Kidney transplant recipients reach this optimum balance generally around 3 to 6 months (although sometimes it takes years) after kidney transplant. When patients have achieved this balance, they are no longer considered *de novo* patients and are considered maintenance patients. These maintenance patients are on a regimen that is both tolerated by their bodies and keeps their immune system from rejecting the organ. Maintenance patients are different from *de novo* transplant recipients, and thus are treated differently. For example, maintenance patients:

- Have lower risk of rejection episodes.
- No longer require treatment with induction antibodies or high dose corticosteroids (unless needed to treat an episode of a high-grade rejection). Are not receiving induction-level immunosuppression, meaning that (among other things) they are receiving lower doses of CNI and a zero to low dose of corticosteroids, and that the long-lasting immunosuppressive effects of the induction treatment received at the time of transplant are starting to disappear.

² Scientific Registry of Transplant Recipients, available on the Internet at http://srtr.org/annual_reports/2011/506d_ki.aspx and http://srtr.org/annual_reports/2011/506a_ki.aspx.

³ Calcineurin inhibitors, including tacrolimus, are considered narrow therapeutic index (NTI) drugs. See FDA's Bioequivalence Recommendations for Specific Products and draft guidances on Tacrolimus (recognizing that tacrolimus is an NTI drug based on certain evidence). FDA updates guidance documents periodically. To make sure you have the most recent version of a drug guidance or a product-specific bioequivalence study guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. The doses and resulting drug trough concentrations needed to achieve efficacy are often associated with toxicity. The goal of dosage adjustments of immunosuppressive drugs is to maintain efficacy and minimize toxicity.

- Receive an immunosuppression regimen that reflects their individual level of immunologic risk as informed by the post-transplant history or absence of rejection episodes.
- Have immunosuppressive drug dosing and targets used in therapeutic drug monitoring (TDM) of whole blood trough concentrations that are optimized for each patient.
- Have a reduced frequency of monitoring, including TDM, to maintain efficacy and minimize toxicity, compared to the early *de novo* post-transplant phase.

The term *conversion* is used to indicate that a kidney transplant patient who has been treated with a regimen of three to four immunosuppressive drugs has one of those drugs discontinued and replaced with another drug. The conversion may be initiated due to toxicity or inadequate efficacy; for example, if the patient is having very serious adverse reactions and cannot tolerate the drug, or if the patient is experiencing rejection. Alternatively, the conversion can be for other reasons, such as choice of once-daily (morning or evening) or twice-daily dosing regimens based on personal convenience or other considerations in the practice of medicine. When a patient is converted to another drug, clinical practice requires additional and/or more frequent monitoring, clinical visits, and laboratory tests (including whole blood trough concentrations), which would not be needed in maintenance patients who continue on their same regimen.

Because immunosuppression in kidney transplant patients is highly individualized and requires a delicate balance between adequate suppression to avoid rejection and adverse events inherent to immunosuppressive therapy, the clinical study design needed to demonstrate the safety and efficacy of immunosuppressants in certain populations is very specialized. Separate studies are needed to support approval in *de novo* patients and conversion patients because the populations, and their inherent risks and goals, are different.

The *de novo* patients start with intense induction regimens consisting of three to four drugs at the time of kidney transplant with the goal of achieving a customized optimum balance between efficacy and toxicity. Once an optimum balance between immunosuppressive toxicity and the risk of rejection has been established in maintenance patients, any disturbance, including a change of immunosuppression regimen (even if it is switching from the immediate release to extended release of the same active moiety), may affect this balance, resulting in organ rejection. Thus, clinical studies in *de novo* patients are designed to evaluate the efficacy and safety of the immunosuppressive regimen in providing adequate protection against rejection. These studies start at the time of transplant and patients are treated and evaluated for safety and effectiveness for a duration of 6 to 12 months.

The goal for studies conducted in conversion patients is to assess the safety and efficacy of conversion because there is a risk of an untoward outcome anytime an alteration, including a change in the immunosuppressive regimen, occurs. Patients who are at least 3 months post-

transplantation can be enrolled in these conversion studies. In a clinical study for conversion, patients are randomized either to continue the maintenance regimen or to be converted to a new drug or formulation to evaluate whether conversion from one product to another (e.g., one tacrolimus formulation to another non-bioequivalent formulation) is safe and effective. Without a controlled clinical study, safety and effectiveness cannot be solely extrapolated from the different pharmacokinetic (PK) characteristics of each product. FDA currently expects separate adequate and well-controlled clinical studies for approval of immunosuppressants in *de novo* and conversion kidney transplant patients.

B. Tacrolimus and Prograf NDA 050708

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*.⁴ Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of the nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression). Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.

The first NDA for tacrolimus was approved by FDA on April 8, 1994, under the trade name Prograf (NDA 050708). The Prograf NDA was submitted pursuant to section 505(b)(1) of the FD&C Act and is currently held by Astellas. Prograf is an IR capsule available in doses equivalent to 0.5, 1, or 5 milligram (mg) of anhydrous tacrolimus.⁵ Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants.⁶ The recommended dosing frequency of Prograf is twice daily.⁷ Prograf is also approved in an

⁴ This paragraph has been excerpted from the Approved Product Labeling for Prograf (NDA 050708) (approved Sept. 4, 2013) (Approved Prograf Product Labeling) (Clinical Pharmacology and Description sections), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050708s043,050709s036lbl.pdf.

⁵ Id. (Description section).

⁶ Id. (Indications and Usage section). The kidney studies for Prograf were conducted in *de novo* patients as described in the Clinical Studies section.

⁷ Id. (Dosage and Administration section).

injectable dosage form (NDA 050709) that should be used only as a continuous IV infusion when the patient cannot tolerate oral administration of Prograf capsules.⁸

Tacrolimus is produced by *Streptomyces tsukubaensis* and meets the statutory definition of an *antibiotic drug*.⁹ This definition turns on the nature of the drug substance rather than on the indication of the drug product. Thus, even though tacrolimus was approved to prevent organ rejection rather than for antimicrobial use, it is considered an antibiotic drug.¹⁰ Because tacrolimus is an antibiotic drug substance that was the subject of an application for marketing received by FDA before November 21, 1997 (i.e., before enactment of the Food and Drug Administration Modernization Act (FDAMA¹¹)), it is commonly referred to as an *Old Antibiotic*.¹² There are no patents or exclusivities listed for the Prograf NDA in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).^{13,14}

C. Astagraf XL

Astagraf XL (NDA 204096) is an oral dosage form (capsule) of tacrolimus developed as an ER formulation and intended for once-daily administration. The approved indication is for the prophylaxis of organ rejection in patients receiving a kidney transplant.¹⁵ Astagraf XL capsules are available in doses equivalent to 0.5, 1 or 5 mg of anhydrous tacrolimus. The Astagraf XL

⁸ Id.

⁹ Section 201(jj) of the FD&C Act (21 U.S.C. 321(jj)) defines *antibiotic drug* as:

any drug . . . composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

¹⁰ Letter from FDA to TG Mahn, JE Mauk, WS Vicente, et al. (Docket No. 2003P-0275/CPI & PSA1) (Dec. 18, 2003) at 15, 29, and 32, available on the Internet at <http://www.fda.gov/ohrms/dockets/dailys/04/apr04/042004/03p-0275-ref0001-090-Tab-39-vol6.pdf>; see the proposed rule "Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs" (65 FR 3623 (Jan. 24, 2000)) (Proposed Rule on Old Antibiotics).

¹¹ Public Law 105-115.

¹² See, e.g., Proposed Rule on Old Antibiotics (listing tacrolimus as an *Old Antibiotic*). See also section II.C., *infra*, for a further discussion of antibiotics and exclusivity.

¹³ See the Orange Book, available on the Internet at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Section 505(j)(7)(A) of the FD&C Act requires FDA to publish and make available to the public certain information, including a list in alphabetical order of the official and proprietary name of each drug that has been approved for safety and effectiveness under section 505(c) of the FD&C Act, the date of approval and application number, and certain patent information. FDA also makes other information, such as exclusivity codes, available in the Orange Book.

¹⁴ FDA has approved several ANDAs referencing Prograf (NDA 050708). See the Orange Book.

¹⁵ Approved Product Labeling for Astagraf XL (NDA 204096) (Feb. 28, 2014) (Indications and Usage section), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204096s002lbl.pdf.

NDA is currently held by Astellas. The Agency summarizes below the relevant history of the NDA.

1. *Astagraf XL NDA 050811 and Withdrawal*¹⁶

On December 19, 2005, Astellas submitted an NDA for Prograf XL (further developed as Advagraf and now approved as Astagraf XL) for once-daily dosing in the prophylaxis of organ rejection following kidney, liver, or heart transplantation (NDA 050811).¹⁷ The NDA was submitted pursuant to section 505(b)(1) of the FD&C Act. The NDA for Astagraf XL cross-referenced animal pharmacology/toxicology data in Astellas' NDA for Prograf IR capsules (NDA 050708).¹⁸ NDA 050811 included one clinical study (Study 158) as primary confirmation of efficacy and supportive data from Phase 2 studies to support the proposed kidney indication.¹⁹

On January 19, 2007, FDA issued an approvable letter for NDA 050811 citing, among other things, deficiencies related to the kidney indication.²⁰ For example: (1) studies in *de novo* and stable kidney transplant patients did not provide sufficient data to support the safe and effective use of Astagraf XL for the prevention of graft rejection in kidney transplant patients or to conclude that the benefit of the drug outweighed its risks; and (2) studies did not demonstrate that the same daily doses of Astagraf XL and Prograf resulted in comparable tacrolimus exposures over the entire treatment period (and the clinical significance of these PK differences had not been fully characterized).²¹ The Agency also advised Astellas to provide additional PK data to support use of an initial dose of Astagraf XL and to submit data from an ongoing clinical trial comparing Astagraf XL to Prograf (Study 12-03) that could provide the additional data needed to support the safety and efficacy of Astagraf XL.²²

¹⁶ Initially, the proposed name for the drug product was Prograf XL and then Advagraf (not Astagraf XL), but for ease of reading, this memorandum refers to the drug product as Astagraf XL throughout.

¹⁷ Astagraf XL Clinical Review (June 19, 2013) (Astagraf XL Clinical Review) at 12. The Agency administratively split the NDA into three separate NDAs for each indication: NDA 050811 (kidney), NDA 050815 (liver), and NDA 050816 (heart). *Id.* To date, Astagraf XL has not been approved for liver or heart transplant patients. Approved Product Labeling for Astagraf XL.

¹⁸ Astagraf XL Clinical Review at 25-26. Manufacturing and controls information for Astagraf XL was incorporated into the application by reference to the Prograf NDA 050708 and the associated Type II DMF 16833. Astagraf XL Division Director Summary Review (July 19, 2013) (Astagraf XL Division Director Summary Review) at 7.

¹⁹ Astagraf XL Division Director Summary Review at 6; Astagraf XL Cross-Discipline Team Leader Review (Astagraf XL CDTL Review) at 1 (citing Astagraf XL Clinical Review at 12-13).

²⁰ Astagraf XL CDTL Review at 1-2 (citing Astagraf XL Clinical Review at 12-13).

²¹ Letter from DTOP to Astellas (Jan. 19, 2007) at 3.

²² Astagraf XL CDTL Review at 2.

On September 12, 2007, Astellas submitted a complete response to the January 19, 2007, approvable letter for NDA 050811.²³ Astellas amended its NDA with results from the PK sub-study of Study 12-03,²⁴ as well as with some limited information on safety and efficacy in the population studied.²⁵

Although this submission addressed the deficiency related to determination of an initial dose of Astagraf XL, it did not address the clinical deficiency.²⁶ In addition, upon reviewing data from NDA 050815 (liver indication), the Agency became concerned that gender-related differences in mortality and post-transplant diabetes mellitus between the Astagraf XL and Prograf treatment groups observed in liver transplant patients may also exist in kidney transplant patients.²⁷

Specifically, while reviewing NDA 050815 (liver indication), FDA found that there was a substantial gender-related difference in 12-month mortality rates between the Astagraf XL and Prograf treatment groups and a gender difference in the onset of post-transplant diabetes mellitus.²⁸ The Agency concluded that data from a PK sub-study of Study 12-03 was insufficient to determine if the observed 20% higher AUC₀₋₂₄ for Astagraf XL, compared with Prograf, was related to this clinically significant higher incidence of tacrolimus-related adverse events for Astagraf XL.²⁹ Although these adverse events were observed in the liver transplant setting, the Agency remained concerned that these adverse events could also exist in kidney transplant patients.³⁰ To address this deficiency in the kidney transplant context, the Agency requested that Astellas submit the full study report for Study 12-03 and study datasets that included, among other things, exposure-response analyses between safety outcomes (i.e., post-transplant diabetes mellitus, renal dysfunction, CMV and other infections, cardiac disorders, and glucose intolerance), efficacy outcomes, and C_{trough} (trough concentrations) as a function of gender and treatment group.³¹ The Agency also requested that Astellas analyze by gender and treatment groups all “adverse events of special interest” for *all* existing Astagraf XL versus Prograf trials in solid organ transplantation, not just Study 12-03 or studies in kidney transplantation.³²

²³ Id.

²⁴ Astellas did not provide the full study report from Study 12-03 at that time.

²⁵ Astagraf XL CDTL Review at 2.

²⁶ Id.

²⁷ Id.

²⁸ Approvable letter from DTOP to Astellas (Mar. 13, 2008) at 1-2.

²⁹ Id.

³⁰ Id.

³¹ Id. at 2.

³² Id.

On January 29, 2009, Astellas requested withdrawal of NDA 050811.³³ In a letter dated February 10, 2009, the Agency informed Astellas that if it decided to resubmit the application, the withdrawal would not prejudice any future decisions on filing.³⁴ The Agency also informed Astellas that it could reference information contained in the withdrawn application in any resubmission and that it should address the deficiencies identified during the Agency's review of the withdrawn application and described in the approvable letter dated March 13, 2008.³⁵

2. *Astagraf XL Pre-NDA/IND 64,148*

Eight months after it withdrew NDA 050811, Astellas met with FDA on September 29, 2009, to discuss its development program for Astagraf XL under IND 64,148.³⁶ Astellas proposed that Study 158 would be the primary basis for the efficacy and safety evaluation of Astagraf XL in the kidney transplant setting and that Study 12-03 would serve as a supportive study.³⁷ Although the Agency agreed that these studies were sufficient to support filing the NDA, it also requested data from PK Study FG-506E-12-01 (Study 12-01); and given the safety issues identified in the Astagraf XL liver transplant program, the Agency also requested a review of the liver studies (with particular attention to the different PK profiles exhibited by Astagraf XL in the liver and kidney patient populations) to augment the safety dossier of the drug in the kidney transplant setting.³⁸

Astellas proposed [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4) The Agency, however, disagreed that the
[REDACTED] (b) (4)

³³ Letter from Astellas to CDER (Jan. 29, 2009).

³⁴ Acknowledgement letter of NDA 050811 Withdrawal from FDA to Astellas (Feb. 10, 2009) at 1.

³⁵ Id.

³⁶ Agency preliminary responses to Astellas' briefing package dated Sep. 9, 2009, for IND 64,148 (Sept. 24, 2009) (Agency Prelim. Resp.). IND 64,148 is the same IND under which studies supporting NDA 050811 were conducted.

³⁷ Agency Prelim. Resp. at 1.

³⁸ Id.

³⁹ Id. at 2. [REDACTED] (b) (4)

⁴⁰ Agency Prelim. Resp. at 2. Astellas' rationale for [REDACTED] (b) (4)

The Agency agreed with Astellas' proposal that the risk of mortality with the potential use of Astagraf XL for organ transplant recipients other than those in the kidney transplant setting could potentially be addressed through labeling and a Risk Evaluation and Mitigation Strategy (REMS), but emphasized that Astellas should continue to elucidate more completely the causes of the safety signals observed in the liver transplant program.⁴³ Given that a difference in the incidence of mortality between males and females was not observed for *de novo* kidney transplant recipients in Studies 158, 12-03, and 12-01, Astellas stated that it would provide the detailed analyses requested in the March 13, 2008, approvable letter to support the lack of clinically significant differences in the safety of Astagraf XL in male and female kidney transplant recipients.⁴⁴

The Agency also agreed that it would review any collected data on dispensing/medication errors that resulted in serious adverse events from those jurisdictions where Astagraf XL had received approval (Europe, Canada, Japan) but also requested that Astellas provide additional information on the labeling and packaging for Astagraf XL in those jurisdictions.⁴⁵ The Agency further stated that it would have to review the adequacy of Astellas' strategies to prevent medication errors.⁴⁶ The Agency agreed that of the two possible approaches Astellas proposed for the resubmission of an NDA—(1) to cross-reference the withdrawn NDA and submit additional/updated summaries, analyses, and reports separately as an electronic common technical document (eCTD) format (Astellas' preferred approach) or (2) to submit an entire new NDA in eCTD—Astellas could adopt its preferred approach.⁴⁷ The Agency also stated that because Astellas withdrew the previous NDA, this application would be a new NDA with a new number and the review clock would be 10 months.⁴⁸ (b) (4)

⁴¹ Agency Prelim. Resp. at 2. The Agency stated that (b) (4)

⁴² Meeting minutes of Sept. 29, 2009, meeting between Astellas and FDA (Oct. 30, 2009) (Sept. 29, 2009, Meeting Minutes) at 3.

⁴³ Agency Prelim. Resp. at 3.

⁴⁴ Id. at 2.

⁴⁵ Id. at 3.

⁴⁶ Id.

⁴⁷ Id. at 3-4.

⁴⁸ Sept. 29, 2009, Meeting Minutes at 7.

⁴⁹ Id.

On November 4, 2011, Astellas submitted a request to the Agency for a pre-NDA Type B meeting to discuss the submission of an NDA for Astagraf XL for the prophylaxis of organ rejection in adults (>18 years old) receiving allogeneic kidney transplants and for the prophylaxis of organ rejection in men (>18 years old) receiving allogeneic liver transplants.⁵⁰ The pre-NDA meeting was held on January 31, 2012.

At this pre-NDA meeting, Astellas once again proposed that (1) Study 158 would be the primary basis to support the safety and efficacy of Astagraf XL in the kidney transplant setting and (2) not only Study 12-03, but also Study 12-01 (the PK study requested by the Agency at the September 29, 2009, meeting held with Astellas) and Study PMR-EC-1210 (or the OSAKA Study, which was a European post-marketing study conducted in the *de novo* setting on the EU-approved version of Astagraf XL (Advagraf)), would provide supportive evidence of efficacy.⁵¹ Astellas chose to characterize Study 12-03 only as supportive because the Prograf regimen used in the control arm of Study 12-03 was different from the FDA-approved regimen.

At this pre-NDA meeting, the Agency generally agreed with Astellas' proposal to submit a new NDA.⁵² The Agency agreed that the studies, including Study 158, could be submitted to support the filing of an NDA for an indication in *de novo* kidney transplant patients but declined to characterize Study 158 as the sole primary study.⁵³ Although Astellas characterized Study 12-03 as only a supportive study, the Agency declined to characterize it as such because the study was requested in the January 19, 2007, approvable letter and the full study reports for Study 12-03 had not been previously reviewed.⁵⁴ The Agency also requested that Astellas include a complete non-inferiority (NI) margin justification for both Study 158 and Study 12-03 and submit final reports for Studies 02-0-131, FG 506E-12-02, and FG 506E-KT01 in conversion kidney patients, including not only the results of the PK analyses, but also the 12-month results for the biopsy-proven acute rejection (BPAR) endpoint (including deaths, graft losses, and losses to follow-up imputed as failures).⁵⁵ Astellas agreed to these requests.⁵⁶

⁵⁰ Meeting minutes of Jan. 31, 2012, meeting between Astellas and FDA (Feb. 28, 2012) (Jan. 31, 2012, Meeting Minutes).

⁵¹ *Id.* at 6.

⁵² *Id.* at 4.

⁵³ *Id.* at 7.

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ *Id.*

As discussed at the September 29, 2009, meeting (and as indicated in the October 30, 2009, FDA meeting minutes), Astellas also proposed [REDACTED] (b) (4)

To meet the requirements for pre-clinical information, Astellas proposed to cross-reference non-clinical data from its previously submitted NDAs for Prograf (NDAs 050708 Prograf capsules [S-008; S-021; S-022] and 050709 Prograf injection [S-006; S-013; S-016]), as well as an Astagraf XL-specific nonclinical pharmacology study (Study CCR980201) to support the NDA.⁵⁸

3. *Astagraf XL NDA 204096*

On September 21, 2012, Astellas submitted a new NDA for Astagraf XL (NDA 204096). The proposed indication was prophylaxis of organ rejection in adult patients receiving kidney transplants.⁵⁹

On July 19, 2013, FDA approved Astagraf XL based on two Phase 3 controlled clinical trials (Studies 158 and 12-03), both of which demonstrated that Astagraf XL was non-inferior to Prograf on the endpoint of BPAR, when used with MMF and corticosteroids, in a regimen with or without basiliximab induction respectively.⁶⁰ Both studies were conducted in *de novo* kidney transplant patients. Consistent with FDA's practice of approving organ-based indications for transplant drug products, the Indications and Usage section of the approved labeling states, in part:

ASTAGRAF XL is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant. It is recommended that ASTAGRAF XL be used concomitantly with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction Therapeutic drug monitoring is recommended for all patients receiving ASTAGRAF XL

The clinical studies conducted by Astellas that were the basis for exclusivity were in *de novo* kidney transplant patients rather than in conversion patients.⁶¹ The Astagraf XL Clinical Review described FDA's understanding that Astellas was seeking approval for Astagraf XL for the

⁵⁷ Id. at 7-8. [REDACTED] (b) (4)

⁵⁸ Id. at 5.

⁵⁹ NDA 204096 was submitted with the proposed trade name Advagraf. Before approval, the trade name was changed to Astagraf XL.

⁶⁰ Astagraf XL Division Director Review at 4. Basiliximab is an antibody used in induction for kidney transplant patients.

⁶¹ Astagraf XL Clinical Review at 32.

prophylaxis of organ rejection in patients receiving *de novo* kidney transplants.⁶² The Astagraf XL Clinical Review indicates that in 2012, Astellas was not seeking a “specific conversion indication, but [was] requesting that [REDACTED] (b) (4)

[REDACTED]

The Agency concluded that Astellas’ studies in stable patients converted from Prograf to Astagraf XL were not adequate and well-controlled trials for the purpose of supporting a specific conversion indication in labeling.⁶⁴ Although Astellas, in its 2012 proposed labeling, originally proposed including [REDACTED] (b) (4)

[REDACTED]

[REDACTED] the Agency did not agree with that approach, as reflected in the currently approved labeling for Astagraf XL.

The PK section of the currently approved labeling includes only limited descriptive PK information from FG 506E-12-02 in the last row of Table 6.⁶⁵ This information was not intended to and does not imply approval of Astagraf XL for the conversion use. The text of the Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling not only is silent on the conversion use but also is specific to *de novo* use in kidney transplant patients.

When Astagraf XL was approved, FDA determined that the NDA should receive 3-year exclusivity because Astellas conducted new clinical investigations essential to approval (Studies 158 and 12-03). This exclusivity covers the once-daily, ER dosage form for the prophylaxis of organ rejection for use in *de novo* kidney transplant patients and is reflected in the Orange Book with the exclusivity code *NDF* or *new dosage form*. The exclusivity expires on July 19, 2016.⁶⁶

D. Envarsus XR

Envarsus XR is an ER tablet formulation of tacrolimus in doses equivalent to 0.75, 1, or 4 mg of anhydrous tacrolimus. Envarsus XR is intended to be dosed once-daily, and the proposed

⁶² Id. at 32. Section 5, entitled Sources of Clinical Data, includes the following sentence: “The Applicant is seeking approval for tacrolimus XL for prophylaxis of organ rejection in patients receiving *de novo* kidney transplants.” (italics added). Studies 158 and 12-03 are also described in section 5.

⁶³ Id. at 39 and 41.

⁶⁴ Id. at 22 and 41. [REDACTED] (b) (4)

⁶⁵ Approved Product Labeling for Astagraf XL (Pharmacokinetics section, Table 6, Pharmacokinetic Parameters of Astagraf XL Once Daily in Healthy Subjects and in Kidney Transplant Patients (Under Fasted Conditions) and Statistical Comparison of PK Parameters with Prograf Twice Daily (Table 6)).

⁶⁶ See the Orange Book.

labeling from Veloxis states that it is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants.

1. *Envarsus XR NDA 206406*

On December 28, 2013, Veloxis submitted NDA 206406 for Envarsus XR pursuant to section 505(b)(2) of the FD&C Act. The Envarsus XR NDA relies on the listed drug Prograf (NDA 050708), which currently is not protected by any patents or exclusivities. Specifically, Envarsus XR relies on FDA's findings of safety and/or effectiveness for Prograf with respect to nonclinical and certain clinical pharmacology information.

To support the Envarsus XR NDA, Veloxis also submitted results from Phase 1, 2, and 3 studies, including two Phase 3 clinical studies: one study in *de novo* kidney transplant recipients (Study 3002)⁶⁷ and one study in stable kidney transplant recipients converted from Prograf to Envarsus XR (≥ 3 months to 5 years post-transplant) (Study 3001).⁶⁸ For both studies, the primary endpoint was the rate of treatment (efficacy) failure, defined as BPAR, graft loss, death, or loss to follow-up by the 12-month post-transplant visit.⁶⁹

The study in the *de novo* population compared Envarsus XR (starting dose of 0.17 mg/kg/day given once daily) to Prograf, (starting dose of 0.1 mg/kg/day given twice daily) with subsequent dosage adjustments based on the attainment of the protocol-specified target tacrolimus trough concentration ranges of 6-11 ng/mL in the first 30 days and 4-11 ng/mL thereafter. Because the trough concentrations in *de novo* patients taking Envarsus XR were higher than observed in *de novo* patients taking IR tacrolimus during the first 2 weeks and higher than the protocol specified target range during the first week post-transplant, the Agency questioned whether the 0.17 mg/kg/day starting dose of Envarsus XR used by Veloxis in Study 3002 would be safe and effective.⁷⁰ A Phase 2 PK study (Study 2017) provided support for a lower 0.14 mg/kg/day starting dose for Envarsus XR in *de novo* patients, which is currently in the proposed labeling.⁷¹

⁶⁷ We note that Veloxis submitted a June 18, 2010, request for a Special Protocol Assessment for Study 3002. FDA reviewed the protocol and, based on the information submitted, agreed that the design and planned analysis of the study adequately addressed the objective to support a regulatory submission. See Letter from DTOP to R Guido (Aug. 5, 2010) (Special Protocol Agreement); see also FDA's guidance for industry, *Special Protocol Assessment* (May 2002).

⁶⁸ Envarsus XR Clinical Review (Sept. 25, 2014) (Envarsus XR Clinical Review) at 8.

⁶⁹ *Id.* at 60.

⁷⁰ Budde, K, S Bunnapradist, JM Grinyo, et al., Dec. 2014, Novel Once-Daily ER Tacrolimus (LCPT) Versus Twice-Daily Tacrolimus in *De Novo* Kidney Transplants: One-Year Results of Phase III, Double-Blind, Randomized Trial, *Am J Transplant*, 14(12):2796-2806.

⁷¹ Veloxis initially submitted its IND results from a Phase 2 PK study conducted in stable kidney transplant patients (Study 2011). FDA, however, requested information in *de novo* transplant patients (End-of-Phase 2 meeting (May 20, 2008)). A protocol for Study 2017 was then submitted on August 13, 2008. One of the key issues identified during the review of the application was that the starting dose of 0.17 mg/kg/day used in Study 3002 resulted in patients having levels above the target trough concentrations (up to 52 ng/mL for the first 2 weeks post-

Separately, in Study 3001, Envarsus XR was studied for converting patients who had previously been stable on Prograf. In the conversion study, stable kidney transplant patients receiving stable doses of Prograf twice daily and having tacrolimus trough concentrations within 4-15 ng/mL at the end of the 7-day run-in period were randomized (1:1) at baseline either to continue treatment with Prograf twice daily at the current dose or to switch to Envarsus XR once daily. Study 3001 and Study 2011, a PK study in stable kidney transplant patients, provided support for a recommended Prograf-to-Envarsus XR daily dose conversion ratio of 1:0.8.⁷²

In Study 3002, Envarsus XR was shown to be non-inferior to Prograf in *de novo* kidney transplant patients, and the outcome met the pre-defined non-inferiority margin. In Study 3001, comparable efficacy was shown between the Prograf and Envarsus XR arms in conversion patients. Overall, the reviewers concluded that the benefits of Envarsus XR outweighed its risk in the prophylaxis of organ rejection in kidney transplant recipients, and that Envarsus XR represented a safe and effective treatment option for the prophylaxis of organ rejection in kidney transplant patients in *de novo* and conversion settings.⁷³ The Indications and Usage section of the proposed labeling currently states that Envarsus XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants. The Clinical Studies and Dosage and Administration sections of the proposed labeling include information for the safe and effective use for the prophylaxis of organ rejection in *de novo* and conversion kidney transplant patients.

On October 30, 2014, FDA concluded that NDA 206406 for Envarsus XR was safe and effective for the prophylaxis of organ rejection in both *de novo* and conversion kidney transplant patients and issued a tentative approval for use in both of these settings. The Envarsus XR NDA would have been fully approved at that time but for a determination that the approval was blocked by the exclusivity of Astagraf XL, as described more fully below.

2. *Veloxis' Request for Orphan Designation*

On July 16, 2013, Veloxis requested orphan designation for tacrolimus for “prophylaxis of organ rejection in patients receiving allogeneic kidney transplant” based on a “plausible hypothesis” that its product in development (then referred to as LCP-tacro and later known as Envarsus XR)

transplantation), whereas in Study 2017, the starting dose of 0.14 mg/kg/day was not associated with trough concentrations significantly outside the target range.

⁷² In Study 2011, the steady state AUC-C_{trough} correlation lines of Envarsus XR and Prograf were found to be superimposable (i.e., the slopes of the lines were comparable and the data points comprising each line overlapped substantially), and the AUC-C_{trough} correlation coefficients ($r \geq 0.79$) were found to be satisfactory. These observations suggested that targeting the same tacrolimus trough concentration range as Prograf would be appropriate for stable kidney transplant patients who had switched from Prograf to Envarsus XR at a daily dose conversion ratio of 1:0.8. Envarsus XR Clinical Review at 41.

⁷³ Id. at 9-10.

was clinically superior to Prograf.⁷⁴ Orphan designation was granted on December 20, 2013.⁷⁵ Astagraf XL had not been approved when the request for designation was made; neither the request for designation nor the reviews of that request considered whether Envarsus XR had a plausible hypothesis of clinical superiority to Astagraf XL.⁷⁶

E. Summary of Communications between FDA, Veloxis & Astellas Regarding the Scope of Astagraf XL’s Exclusivity and of FDA’s Initial Consideration of the Scope of Exclusivity

As noted above in section I.C., FDA determined that the NDA for Astagraf XL was eligible for 3-year exclusivity because Astellas conducted new clinical investigations essential to approval of the NDA. The Orange Book lists the exclusivity code as *NDF*, and the exclusivity expires on July 19, 2016.

On September 12, 2014, Astellas submitted a letter to FDA requesting that the Agency clarify the scope of Astagraf XL’s exclusivity.⁷⁷ As stated in the letter, Astellas believes that Astagraf XL’s “conditions of approval protected by [section 505(c)(3)(E)(iii) of the FD&C Act] encompass the once[-]daily formulation of tacrolimus indicated for the prophylaxis of organ rejection in transplant recipients regardless of patient setting, and no application for those conditions can be approved until expiration of the exclusivity period on July 19, 2016.”⁷⁸ The letter also conveyed Astellas’ belief, based on public information, that the Envarsus XR NDA covers the same active ingredient and dosing frequency and asked whether another once-daily tacrolimus product (e.g., Envarsus) can be approved by FDA during the period of Astellas’ exclusivity.

On October 17, 2014, the CDER Exclusivity Board issued a letter to Astellas seeking additional information regarding exclusivity for Astagraf XL.⁷⁹ On October 27, 2014, Astellas’ outside

⁷⁴ Letter from R Guido to G Rao re: Request for Designation of an Orphan Drug (July 16, 2013).

⁷⁵ Letter from G Rao to R Guido re: Designation Request # 13-4071 (Dec. 20, 2013).

⁷⁶ A sponsor who seeks orphan-drug designation for a drug that is the same drug (same active moiety) as a previously approved drug for the same rare disease or condition as that previously approved drug must submit a plausible hypothesis that it is clinically superior to the previously approved drug (21 CFR 316.20(a)). If FDA agrees that the hypothesis is plausible and that the drug otherwise meets all the applicable statutory and regulatory requirements for designation, the Agency will grant the request for designation.

⁷⁷ Letter from Astellas to DTOP (Sept. 12, 2014) (indicating that in August 2014 there was a conversation between a representative from FDA and a representative from Astellas, during which the company first posed the issue).

⁷⁸ *Id.* at 2.

⁷⁹ Letter from CDER Exclusivity Board to Astellas (Oct. 17, 2014).

counsel submitted a letter asserting that the Agency had properly determined that Astagraf XL was eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) and 505(v) of the FD&C Act.⁸⁰

After receiving Astellas' letter, on October 27, 2014, FDA sent an Information Request to Veloxis, requesting the company's position on whether approval of the Envarsus XR 505(b)(2) NDA would be affected by Astagraf XL's exclusivity.⁸¹ On October 29, 2014, Veloxis responded by submitting a letter to the Envarsus XR NDA stating that Astagraf XL's "exclusivity does not affect the type of action letter FDA can issue for Envarsus XR, which has a different dosage form and different proposed conditions of use."⁸² Further, Veloxis claimed that the "Envarsus XR development program did not rely upon any of the studies Astellas performed which were essential to the approval of Astagraf XL."⁸³

FDA considered Veloxis' reply in determining whether the Envarsus XR NDA was blocked by Astagraf XL's exclusivity. FDA concluded that the exclusivity for Astagraf XL covers its ER dosage form and its once-daily dosing regimen, both of which were changes from the previously approved tacrolimus drug, Prograf, and were supported by new clinical investigations essential to the approval of Astagraf XL. Because Envarsus XR is also an ER dosage form of tacrolimus with a once-daily dosing regimen, FDA determined at that time that Envarsus XR shares Astagraf XL's exclusivity-protected conditions of approval.

On October 30, 2014, FDA issued a tentative approval letter to Veloxis for Envarsus XR, stating that, "[a]s noted in the . . . Orange Book . . . , the listed drug product Astagraf XL (NDA 204096), with which you share conditions of approval for which new clinical studies were essential, is subject to a period of exclusivity protection under section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until that product's exclusivity period has expired."⁸⁴

Counsel for Veloxis contacted the Office of the Chief Counsel (OCC) on October 31, 2014, requesting a meeting with FDA and asking FDA to retract its tentative approval and to issue a letter approving the Envarsus XR NDA. On November 6, 2014, representatives of Veloxis met with representatives of FDA, including representatives from DTOP, OAP, OCP, ORP, and OCC. At this meeting, Veloxis explained that it believed FDA had issued the tentative approval letter for Envarsus XR in error because the "[c]onditions of approval of Envarsus XR do not overlap

⁸⁰ Letter from Covington & Burling to CDER Exclusivity Board (Oct. 27, 2014).

⁸¹ Letter from DTOP to Veloxis (Oct. 27, 2014).

⁸² Letter from Veloxis to DTOP (Oct. 29, 2014) at 1.

⁸³ *Id.* at 1-2.

⁸⁴ Letter from DTOP to Veloxis (Oct. 30, 2014) at 1-2.

with Astagraf XL.”⁸⁵ Specifically, Veloxis claimed that Envarsus XR differs from Astagraf XL in, among other things, its dosage form, dosing regimen, strengths, and PK profile. Veloxis identified examples of past drug approval actions that it believed support approval of Envarsus XR, notwithstanding Astagraf XL’s exclusivity. Veloxis also brought to the meeting a kidney transplant physician, Dr. Roy Bloom, who discussed the anecdotal benefits he observed using Envarsus XR, particularly in African-American patients whom he characterized as “rapid metabolizers” of tacrolimus.⁸⁶ Further, Veloxis reiterated that Envarsus XR’s development program did not rely on the Astagraf XL NDA.

On November 10, 2014, FDA issued a General Advice/Information Request letter to Veloxis, explaining that at the November 6 meeting, Veloxis had presented new information for the Agency to evaluate and had asked FDA to reconsider its decision to tentatively approve the Envarsus XR NDA.⁸⁷ FDA requested that this new information be submitted as an amendment to the Envarsus XR NDA, identified as a “Request For Final Approval.” Veloxis submitted the “Request For Final Approval” on November 14, 2014.⁸⁸ This submission contained an 18-page letter with six exhibits detailing Veloxis’ position that FDA should immediately approve the NDA. The submission also included declarations from Dr. Bloom and a representative of the National Kidney Foundation.⁸⁹

On December 2, 2014, Veloxis submitted an amendment to its “Request For Final Approval.”⁹⁰ In this letter, Veloxis asserted for the first time that Astagraf XL was ineligible to receive 3-year exclusivity under section 505(v) of the FD&C Act because Astagraf XL (NDA 050811) was the subject of a pending application prior to October 8, 2008, the date of enactment of the QI Program Supplemental Funding Act of 2008 (QI Act),⁹¹ and was therefore specifically excluded from eligibility for 3-year exclusivity under the timing provisions of the QI Act.⁹² Veloxis claimed that Astellas performed no new studies in support of its application between the time of withdrawal and submission of the Astagraf XL NDA in 2012. According to Veloxis, its NDA for Envarsus XR could not be blocked by Astagraf XL’s exclusivity because Astagraf XL was

⁸⁵ Veloxis subsequently submitted the meeting slides as part of a submission to its NDA. Veloxis Submission (Nov. 14, 2014) (Veloxis Submission) (Exhibit 4 at slide 4).

⁸⁶ Veloxis also submitted a declaration by Dr. Bloom. Veloxis Submission (Exhibit 2).

⁸⁷ Letter from DTOP to Veloxis (Nov. 10, 2014).

⁸⁸ Veloxis Submission.

⁸⁹ Id. (Exhibit 1).

⁹⁰ Letter from Veloxis to DTOP (Dec. 2, 2014).

⁹¹ QI Program Supplemental Funding Act of 2008, Public Law 110-379, section 4, entitled “Incentives for the Development of, and Access to, Certain Antibiotics.”

⁹² Letter from Veloxis to DTOP (Dec. 2, 2014) at 1.

not entitled to any exclusivity under this QI Act limitation. Veloxis again urged FDA to immediately approve the Envarsus XR NDA.

After meeting with Veloxis on November 6, 2014, and receiving its subsequent submissions, FDA had numerous internal meetings. On December 2, 2014, Agency representatives met with Astellas regarding the scope of exclusivity for Astagraf XL. At this meeting, Astellas stated that

(b) (4)

While reviewing the issues raised by Veloxis and Astellas, FDA preliminarily determined that the new clinical investigations essential to Astagraf XL's approval demonstrated the safety and effectiveness of the drug only in *de novo* patients but not in conversion patients and that, therefore, Envarsus XR's approval for conversion use would not be blocked by Astagraf XL's exclusivity. To that end, FDA held a teleconference with Veloxis on December 5, 2014, in which FDA suggested that Veloxis seek approval only for conversion of patients who are stable on IR tacrolimus to Envarsus XR, subject to submission and approval of revised labeling for Envarsus XR. In response to Veloxis' questions, FDA discussed potential revised labeling for Envarsus XR that would omit the information regarding use of Envarsus XR in *de novo* patients while permitting approval for the conversion use.

On December 8, 2014, Veloxis sent a letter to FDA declining to pursue the proposed option discussed on December 5, 2014.⁹³ In its letter, Veloxis reiterated its position that FDA should immediately approve Envarsus XR for all of the uses reflected in the labeling previously submitted in the Envarsus XR NDA. With the December 8, 2014 submission, Veloxis also submitted a declaration from Dr. Anthony Langone regarding the Envarsus XR NDA. Veloxis later submitted a letter on December 12, 2014, containing an additional exclusivity precedent for the Agency's consideration.⁹⁴

On December 12, 2014, FDA sent a letter to Veloxis indicating that although FDA had initially estimated that it could respond during the week of December 8, the Agency had not had adequate time to fully consider the entire record and all of Veloxis' submissions.⁹⁵ The Agency's letter detailed the activity that had taken place since Veloxis' initial request on October 31, 2014, and indicated that due to the complexity of the issues involved, the Agency was not issuing a final decision at the time and intended to respond no later than January 12, 2015.

Veloxis' counsel requested a call with OCC on December 14, 2014. During that call, Veloxis' counsel requested immediate final approval by December 23, 2014. On December 15, 2014,

⁹³ Letter from Veloxis to DTOP (Dec. 8, 2014).

⁹⁴ Letter from Veloxis to DTOP (Dec. 12, 2014).

⁹⁵ Letter from DTOP to Veloxis (Dec. 12, 2014).

OCC responded by letter conveying that the Agency could not commit to the time frame requested by Veloxis and referred to FDA's December 12, 2014, letter for additional explanation.

On December 16, 2014, Veloxis sent a letter to the Agency stating the company's intent of pursuing "court intervention" to require FDA to "grant final approval to the Envarsus XR NDA."⁹⁶ Although it knew the Agency had not yet reached a final decision, Veloxis filed a complaint in the U.S. District Court for the District of Columbia on the same day. On December 17, 2014, FDA moved to stay the proceedings pending final Agency action. The Court granted FDA's motion to stay on December 18, 2014.

II. STATUTORY AND REGULATORY BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) abbreviated new drug applications (ANDAs).

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.⁹⁷ NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

A 505(b)(1) NDA must also include:

- a full list of the articles used as components of such drug;
- a full statement of the composition of such drug;
- a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
- samples of the drug as necessary;
- proposed labeling for the drug; and
- pediatric assessments.⁹⁸

FDA will approve a 505(b)(1) NDA if it finds the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed,

⁹⁶ Letter from Veloxis to DTOP (Dec. 16, 2014).

⁹⁷ See section 505(b)(1)(A) of the FD&C Act.

⁹⁸ See section 505(b)(1) of the FD&C Act.

recommended, or suggested in the proposed labeling.⁹⁹

2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)¹⁰⁰ created section 505(b)(2) and 505(j) of the FD&C Act. These provisions established abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.¹⁰¹ The Hatch-Waxman Amendments reflected Congress’s efforts to balance the need to “make available more low cost generic drugs by establishing a generic drug approval procedure” with new incentives for drug development in the form of marketing exclusivity and patent term extensions.¹⁰² These pathways permit sponsors to rely on what is already known about the previously approved drug, which allows for a speedier market entry than would be possible under the 505(b)(1) pathway and leads to increased competition.¹⁰³

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act and must meet the “full reports” requirement in 505(b)(1)(A). Unlike a stand-alone NDA, in a 505(b)(2) NDA some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.¹⁰⁴ Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may conduct its own studies; rely on published reports of studies to which the applicant has no right of reference; rely on Agency findings of safety and/or effectiveness for a previously approved drug, i.e., a listed drug; or use a combination of these sources to support approval.¹⁰⁵

⁹⁹ See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

¹⁰⁰ Public Law 98-417.

¹⁰¹ Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(1) and 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

¹⁰² See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

¹⁰³ See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. v. Royce Laboratories, Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

¹⁰⁴ Section 505(b)(2) of the FD&C Act provides for approval of an application:

for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted

¹⁰⁵ See FDA’s Response to Sanzo, Chasnow, Lawton, et al. (Docket Nos. 2001P-0323, 2002P-0047, and 2003-0408) (Oct. 14, 2003).

When the sponsor of a 505(b)(2) NDA chooses to rely on a listed drug, the 505(b)(2) pathway allows the sponsor to streamline drug development by relying on the Agency's finding of safety and effectiveness for the listed drug to the extent it is applicable and only requiring a sponsor to conduct the studies necessary to support any differences between the drug proposed for approval and the listed drug relied on.

Consistent with Congress' goal to advance both competition and innovation, the Hatch-Waxman Amendments balance the competitive advantages that an abbreviated pathway provides by also imposing on a 505(b)(2) applicant "additional requirements with respect to patent certification, notification of such certification to the patent owner, and exclusivity."¹⁰⁶ These additional requirements, which are designed to recognize certain market protections for previously approved drugs, have the potential to delay approval of 505(b)(2) applications but do not apply to delay approval of stand-alone NDAs.

B. 3-Year Exclusivity

The Hatch-Waxman Amendments provide NDA holders (including 505(b)(2) NDA holders) with certain periods of limited protection from competition from certain potential competitors for the innovation represented by the NDA holders' approved products. These periods are referred to generally as *exclusivity*.

At issue here is 3-year exclusivity, which operates by delaying the date that FDA can give final, effective approval to a 505(b)(2) NDA for the conditions of approval for which exclusivity was granted.¹⁰⁷ Specifically, section 505(c)(3)(E)(iii) of the FD&C Act states:¹⁰⁸

If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application

¹⁰⁶ Proposed rule "Abbreviated New Drug Application Regulations." (54 FR 28872 (July 10, 1989)) (1989 Proposed Rule).

¹⁰⁷ 1989 Proposed Rule at 28896 ("Section[] 505(j)(4)(D) and 505(c)(3)(D) of the [FD&C Act] partially protect certain listed drugs, or certain changes in listed drugs, from competition in the marketplace for specified periods . . . by delaying the effective date of approval of ANDAs and 505(b)(2) applications for those listed drug products").

¹⁰⁸ A parallel provision applies 3-year exclusivity to ANDAs, but it is not relevant here. See section 505(j)(5)(F)(iii) of the FD&C Act.

were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Thus, to be eligible for 3-year exclusivity under this provision, an application must have met each of the following requirements:

- be a 505(b)(1) or a 505(b)(2) NDA (submitted under subsection (b) of this section)
- have been approved after the enactment of the Hatch-Waxman Amendments (approved after September 24, 1984)
- be for a drug that contains a previously approved active moiety (an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section)
- contain at least one new clinical study that is not a bioavailability study that is essential to approval of the application and was conducted by or for the sponsors (reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant).

FDA's implementing regulations further interpret certain aspects of the statutory language regarding eligibility for 3-year exclusivity. They define a *clinical investigation* as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects."¹⁰⁹ They further define *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 effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.¹¹⁰

FDA regulations also define what *essential to approval* means with regard to an investigation, i.e., "there are no other data available that could support approval of the application."¹¹¹

After FDA determines that new clinical investigations have qualified an application for exclusivity, FDA determines the scope of that exclusivity. Section 505(c)(3)(E)(iii) of the FD&C Act provides that, if the NDA receives 3-year exclusivity, the Agency may not approve a 505(b)(2) NDA for the "conditions of approval" of such drug for a period of 3 years. The regulations similarly state that if an application submitted under section 505(b) contained new clinical investigations that were essential to approval and conducted or sponsored by the applicant, the Agency "will not make effective for a period of 3 years after the date of approval

¹⁰⁹ 21 CFR 314.108(a).

¹¹⁰ Id.

¹¹¹ Id.

of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application”¹¹²

Although neither the statute nor the regulations defines the phrase *conditions of approval* for purposes of determining the scope of 3-year exclusivity,¹¹³ the preamble to the 1989 Proposed Rule provides the Agency’s interpretation. It makes clear FDA’s view that 3-year exclusivity covers the innovative change that is supported by the new clinical investigations:

Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.¹¹⁴

FDA thus interprets the scope of exclusivity to be related to the scope of the underlying *new clinical investigations* that were essential to the approval. Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Courts have upheld FDA’s view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.¹¹⁵

Because the relevant conditions of approval for exclusivity purposes are those changes for which the new clinical investigations were essential, under the Agency’s interpretation, a 505(b)(2) NDA can differ in certain respects from the previously approved product with exclusivity and nonetheless be blocked. If the 505(b)(2) NDA shares the exclusivity-protected conditions of approval, the NDA may differ in other ways from the exclusivity-protected product and nonetheless be blocked from approval for the exclusivity-protected approval conditions.

¹¹² 21 CFR 314.108(b)(4)(iv).

¹¹³ 21 CFR 314.108(a) and 314.108 (b)(4)(iv).

¹¹⁴ 1989 Proposed Rule at 28896-97.

¹¹⁵ *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff’d*, 213 F.3d 161 (4th Cir. 2000) (“The exclusivity extends only to the ‘change approved in the supplement’”); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff’d*, 713 F.3d 1134 (D.C. Cir. 2013) (“[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . .”). Although these cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA’s interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

This interpretation strikes a balance between rewarding innovation and increasing access as Congress intended. If the Agency was to take the position that any differences between two products, including differences in aspects of the product for which new clinical investigations were not essential, means that the two products do not share conditions of approval and that the second product is not blocked, the 3-year exclusivity provision governing the approval of 505(b)(2) NDAs could be rendered meaningless. Under this hypothetical interpretation, only a true duplicate version of the product would be blocked. Subsequent 505(b)(2) sponsors could make simple changes that make little therapeutic difference (including changes that could be approved in a suitability petition, such as a change from tablet to capsule supported by no more than a PK study) to avoid being blocked. In rejecting this approach, the Agency's interpretation balances the dual goals of Hatch-Waxman to encourage innovation and to make available potentially less costly alternatives by providing exclusivity for the changes for which new clinical investigations were essential, by limiting that exclusivity to those changes, and by prohibiting other sponsors from easily circumventing that exclusivity by making minor changes to their drug products. It also recognizes that Congress created a separate pathway for true duplicates (i.e., ANDAs) and ensures the provisions of section 505(c)(3)(E)(iii) would not be superfluous.

FDA has also determined that if two 505(b)(2) applications are both under review, and the first to be approved receives exclusivity for an innovative change, the second will be blocked from obtaining approval for that innovative change during the exclusivity period. Specifically, the preamble to the 1989 Proposed Rule states:

The exclusivity provisions . . . delay the effective date of approval of any 505(b)(2) application that is for the conditions of use of a previously approved application that contained new clinical investigations essential for approval. Consequently, if two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be approved will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity.¹¹⁶

FDA has also indicated more generally that if an application has 3-year exclusivity for a change to a previously approved drug product, a subsequent 505(b)(2) NDA containing that same change will be subject to the 3-year exclusivity regardless of whether the 505(b)(2) NDA relies on the product with exclusivity.¹¹⁷ Specifically, in the preamble to the 1989 Proposed Rule,

¹¹⁶ 1989 Proposed Rule at 28901.

¹¹⁷ Notably, the regulation implementing the 3-year exclusivity provisions of the statute refers to reliance only in the context of applications approved under a suitability petition under section 505(j)(2)(C) of the FD&C Act. In discussing the scope of exclusivity, the regulation states that:

the [A]gency will not make effective for a period of 3 years after the date of approval of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original

FDA considered and endorsed a broad view of 3-year exclusivity that “covers . . . changes in non-new chemical entities rather than covering only specific drug products.” Under this view, the preamble states, “a 505(b)(2) application for a drug with . . . the innovator’s change . . . could not be approved until the innovator’s exclusivity expired, even if the . . . 505(b)(2) relied on another approved version of the innovator’s drug.”¹¹⁸ It further states:

[W]hen exclusivity attaches to . . . an innovative change in an already approved drug, the . . . effective date of approval of . . . 505(b)(2) applications for a drug with that . . . innovative change will be delayed until the innovator’s exclusivity has expired . . . regardless of the specific listed drug product to which the . . . 505(b)(2) application refers.

(emphasis added).¹¹⁹

In sum, the Agency has interpreted the scope of 3-year exclusivity to cover the “innovative change” in the drug product and to be circumscribed by the scope of the “new clinical investigations” essential to the approval of the change. A 505(b)(2) NDA for the conditions of approval that have received 3-year exclusivity will be blocked regardless of whether the 505(b)(2) NDA relies on the drug product with 3-year exclusivity.

C. Antibiotics and Exclusivity

As noted above in section I.B, tacrolimus is produced by *Streptomyces tsukubaensis*, and meets the statutory definition of an *antibiotic* drug.¹²⁰ This definition turns on the nature of the drug substance rather than on the indication of the drug product. Thus, even though tacrolimus was approved to prevent organ rejection rather than for antimicrobial use, it is considered an antibiotic.¹²¹ This is relevant to this exclusivity inquiry because additional considerations apply to antibiotic drugs such as tacrolimus in determining eligibility for 3-year exclusivity as discussed below.

Before enactment of the FDAMA, antibiotic drugs were approved under section 507 of the FD&C Act and non-antibiotic drugs were approved under section 505 of the FD&C Act. The exclusivity and patent listing provisions of the Hatch-Waxman Amendments (Hatch-Waxman

application or an [ANDA] submitted pursuant to 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.

(emphasis added).

¹¹⁸ 1989 Proposed Rule at 28897.

¹¹⁹ *Id.*

¹²⁰ Section 201(jj) of the FD&C Act (21 U.S.C. 321).

¹²¹ Letter from FDA to TG Mahn, JE Mauk, WS Vicente, et al. (Docket No. 2003P-0275/CP1 & PSA1) (Dec. 18, 2003) at 15, 29, and 32, available on the Internet at <http://www.fda.gov/ohrms/dockets/dailys/04/apr04/042004/03p-0275-ref0001-090-Tab-39-vol6.pdf>; see Proposed Rule on Old Antibiotics (listing tacrolimus as an Old Antibiotic).

benefits) applied only to approvals under section 505 of the FD&C Act and therefore did not apply to antibiotic drugs approved under section 507 of the FD&C Act. In 1997, FDAMA repealed section 507 of the FD&C Act and required that all applications for antibiotic drugs be submitted under section 505 of the FD&C Act.¹²² FDAMA included a transition provision declaring that an application approved under section 507 of the FD&C Act before enactment of FDAMA must be considered an application submitted, filed, and approved under section 505 of the FD&C Act (transition provision).¹²³ Congress created an exception to this transition provision in section 125(d)(2) of FDAMA, which exempted certain applications for antibiotic drugs from those provisions of section 505 of the FD&C Act that provide Hatch-Waxman benefits.¹²⁴ Specifically, section 125(d)(2) of FDAMA exempts an application from Hatch-Waxman benefits when “the drug that is the subject of the application contains an antibiotic drug[,] and the antibiotic drug was the subject of any application” received by FDA before the enactment of FDAMA (i.e., November 21, 1997).¹²⁵

Thus, Congress created a distinction between antibiotic drugs for which the first application was received *after* FDAMA’s effective date (November 21, 1997) and those antibiotic drugs for which the first application was received *before* that date (*Old Antibiotics*).¹²⁶ Initially, the former were eligible for Hatch-Waxman benefits and the latter were not.¹²⁷ FDA determined that the FDAMA exemption from Hatch-Waxman benefits for Old Antibiotics applied to all antibiotic moieties of antibiotic drugs that were the subjects of marketing applications received by FDA before November 21, 1997.¹²⁸

On October 8, 2008, the FD&C Act was amended again through section 4 of the QI Act. The QI Act incorporated Old Antibiotics into the Hatch-Waxman regulatory scheme and provided certain Hatch-Waxman benefits for such Old Antibiotics for the first time. Among other things, it removed FDAMA’s enumerated exemptions for Old Antibiotics and created an opportunity for an Old Antibiotic application to obtain Hatch-Waxman exclusivity if that application (or supplement thereto) was submitted after the QI Act’s enactment. Thus, section 505(v)(1)(A) of the FD&C Act, as amended by the QI Act, provides that:

Notwithstanding any provision of [FDAMA] or any other provision of law, a sponsor of [an Old Antibiotic] shall be eligible for, with respect to the drug, the 3-year exclusivity

¹²² Section 125(d)(1) of FDAMA.

¹²³ Section 125(d)(1) of FDAMA.

¹²⁴ Section 125(d)(2) of FDAMA.

¹²⁵ *Id.*

¹²⁶ *ViroPharma, Inc. v. Hamburg, et al.*, 898 F. Supp. 2d 1 (D.D.C. 2012) (*ViroPharma*) at 8.

¹²⁷ *Id.*

¹²⁸ Proposed Rule on Old Antibiotics.

period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of section (j)(5)(F), subject to the requirements of such clauses, as applicable.

The statute further explains that such exclusivity applies to “an application . . . submitted . . . after the date of the enactment of [the QI Act] in which the drug that is the subject of the application contains [an Old Antibiotic].”¹²⁹

However, the QI Act did not make applications for Old Antibiotics submitted after the date of enactment of the QI Act eligible for exclusivity and other Hatch-Waxman benefits to the same extent as other section 505 drugs. Instead, for Old Antibiotics, such as tacrolimus, the exclusivity described in section 505(v)(1) of the FD&C Act is subject to the limitation in section 505(v)(3)(B) of the FD&C Act, which provides that 3-year exclusivity is not available for “any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act].”

In interpreting this language, FDA concluded that, for section 505(v)(3)(B) of the FD&C Act not to be rendered superfluous, Congress must have intended to create a higher hurdle for 3-year exclusivity for Old Antibiotics than exists for non-antibiotic drugs.¹³⁰ Thus, FDA interpreted section 505(v)(3)(B) to permit 3-year exclusivity for Old Antibiotics “only for a *significant new use* for an Old Antibiotic (such as a new indication for a previously approved antibiotic, or a new

¹²⁹ Section 505(v)(1)(B)(i) of the FD&C Act (emphasis added).

¹³⁰ See Letter from FDA to ViroPharma, Inc. (Docket No. FDA-2006-P-0007) (Apr. 9, 2012) (Vancocin CP Response). In the Vancocin CP Response, the Agency stated:

[The] availability of 3-year exclusivity for Old Antibiotics was not without limitation. Rather than simply placing new applications and supplements for Old Antibiotics under the pre-existing Hatch-Waxman regulatory scheme, Congress prescribed specific limits to this eligibility under section 505(v)(3)(B) of the FD&C Act. The QI Act provides that 3-year exclusivity period is not available for “any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act].”

The QI Act does not expressly define what constitutes a “condition of use . . . approved before the date of enactment.” As an initial matter, FDA concludes that this limitation must exclude from exclusivity some applications and supplements containing new clinical studies that otherwise would qualify a non-Old Antibiotic product for 3-year Hatch-Waxman exclusivity Thus, to give content to this limitation, FDA must find that *there is a higher hurdle for exclusivity* for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity.

(emphasis added).

See also *ViroPharma* at 13 (quoting the Agency’s position that “[t]o give content to this limitation, FDA must find that there is a higher hurdle for exclusivity for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity”).

approval for a submitted but never previously approved antibiotic), not for refinements in labeling related to previously approved uses for Old Antibiotics.”¹³¹

The only court to have considered the matter has upheld this FDA interpretation as reasonable.¹³² The court noted that the Agency’s interpretation of “conditions of use” “encompass[ed] how, to whom, and for which purposes a drug product [was] used.”¹³³ The court further noted that, in denying exclusivity for new labeling changes for the Old Antibiotic Vancocin under section 505(v)(3) of the FD&C Act, FDA had concluded, among other things, that the labeling changes for the Old Antibiotic at issue “did not prescribe a new dosing regimen.” FDA’s conclusion implied that if there had been a new dosing regimen, exclusivity would have been available despite the limitation in section 505(v)(3). In the court’s opinion, FDA’s conclusion confirmed that the Agency’s interpretation of “significant new use” was broader than just a new indication.¹³⁴ As noted above, the court upheld that interpretation as reasonable.

III. DISCUSSION

Veloxis has made multiple assertions that Astagraf XL is not eligible for 3-year exclusivity and, in the alternative, even if it was eligible, that exclusivity does not block approval of Envarsus XR for use in *de novo* and conversion patients. In determining eligibility of Astagraf XL for 3-year exclusivity and in evaluating whether Envarsus XR is within its scope and therefore blocked, FDA has considered arguments from Veloxis and Astellas, the studies conducted to support both the Astagraf XL and Envarsus XR NDAs, and relevant precedent.

The Agency first evaluated whether Astagraf XL was ineligible for 3-year exclusivity due to the limitation on timing of the NDA submission under section 505(v) of the FD&C Act. Upon concluding that the timing of Astagraf XL’s submission did not preclude eligibility for exclusivity, the Agency considered another issue that was not raised by Veloxis regarding whether Astagraf XL obtained approval only for a previously approved condition of use and therefore was ineligible for exclusivity under section 505(v)(3). After determining that Astagraf XL obtained approval for a new condition of use, was eligible for 3-year exclusivity, and was not otherwise barred by any of the limitations in section 505(v)(3), the Agency determined the scope of that exclusivity.

As described more fully below, FDA has concluded that Astagraf XL has exclusivity for a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. That exclusivity will block approval of Envarsus XR for use in *de novo*

¹³¹ Vancocin CP Response at 70 (emphasis added).

¹³² *ViroPharma* at 22.

¹³³ *Id.*

¹³⁴ *Id.*

kidney transplant patients but will not block approval of Envarsus XR for the conversion use in kidney transplant patients stabilized on IR tacrolimus (i.e., Prograf and therapeutically equivalent generics).

A. Eligibility of Astagraf XL for Exclusivity Under Section 505(v) of the FD&C Act

1. Timing of Submission of Astagraf XL NDA

Veloxis has raised several arguments concerning Astagraf XL’s exclusivity under section 505(v)(1) of the FD&C Act.

First, Veloxis asserts that the Astagraf XL NDA was not eligible for exclusivity under the timing limitations of the QI Act because the NDA was pending prior to the enactment of the QI Act.¹³⁵ FDA rejects this argument. Astellas submitted the NDA for Astagraf XL (NDA 204096) on September 20, 2012—a date four years *after* the QI Act was enacted. As noted above in section II.C, section 505(v)(1)(B)(i) of the FD&C Act only permits exclusivity under section 505(v) of the FD&C Act for Old Antibiotics with applications submitted after the date of enactment of the QI Act. On its face, Astagraf XL is an application submitted after enactment of the QI Act that is eligible for exclusivity under section 505(v) based on the plain text of section 505(v)(1)(B)(i).

Second, Veloxis argues that although “a separate but related” NDA for Astagraf XL was submitted after enactment of the QI Act, this NDA had been submitted before enactment of the QI Act and should be disqualified on this basis.¹³⁶ FDA does not agree. There is no indication in the text of the QI Act that a second application submitted after enactment would be disqualified if another related application was also submitted before enactment. Congress knew how to use different terms to capture the status of an antibiotic application that had previously been submitted for review before the QI Act was enacted but chose not to use such language in section 505(v)(1)(B)(i) of the FD&C Act.¹³⁷ Instead, Congress provided that any application submitted after enactment of the QI Act is eligible for exclusivity without regard to whether a version of such an application may have been previously submitted. Given that Congress has spoken to timing and does not explicitly exclude submissions of applications that have

¹³⁵ Letter from Veloxis to DTOP (Dec. 2, 2014) at 1-2.

¹³⁶ *Id.* at 2.

¹³⁷ See, e.g., section 505(v)(2) of the FD&C Act (referring to *pending* applications). Congress also explicitly distinguished between different antibiotic applications based on the timing of submission and approval when it intended to do so. See, e.g., section 125(d)(1) of FDAMA (stating that an application approved by FDA before the date of enactment for the marketing of an antibiotic drug under section 507 of the FD&C Act is “in effect on the day before the date of enactment [of FDAMA]” and “shall on and after such date of enactment[] be considered to be an application that was submitted and filed under section 505(b)"); section 125(d)(2) of FDAMA (stating that certain sections of the FD&C Act shall not apply to “any 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 any application for marketing received” by FDA under section 507 of the FD&C Act before the date of the enactment.).

previously been submitted and withdrawn prior to approval, FDA declines to adopt this additional limitation here. FDA's interpretation of this provision is consistent with Congress' intent to balance the need to encourage development of new antibiotic drugs with its desire to ensure access to previously approved antibiotics through approval of generic versions of such antibiotics.¹³⁸ If, instead, FDA adopted the limitation advocated by Veloxis, public health could be adversely affected by discouraging sponsors from continuing to study, analyze data, and submit an NDA for an antibiotic drug product in situations where the drug product had been the subject of a previously submitted and withdrawn NDA.

Third, Veloxis states that although the subsequent application may have been assigned a new NDA number for administrative purposes, Astellas' second NDA must be treated as a continuation of the original NDA (submitted before enactment of the QI Act) for exclusivity purposes because Astellas performed no new studies in support of its second NDA between the time of withdrawal and resubmission of its NDA.¹³⁹ Specifically, Veloxis states that Studies 158 and 12-03 were cited by FDA as the clinical trials that had provided the basis for 3-year exclusivity and that the studies were completed before Astellas withdrew the original NDA in 2009.¹⁴⁰

Contrary to Veloxis' assertions, Astellas was asked to, and did, submit in the new NDA the following studies and information: complete justification for non-inferiority (NI) margins for both Studies 158 and 12-03; final reports for Studies 02-0-131, FG 506E-12-02 and FG 506E-KT01 including not only the results of the PK analyses, but also the 12-month results for the BPAR endpoint (including deaths, graft losses, and losses to follow-up imputed as failures); results from the OSAKA Study; and additional safety analyses.¹⁴¹ This information had not been submitted to the previously filed and withdrawn NDA.

Finally, Veloxis notes that although the Astagraf XL NDA that FDA ultimately approved was submitted after enactment of the QI Act, the FD&C Act user fee provisions "highlight[] the relatedness and connection between a withdrawn NDA and a subsequent application submitted by the same applicant for the same product."¹⁴² Specifically, Veloxis notes that under the FD&C Act, if a sponsor pays an application fee for an initial NDA that is withdrawn prior to approval, a subsequent application "for the same product by the same person" shall not be subject to another

¹³⁸ *ViroPharma* at 20 (citing Senator Kennedy's statements in the Congressional Record that the QI Act "includes limits that would prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs").

¹³⁹ Letter from Veloxis to DTOP (Dec. 2, 2014) at 2-3.

¹⁴⁰ *Id.* at 3.

¹⁴¹ Meeting Minutes (Jan. 31, 2012) at 6-7.

¹⁴² Letter from Veloxis to DTOP (Dec. 2, 2014) at 1-2.

application fee.¹⁴³ Veloxis states that the statute treats two applications as related, “recognizing that FDA’s work reviewing the first application can be applied in large measure to its review of the subsequent related application[,] and thus that a separate fee is not warranted.”¹⁴⁴ Veloxis also speculates that Astellas did not pay a user fee for its “subsequent NDA for Astagraf XL” submitted in 2012.¹⁴⁵

As a factual matter, Astellas paid a user fee for the Astagraf XL NDA submitted after the enactment of the QI Act.¹⁴⁶ The user fee provision, however, has no bearing on exclusivity under section 505(v) of the FD&C Act. As noted above, the relevant factors for whether Astagraf XL was eligible for exclusivity under section 505(v) of the FD&C Act are: (1) whether the drug contains an Old Antibiotic; (2) whether the drug is the subject of an application for marketing approval submitted after October 8, 2008 (the date of enactment of the QI Act); and (3) whether the drug is seeking exclusivity for a condition of use approved before the date of enactment of the QI Act. In other words, regardless of whether Astellas paid a user fee for the Astagraf XL NDA, Astagraf XL would still be eligible for 3-year exclusivity under section 505(v) of the FD&C Act.

2. *Approved Conditions of Use for Astagraf XL*

Because Astagraf XL is an Old Antibiotic subject to section 505(v) of the FD&C Act, the drug product’s exclusivity depends on whether it falls within the limitation described in section 505(v)(3) (i.e., whether it is approved for conditions of use that had not been previously approved for that Old Antibiotic). If the conditions of use for which Astagraf XL would otherwise have received exclusivity had been previously approved for Prograf or another tacrolimus product, Astagraf XL would not be entitled to 3-year exclusivity.¹⁴⁷

In its submission of October 27, 2014, Astellas asserted that the clinical studies that were essential for Astagraf XL’s approval established the safety and effectiveness of its once-daily dosing regimen, which is different from Prograf’s previously approved twice-daily dosing regimen.¹⁴⁸ According to Astellas, Astagraf XL’s new dosing regimen falls outside of the

¹⁴³ Id.

¹⁴⁴ Id.

¹⁴⁵ Id.

¹⁴⁶ Prescription Drug User Fee CoverSheet (Sept. 13, 2012).

¹⁴⁷ Although Veloxis did not raise this issue, the Agency nevertheless considered it as part of its review of the matter.

¹⁴⁸ Letter from Covington & Burling to CDER Exclusivity Board (Oct. 27, 2014) at 3.

limitation under section 505(v)(3)(B) such that Astagraf XL's exclusivity is for a condition of use that was not approved before enactment of the QI Act.¹⁴⁹

As explained in section II.C, FDA has interpreted the conditions of use in section 505(v)(3) of the FD&C Act to require a significant new use for an Old Antibiotic, not merely a refinement in labeling related to previously approved uses. Although the Agency does not agree with Astellas that the scope of exclusivity for Astagraf XL includes once-daily dosing for all kidney transplant patients, FDA agrees that for purposes of section 505(v)(3), the clinical studies conducted by Astellas to demonstrate the safety and effectiveness of Astagraf XL for once-daily dosing of tacrolimus in the *de novo* kidney transplant population resulted in a significant new use of tacrolimus compared to the twice-daily dosing approved for Prograf in this patient population. Because this once-daily dosing regimen is not encompassed within the previously approved twice-daily dosing regimen for Prograf and represents a change in how, by whom, and for what purposes the drug is used, FDA has concluded that this change is eligible for exclusivity.¹⁵⁰

B. Scope of 3-Year Exclusivity for Astagraf XL

Because we have determined that the limitations on exclusivity for Old Antibiotic drugs established under section 505(v) of the FD&C Act do not apply to the Astagraf XL NDA, the Agency must recognize 3-year exclusivity for the Astagraf XL NDA under subsections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and the implementing regulations in 21 CFR part 314.108. Specifically, Study 158 and Study 12-03 were “new clinical investigations” (other than bioavailability studies) that were “essential to the approval of the application” and “conducted or sponsored” by Astellas within the meaning of the FD&C Act and implementing regulations.¹⁵¹

At issue here is the scope of 3-year exclusivity for Astagraf XL. The scope of exclusivity under section 505(c)(3)(E)(iii) turns on the key phrase “conditions of approval.” Although the FD&C Act and implementing regulations do not define “conditions of approval,” as discussed above in section II.B., the Agency interprets the scope of 3-year exclusivity to cover the “innovative

¹⁴⁹ Id. at 4-5.

¹⁵⁰ The Exclusivity Board acknowledged that the reviews for Astagraf XL state that there is no substantial evidence of a clinical benefit with respect to potential improved patient adherence with once-daily dosing of Astagraf XL compared to Prograf. See, e.g., Astagraf XL Clinical Review (June 19, 2013) at 6; Astagraf XL Cross-Discipline Team Leader Review at 18, 37. However, the Exclusivity Board observed that the once-daily dosing for Astagraf XL is a new dosing regimen. The Exclusivity Board concluded that at this time, FDA does not consider a demonstration of a clinical benefit of a new dosing regimen compared to a past dosing regimen to be a prerequisite to establishing a significant new condition of use for exclusivity purposes under section 505(v). See Exclusivity Board Memorandum re Astagraf XL (tacrolimus extended-release capsules) 3-year exclusivity (Jan. 8, 2015).

¹⁵¹ As no party disputes that Astagraf XL is entitled to 3-year exclusivity under section 505(c)(3)(E)(iii) of the FD&C Act (see Veloxis Submission at 11), it is not necessary to include a more detailed analysis of this provision here.

change” which is related to the scope of the underlying “new clinical investigations” that were essential to the approval. Accordingly, the Agency must determine the innovation for which Astellas received exclusivity. Applying this interpretation to the facts at issue, we begin with a description of the “new clinical investigations” that were essential to the approval of Astagraf XL.

The approval of the Astagraf XL NDA for the prophylaxis of organ rejection in patients receiving kidney transplants was supported by two 12-month, Phase 3, randomized studies in *de novo* kidney transplant patients that included treatment arms for both Astagraf XL and Prograf: Study 158¹⁵² and Study 12-03.¹⁵³

Study 158 was a comparative trial comprising three arms in *de novo* kidney transplant patients, all with basiliximab (antibody) induction: Astagraf XL (0.15-0.20 mg/kg once daily) + MMF + corticosteroids; Prograf (0.075-0.10 mg/kg twice daily) + MMF + corticosteroids; and the active comparator cyclosporine Neoral (4.5 mg/kg twice daily) + MMF + corticosteroids.¹⁵⁴ The study was designed to demonstrate non-inferiority of Astagraf XL/MMF and of Prograf/MMF to Neoral/MMF within a 10% margin in *de novo* kidney transplant patients such that the primary efficacy comparison was between the Astagraf XL and Neoral arms and that the comparison of Astagraf XL versus Prograf served as the secondary clinical endpoint.¹⁵⁵ The study included a 1-year primary analysis period and a clinical continuation period of treatment for up to 60 months post-transplant. The protocol-defined primary analysis was efficacy failure rate (biopsy-confirmed (Banff grade \geq 1) acute rejection (BCAR), graft failure, death or lost to follow-up at 1 year).¹⁵⁶

Study 12-03 was conducted as a double-blind, double-dummy study during the first 24 weeks post-transplantation in *de novo* kidney transplant patients, continuing as an open-label study until the last patient completed the 12-month visit.¹⁵⁷ The study compared the efficacy and safety of Astagraf XL (0.2 mg/kg once daily) and Prograf (0.1 mg/kg twice daily), both in the presence of MMF and steroids, but without basiliximab induction. The intent of the study was to demonstrate that Astagraf XL was non-inferior to Prograf with respect to the primary endpoint, i.e., event rate of patients with BPAR within the first 24-weeks following transplantation.¹⁵⁸

¹⁵² Astagraf XL Clinical Review at 32.

¹⁵³ Id.

¹⁵⁴ Id..

¹⁵⁵ Id. at 42.

¹⁵⁶ Id. at 32 and 42. BCAR is synonymous with BPAR.

¹⁵⁷ Id. at 32.

¹⁵⁸ Id. at 32 and 51.

Although different primary endpoints were used in Studies 158 and 12-03, data for efficacy failures (BPAR, death, graft loss, or loss to follow-up) were collected and analyzed by the statistical reviewer for both studies.¹⁵⁹ Astellas considered Study 158 to be the primary study to support the demonstration of the efficacy and safety of Astagraf XL because the study was more consistent with the U.S. standard of care and population demographics. Study 12-03 provided information on a combination of tacrolimus + MMF without the use of antibody induction (which represents 15% of the use of this combination), and thus FDA also considered Study 12-03 to be a primary study to support the efficacy and safety of Astagraf XL in the *de novo* kidney transplant population.¹⁶⁰

Because Prograf capsules had been previously approved as a twice-daily, IR dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients, the change in Astagraf XL for which new clinical investigations were needed was the change to a once-daily, ER version of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients. Studies 158 and 12-03 were essential to the approval of Astagraf XL for this change.¹⁶¹

C. Veloxis' Assertions That Approval of the Envarsus XR NDA Is Not Blocked

Veloxis has made several assertions that 3-year exclusivity for Astagraf XL does not block approval of the Envarsus XR NDA for use in *de novo* and conversion patients. FDA disagrees with these assertions.

1. Differences Between Envarsus XR and Astagraf XL

Veloxis asserts that Envarsus XR is not blocked by Astagraf XL's exclusivity because, although it shares some conditions of approval with Astagraf XL, it does not share all of the conditions of approval of Astagraf XL. Specifically, Veloxis argues that Envarsus XR differs from Astagraf XL in dosage form (capsule versus tablet), certain strengths, dosing regimen (although it is also a once-daily, ER dosage form, it has a different starting dose, target trough level, timing for step-down target trough levels), and PK profiles, and that these differences may have clinical significance, which take Envarsus XR outside the scope of Astagraf XL's exclusivity.¹⁶²

¹⁵⁹ Id. at 36. Data from the OSAKA Study on Advagraf, the EU-approved version of Astagraf XL, was also reviewed. The OSAKA Study was a non-IND, open-label, post-marketing study, exploring three different regimens using various doses and a combination of Advagraf compared to a Prograf + MMF + corticosteroids control arm that resembled the regimen used in the Prograf arm of Study 12-03 but without antibody induction. Although one of the Advagraf treatment arms approximated that used in the Astagraf XL treatment arm of Study 12-03, the open-label design, the limitation of assessment of efficacy and safety to 24 weeks, and the multiple comparisons involved limited the utility of this study to support labeling of the efficacy and safety of an Astagraf XL regimen in the U.S. Astagraf XL Clinical Review at 40.

¹⁶⁰ Id. at 38.

¹⁶¹ Astagraf XL Division Director Summary Review at 10-11.

¹⁶² Veloxis Submission at 8-11.

We disagree with Veloxis as both a legal and factual matter. The differences that Veloxis refers to are not relevant to the exclusivity analysis in this case; moreover, they have not been demonstrated to be clinically meaningful. Astagraf XL received exclusivity neither for the capsule nature of its dosage form (Prograf had been approved previously as a capsule) nor for the particular strengths for which it was approved (Prograf had been approved previously in the same strengths: 0.5, 1, and 5 mg). Astagraf XL also did not obtain exclusivity for its precise PK profile as the Agency has not yet determined, and no sponsor has yet established, the correlation between the changes in PK profile and clinically significant differences in safety and effectiveness for tacrolimus products. Instead, Astellas' innovation for Astagraf XL was the ER nature of its dosage form that permitted once-daily dosing (whereas Prograf was an IR dosage form for twice-daily dosing). The new clinical investigations essential to this innovation studied Astagraf XL for the prophylaxis of organ rejection in *de novo* kidney transplant patients. Astellas' exclusivity is circumscribed by the scope of these new clinical investigations and cannot extend beyond this condition of approval. Therefore, Astellas' new clinical investigations supported and Astagraf XL got exclusivity for establishing the safety and effectiveness of a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients.

Because Envarsus XR clearly shares with Astagraf XL the exclusivity-protected conditions of approval—i.e., once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* patients receiving kidney transplants—Envarsus XR is blocked from approval for this use. As noted above in section II.B, under the Agency's interpretation, a 505(b)(2) application can differ in certain ways from the previously approved product with exclusivity and nonetheless be blocked if it shares the conditions of approval for which exclusivity was granted.

Because the Agency disagrees with Veloxis' interpretation that only an application that shares every condition of approval with an exclusivity-protected drug will be blocked,¹⁶³ and because the Agency notes that Envarsus XR shares the conditions of approval for which Astagraf XL obtained exclusivity, it is irrelevant whether Envarsus XR is different from Astagraf XL in the ways that Veloxis asserts. Nonetheless, for the sake of completeness, FDA notes that it also disputes many of the assertions made by Veloxis regarding the clinical significance of differences between the two products, as discussed below.

- *PK Profiles*

Veloxis asserts that Envarsus XR and Astagraf XL have “drastically different” PK profiles and that these PK differences “may” have clinical significance, particularly for African-American

¹⁶³ As noted above in section II.B, such a narrow interpretation would render 3-year exclusivity virtually meaningless because any change (including changes that could be approved in a suitability petition such as a change from tablet to capsule supported by no more than a PK study) would be sufficient to take a subsequent drug outside the scope of another's exclusivity.

patients.¹⁶⁴ Although FDA acknowledges that there are some differences in the PK profiles for Astagraf XL and Envarsus XR, the clinical significance of the different tacrolimus PK profiles of Envarsus XR and Astagraf XL (and Prograf) has not been established. Specifically, despite Veloxis' claims, the clinical significance of the potential differences in PK profiles of these formulations *has not been demonstrated* in African-American patients in the Phase 3 clinical trials. A clinical study evaluating the significance of a potential difference of PK profiles between Envarsus XR and IR tacrolimus in African-American patients is underway but has not yet been completed. In particular, Veloxis has initiated a study entitled "Prospective, Randomized, Open-label, Single-center, Two Sequence, Three Period Crossover Study to Compare the Steady State Pharmacokinetics of Once-Daily-Extended Release Melt Dose Tacrolimus Tablets (LCP-Tacro) to Generic Tacrolimus Capsules Twice Daily in Stable African American Renal Transplant Patients."¹⁶⁵ This study is still ongoing, and whether the results will support a difference in PK between Envarsus XR and IR tacrolimus that is clinically significant is still unknown and will not be determined until after a review of the complete data and analyses. This study is not designed to detect the clinical significance, if any, of differences in PK profiles between Envarsus XR and Astagraf XL.

- *Tremors*

Veloxis claims that the results of the Envarsus XR STRATO Study (Study LCP-Tacro 3003) reveal that the majority of kidney transplant patients who were experiencing tacrolimus-induced hand tremors experienced significant improvement after conversion to Envarsus XR.¹⁶⁶ The claim of reduction in tremors is not supported by data from adequate and well-controlled trials. The two Phase 3 studies of Envarsus XR (LCP-Tacro 3002 and LCP-Tacro 3001) compared Envarsus XR to Prograf (not Astagraf XL) and did not show a reduction in tremors in the Envarsus XR group. Additionally, the STRATO Study was a Phase 2 study and was not considered by FDA to be an adequate, well-controlled study designed to support a claim for the reduction of tremor in kidney transplant recipients who had switched to Envarsus XR from a tacrolimus IR product. In particular, the STRATO Study did not have a double-blind design that would have been needed to minimize the potential for bias, as had been recommended by the Agency.¹⁶⁷

- *Dosage Forms, Strengths, and Dosing Regimens*

¹⁶⁴ Veloxis Submission at 8-9 (Exhibit 2).

¹⁶⁵ See "Crossover Study to Compare PKs of Once Daily [ER] Tacrolimus Tablets to Generic Tacrolimus Capsules Twice Daily," available on the Internet at <https://www.clinicaltrials.gov/ct2/show/NCT01962922?term=LCP-tacro&rank=10>.

¹⁶⁶ Letter from Veloxis to DTOP (Dec. 8, 2014) (Declaration of Dr. Anthony Langone).

¹⁶⁷ Letter from DTOP to Veloxis re: IND 75,250 (Oct. 18, 2011).

Veloxis argues that Envarsus XR and Astagraf XL have different dosing regimens, dosage strengths, and dosage forms.¹⁶⁸ Contrary to Veloxis' assertions, Envarsus XR and Astagraf XL are both once-daily, ER dosage forms of tacrolimus. As noted above, even though Astagraf XL is a capsule and Envarsus XR is a tablet, these differences are not relevant for exclusivity purposes because neither Astellas' nor Veloxis' Phase 3 clinical investigations evaluated the safety and effectiveness of the specific dosage form (i.e., the capsule property of Astagraf XL and the tablet property of Envarsus XR). Rather, the focus of the clinical investigations was the once-daily, ER aspect of the drugs for the specific population. Astagraf XL did not get exclusivity for the capsule aspect of its dosage form. Similarly, although Envarsus XR and Astagraf XL share only one common dosage strength,¹⁶⁹ the Phase 3 clinical investigations for both drug products did not evaluate the specific strengths for each product because dosing for tacrolimus products is individually titrated based on the patient's weight. Moreover, although the two products have different starting doses, target trough levels and timing for step-down target trough levels, Veloxis has not demonstrated that Envarsus XR and Astagraf XL dosing regimens are clinically different. Astellas obtained exclusivity for the ER dosage form that permitted once-daily dosing for Astagraf XL, a characteristic that Envarsus XR shares. If FDA were to accept Veloxis' arguments for why Envarsus XR should not be blocked by Astagraf XL's exclusivity, 3-year exclusivity would block only ANDAs approved under section 505(j) of the FD&C Act and the provisions of section 505(c)(3)(E)(iii) would then be superfluous.

2. *Orphan Designation*

Veloxis attempts to make much of its receipt of orphan designation for Envarsus XR.¹⁷⁰ To the extent Veloxis argues that this orphan designation means that the approval of Envarsus XR should not be blocked by the exclusivity of a previously approved drug product, this argument has no merit.

Envarsus XR's status as an orphan-designated drug has no bearing on whether, if approved, the drug product would be approved for the exclusivity-protected conditions of approval for Astagraf XL. The conditions of approval for which Astagraf XL has exclusivity are once-daily, ER dosage forms of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. To be blocked by 3-year exclusivity, a drug need not share all of the conditions of approval (i.e., be a duplicate).

¹⁶⁸ Veloxis Submission at 9-11.

¹⁶⁹ Astagraf XL is available in 0.5, 1, and 5 mg strengths. Envarsus XR has 0.75, 1, and 4 mg strengths. The Agency requested that Veloxis develop different strengths from Prograf due to concerns about the potential for medication errors. Letter from DSPTP to LifeCycle Pharma re IND 75350 (Oct. 27, 2009).

¹⁷⁰ Veloxis Submission at 9-11.

Moreover, even if Veloxis' view that a superior product should not be blocked by exclusivity was to prevail, Veloxis' orphan designation does not establish that FDA has concluded that Envarsus XR is a superior product to Astagraf XL. FDA acknowledges that Envarsus XR was designated for an indication for which tacrolimus had previously been approved and notes that a sponsor who seeks orphan-drug designation for a drug that is otherwise the same drug (same active moiety) as a previously approved drug for the same indication as that previously approved drug must submit a "plausible hypothesis" that it is clinically superior to the previously approved drug to obtain orphan designation.¹⁷¹ If FDA agrees that the hypothesis is in fact plausible and that the drug otherwise meets all the applicable statutory and regulatory requirements for designation, the Agency will grant the request for designation. However, orphan designation does not indicate that, if approved, the relevant conditions of approval of Envarsus XR will differ from those of Astagraf XL. The "plausible hypothesis" standard for orphan designation presents a relatively low threshold and is not the same standard that would need to be met for a superiority claim in labeling.¹⁷² Specifically, although more than "a hypothetical claim of clinical superiority" is needed to receive orphan designation, clinical superiority has not been proven at this stage in the process.¹⁷³ When FDA designates a drug, such as Envarsus XR, based on a plausible hypothesis of clinical superiority over a previously approved drug, the Agency makes no determination that the drug is in fact clinically superior to the previously approved drug or whether its ultimate approval would result in a different condition of approval.

Further, in applying for orphan designation, Veloxis hypothesized that Envarsus XR would be clinically superior to Prograf, the older, IR formulation of tacrolimus that was approved at the time the orphan designation was requested, not to Astagraf XL. FDA reviewed the Veloxis designation request on this basis and agreed that there was a plausible hypothesis that Envarsus

¹⁷¹ 21 CFR 316.20(a) ("[A] sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug"); 21 CFR 316.25(a)(3); see 21 CFR 316.3(b)(3) and (14).

¹⁷² See the proposed rule "Orphan Drug Regulations" (56 FR 3338, 3340 (Jan. 29, 1991)):

FDA considered proposing a rule under which it would designate drugs apparently the same as drugs that already have orphan-drug exclusive approval only where the agency believed that there was a high probability of eventual approval. FDA decided on a liberal designation policy, however, because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval.

See also Letter from L Kux to P Turner, (Docket No. FDA-2011-P-0213) (Aug. 8, 2012) (Wilate CP response) at 4 ("Though the sponsor of a subsequent orphan drug must set forth a plausible hypothesis of clinical superiority over the previously approved drug at the designation stage, such a sponsor faces a higher standard at time of approval" (footnote omitted)).

¹⁷³ Wilate CP Response at 13.

XR would be clinically superior to Prograf. FDA's decision to designate Envarsus XR as an orphan drug did not involve any comparison of Envarsus XR to Astagraf XL.

For these reasons, although Envarsus XR has orphan-drug designation for the prophylaxis of organ rejection in patients receiving an allogeneic kidney transplant, this has no impact on the analysis of whether its conditions of approval differ from those of Astagraf XL and, more specifically, of whether Envarsus XR can be approved in the face of Astagraf XL's exclusivity.

3. *Lack of Reliance on Astagraf XL*

Veloxis asserts that because Envarsus XR did not reference or rely on the Agency's previous findings of safety and/or effectiveness for Astagraf XL, it should not be blocked.¹⁷⁴ Veloxis argues that section 505(c)(3)(E)(iii) uses the term "relied upon"¹⁷⁵ and that therefore the plain language of the statute requires reliance on a drug with exclusivity for a subsequent 505(b)(2) NDA to be blocked by that drug's exclusivity.

The scope of 3-year exclusivity for Astagraf XL does not depend on whether Envarsus XR relies on Astagraf XL for approval. Veloxis' assertion is misplaced because the phrase "relied upon," in section 505(c)(3)(E)(iii) of the FD&C Act, does not indicate that only drugs that rely on a particular drug with exclusivity are blocked; it simply distinguishes a 505(b)(2) NDA from a stand-alone NDA (and thereby identifies 505(b)(2) NDAs as those that have the potential to be blocked under that provision). This is plain from a review of the statutory text below.

Section 505(b)(2) of the FD&C Act provides that a 505(b)(2) NDA is

[a]n application submitted under paragraph (1) for a drug for which the *investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted*

(emphasis added). In describing what applications are blocked by exclusivity, section 505(c)(3)(E)(iii) of the FD&C Act mirrors this language as follows:

If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective

¹⁷⁴ Veloxis Submission at 11-14.

¹⁷⁵ *Id.* at 11.

before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the *investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.*

(emphasis added). Although Veloxis misquotes the statute to read in an element of *reliance* on the drug with exclusivity, the plain text of the statute does not include such an element.

Similarly, in FDA regulations, the use of the words “relies on” in 21 CFR 314.108(b)(4)(iv) only modifies ANDAs submitted under suitability petitions pursuant to section 505(j)(2)(C) of the FD&C Act. Neither the statute nor the regulation requires a 505(b)(2) NDA to rely on a drug with exclusivity for that 505(b)(2) NDA to be blocked. To the contrary, the operative statutory term for the scope of exclusivity is “conditions of approval”; this phrase and others in section 505(c)(3)(E)(iii) and in the sections of the regulation at 314.108(b)(4)(iv) that apply to 505(b)(2) NDAs do not refer to any such reliance.

Veloxis also refers to the structure and purpose of the Hatch-Waxman Amendments to support its argument that an application cannot be blocked by a drug with exclusivity if it did not rely on the finding of safety or effectiveness for the exclusivity-protected drug. Even assuming *arguendo* that the statute is ambiguous, the Agency’s interpretation is reasonable; the Agency interprets 3-year exclusivity to protect the change supported by the new clinical investigations regardless of reliance, thereby preserving the incentive to make exclusivity-protected changes.

In fact, as noted above, FDA specifically stated in the Preamble to the 1989 Proposed Rule describing the Agency’s interpretation of 3-year exclusivity that

when exclusivity attaches to an active moiety or to an innovative change in an already approved drug, the submission or effective date of approval of ANDAs or 505(b)(2) applications for a drug with that active moiety or innovative change will be delayed until the innovator’s exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, *and regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers.*¹⁷⁶

The Agency’s interpretation balances the goals of the Hatch-Waxman Amendments by giving full effect to protections available for innovative changes and by preventing those protections from being undercut by a competitor’s simple decision to reference a different listed drug.

Finally, Veloxis asserts that FDA has previously taken the position that a 505(b)(2) NDA is barred by another drug’s marketing exclusivity only if it relies upon the subject drug. Veloxis refers to the Parkman Letter, the 505(b)(2) guidance, and certain citizen petition responses in

¹⁷⁶ See 1989 Proposed Rule at 28897 (emphasis added).

support of this assertion.¹⁷⁷ For example, in its November 14 submission, Veloxis quotes a Citizen Petition response where FDA stated: “A 505(b)(2) applicant is subject to applicable periods of marketing exclusivity *granted to the listed drug relied upon . . .*”¹⁷⁸ This statement (and other similar statements in other Agency documents) is correct (a 505(b)(2) applicant is subject to exclusivity granted to the listed drug relied upon), but does not describe the entire universe of ways in which a 505(b)(2) application can be blocked.¹⁷⁹ These statements merely address the most common scenario that arises – where a 505(b)(2) NDA that relies, in part, on a listed drug will be subject to the exclusivity periods covering the listed drug. These documents do not address the circumstance at issue here where a 505(b)(2) NDA may be blocked regardless of whether it relies on the exclusivity-protected drug – an interpretation supported by the statutory language and clearly contemplated by the Agency’s preamble statements.¹⁸⁰ As noted above, there is nothing in this statement that precludes the Agency from concluding that a 505(b)(2) NDA is also blocked from approval, in whole or part, by the exclusivity of a drug product that it did not rely upon.

4. *The Orange Book Exclusivity Code*

Veloxis also asserts that it relied, to its detriment, on the NDF exclusivity code in the Orange Book, which put applicants on notice regarding the scope of exclusivity.¹⁸¹ Veloxis asserts that because the NDF exclusivity code suggests that Astagraf XL obtained exclusivity for its dosage form and because Astagraf XL’s dosage form is an ER capsule and Envarsus XR is an ER tablet,

¹⁷⁷ Veloxis Submission at 13-14.

¹⁷⁸ Veloxis Submission (Exhibit 4 at slide 15) (citing Letter from J. Woodcock to D. Clissold, Docket Nos. FDA-2011-P-0869 & FDA 2013-P-0995, September 18, 2013) (Suboxone CP Response) (emphasis added by Veloxis).

¹⁷⁹ We note as an aside that in responding to that petition, FDA was not considering directly whether a 505(b)(2) NDA would be blocked by 3-year exclusivity for buprenorphine/naltrexone, only whether such an NDA must reference Suboxone sublingual film and certify to its patents. We further note that in answering that petition, FDA did state, “During [the 3-year exclusivity] period, the Agency will not make effective the approval of a 505(b)(2) application for the conditions of approval of the application covered by the exclusivity.” Suboxone CP Response at 5.

¹⁸⁰ We note that Veloxis’ citation to language in FDA Response to Kevin McKenna, Ph.D., Docket No FDA 2011-P-0662 (March 27, 2012), is also inapposite, since this petition dealt with patent certifications not exclusivity considerations and involved interpretation of a statutory provision that is different than the one at issue here. In contrast to the 3-year exclusivity provision at 505(c)(3)(E)(iii), which prohibits approval for the conditions of approval for which exclusivity was granted without reference to reliance on the exclusivity-protected drug, section 505(b)(2)(A) regarding patent certifications for 505(b)(2) applications specifically ties the need for certification to the listed drug relied on for approval. It states, that an application “for which the investigations described in clause (A) . . . and relied upon by the applicant on for approval of the application were not conducted by of for the applicant . . .” shall include a patent certification “for each patent which claims the drug for which such investigations were conducted.” The latter thus links the investigations relied on for approval with the patent certifications that are required. Because a 505(b)(2) NDA cannot rely for approval on investigations in another NDA without citing that NDA as a listed drug, the patent certification provision necessarily limits the patent certification obligation to a listed drug relied upon.

¹⁸¹ Veloxis Submission at 8.

these two products do not share the same condition of approval and Envarsus XR should therefore not be blocked.¹⁸²

The NDF code corresponding to “new dosage form” in this case refers to the approval of an ER dosage form.¹⁸³ It is clear that the NDF code was not intended to refer to the capsule nature of the Astagraf XL product because Prograf had been previously approved for the same indication in capsule form; therefore, the capsule aspect of the product could not have been the innovation protected by exclusivity.

In any event, FDA notes that the scope of 3-year exclusivity is not intended to be defined or circumscribed by the exclusivity code listed in the Orange Book. In fact, “[i]t has been FDA’s long-standing position that the exclusivity code listed in the Orange Book does not necessarily identify, with specificity, the actual scope of exclusivity (i.e., the conditions of approval for which new clinical investigations were essential and which are therefore protected).”¹⁸⁴

As discussed above, FDA determined that the new clinical investigations essential to the approval of Astagraf XL, Studies 158 and 12-03, encompassed the once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney patients. Both Astagraf XL and Envarsus XR are once-daily, ER dosage forms of tacrolimus for the prophylaxis of organ rejection for use in *de novo* kidney patients.

D. Conversion Kidney Transplant Setting Is Not Within the Scope of 3-Year Exclusivity for Astagraf XL

Astellas argues that the scope of its exclusivity for Astagraf XL encompasses and prevents approval of any once-daily dosage form of tacrolimus indicated for prophylaxis of organ rejection in kidney transplant patients “regardless of patient setting.”¹⁸⁵ However, Astellas did not obtain approval of Astagraf XL in conversion patients and thus its exclusivity cannot extend to block approval for this population.

Although Astellas indicated during the pre-NDA development stages of Astagraf XL that it intended to (b) (4)

¹⁸² Id.

¹⁸³ The Patent and Exclusivity Terms section of the Orange Book does not have an exclusivity code that is more specific to ER dosage forms. See the Orange Book (Patent and Exclusivity Terms).

¹⁸⁴ FDA Response to GL Veron (Docket No. FDA-2010-P-0614) (May 25, 2011) at 22-23 (FDA determined that although the descriptor in the Orange Book stated that Colcrys’ exclusivity covered “gout flares,” the single clinical trial essential to the approval of Colcrys was for the treatment of acute gout flares, not prophylaxis of gout flares and therefore acute gout flairs was the exclusivity-protected indication.).

¹⁸⁵ Letter from Astellas to DTOP (Sept. 12, 2014) at 2.

¹⁸⁶ See, e.g., Medical Officer Review of IND 64,148 for Modified Release Tacrolimus (April 1, 2003) (Astellas’ early development plan submitted to FDA in 2002 included plans for (b) (4))

(b)(4) the Astagraf XL Clinical Review indicates that Astellas was not seeking a “specific conversion indication, but [was] requesting (b)(4)

”¹⁸⁷ Upon review of the data, however, the Agency concluded that Astellas’ studies in stable patients converted from Prograf to Astagraf XL were not adequate and well-controlled trials for the purpose of supporting approval for conversion of kidney transplant patients from an IR version of tacrolimus to Astagraf XL (and vice versa) in proposed labeling.¹⁸⁸ Not only were the studies single arm and not randomized, they were also inherently not designed to meet the standard of providing substantial evidence of safety and efficacy of conversion from Prograf to Astagraf XL (i.e., not designed to collect systematic long-term information on BPAR), and thus were not reviewed for safety and efficacy.¹⁸⁹

(b)(4)

The PK section of the currently approved labeling includes only limited descriptive PK information from Study FG 506E-12-02 in the last row of Table 6.¹⁹⁰ The Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling are not only silent on the conversion use, but are specific to *de novo* use.¹⁹¹ The PK studies conducted in the conversion population were relative

(b)(4)

¹⁸⁷ Astagraf XL Clinical Review at 39 and 41.

¹⁸⁸ *Id.* at 22 and 41 (stating that the issue of making recommendations for conversion of stable transplant patients from Prograf to Astagraf XL in the proposed label is moot because Studies 02-0-131, FG 506E-12-02, and FG 506E-KT01, which are single arm and non-randomized, do not represent adequate well controlled studies).

¹⁸⁹ *Id.* at 41. Although Astellas submitted some 12-month follow-up data from these short studies, FDA concluded that such data was neither readily interpretable without a randomized concurrent control group nor included a systematic collection of safety data, or episodes of allograft rejection, beyond the completion of the short period of PK sampling. In addition, FDA concluded that the range of duration from time-of-transplant to time-of-conversion rendered data on 12-month graft and patient survival even more difficult to interpret in a clinically meaningful way that could inform an individual clinician or patient on the safety or efficacy of such conversion. *Id.*

¹⁹⁰ Approved Product Labeling for Astagraf XL (PK section, Table 6). FDA also notes that the same table includes PK information in healthy subjects as well.

¹⁹¹ For example:

- The *Dosage in Adult Kidney Transplant Recipients* subsection of the Dosage and Administration section, describes dosing and administration instructions with and without basiliximab induction, which is specific to *de novo* kidney transplant patients. The use of the phrase “with or without basiliximab induction” implies that Astagraf XL is indicated for use in *de novo* patients because basiliximab (Simulect) induction

bioavailability studies and they were not “new clinical investigations” essential to the approval of Astagraf XL within the meaning of the statute and regulations.

Further, it is clear that the new clinical investigations (Studies 158 and 12-03) for which Astagraf XL received exclusivity did not also demonstrate the safety and effectiveness of the Astagraf XL once-daily, ER dosage form for every use (or even just for conversion use), but rather only for *de novo* use in kidney transplant patients.¹⁹² FDA has previously required adequate and well-controlled studies to demonstrate safety and effectiveness of other immunosuppressants for the conversion use¹⁹³ and such studies would have been needed for approval for conversion for Astagraf XL as well. Astellas did not conduct those clinical investigations that would have been necessary to support that use. Consequently, the scope of 3-year exclusivity for Astagraf XL does *not* extend to a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for converting kidney transplant patients who are stable on IR tacrolimus.¹⁹⁴

refers to the two doses of basiliximab administered during the first week after kidney transplantation. The use of that phrase also reflects that both studies 158 and 12-03 were essential to approval.

- The Clinical Studies section specifically states that “[t]he efficacy and safety of ASTAGRAF XL in *de novo* kidney transplantation were assessed in two randomized, multicenter, active-controlled trials [(Studies 158 and 12-03)].”

¹⁹² Astellas recognized the limitations of the Astagraf XL once-daily, ER dosage studies in its August 2012 submission:

In this NDA, Astellas is providing two new clinical investigations (one for the *de novo* kidney transplant indication [Study 158] and one for the *de novo* male liver transplant indication[,]) and each one is essential to the approval of the application . . . [so that 3-year] exclusivity can be obtained for the *de novo* kidney and the *de novo* male liver transplant indication.

(Note that Astellas ultimately did not receive approval for the *de novo* male liver transplant indication). See Exclusivity Request submitted Aug. 2012 at 7-8, available on the Internet at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204096Orig1s000AdminCorres.pdf.

¹⁹³ As noted above in section I.A, immunosuppressants indicated for prophylaxis of organ rejection in patients receiving kidney transplants include organ-based indications. Because *de novo* patients and conversion patients are considered two distinct populations, however, the Agency generally expects adequate and well-controlled clinical studies to support the safe and effective (and approved) use in each respective population. See, e.g., Approved Product Labeling for Myfortic (mycophenolic acid) (NDA 50791) (approved Sept. 27, 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050791s019lbl.pdf. The Indications and Usage section of that label states, in part, that Myfortic is indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Specifically, the conversion study (conducted in adults) was one in which renal transplant patients (ages 18-75 years), who were at least 6 months post-transplant receiving MMF (brand name, CellCept) 2 g/day in combination with cyclosporine with or without corticosteroids for at least two weeks prior to entry in the study were randomized to Myfortic 1.44 g/day or MMF 2 g/day for 12 months. In that approved labeling, the Clinical Studies section, for example, includes conversion information.

¹⁹⁴ Any attempt by Astellas to argue that

(b) (4)

□

While reexamining these exclusivity issues at the request of Veloxis, on December 5, 2014, the Agency informed Veloxis that before the expiry of Astagraf XL's exclusivity, Envarsus XR could potentially be approved for prophylaxis of organ rejection for conversion use only in kidney transplant patients who were stable on IR tacrolimus. This is because, in contrast to the studies Astellas submitted for Astagraf XL, Veloxis submitted to the Envarsus XR NDA the results of a clinical study for conversion use, i.e., kidney transplant recipients converted from Prograf to Envarsus XR (Study 3001). This study (along with the other studies submitted in the Envarsus XR NDA) provided substantial evidence of the effectiveness and safety of Envarsus XR to support approval in the conversion population.¹⁹⁵ Study 3001 also provided adequate data and information to support the appropriate dosing and administration of Envarsus XR for conversion use and the other necessary aspects of the labeling.¹⁹⁶ The Agency determined, as a preliminary matter, that it was feasible for Veloxis to obtain approval for the once-daily, ER dosage form of tacrolimus for conversion use only during the Astagraf XL exclusivity period and that such use would not be blocked by Astagraf XL's exclusivity. In short, the Agency concluded that the conversion use is a different "condition of approval" from the *de novo* use for which Astagraf XL received exclusivity and that Astagraf XL did not conduct new clinical investigations essential to the approval of Astagraf XL for the conversion use. Therefore, FDA informed Veloxis of its preliminary determination that Envarsus XR would not be blocked for this condition of approval and asked Veloxis to submit proposed labeling seeking approval only for the conversion use.¹⁹⁷ Veloxis declined to pursue this option.

(b) (4)

¹⁹⁵ Envarsus XR Clinical Review at 8.

¹⁹⁶ The Tentatively Approved Product Labeling for Envarsus XR (NDA 206406) (October 30, 2014), states, in relevant part: "To convert from a tacrolimus immediate release product to ENVARSUS XR, administer an ENVARSUS XR daily dose that is 80% of the total daily dose of the tacrolimus immediate release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL."

¹⁹⁷ The Agency informed Veloxis of this option after extensive consideration of the issues prompted by meetings with Veloxis and Astellas, respectively, and review of Veloxis' submissions and other relevant information in the respective NDAs. The Agency considered, for example, the October 30, 2014, CDER Memorandum summarizing the Agency's conclusion that Envarsus XR was blocked by Astellas' 3-year exclusivity. At that time, however, Veloxis was seeking approval of Envarsus XR for prophylaxis of organ rejection for both conversion use and for use

IV. ANALYSIS OF PRECEDENT CITED BY VELOXIS

The Agency has reviewed its prior actions regarding 3-year exclusivity in light of Veloxis' arguments. The fact that Veloxis has not identified any examples where FDA tentatively approved (rather than fully approved) a 505(b)(2) NDA based on a determination that the 505(b)(2) application was blocked by 3-year exclusivity for a listed drug on which it did not rely does not establish that the Agency interprets the relevant statutory and regulatory provisions such that a 505(b)(2) NDA cannot be blocked by 3-year exclusivity for a listed drug on which it did not rely. Indeed, FDA's policy as stated in preamble statements is the opposite — that a 505(b)(2) NDA can be blocked by the exclusivity of another NDA even if there is no reliance.¹⁹⁸ Our review of Agency precedent provides no indication that the Agency has abandoned this explicitly stated interpretation.

Questions about the scope of 3-year exclusivity and its potential to block approval of 505(b)(2) NDAs are not presented often, which can be explained by a combination of several factors, including the rarity of the factual scenario and rational decision-making by knowledgeable industry actors. Three years is relatively short in relation to the time required to develop an NDA. It generally takes a longer time for an NDA to be developed, filed, and reviewed. Therefore, for this question to be presented, two applicants would generally have to proceed on parallel development paths for the same innovation. In addition, the later-in-time application would have to be a 505(b)(2) NDA, which would have to become ready for an approval decision during the pendency of the 3-year exclusivity period of a protected drug on which it did not rely. Moreover, for the question of reliance to arise, there must also exist another version of the exclusivity-protected drug (or a significant quantity of non-product specific published literature) such that the 505(b)(2) NDA is able to refer to the other drug as its listed drug or rely on the non-product specific published literature to fill gaps in its application, rather than relying on the exclusivity-protected drug product.

Even in the relatively rare cases where a 505(b)(2) NDA has the potential to be blocked by exclusivity for a previously approved application on which it did not rely because it seeks approval for an exclusivity-protected condition of approval, it is likely that sponsors and applicants will strategically avoid situations where FDA must determine whether their applications fall within the scope of another sponsor's exclusivity. For example, applicants may shape their NDA submissions to avoid submitting an application that may be delayed by existing exclusivity. Similarly, because (in contrast to an ANDA) a 505(b)(2) NDA is not required to be the same as any previously approved application in any respect, in many cases a 505(b)(2) applicant can seek approval for conditions of approval that are no longer (or never were)

in *de novo* kidney transplant patients. The Agency's further consideration of the issues prompted a closer review of the nature of the studies conducted by Astellas and of the scope of 3-year exclusivity for Astagraf XL.

¹⁹⁸ 1989 Proposed Rule at 28872, 28897.

protected by exclusivity. For example, Veloxis had the opportunity to do that here by seeking approval only for the unprotected conversion use but chose not to do so.

Sponsors have also developed alternative business arrangements to avoid conflicts involving 3-year exclusivity issues for competing products. For example, two firms recently announced an exchange of waivers of exclusivity for their respective competing single entity extended-release hydrocodone products.¹⁹⁹ Zogenix's single entity extended-release hydrocodone capsule, Zohydro ER (NDA 202880), was approved first and is listed in the Orange Book as having 3-year exclusivity, which will expire on October 25, 2016.²⁰⁰ Purdue's single entity extended-release hydrocodone tablet, Hysingla (NDA 206627), a 505(b)(2) NDA that did not rely on Zohydro for approval, was approved shortly after the mutual waiver agreement was announced.²⁰¹

A search of the Agency's records has not produced another instance where FDA refused to fully approve a 505(b)(2) application due to the 3-year exclusivity of another NDA on which the subsequent application did not rely. However, in instances where the Agency has considered this situation, it has applied considerations consistent with this interpretation of the scope of 3-year exclusivity. For example, on October 24, 1996, FDA approved Combivent (NDA 020291), a metered dose aerosol for inhalation and the first fixed-combination drug of albuterol sulfate and ipratropium bromide for use in patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. Because its sponsor had conducted new clinical investigations essential to its approval, Combivent was eligible for 3-year exclusivity, which expired on October 24, 1999. The scope of Combivent's exclusivity was related to the new clinical investigations that studied the fixed-combination of albuterol sulfate and ipratropium bromide for use in patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.²⁰²

¹⁹⁹ E.g., Reuters, *Zogenix and Purdue Pharma Exchange Waivers of Regulatory Exclusivity for Extended-Release Hydrocodone Products* (Oct. 31, 2014), available at <http://www.reuters.com/article/2014/10/31/idUSnGNXtRGsC+ed+GNW20141031> (last accessed on Jan. 11, 2015). The companies, Zogenix, Inc. and Purdue Pharma L.P., announced their decision the day after the PDUFA goal date for Hysingla had passed.

²⁰⁰ The Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202880&Product_No=006&table1=OB_Rx.

²⁰¹ CBS, *FDA approves new, hard-to-abuse hydrocodone painkiller* (Nov. 20, 2014), available at <http://www.cbsnews.com/news/fda-approves-new-hard-to-abuse-hydrocodone-painkiller/> (last accessed on Jan. 11, 2015).

²⁰² Combivent Exclusivity Summary and Approved Product Labeling for Combivent (NDA 020291) (approved Oct. 24, 1996); see also Combivent Division Director Review (Oct. 3, 1996).

On May 27, 1999, FDA considered the approvability of Duoneb (NDA 020950), which was a solution for inhalation and also a fixed-combination of albuterol sulfate and ipratropium bromide for the same indication as Combivent. Duoneb had been submitted as a 505(b)(2) application that did not rely on Combivent.²⁰³ FDA noted that the Duoneb applicant conducted its own clinical trials to establish the safety and effectiveness of the fixed-combination, but FDA concluded that it likely would not be able to fully approve Duoneb's 505(b)(2) NDA at that time due to Combivent's existing exclusivity, which was due to expire on October 24, 1999.²⁰⁴

Similarly, in May 2010, when considering whether Cipher's tramadol hydrochloride ER capsules (NDA 022370) were blocked by exclusivity for Labopharm's Ryzolt (tramadol hydrochloride ER tablets) (NDA 021745), FDA noted that Cipher's product had the potential to be blocked if it was "seeking the same conditions of approval as are protected for Ryzolt."²⁰⁵ FDA made this observation even though Cipher's product differed in dosage form from the Labopharm product and Cipher's product did not rely on Ryzolt for approval. Although the Agency ultimately concluded that Labopharm's clinical studies were essential only to approval of the specific titration schedule approved for Ryzolt and that Cipher's product (which had a different non-protected titration schedule previously approved for another tramadol product) was not blocked, the Agency's analysis contemplated that Cipher's product would have been blocked had it sought approval for the exclusivity-protected titration schedule. FDA further noted that although Cipher's tramadol product was an ER capsule and Ryzolt was an ER tablet, "[a] difference in dosage form alone for a proposed product would not necessarily be a basis for concluding that a previous applicant's exclusivity does not delay approval."²⁰⁶

In the case of colchicine products too, FDA acknowledged that exclusivity for a drug that a 505(b)(2) NDA did not reference, nonetheless had the potential to block approval of that 505(b)(2) NDA. In that case, Mutual (the sponsor for Colcris colchicine tablets) had exclusivity for use of colchicine for acute gout flares that was due to expire on July 30, 2012. Mutual submitted a citizen petition requesting that FDA "refrain from filing or approving any . . . 505(b)(2) application for a single-ingredient oral colchicine product that does not reference Colcris" and further requested that FDA "[r]efrain from approving any . . . 505(b)(2) application for a single-ingredient oral colchicine product until the existing 3-year exclusivity awarded to

²⁰³ Duoneb (NDA 020950) Division Director's Memorandum (May 27, 1999) at 1, Administrative Documents, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20950_DuoNeb_admindocs.pdf.

²⁰⁴ Id. at 2. FDA also concluded that outstanding significant chemistry, manufacturing and controls issues precluded approval of Duoneb's application. By the time all outstanding issues were addressed and FDA was able to approve the application for Duoneb on March 21, 2001, Combivent's exclusivity had expired. FDA reached this conclusion despite the fact that Duoneb differed from Combivent in its dosage form and dosing regimen.

²⁰⁵ See Memorandum from Division of Anesthesia and Analgesia Products to Office of Generic Drugs re: Scope of Three-year Exclusivity Granted to Ryzolt (tramadol hydrochloride) extended release tablets (May 7, 2010) at 3.

²⁰⁶ See id. at 6, fn. 9.

Colcrys expires on July 30, 2012.”²⁰⁷ FDA denied Mutual’s request that “any 505(b)(2) application for a single-ingredient oral colchicine product must necessarily cite Colcrys as its listed drug, irrespective of whether the proposed product shares the same strength, pharmacokinetic (PK) profile, or other characteristics such as dosage form or conditions of use.”²⁰⁸ Nonetheless, the Agency found that “the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares must inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use, and thus *the approval of such a product must await expiration of Colcry’s 3-year exclusivity for acute gout flares . . .*”²⁰⁹ Thus the Agency recognized that although a 505(b)(2) NDA that was not a duplicate of Colcrys tablets need not reference Colcrys as a listed drug, it might nonetheless be subject to exclusivity for Colcrys and would have to await expiration of that exclusivity before it could obtain approval.

These examples demonstrate that, although it does not arise often, when FDA is aware of exclusivity for a product on which a 505(b)(2) NDA did not rely, FDA has continued to interpret the 3-year exclusivity provisions in a manner consistent with the interpretation set forth in the Agency’s preamble statements and consistent with its position set forth here.

The Agency has carefully evaluated the precedents cited by Veloxis.²¹⁰ As discussed below, we disagree that the only plausible explanation for approval of the products cited is that FDA interprets 3-year exclusivity such that it blocks only a 505(b)(2) NDA that relies on an exclusivity-protected drug.²¹¹

²⁰⁷ FDA Response to GL Veron (Docket No. FDA-2010-P-0614) (May 25, 2011) at 1-2.

²⁰⁸ *Id.* at 3.

²⁰⁹ *Id.* (emphasis added).

²¹⁰ Although the Veloxis letter cites only methylphenidate and testosterone as precedent for approving Envarsus XR, in its Exhibit 4, which includes slides from a presentation to FDA on November 6, 2014, Veloxis identified two additional examples: somatropin recombinant injections and timolol ophthalmic solution drops as support for its argument that a subsequent 505(b)(2) application is not blocked by 3-year exclusivity in the absence of reliance. The Agency reviewed the administrative records for the somatropin and timolol NDAs cited by Veloxis and found that in each case, approval of the later-in-time 505(b)(2) NDA could be explained by a closer examination of the scope of the clinical studies that earned exclusivity for the previously approved product. For example, the two somatropin products in the somatropin example did not share the same indication and since the new clinical studies for the first product which earned exclusivity established the safety and effectiveness of the product for the indication, the second one was not blocked. The timolol ophthalmic solution example could also be explained by a narrow scope of exclusivity (i.e., once-daily dosing) that did not block the approval of the subsequent NDA which was administered twice daily. Thus, these examples do not demonstrate that FDA interprets 3-year exclusivity such that it blocks only a 505(b)(2) NDA that relies on the exclusivity-protected NDA. Because Veloxis focuses on methylphenidate and testosterone, the remainder of this discussion likewise focuses on those products.

²¹¹ FDA makes exclusivity decisions in the context of individual applications because such decisions are fact- and circumstance-specific. Therefore, we have closely reviewed the records of the clinical studies essential to approval that gave rise to exclusivity and the basis for approval of a subsequently-approved 505(b)(2) NDA. We have reviewed the examples that Veloxis has cited, and we have not found a stand-alone document that summarizes

A. Methylphenidate

One of the precedents cited by Veloxis is the Agency's approval of a 505(b)(2) NDA for Metadate CD (ER methylphenidate capsules) (NDA 021259) on April 3, 2001, during the 3-year exclusivity period of another ER methylphenidate product, Concerta (ER methylphenidate tablets) (NDA 021121), that was approved on August 1, 2000.²¹² Veloxis claims that "[l]ike Envarsus XR and Astagraf XL, Concerta and Metadate CD are approved to treat the same indication and both are once-daily extended-release formulations of the same active ingredient," but "[a]lso like the current situation, Concerta and Metadate CD are approved in different dosage forms (i.e., extended-release tablets and extended-release capsules, respectively)."²¹³ Veloxis, thus, concludes that "[a]s a result of this critical difference, Concerta's exclusivity did not block approval of Metadate CD."²¹⁴ In addition, Veloxis asserts that this example supports its view that a later-in-time 505(b)(2) NDA is not blocked if it does not rely on the NDA with exclusivity.²¹⁵

The administrative records for the approvals of Concerta and Metadate CD do not, however, support Veloxis' conclusions. There is no evidence that FDA decided that Metadate CD was not blocked because it was a capsule rather than a tablet or because it did not rely on Concerta. Veloxis has not cited any evidence in the administrative record for Concerta that supports the notion that the ER tablet dosage form of Concerta was a condition of approval for which clinical studies were necessary, and that the exclusivity protected Concerta only against another ER tablet. In fact, given the prior approvals of Ritalin (an IR methylphenidate tablet) and Ritalin SR (an ER methylphenidate tablet), Concerta would not have obtained exclusivity for being a methylphenidate tablet or an ER methylphenidate tablet.²¹⁶ It follows that the scope of Concerta's exclusivity was narrower than the scope of Astagraf XL's exclusivity here because Astagraf XL was the first extended-release tacrolimus product and the first with once-daily dosing. It would be reasonable to conclude that Concerta's condition of approval for which

FDA's reasoning why the particular drugs reviewed were or were not blocked. In addition, prior to the recent establishment of the CDER Exclusivity Board, there was no formal mechanism for vetting exclusivity decisions and their implications for approval of other applications. Many of the methylphenidate and testosterone products cited by Veloxis were approved more than a decade ago and all were approved prior to the establishment of the CDER Exclusivity Board so we have drawn reasonable conclusions based on the available records.

²¹² Veloxis Submission at 15.

²¹³ *Id.*

²¹⁴ *Id.*

²¹⁵ *Id.* at 15-16.

²¹⁶ FDA first approved methylphenidate on December 5, 1955, in an IR tablet form (Ritalin NDA 010187). Ritalin SR (NDA 018029), a sustained-release form of methylphenidate, was approved on March 30, 1982. Ritalin SR was designed to exert an effect equivalent to two 10 mg tablets of IR methylphenidate given 4 hours apart.

clinical investigations were essential was the specific PK profile that results from its proprietary drug release mechanism that has both specific IR and ER release components.²¹⁷

There is no explicit contemporaneous documentation in the record for why FDA determined that the subsequent methylphenidate product, Metadate CD, was not blocked by Concerta's exclusivity. However, Metadate CD had a different PK profile that was associated with a different drug release mechanism, and a clinical study that was essential for the approval of Metadate CD was designed to demonstrate the safety and efficacy of the specific PK profile for Metadate CD. Consistent with the views stated here, it is reasonable to conclude that Concerta's exclusivity extended only to the specific PK profile associated with its formulation and drug release mechanism, and thus would not block the approval of Metadate CD.

B. Testosterone

Veloxis refers to FDA's approvals of certain NDAs for testosterone transdermal products during the 3-year exclusivity period of previously approved testosterone transdermal products and speculates that the NDAs were not blocked "presumably" because the applicants did not rely on the previously approved testosterone transdermal products with exclusivity.²¹⁸ The Agency disagrees that the only reasonable explanation for these approvals is that FDA interprets 3-year exclusivity such that it blocks only a 505(b)(2) NDA that relies on the exclusivity-protected product. The Agency's review shows that it has not abandoned its interpretation that a 505(b)(2) NDA can be blocked by the exclusivity of a previously approved product regardless of reliance on that product.

As a predicate to analyzing Veloxis' arguments, it is important to summarize some background regarding the approval of testosterone products. Testosterone was first approved in 1941 in the form of methyltestosterone (NDA 003158), and generally has been indicated as a replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Prior to February 2000, i.e., before approval of the transdermal testosterone products cited by Veloxis, testosterone had been approved for this use in the form of intramuscular injectables, oral tablets, and transdermal patches.²¹⁹ Efficacy of testosterone products has generally been established by demonstrating serum testosterone levels within the

²¹⁷ See Concerta (NDA 021121) Exclusivity Checklist ("New PK profile of formulation requires a clinical study."), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-121_Concerta_admincorres.pdf. Unlike the methylphenidate products, which have a narrow scope of exclusivity related to the particular PK profile because an ER methylphenidate had already been approved by FDA, Astagraf XL had a broader scope of exclusivity because it was the first approved NDA for an ER tacrolimus product and Astellas conducted clinical studies that were necessary for the approval of its ER dosage form and once-daily dosing regimen for use in *de novo* kidney transplant patients.

²¹⁸ Veloxis Submission at 15-16; letter from Veloxis to DTOP (Dec. 12, 2014).

²¹⁹ AndroGel 1% Medical Review dated February 25, 2000 at 7.

normal ranges. Testosterone products have also been associated with certain safety issues, including the risk of secondary exposure to women and children for topically applied testosterone gels.²²⁰

Based on FDA's review of the record, FDA has prepared a table attached as an Appendix that includes for the relevant testosterone transdermal products the following information: the trade name, NDA number, date of approval, expiration date of exclusivity, exclusivity code, active ingredient, indication, dosage form, strength, application site, and summary description of the new clinical investigations essential to approval. This table provides an overview of the testosterone products cited by Veloxis to aid in understanding how these products relate to each other and the nature of the new clinical investigations that were essential to approval. Given the number of products and the extensive record for each NDA, the table is a summary only and is not intended to be comprehensive.

In its initial submission, Veloxis cites as precedent for its view the approvals of NDAs for Axiron (NDA 022504), Fortesta (NDA 021463), and AndroGel 1.62% (NDA 022309).²²¹ Veloxis states that FDA approved the 505(b)(2) NDA for Fortesta notwithstanding exclusivity for the Axiron 505(b)(2) NDA, and FDA approved the 505(b)(2) NDA for AndroGel 1.62% notwithstanding exclusivity for the Axiron and Fortesta 505(b)(2) NDAs. Veloxis states that FDA did so even though Axiron, Fortesta, and AndroGel 1.62% all share active ingredients and indications; and the AndroGel 1.62% 505(b)(2) NDA was approved notwithstanding exclusivity for the Fortesta 505(b)(2) NDA even though they share the same dosage form (transdermal gel). Veloxis hypothesizes that the later-in-time approvals were permitted because they did not rely on the previously approved product(s) with exclusivity. FDA's review of the administrative records for each of these applications reveals that approval of the later-in-time 505(b)(2) NDA could be

²²⁰ For example, in 2009, FDA became aware of cases of secondary exposure of women and children to topical testosterone gel products caused by inadvertent drug transfer from adult males using the products ("risk of secondary transfer"). The risk of secondary transfer associated with testosterone gel products has been reported to cause virilization in women and children, some of which is irreversible. Signs and symptoms of secondary exposure have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. FDA addressed this risk in April 2009, by requiring safety-related labeling changes, including requiring a boxed warning cautioning about secondary exposure to testosterone, and a Medication Guide (a form of FDA-approved patient labeling) discussing these risks. In light of this information, FDA determined, in the context of ANDAs for topical testosterone gel products, that some differences in inactive ingredients, including, but not limited to, differences in penetration enhancers, trigger the need for a study to evaluate the risk of secondary transfer (or transfer potential study), as well as a hand washing study to determine whether hand washing affects the amount of residual product on the skin. See, e.g., Letter from CDER to Auxilium Pharmaceuticals, Inc.(Docket No. FDA-2009-P-0123) (Aug. 26, 2009).

²²¹ Veloxis Submission at 15-16;

explained by the scope of the clinical studies that earned exclusivity for the previously approved product.

The Fortesta and AndroGel 1.62% approvals are consistent with the Agency's interpretation of the scope of 3-year exclusivity in that the approvals would not have otherwise been blocked due to the scope of 3-year exclusivity for the respective exclusivity-protected drugs. First, FDA has not uncovered any express statements in the record stating that approval of Fortesta or AndroGel 1.62% was permitted due to the fact that the later-in-time application did not rely on the exclusivity-protected drug in its 505(b)(2) NDA, nor has Veloxis cited any such statements. Second, Veloxis fails to consider that a subsequent 505(b)(2) NDA for testosterone would not be blocked if that drug did not share any exclusivity-protected conditions of approval with a previously approved drug. Axiron's 3-year exclusivity was not, as Veloxis suggests, for the active ingredient (testosterone) or indication (i.e., replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone) as those aspects of the drug product had been previously approved in other testosterone NDAs. As a result, sharing these characteristics would not have precluded approval of the Fortesta 505(b)(2) NDA. Likewise, the approval of AndroGel 1.62% would not have been blocked by virtue of sharing these characteristics (active ingredient and indication) with Axiron and Fortesta for the same reason. Furthermore, the fact that Fortesta and AndroGel 1.62% share the same dosage form (transdermal gel) is also irrelevant as this dosage form, too, was previously approved in the AndroGel 1% NDA in February 2000 and therefore was not the basis of exclusivity for the Fortesta 505(b)(2) NDA. Therefore, the fact that Fortesta and AndroGel 1.62% share the same dosage form would not have precluded approval of AndroGel 1.62% during Fortesta's exclusivity period.

Instead, FDA's review of the record shows the approval of 505(b)(2) NDAs for Fortesta and AndroGel 1.62% can be explained by the scope of 3-year exclusivity for the exclusivity-protected product supported by the new clinical investigations essential to the approval. The sponsors of the exclusivity-protected drugs conducted new clinical investigations to demonstrate, for example, the safety and effectiveness of each unique dosage form, formulation (e.g., strength), or application site for their particular testosterone product, and these new clinical investigations determined the scope of each product's exclusivity. Thus, a subsequent 505(b)(2) NDA for testosterone would not be blocked if that drug did not share exclusivity-protected conditions of approval with a previously approved drug.

In a later submission, Veloxis asserts that FDA approved Testim notwithstanding the exclusivity for AndroGel 1%; and that the Testim NDA did not reference AndroGel 1%, nor did it rely on any clinical studies performed in connection with the approval of AndroGel 1%.²²² Based on a

²²² Letter from Veloxis to DTOP (Dec. 12, 2014) at 2.

Medical Officer's statements in the record relating to FDA's policy on the need for premarket approval site inspections, Veloxis speculates that "it would appear" that FDA concluded that the lack of reliance on AndroGel precluded the application of AndroGel's exclusivity to block final approval of Testim.²²³

Again, FDA's review has not uncovered any express statement in the record stating that approval of the Testim NDA was permitted due to the fact that it did not rely on AndroGel 1%, nor has Veloxis cited any such statements. To the extent Testim could be viewed as sharing certain characteristics with AndroGel 1% for which clinical investigations were essential and to the extent those characteristics could be viewed as exclusivity-protected conditions of approval, it is possible that Testim was approved prematurely four months before expiration of the 3-year exclusivity for AndroGel 1%. However, this single approval does not establish that FDA has interpreted the statute to require reliance for a subsequent 505(b)(2) application for the exclusivity-protected conditions of approval to be blocked. Instead, some aspects of the administrative record indicate the Testim NDA had been reclassified by the Agency as a 505(b)(1) NDA before expiration of exclusivity for AndroGel 1%.²²⁴ Regardless of whether the application was correctly reclassified, this issue is significant because if FDA had believed that Testim was a 505(b)(1) NDA, its approval would not have been blocked by 3-year exclusivity of another drug. Finally, given that the Testim approval appears to be an outlier, this example should not be viewed as precedent that binds the Agency.

V. CONCLUSION

Based on a thorough review of submissions by Veloxis and Astellas, including the studies conducted in support of their applications, the relevant provisions of the FD&C Act and FDA regulations, and Agency precedent, FDA concludes that Astagraf XL obtained 3-year exclusivity for once-daily ER tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients and Envarsus XR is blocked from obtaining approval for that condition of approval until Astagraf XL's exclusivity expires on July 19, 2016. However, if appropriate labeling is submitted to the Agency, Envarsus XR may be approved now for its once-daily, ER dosage form of tacrolimus for conversion of stable kidney transplant patients from tacrolimus IR to tacrolimus

²²³ Id. (citing Medical Officer Review, "The decision to not have any site inspections was a result of the new draft policy from DSI which states that new NDAs do not automatically require clinical site inspections. Testim is not an NME, not first in its class, not intended for a novel population, not used for a new diagnostic category, and not delivered via new route of administration. Site inspections were not indicated under these circumstances." (italics omitted)).

²²⁴ See, e.g., Testim (NDA 021454) Exclusivity Determination Checklist (stating that the NDA had been reclassified from a 505(b)(2) to a 505(b)(1)). Testim Supervisory Pharmacologist Memo to the NDA (Jan. 21, 2003) (stating that "[t]he literature cited by Auxilium did not contain investigations necessary to approval of the NDA"); Letter from CDER to Auxilium (Jan. 17, 2003) (stating that "[a]lthough the NDA was submitted as a 505(b)(2) application, it was determined that it was submitted under 505(b)(1)").

ER. In approximately eighteen months, after the expiration of exclusivity for Astagraf XL, Envarsus XR can be approved for the prophylaxis of organ rejection in *de novo* and conversion kidney transplant patients.

APPENDIX

Drug Name/ NDA #	Approval/Ex clusivity Expiration Date/Code	Active Ingredient/ Indication	Dosage Form, Strength, Application Site	New Clinical Investigations Essential to Approval ^a
AndroGel 1% NDA 021015	02/28/2000 2/28/2003 NDF	Testosterone Indicated for replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone	<ul style="list-style-type: none"> • Transdermal gel • 25 mg/2.5 g packet • 50 mg/5 g packet • Transdermal gel- metered dose pump • 12.5 mg/1.25 g actuation (approved on 09/23/2003 in supplement 10) • shoulders, upper arms, and/or abdomen 	UMD-96-017 Randomized, active-controlled, parallel- group trial that compared two doses of AndroGel with a testosterone patch (Androderm). Three treatment arms: 5gm of AndroGel daily (containing 50 mg of testosterone), 10 gm of AndroGel daily (containing 100 mg of testosterone), and two Androderm patches daily (containing total of 5 mg absorbed testosterone). Primary endpoint was proportion of patients in each treatment group with both C_{avg} and C_{min} values for serum testosterone within the normal range (298-1043 ng/dl) on Day 30. ^b
Testim [1%] NDA 021454	10/31/2002 10/31/2005 NP	Same	<ul style="list-style-type: none"> • Transdermal gel • 50 mg/5 g packet • Shoulders and upper arms 	AUX-TG-201-02 ^c Randomized, active-and placebo- controlled, four arm, parallel-group, multicenter trials in adult males with morning serum testosterone levels \leq 300 ng/dl. Four treatment arms were Testim 50 and 100 mg gel, matching placebo gel, and Androderm transdermal patches (2 x 1.5 mg). Primary efficacy parameter was the C_{avg} and C_{min} of serum total testosterone levels within normal range. AUX-TG-207-01 Evaluated effect of washing on testosterone levels. AUX-TG-206-00 Evaluated potential for dermal transfer of testosterone. AUX-TG-209-00 Evaluated potential for dermal transfer of testosterone. ^d
Axiron [2%] NDA 022504	11/23/2010 11/23/2013 NP	Same	<ul style="list-style-type: none"> • Transdermal solution – metered • 30 mg/1.5 mL actuation (pump is capable of dispensing 90 mL of solution in 60 metered pump actuactions) • Axillae (armpit) 	MTE08 Phase 3, open-label titration trial to evaluate the effectiveness and safety of a dermal application of Axiron (testosterone transdermal solution) in hypogonadal men. Initial dose 60 mg to each axilla once daily. Primary efficacy endpoint was C_{avg} for testosterone in defined normal range. ^e

Drug Name/ NDA #	Approval/Exclusivity Expiration Date/Code	Active Ingredient/ Indication	Dosage Form, Strength, Application Site	New Clinical Investigations Essential to Approval ^a
Fortesta [2%] NDA 021463	12/29/2010 12/29/2013 NP	Same	<ul style="list-style-type: none"> • Transdermal gel – metered • 10 mg/0.5 g actuation (60 g canisters, with 120 metered pump actuations) • Front and inner thighs 	FOR01C Phase 3, open-label, non-comparative trial in hypogonadal males. Fortesta (testosterone gel) was applied to thighs at starting dose of 40 mg once daily. Primary efficacy endpoint was serum total testosterone C _{avg} within physiological range. ^f
AndroGel 1.62% NDA 022309	04/29/2011 4/29/2014 NP	Same	<ul style="list-style-type: none"> • Transdermal gel – 1-metered • 20.25 mg/1.25 g actuation (pump can dispense 60 actuations) • Transdermal gel • 20.25 mg/1.25 g packet • 40.5 mg/2.5 g packet • shoulders and upper arms 	S176.3.104 Phase 3, randomized, double-blind, placebo-controlled study in hypogonadal males. AndroGel 1.62% (testosterone gel) was applied at starting dose of 2.5g of testosterone which could, over any seven day period, be rotated between the upper arms/shoulders or abdomen provided correct application technique (arms/shoulder only application) occurred during PK visits. Primary efficacy endpoint was serum testosterone C _{avg} within normal serum testosterone range. Additional 6-month open-label extension. ^g

^a Refers to new clinical investigations listed on Exclusivity Summary.

^b AndroGel 1% Medical Officer Review (February 15, 2000) at 4, 9.

^c Exclusivity Summary lists AUX-TG-201-02. The Testim NDA reviews refer to AUX-TG-202.01R or Study AUX-TG-202 (Study described in text). The NDA reviews also refer to AUX-TG-201.01 or Study AUX-201 (single-dose pharmacokinetic, crossover design with AndroGel active comparator). The Exclusivity Summary is likely referring to Study AUX-TG-202.

^d Testim Medical Officer's Clinical Review (October 30, 2002) at 5, 7, 9, 11.

^e Axiron Deputy Division Director Summary Review for Regulatory Action (November 23, 2010) at 5, 6, 7, 12.

^f Fortesta Deputy Division Director Summary Review for Regulatory Action (December 29, 2010) at 7.

^g AndroGel 1.62% Summary Review for Regulatory Action (April 29, 2011) at 9-10.

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/s/

LOIS A ALMOZA

01/12/2015

Envarsus XR Decisional Memorandum archived on behalf of the Exclusivity Board

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 30, 2014

FROM: Renata Albrecht, M.D.
Division of Transplant and Ophthalmology Products (DTOP)

J.S. Jay Sitlani, J.D., Senior Regulatory Counsel
Office of Regulatory Policy (*Acting in his Capacity as Chair of the CDER
Exclusivity Board*)

SUBJECT: Tentative Approval of NDA 206406 for Envarsus XR (tacrolimus extended-release tablets)

TO: NDA 206406 for Envarsus XR (tacrolimus extended-release tablets)

OVERVIEW

This memorandum addresses the decision by the Food and Drug Administration (FDA or the Agency) to tentatively approve Veloxis's new drug application (NDA) 206406 for Envarsus XR (tacrolimus extended-release tablets), in light of the existing 3-year exclusivity for Astagraf XL, a previously approved extended-release tacrolimus product. That exclusivity expires on July 19, 2016. Upon approving Astagraf XL, DTOP determined that it was eligible for exclusivity for new clinical investigations that were essential to its approval. In addition, after consulting with the Exclusivity Board within the Center for Drug Evaluation and Research (CDER), and based on the Exclusivity Board's determination that the conditions of approval for which Astagraf XL currently has exclusivity are shared by Envarsus XR, DTOP may only tentatively approve Envarsus XR at this time.

The Exclusivity Board has, however, become aware that an analysis under section 505(v)(3)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which applies to "Old Antibiotics"¹ such as tacrolimus, and requires an assessment of whether the NDA was approved for a new "condition of use," was not conducted as part of Astagraf XL's exclusivity determination. At

¹ Old Antibiotics are those for which a first application was received by the Agency prior to November 21, 1997, the date of enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA repealed section 507 of the FD&C Act under which antibiotics were approved, and provided that drugs approved under section 507 would thereafter be considered to have been reviewed and approved under section 505. Antibiotics for which applications were received after FDAMA was enacted could avail of 3-year exclusivity (among other Hatch-Waxman provisions), but Old Antibiotics were excluded from such incentives until the enactment of the QI Program Supplemental Funding Act of 2008 (the QI Act, also entitled "Incentives for the Development of, and Access to, Certain Antibiotics"). The QI Act amended the FD&C Act to create section 505(v) that provided Old Antibiotics an opportunity for 3-year exclusivity, subject, however, to certain statutory limitations.

this time, the Exclusivity Board is in the process of conducting such an assessment. Upon the conclusion of the Exclusivity Board's assessment, should the Agency determine that Astagraf XL was in fact not eligible for 3 years of exclusivity under the limitations described in section 505(v)(3)(B) of the FD&C Act for Old Antibiotics, and that the existing 3-year exclusivity for Astagraf XL was recognized in error, the Agency intends to make the approval of Envarsus XR effective at that time.

BACKGROUND

Tacrolimus, a calcineurin inhibitor, indicated for prophylaxis of organ rejection in liver, kidney and heart transplant recipients was first approved by FDA in 1994 under the trade name Prograf. Developed by Astellas Pharma US, Inc. (Astellas), Prograf is an immediate-release tacrolimus product that is dosed twice daily (BID) in capsule form. On July 19, 2013, FDA approved NDA 204096 for Astagraf XL, an extended-release tacrolimus product that is formulated as a capsule and intended to be dosed once-daily (QD) for the same indications as for Prograf. The Agency recognized 3-year exclusivity for Astagraf XL under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act, notated in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) as new dosage form (NDF) exclusivity. These statutory provisions bar FDA from approving a drug with the same "conditions of approval" as a drug product that has 3-year exclusivity until that exclusivity expires. DTOP found that the Astagraf XL NDA met the statutory and regulatory conditions for 3-year exclusivity because it was supported by new clinical investigations (that were not bioavailability studies) conducted or sponsored by Astellas that were essential to approval of the NDA (see Exclusivity Summary for Astagraf XL).² The exclusivity-supporting clinical investigations were two Phase 3 controlled clinical trials of 12-month duration (Study 158 and 12-03), both of which demonstrated that Astagraf XL was non-inferior to Prograf on the endpoint of biopsy-proven acute rejection (BPAR), when used with mycophenolate mofetil (MMF) and corticosteroids, in a regimen with or without basiliximab induction.

On September 12, 2014, Astellas submitted a letter to DTOP requesting that the Agency clarify the types of products that would be blocked from approval during Astagraf XL's 3-year exclusivity period. DTOP referred this letter to the Exclusivity Board. Upon review of the letter and the administrative record for Astagraf XL, the Exclusivity Board determined that that the exclusivity analysis had not included an inquiry on whether Astagraf was eligible for 3-year exclusivity in light of the limitations imposed by section 505(v) of the FD&C Act for Old Antibiotics such as tacrolimus. Specifically, section 505(v)(3)(B) of the FD&C Act prohibits FDA from granting 3-year exclusivity for Old Antibiotics for "any condition of use for which the [Old Antibiotic] ... was approved before the date of the enactment [of the QI Act]," i.e., October 8, 2008.³

On October 27, 2014, FDA sent Veloxis an information request, in which the Agency sought Veloxis's views on whether Envarsus XR shared Astagraf XL's exclusivity –protected

² NDA 204096, Exclusivity Summary.

³ Three-year exclusivity is thus available for an application of an Old Antibiotic if it (1) otherwise meets the requirements of sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act, and (2) is not for a "condition of use" approved for the Old Antibiotic before October 8, 2008.

conditions of approval. On October 28, 2014, Veloxis submitted a response to FDA in which it indicated that the scope of Astagraf XL's exclusivity does not block final approval of Envarsus XR during Astagraf XL's exclusivity period, because: (1) the reference listed drug is not Astagraf XL, (2) Veloxis does not rely on Astagraf XL's data, and (3) Envarsus XR differs from Astagraf XL in its dosage form, strengths, dosing regimen, and pharmacokinetics.

DISCUSSION

The Exclusivity Board is currently considering whether FDA properly recognized 3-year exclusivity for Astagraf XL notwithstanding the limitations on such exclusivity for Old Antibiotics established under section 505(v) of the FD&C Act. The Exclusivity Board has determined that Astagraf XL otherwise met the requirements of sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and the Agency's implementing regulations in 21 CFR Part 314.108.

As noted above, for the approval of NDA 204096, Astellas submitted two Phase 3 controlled clinical trials of 12-month duration (Study 158 and 12-03), both of which demonstrated that Astagraf XL's extended-release capsules, when dosed once-daily, are non-inferior to Prograf's immediate-release capsules, when dosed twice-daily. Studies 158 and 12-03 were "new" clinical studies conducted by Astellas. Consequently, the exclusivity for Astagraf covers its extended-release dosage form and its once-daily dosing regimen. Because Envarsus XR is also an extended-release dosage form for a once-daily dosing regimen, it shares Astagraf XL's exclusivity-protected conditions of approval. Therefore, FDA is currently barred from making Envarsus XR's approval effective.

The Exclusivity Board, however, continues to assess whether Astagraf XL's conditions of approval described above and determined to be eligible for 3-year exclusivity, met the higher hurdle for Old Antibiotics under section 505(v) of the FD&C Act.⁴

CONCLUSION

For the reasons described above, the Agency has decided to tentatively approve Envarsus at this time based on the existing exclusivity for Astagraf, but will continue to evaluate whether that exclusivity was properly granted under 505(v) of the FD&C Act. If the Agency determines that the exclusivity was improperly granted, the eligibility of Envarsus XR for a full and final approval will be considered at that time.

⁴ Upon review of the statute and the available legislative history, the Agency previously concluded that there is a higher hurdle for exclusivity for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity, and that only significant new uses (as opposed to a refinement of an existing condition of use) for an Old Antibiotic would meet the standard for exclusivity under section 505(v) of the FD&C Act. Letter regarding 3-year exclusivity determination for Vancocin from Janet Woodcock, Director, CDER, to Thomas Doyle, Docket No. FDA-2006-P-0007 at 69-70 (April 9, 2012).

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/s/

LOIS A ALMOZA
10/30/2014

RENATA ALBRECHT
10/30/2014

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Ozlem Belen MD, MPH and Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Cross-Discipline Team Leader Review/ Division Director Summary Review
NDA Number	NDA 206406
Related IND	IND 75250
Applicant Name	Veloxis Pharmaceuticals, Inc
Date of Submission	December 28, 2013
Date of Receipt	December 30, 2013
PDUFA Goal Date	October 30, 2014
Proprietary Name / Established (USAN) Name	Envarsus XR tacrolimus extended-release tablets
Formulation Strength	Oral tablets 0.75, 1, and 4 mg
Proposed Indication(s)	Prophylaxis of organ rejection in kidney transplant patients
Action for Application	<i>Tentative Approval</i>

NDA 206406, Envarsus XR (tacrolimus extended-release tablets)
 Prophylaxis of organ rejection in kidney transplant patients
 Summary Review

Material Reviewed/Consulted Action package and the following	Names of discipline reviewers
Medical Officer Review	Huseyin E Velidedeoglu, Ozlem Belen, Renata Albrecht 9/25/14
CDTL Review	Ozlem Belen, Renata Albrecht 10/15/2014
Statistical Review	Hongling Zhou, Yan Wang 9/24/2014
Pharmacology/Toxicology Review	Aaron Ruhland, Lori Kotch 9/24/2014, 10/30/2014 Lori Kotch 10/29/2014
Immunology Review	Shukal Bala, Renata Albrecht 7/24/2014
Clinical Pharmacology Review	Gerlie Gieser, Jeffry Florian, Yaning Wang, Phil Colangelo 9/25/2014, 10/16/2014
Product Quality Manufacturing Review, PMCs	Mark Seggel, Celia Cruz 9/25/2014, 10/29/2014 Mark Seggel, Celia Cruz 10/24/2014
Biopharmaceutics Review	Banu S Zolnik, Angelica Dorantes 9/25/2014, 10/16/2014
Product Quality Microbiology	Bryan S Riley, Stephen E Langille 1/13/2014
CDER/OC/Facilities Inspection	Acceptable (see CMC review 3/13/2014)
OSI/DGCPC	Roy A Blay, Janice K Pohlman, Kassa Ayalew 9/25/2014
OSE/DMEPA Proprietary Name Review Letter	Rachna Kapoor, Yelena Maslov, Lubna A Merchant 4/15/2014 Kellie Taylor 4/18/2014
OSE/DMEPA Labeling Review	Rachna Kapoor, Yelena Maslov, Lubna Merchant 8/26/2014 Rachna Kapoor, Yelena Maslov 10/2/2014 , 10/7/2014
OPDP/DPDP (formerly DDMAC)	Christine Corser 10/9/2014
(b) (4)	Christine Corser 10/15/2014
OMP/DMPP MedGuide Review	Shawna Hutchins, Christine Corser, Melissa Hulett 10/8/2014
Project Management Review	Lois Almoza, Diana Willard 3/12/2014
Orphan Designation	Gayatri Rao 12/20/2013
Office of Regulatory Policy	Jay Sitlani, Renata Albrecht 10/30/2014

CDTL=Cross-Discipline Team Leader
 OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI))
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
 (b) (4)
 OC = Office of Compliance
 PMCs = post-marketing commitments

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1. Summary and Recommendations

Tacrolimus is a calcineurin inhibitor. It was approved in 1994 under the trade name Prograf (tacrolimus capsules), and is currently indicated for prophylaxis of organ rejection in liver, kidney and heart transplant recipients. Prograf is an immediate release formulation and is given twice daily. Generic versions of Prograf are now approved. Tacrolimus as an extended release capsule formulation; dosed once-daily was approved in 2013 under the name Astagraf XL (tacrolimus extended-release capsules) for the indication of prophylaxis of organ rejection in kidney transplant recipients, and granted 3-year marketing exclusivity. These two products are manufactured by Astellas.

Veloxis has developed an extended release tablet formulation which is dosed once-daily, and will be marketed under the trade name Envarsus XR; the trade name has been found to be acceptable by DMEPA.

Veloxis submitted results of multiple Phase 1, Phase 2 and Phase 3 studies. The results of Study 2017 and Study 3002 in de novo kidney transplant recipients and the results of Study 3001 in kidney transplant recipients converted from Prograf to Envarsus XR provide substantial evidence of safety and efficacy to support approval, for the following use:

1 INDICATIONS AND USAGE:

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants.

Limitations of Use

ENVARSUS XR extended-release tablets are not interchangeable or substitutable with other tacrolimus products [see *Warnings and Precautions (5.3)*].

(b) (4)

(b) (4) Three strengths of Envarsus XR capsules will be marketed: of 0.75 mg, 1 mg and 4 mg.

The overall safety profile for Envarsus XR was not significantly different from Prograf in the Phase 3 studies. (b) (4)

(b) (4) This includes information that when Envarsus XR (or immediate release tacrolimus) is coadministered with mycophenolate products, exposure to MPA is higher than with cyclosporine coadministration because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. (b) (4) monitor for MPA associated adverse events and reduce the dose of concomitantly administered mycophenolic acid products, if needed.

Facility inspections are acceptable, clinical site inspections recommend the data are considered reliable, labeling has been finalized, and several PMCs have been agreed-to by the applicant. All review disciplines have recommended that the application be approved and labeling is acceptable.

Several issues were raised by this application:

- Medication Errors during dispensing and administration between immediate-release formulation and extended-release formulation:

The Astellas extended release formulation (Astagraf XL) has been marketed under the name Advagraf in Europe since 2007 and as Graceptor in Japan. During the initial marketing, medication errors were reported when the products were inadvertently interchanged during dispensing or when patients took the wrong drug/dose. The information regarding these events was reviewed in detail by DMEPA, the corrective measures implemented in Europe examined, and multiple strategies to minimize medication errors introduced, including distinct shape and sizes of bottles, different colors for capsules, a warning in the product labeling, and plans to issue letters to health care providers informing them of the difference in the formulations and presentations. The biggest medication error concern related to Envarsus XR tablets is the potential confusion with Prograf and Astagraf XL due to overlap in 1 mg strength. In order to mitigate this potential error, Veloxis Pharmaceuticals proposed to differentiate this formulation of tacrolimus from Prograf and Astagraf XL by the following features:

- Unique proprietary name (i.e., Envarsus XR);
- Differentiating the dosage form by manufacturing the product as extended-release tablets versus Prograf, generic and Astagraf XL capsules;
- Use of the frequency of administration statement “Once daily” on the container label and carton labeling;
- Use of different color schemes to highlight the strengths of Envarsus XR;
- Including a warning statement in Envarsus XR’s prescribing information regarding risk of medication errors with unintentional substitution of Prograf with Astagraf XL;

- Including a labeling statement in Envarsus XR’s prescribing information that it is not interchangeable for, or substitutable with, tacrolimus immediate-release formulations or other extended-release formulations without a physician;
- Including a statement in Envarsus XR’s prescribing information and medication guide for the patient to inspect the Envarsus XR medication when it is refilled and make sure the tablets look the same before taking it;
- Including a statement in Envarsus XR’s prescribing information about conversion from tacrolimus immediate-release formulations to Envarsus XR:

(b) (4)

These medication error reducing strategies were found to be acceptable by DMEPA given the fact omitting the 1 mg strength is not an option. These strategies were used for Astagraf XL in the US and European Union and to date medication errors related to confusion between Astagraf XL and Prograf have been identified. DMEPA recommended that Veloxis employ strategies consistent with the Astagraf XL program, and recommended Veloxis Pharmaceuticals also develop a Dear Pharmacist Letter and Dear Professional Society Letter (b) (4) to ensure further communication and reinforce the information that the three formulations are different and are not interchangeable and warn of the potential for confusion between these products.

- Envarsus XR is a submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act, and relies on Prograf NDA 50708 for non-clinical information.
- Veloxis conducted clinical studies that are required for approval (b) (4) for Envarsus XR. (See Section 2.2)
- Envarsus XR was granted orphan designation for the indication and Veloxis is requesting orphan exclusivity. (See Section 2.3)
- Astagraf XL has 3- years marketing exclusivity; based on the memorandum from the Office of Regulatory Policy/Exclusivity Board, the exclusivity listed in the Approved Drug Products with Therapeutic Equivalence Evaluations means that Envarsus XR can be given *Tentative Approval* (TA) at this time.

1.1 Deficiencies

None

1.2 Post-Marketing Studies

Veloxis has agreed to a number of post-marketing commitments summarized in Section 13.3. These commitments will be reassessed at the time the application is eligible for full approval.

1.3 Other Issues

See Section 2 regarding exclusivity and related issues.

2. Background and Regulatory Issues

Kidney transplantation is the generally-preferred treatment for end-stage kidney disease. The other available management is dialysis, however, studies have shown that survival after kidney transplantation is improved compared to survival while on dialysis. Because the transplanted kidney is an allograft, patients need to receive chronic immunosuppressive treatment (drugs or biologics) to prevent the recipient's immune system from rejecting the kidney. At present, there is no treatment that can reliably induce a recipient's tolerance for the allograft; therefore, patients with kidney transplants need chronic immunosuppression.

There are a number of approved immunosuppressants available, including calcineurin inhibitors (cyclosporine or tacrolimus), mammalian target-of-rapamycin inhibitors (sirolimus or everolimus), azathioprine, mycophenolate mofetil, mycophenolic acid, therapeutic proteins, antibodies, and corticosteroids. An extended-release formulation of tacrolimus was approved in 2013 as Astagraf XL (tacrolimus extended-release capsules) for once-daily dosing.

2.1 Regulatory History

Envarsus XR, developed under the name LCP-Tacro, was submitted under IND 75250 on May 30, 2006 and a pre-IND meeting was held on August 2, 2006 to discuss the development of this extended release formulation of tacrolimus, including the plan to submit this as a 505(b)(2) application.

The end of Phase 2 meeting was held May 20, 2008, during which results from Study 2011 in stable kidney patients were summarized and further development discussed. FDA requested information on de novo transplant patients, therefore a protocol for Phase 2 Study 2017 in de novo kidney transplant patients was submitted August 13, 2008 (b) (4)

Over the subsequent months, the Phase 3 protocols for Studies 3002 (de novo) and 3001 (conversion) were discussed. The main topics included blinding, the choice of a control regimen, and justification of the non-inferiority margin. FDA approved the use of Prograf with MMF on May 19, 2009; the sponsor chose to use this regimen in the control arm.

A second end-of-phase 2 meeting was held February 16, 2010 during which various new dosage strengths of LCP-Tacro were proposed for evaluation as a strategy to avoid medication errors, and the NI margins were discussed. For Study 3001, the applicant proposed a (b) (4) NI margin but FDA did not accept this. FDA noted that the information provided in the briefing package, using only the acute rejection rates, would support a margin no larger than (b) (4). For Study 3002, there was discussion that a 10% NI margin may be acceptable, if a justification using the appropriate putative placebo were provided. The initial starting dose of 0.14 mg/kg/day studied in Study 2017 was proposed for Phase 3 Study 3002.

Protocol 3002 was submitted for a Special Protocol Assessment (SPA) on March 31, 2010, and after revisions, SPA agreement was reached August 5, 2010.

A protocol for Study 3003 to evaluate tremors after switching from Prograf to LCP-tacro was submitted September 19, 2011; however, the revisions proposed by the Division were not included in the protocol for this one-way crossover study of 2-week duration.

On December 30, 2011, the applicant requested a Type C meeting to discuss (b) (4)

The applicant submitted the protocol for Study 2019 to evaluate PK of LCP-Tacro and Prograf in de novo kidney patients; this separate protocol was submitted in lieu of conducting a PK sub-study in Study 3002.

At the pre-NDA meeting held on August 7, 2013, the Division discussed the proposed content and format of the NDA, the sponsor's plan to mitigate potential medication errors related to inadvertent switching with other tacrolimus products, by providing information in labeling, MedGuide and other strategies (e.g., (b) (4))

The NDA was submitted December 28, 2013, for the indication of prophylaxis of organ rejection in kidney transplant patients.

2.2 (b) (4)

DTOP agrees that the two Phase 3 Studies (3001 and 3002) are required for approval of the applicant's proposed labeling of this application, along with the results of Study 2017 that provides support for the 0.14 mg/kg/day starting dose. However, Astagraf XL, NDA 204096, approved July 19, 2013¹ requested and was granted 3-year marketing exclusivity as a new dosage form (NDF). Astellas, the applicant for Astagraf XL, sent a letter to the Agency on September 12, 2014, asking whether the agency agreed that Astellas' exclusivity blocked approval of Envarsus XR.²

DTOP met with the Exclusivity Board³ on September 24 and October 14, 2014, during which time the scope of the Astagraf XL exclusivity was discussed. Astellas stated in August 2012 that the exclusivity was supported by the new condition of use, namely the change in dosage regimen. However, at the October 14 meeting, the Board noted that tacrolimus was an old antibiotic and although Section 507 of the FD&C Act had been repealed, a new Section 505(v) enacted in 2008, and this section was being interpreted to mean that old antibiotics needed to show significant innovation, meet a 'higher' hurdle than 505(c) drugs. The Board advised that applications for new indications were considered to meet that higher standard: (b) (4), (b) (5)

¹ Drugs@FDA

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

² Press release that in December 2013 Veloxis Pharmaceuticals submitted a New Drug Application FDA to market Envarsus for kidney transplant recipients.

<http://www.thepharmaletter.com/article/veloxis-pharma-submits-nda-for-envarsus-in-kidney-transplant-recipients>
<http://www.pharmabiz.com/NewsDetails.aspx?aid=79577&sid=2>

³ Jay Sitlani, Nisha Shah, Nancy Hayes, Melissa Matles, Mustafa Unlu

On October 17, 2014, the Exclusivity Board sent a letter to Astellas requesting an analysis of how Astagraf XL (NDA 204096) qualifies for 3-year exclusivity under the Agency’s interpretation of section 505(v) of the Federal Food, Drug, and Cosmetic (FD&C) Act as set forth in the Agency’s April 9, 2012 letter from Janet Woodcock, Director, CDER, to Thomas Doyle, Docket No. FDA-2006- P-0007.1⁴ A copy of that letter summarizing the Agency decision on Vancocin was attached to the request sent to Astellas (and archived under NDA 204096).

Astellas responded with a letter from Covington & Burling, LLC dated October 27, 2014, (received officially on October 30, 2014) commenting that the once-daily regimen represents a new condition of use, whereas the Vancocin regimen was judged to be a refinement of a regimen. Astellas further adds that Astagraf XL’s once-daily dosing regimen was considered a new condition of use that triggered the Pediatric Research Equity Act (PREA), whereas for the Vancocin approval the FDA acknowledged PREA was not triggered by the supplemental NDA.

On October 27, 2014, an information request was sent to Veloxis for NDA 206406 asking Veloxis whether the NDF 3-year exclusivity listed for Astagraf XL in the Approved Drug Products with Therapeutic Equivalence Evaluations (orange book) affects the type of action letter than can be issued. Assuming there are no outstanding deficiencies for NDA 206406, the choices would be a Tentative Approval letter if Astagraf XL exclusivity blocks approval at this time, or [Full] Approval letter if Astagraf’s exclusivity does not block approval.

In a letter dated October 29, 2014, Veloxis responded that they relied on Prograf for their 505(b)(2) application and did not rely on Astagraf XL. They further note they are a different dosage form, with different strengths, different bioavailability and PK characteristics, and do not believe Envarsus XR is affected by the Astagraf XL exclusivity. (See Figure 1)

Table 2. Summary of Various Characteristics for the Three Tacrolimus Products

	Envarsus XR	Astagraf XL	Prograf
NDA number	N206406	N204096	N050708
Applicant	Veloxis	Astellas	Astellas
NDA type	505(b)(2)	505(b)(1)	505(b)(1)
Dosage Form	Tablet	Capsule	Capsule
Formulation	Extended release	Extended release	Immediate release
Dosing frequency	Once daily	Once daily	Twice daily
Strengths (mg)	0.75, 1, 4	0.5, 1, 5	0.5, 1, 5
Dose adjustment by therapeutic drug monitoring (TDM)	TDM	TDM	TDM

⁴ The Agency’s interpretation was subsequently upheld in ViroPharma, Inc. v. Hamburg, 898 F.Supp.2d 1 (D.D.C.2012).

Indication: prevention of rejection in	Kidney transplant	Kidney transplant	Kidney transplant
Concomitant medications	MMF and steroids	MMF and steroids	MMF and steroids
Approval date	<i>PDUFA:</i> <i>October 30, 2014</i>	Approved: July 19, 2013	Approved April 8, 1994
Market exclusivity	Requested	July 19, 2016 NDF	Expired
Basis for approval	Clinical studies	Clinical studies	Clinical Studies
Patents		March 25, 2019	Expired
Listed Drug	Prograf	None (b)(1)	None (b)(1)
Orphan Designation	Yes	No	No
Manufacturing	"MeltDose technology"		

On October 30, 2014, the Office of Regulatory Policy submitted a Memorandum summarizing the Exclusivity Board's findings regarding the Astagraf XL exclusivity and effect on Envarsus XR approval:

This memorandum addresses the decision by the Food and Drug Administration (FDA or the Agency) to tentatively approve Veloxis's new drug application (NDA) 206406 for Envarsus XR (tacrolimus extended-release tablets), in light of the existing 3-year exclusivity for Astagraf XL, a previously approved extended-release tacrolimus product. That exclusivity expires on July 19, 2016. Upon approving Astagraf XL, DTOP determined that it was eligible for exclusivity for new clinical investigations that were essential to its approval. In addition, after consulting with the Exclusivity Board within the Center for Drug Evaluation and Research (CDER), and based on the Exclusivity Board's determination that the conditions of approval for which Astagraf XL currently has exclusivity are shared by Envarsus XR, DTOP may only tentatively approve Envarsus XR at this time.

Comment: The application is eligible for Tentative Approval at this time.

2.3 Orphan designation, request for orphan exclusivity

The Office of Orphan Products Development (OOPD) granted orphan designation to Envarsus XR for the indication of prophylaxis of organ rejection in patients receiving allogeneic kidney transplant on December 20, 2013. The designation was based on a plausible hypothesis that the Applicant's drug may be clinically superior to the approved tacrolimus products for the same indication.

It is not clear what impact the recent ruling⁵ to "recognize orphan drug exclusivity for Gralise (gabapentin) Tablets without requiring any proof of clinical superiority or imposing any additional conditions on Depomed," may have on the determination of Envarsus and Orphan Exclusivity.

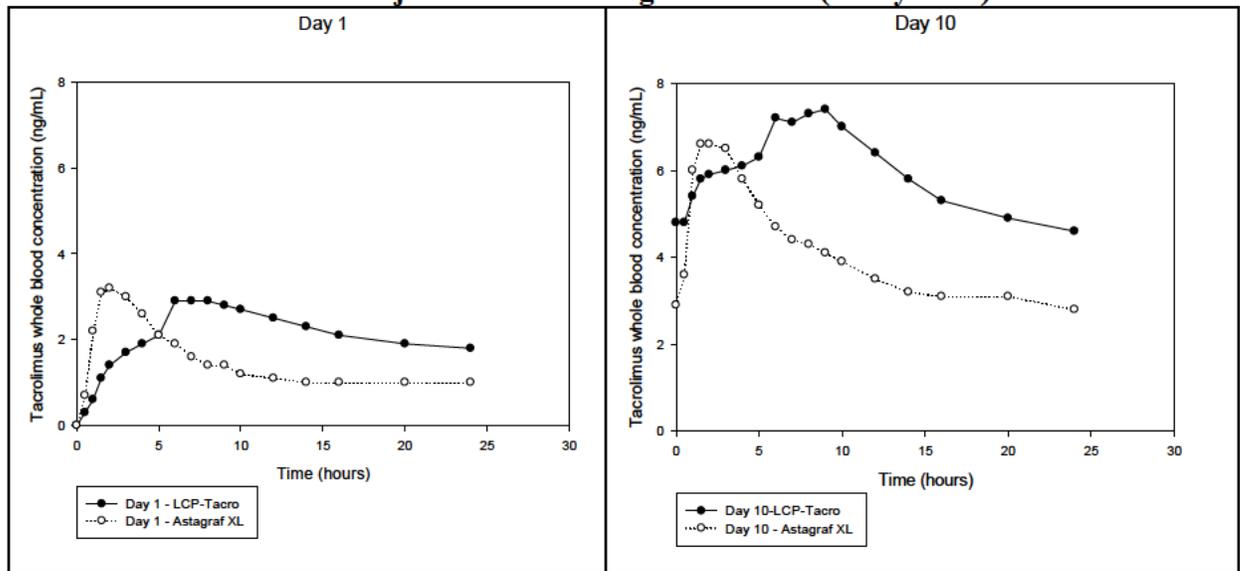
During a meeting with OOPD staff on October 14, 2014, OOPD commented that (b) (4)

⁵ Court Upends FDA's Clinical Superiority Requirement for Granting Orphan Drug Exclusivity; Decision Leaves a Lot of Questions to be Answered http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/09/court-upends-fdas-clinical-superiority-requirement-for-granting-orphan-drug-exclusivity-decision-lea.html

(b) (4) in order to qualify for orphan exclusivity. DTOP stated that the clinical trials showed that Envarsus XR was non-inferior to the control, Prograf, and that there was no demonstrated superiority in terms of safety. Although the applicant claimed that Study 3003 demonstrated a lower tremor rate, DTOP determined there were many limitations to the study, including that it was a single-crossover trial of 2 weeks duration. By comparison, the two Phase 3 trials did not demonstrate any significant difference in tremor rates between Envarsus XR and Prograf; the tremor rates for the Prograf were actually numerically lower. The applicant's claim that the Melt®Dose technology provided a superior product with consistent bioavailability did not translate to documented clinical superiority for the product. The applicant reports that the "PK profile of Envarsus XR is significantly different from Astagraf XL: bioavailability is greater, Tmax is later, Cmax is lower, peak-to-through ratio is later, fluctuation and swing are lower. In all cases the differences are both clinically and statistically significant. The products are not substitutable and consequently the Envarsus XR development program required" clinical trials. The requirement for the clinical trials was because these products were not bioequivalent (e.g., these are not generics of each other) and clinical trials are needed for this narrow therapeutic index (NTI) calcineurin inhibitor.

Veloxis conducted a study comparing the PK of Envarsus XR and Astagraf XL, and the results of these PK studies are summarized in Figure 1.

Figure 1. Mean Tacrolimus Whole Blood Concentration – Time over 24 hour Profiles of ENVARSUS® XR QD and Astagraf XL QD on Day 1 and Day 10 of dosing in 19 Healthy Caucasian Subjects under Fasting Conditions (Study 1017)



LCP-Tacro = ENVARSUS® XR

Source: Clinical Pharmacology Review, page 65

Comment: Determination of Orphan Exclusivity will also need to wait until the issue regarding (b) (4) is addressed.

3. CMC/Product Quality Microbiology

For complete details, see the reviews by the product quality reviewers. The following summary is excerpted from these reviews:

The CMC reviewer concluded that the quality of the drug substance, tacrolimus monohydrate, has been adequately documented and the sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of tacrolimus extended-release tablets. The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. An overall recommendation of Acceptable was issued by the Office of Compliance on September 1, 2014.

Envarsus XR (tacrolimus extended-release tablets) 0.75, 1 and 4 mg is a once-daily formulation of the calcineurin-inhibitor, tacrolimus. Approved formulations of tacrolimus include tacrolimus injection, tacrolimus capsules (e.g., Prograf and generic versions), and tacrolimus extended-release capsules, Astagraf XL, 0.5, 1, and 5 mg.

Tacrolimus, the active ingredient in Envarsus XR, is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. There is a significant body of literature covering the characterization of tacrolimus. Tacrolimus monohydrate used in the manufacture of Envarsus XR is sourced from (b) (4). Drug substance CMC is documented in DMF (b) (4).

The drug product is manufactured in (b) (4)

The drug product specification includes (b) (4)

(b) (4)

(b) (4)

(b) (4), and the absence of an analytical procedure sufficiently sensitive and robust to detect such crystallization, the applicant has agreed to develop and implement an X-ray powder diffraction test (XRPD) and the following post-marketing commitments (PMC): (1) develop and validate a regulatory X-ray powder diffraction (XRPD) test for the determination of crystalline content in the drug product, (2) develop an XRPD test for (b) (4), (3) test legacy samples for crystalline content by XRPD, (4) evaluate conditions that might promote crystallization, and (5) evaluate impact of manufacturing process parameters on crystalline content. These post-marketing commitments will provide additional assurance that potential crystallization of tacrolimus does not adversely impact product performance.

When protected from heat, light and moisture, tacrolimus exhibits good chemical stability as demonstrated by little increase in related substances on stability. Originally, the applicant intended to (b) (4). However, the final approved shelf-life of 24 months will begin at the time of (b) (4).

Inactive ingredients include hypromellose, lactose monohydrate, polyethylene glycol, poloxamer, magnesium stearate, tartaric acid, butylated hydroxytoluene, and dimethicone. All excipients meet USP/NF compendial requirements.

The CMC review notes that labeling should not list (b) (4) as the manufacturer; rather Envarsus XR is manufactured by Rottendorf Pharma GmbH. Veloxis Pharmaceuticals A/S is (b) (4) responsible for regulatory oversight of the release of the finished product. In addition, the reviewer recommends any references to (b) (4) be removed from the labeling. The mention is considered promotional in nature and does not provide information that is useful for the safe prescribing of the product by healthcare provider or use by the patient.

Environmental Assessment

Veloxis Pharmaceuticals request for categorical exclusion from the requirement to submit an Environmental Assessment (EA) according to 21 CFR 25.31(b) was considered acceptable.

Formulation Development

Formulation development was driven by (b) (4), BE/BA studies, and stability studies. Multiple strengths of the various formulations were evaluated. Several strengths of the final commercial formulation (G) were developed (0.75 mg, 1 mg, (b) (4) and 4 mg; the (b) (4) [Astagraf XL (tacrolimus extended-release capsules) is available in 0.5, 1 and 5 mg strengths.]

Selection of commercial strengths was influenced by DMEPA concerns about common, overlapping strengths of approved tacrolimus products (0.5 mg, 1 mg and 5 mg) although the 1 mg tablet was retained to make dosing manageable.

Comment: The application can be approved from the CMC perspective.

4. Nonclinical Pharmacology/Toxicology

For detailed information, see Pharmacology /Toxicology (P/T) Reviews.

The applicant has submitted a 505(b)(2) NDA application for an extended release formulation of tacrolimus, Envarsus XR, and relies on the approval of Prograf capsules (NDA 050708) to support nonclinical safety of Envarsus XR. Revisions to the nonclinical sections of the product labeling predominantly reflect changes in the safety margins resulting from comparing the dose based on body surface area (mg/m²) or exposure (AUC) following oral administration, based on the starting dose of 0.14 mg/kg/day. These revisions have been incorporated in the package insert.

Comment: The application can be approved from the Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

For complete information, see the Clinical Pharmacology review.

Based on the reviewer's analyses of tacrolimus PK, concentration and dose data from two Phase 2 studies and two Phase 3 studies in de novo kidney transplant patients and stable kidney transplant patients switched from tacrolimus immediate release capsules (Prograf®), as well as Phase 1 PK studies in healthy subjects, the reviewer's recommendations regarding the dosage and administration of Envarsus XR are as follows:

Envarsus XR Starting Dosage and Dosage Titration

- *De novo kidney transplant patients* [redacted] (b) (4)

[redacted] (b) (4)

- *Stable kidney transplant patients*
When switching from tacrolimus immediate release (e.g., Prograf) to ENVARSUS® XR, use a daily dose conversion ratio of 1:0.80 (i.e., upon conversion, the daily dose of Envarsus XR should be 80% of the daily dose of Prograf prior to conversion)
If needed, adjust Envarsus XR dosage to achieve tacrolimus trough concentrations within a 4 to 11 ng/mL range, and preferably similar to the pre-conversion level.

Administration

- To achieve maximum possible and consistent tacrolimus exposures, take Envarsus XR without food (i.e., at least 1 hour before a meal or 2 hours after a meal), and at the same time each day (preferably in the morning).

Therapeutic Drug Monitoring

Monitor tacrolimus whole blood trough concentrations frequently during the first 7 days post-transplant. When interpreting measured concentrations, clinicians should be aware that the time to achieve steady state is approximately 7 days after initiating or changing the Envarsus XR dose; however, administration of a higher Envarsus XR starting dosage (e.g., ≥ 0.17 mg/kg/day) could potentially result in higher than expected initial tacrolimus concentrations and/or systemic exposure.

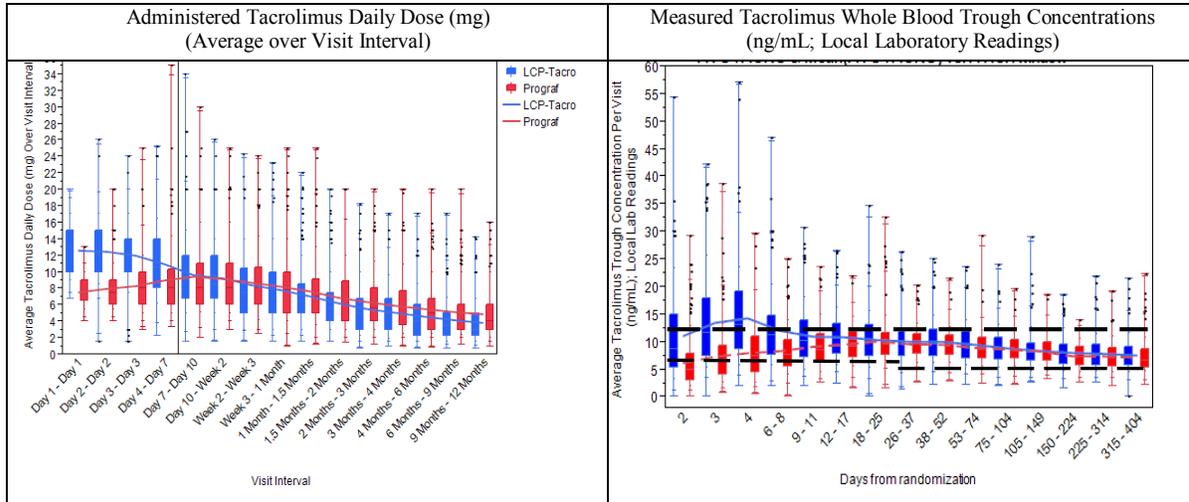
Studies in De Novo Kidney Transplant Patients

Phase 2 Study 2019 determined tacrolimus PK parameters in de novo kidney transplant patients, a starting Envarsus XR daily dose of 0.17 mg/kg/day (regardless of race) would result in a 2.0 to 2.6 -fold higher tacrolimus AUC₀₋₂₄/C_{max}/C_{trough} on Day 1, as compared to Prograf starting at 0.1 mg/kg/day (given twice daily).

In Study 2017, the mean/median tacrolimus whole blood trough concentrations (C_{trough}) achieved in Envarsus XR patients at a starting dose of 0.14 mg/kg/day were within the protocol defined target tacrolimus C_{trough} range (7-20 ng/mL), and increased steadily during the first 7 days post-transplant. Per the applicant, no patients in Phase 2 Study 2017 experienced graft failure or died during the 12-month study; there was no statistically significant difference between Envarsus XR and Prograf in terms of the cumulative incidence of freedom from biopsy-proven acute rejection (BPAR), and severity of BPAR episodes.

Envarsus XR was prospectively evaluated in de novo kidney transplant patients in the 12-month Phase 3 Study 3002, comparing Envarsus XR, starting dose of 0.17 mg/kg/day (given QD) vs. Prograf, starting dose of 0.1 mg/kg/day (given BID), with subsequent dosage adjustments based on the attainment of the protocol-specified target tacrolimus trough concentration ranges of 6-11 ng/mL (first 30 days), and 4-11 ng/mL thereafter. The mean/median tacrolimus whole blood trough concentrations measured in Envarsus XR patients were higher than the upper limit of the protocol specified target range during the first 7 days, and higher than that achieved in the Prograf twice daily arm during the first 14 days, due at least in part to the higher administered daily doses of Envarsus XR than Prograf during the first week post-transplant, and dosing was higher on LCP-Tacro (blue bars) compared to Prograf (red bars) during this time, as shown in Figure 2.

Figure 2. Administered Tacrolimus Daily Dose (mg) and Measured Tacrolimus Trough Concentrations (ng/mL) of De Novo Kidney Transplant Patients by Treatment – Study 3002



Legend: LCP-Tacro = ENVARSUS® XR (blue bars with solid blue line); PROGRAF (red bars with broken red line); protocol defined target tacrolimus trough concentrations (dashed horizontal lines)
 *reviewer's analysis includes 12-month study completers
 Source: page 7 of Clinical Pharmacology review.

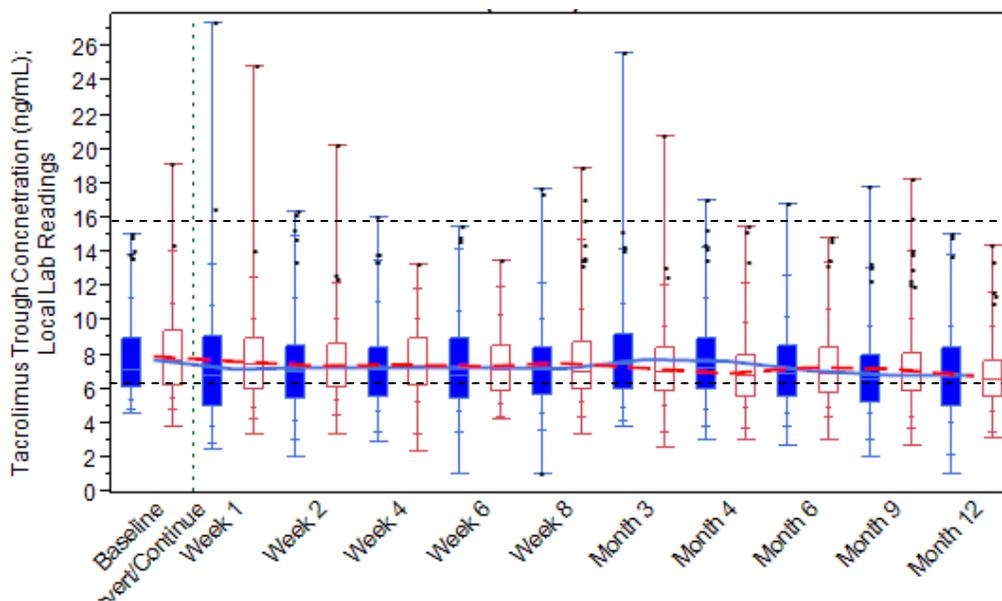
Studies in Stable Kidney Transplant Patients

In Study 2011, the steady state AUC-C_{trough} correlation lines of Envarsus XR and Prograf were superimposable (i.e., the slopes of the lines were comparable, and the data points comprising each line overlapped substantially); the AUC-C_{trough} correlation coefficients ($r \geq 0.79$) were satisfactory. This observation suggests that targeting the same tacrolimus trough concentration range as Prograf would be appropriate for stable kidney transplant patients switched from Prograf to Envarsus XR (at a daily dose conversion ratio of 1:0.8).

In Study 3001, stable kidney transplant patients (30 African Americans/Blacks and 120 non-African Americans/non-Blacks) receiving stable doses of Prograf twice daily and with tacrolimus trough concentration within 4-15 ng/mL at the end of the 7-day run-in period were randomized (1:1) at baseline to either continue treatment with Prograf twice daily at the current dose, or switch to Envarsus XR once daily. The Prograf-to-Envarsus XR daily dose conversion ratio was 1:0.85 for Blacks/African Americans, or 1:0.7 for non-African Americans/non-Blacks (slightly different from that used in Phase 2 Study 2011).

The reviewer stated that the baseline-to-Week 1 ratio of mean tacrolimus daily doses administered in Study 3001 were 0.8 for Envarsus XR conversion patients and 1.0 for Prograf continuation patients. This observation provided support for the reviewer's proposal to recommend a Prograf-to- Envarsus XR daily dose conversion ratio of 1:0.8 (regardless of race). After the first month, the target trough concentrations should be 4-11 ng/mL, similar to the pre-conversion level. Figure 3 presents the results of the tacrolimus trough concentrations in stable kidney transplant patients from Study 3001.

Figure 3. Daily Tacrolimus Trough Concentrations (ng/mL) in Stable Kidney Transplant Patients in Study 3001, by Treatment



Legend: ENVARUSUS® XR (blue solid boxes with blue solid line); PROGRAF (red open boxes with red broken line); protocol defined target tacrolimus trough concentrations (black horizontal broken lines)
Source: Clinical Pharmacology Review, page 10

Comment: The application can be approved from a Clinical Pharmacology perspective.

6. Immunology

For detailed information, see Immunology Review.

Based on the review of multiple published studies, the Immunology reviewer recommended that revisions be made to the labeling in Section 12.1 Mechanism of Action:

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (an ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

Comment: The application can be approved from a Immunology perspective.

7. Clinical/Statistical-Efficacy

7.1 Phase 3 and Phase 2 Clinical Trials Supporting Approval

For complete details regarding the study design and outcome of the clinical studies, see Clinical and Statistical Reviews. The summary below is excerpted from these reviews.

This NDA contains two Phase 3 studies, 12-months in duration: Study 3002 was conducted in de novo kidney transplant patients and Study 3001 was conducted in stable renal transplant patients, 3 months to 5 years post-transplant. Phase 2 Study 2017 was designed primarily as a pharmacokinetic study, was smaller and not powered to demonstrate efficacy and followed patients for 12 months to assess safety. The results for study 2017 are relevant because this trial evaluated the starting dose of 0.14 mg/kg/day.

Phase 3 Studies 3002 and 3001, and Phase 2 Study 2017 served to support the evaluation of efficacy and safety for this NDA and an overview of these studies is presented in Table 3.

Table 3. Overview of Phase 3 Studies 3002 and 3001, and Phase 2 Study 2017 in Kidney Transplant Patients

Study	Phase and Design	Primary endpoint and objective	LCP-Tacro	Prograf	Study Population
3002	Phase 3, double-blind, double-dummy, multi-center, prospective, randomized study of the efficacy and safety of LCP-Tacro once daily compared to Prograf capsules twice daily with MMF	Death, graft failure, BPAR or lost to follow-up within 12 months after randomization. To show NI.	N= 268 LCP-Tacro tablets, 0.75, 1 and 4 mg once daily (QD)	N=275 Prograf capsules (tacrolimus), 0.5 mg, 1 mg, and 5 mg twice daily (BID)	Adult <i>De Novo</i> Kidney transplant recipients
3001	Phase 3, open-label, multicenter, randomized study of the efficacy and safety of conversion from Prograf capsules twice daily to LCP-Tacro tablets once daily	Efficacy failure defined as death, graft failure, BPAR or LTFU at 12 months after the first dose of study drug. To show NI.	N=163 LCP-Tacro 0.5, 1, 2, and 5 mg tablets (QD). Initial dosing 0.7 of total daily dose of Prograf being taken for non-blacks, 0.85 multiple for blacks	N=163 Prograf 0.5-, 1-, and 5-mg capsules(BID). Only patients taking a stable total daily dose of at least 2 mg of Prograf were eligible for entry into the study.	Stable kidney transplant patients

2017	Phase 2, open-label, multi-center, randomized trial to demonstrate the PK of LCP-Tacro tablets once daily and Prograf® capsules twice daily.	Tacrolimus PK on Days 1, 7, and 14 and the proportion of patients achieving tacrolimus trough levels of 7 to 20 ng/mL on Days 1, 2, 3, 4, 7, 10, 12, and 14. Efficacy also assessed.	N=32 LCP-Tacro 0.5, 1, 2 and 5 mg tablets once daily (QD)	N=31 Prograf 0.5 1 and 5 mg capsules twice daily (BID)	Adult <i>de novo</i> kidney transplant patients
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Source: Adapted from Statistical Review, page 8.

The primary endpoint was the rate of treatment (efficacy) failure, defined as biopsy-proved acute rejection, graft loss, death or loss to follow-up by the 12-month post-transplant visit.

For Study 3002, the treatment failure rate was 18.7% in the LCP-Tacro group and 19.6% in the Prograf group. The difference between the two groups (LCP-Tacro – Prograf) is -1.0% and the 95% confidence interval is (-7.6%, 5.6%). The upper bound of this CI is smaller than the pre-specified non-inferiority (NI) margin of 10%. The sponsor’s justification for the 10% non-inferiority (NI) margin was found to be appropriate (see Section 7.2).

Table 4. Efficacy Failure Results* from Studies 3002, 3001, and 2017

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

Source: Statistical Review, page 5.

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

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

***The sponsor’s results for Study 3002 exclude one patient (patient ID 034154017) from the LCP-Tacro arm, considered as an efficacy failure in the statistical review because the patient had a clinically suspected acute rejection within the 12 month study period, although the biopsy was not done until day 366; the protocol defined an efficacy failure as a BCAR through day 365.

**** In Study 300, 326 patients were randomized to the two treatment groups with 163 patients in each treatment group. One patient in each treatment group did not receive study drug, therefore, there were 162 in LCP-Tacro group and 162 in Prograf group included in the analysis of efficacy.

The 95% CI for the BPAR rate is (-3.4, +3.4)

The incidence rates in Study 3002 were comparable for each individual components of the efficacy failure endpoint (BPAR, death, graft loss, lost to follow-up). Treatment differences were also comparable across demographic subgroups with no statistically significant differences observed. The conclusion on efficacy outcome showed similar results and the same conclusion of non-inferiority between LCP-Tacro and Prograf based on local BPAR reading.

The efficacy results from Study 3001 in stable kidney patients were comparable between the LCP-Tacro group and the Prograf group. There were 4 efficacy failures in each treatment group based on local laboratory readings, with a 95% confidence interval of the difference of the efficacy failure rates between the two groups (-4.2%, 4.2%) and for BPAR, there were 2 failures in each arm with a 95% CI (-3.4, +3.4). There was no statistically significant difference of the efficacy failure rates between the two groups ($p=1.0000$, Fisher's exact test). The sponsor's proposed ^{(b) (4)} NI margin was not justified for this study. FDA advised that margin no larger than ^{(b) (4)} for acute rejection could be calculated. The efficacy conclusion did not change when slides were read in a central lab.

In Study 2017, the efficacy results appeared to be comparable between the two groups for the small number of patients in the study. Because the size of the study was small, the confidence interval is large and no definite conclusions can be made; it is noted that the difference between the treatment arms is -3.4%.

7.2 Non-Inferiority Margin

The sponsor proposed a 10% NI margin for the primary efficacy endpoint of treatment failure (defined as death, graft failure, BPAR, or loss to follow-up at month 12 post-transplant). The following treatment arms were considered in the non-inferiority (NI) margin calculation:

- Experimental: basiliximab (B) + MPA + corticosteroids (CS) + LCP-Tacro
- Active control: basiliximab (B) + MPA + corticosteroids + Prograf
- Putative placebo: basiliximab + MPA + corticosteroids

To assess the non-inferiority of LCP Tacro compared to Prograf in Study 3002, the effect of active control compared to the putative placebo was estimated using data from previously conducted clinical trials in the published literature. Details are provided in the Statistical review, Appendix 1.

Regarding the non-inferiority margin for Study 3001, the meeting minutes from the end-of-phase 2 meeting for IND 75250 on February 16, 2010, the Division commented that based on the information provided in the briefing package, using only the acute rejection rates, the data referenced by the sponsor would support a margin no larger than ^{(b) (4)} (See DARRTS entry IND 75250 dated 03/12/2010.)

The non-inferiority of LCP-Tacro with respect to treatment failure within 12 months was assessed using a 2-sided 95% CI based on the difference in treatment failure rates between the treatment groups at 12 months, i.e., LCP Tacro minus Prograf.

8. Safety

The details of the safety evaluation are included in the Clinical and Statistical reviews.

Studies 3002, 3001 and 2017 were also reviewed for safety. Overall, there were 463 LCP-Tacro and 469 Prograf patients enrolled in these trials and treated for up to 12 months. In Study 3002, *de novo* kidney transplant patients were treated with LCP-Tacro (N=268) or tacrolimus immediate-release product (N=275) and concomitant immunosuppressants. The clinical reviewer noted that an adequate number of kidney transplant patients demographically representative of the US kidney transplant population, both *de novo* and stable, received LCP-Tacro extended release tablets at appropriate doses and with sufficient duration to permit an adequate safety analysis. Because of the differences in the population (*de novo* and stable) and in design (difference in starting doses), the results from these trials are not pooled. More detailed presentation of data is presented for the *de novo* Study 3002, which evaluated a starting dose of LCP-Tacro 0.17 mg/kg/day. For Study 3001, similar events were seen, but rates were lower, as would be expected in a stable population. For the Phase 2 Study 2017, similar types of events were also seen; this study evaluated a lower starting dose of LCP-Tacro 0.14 mg/kg/day.

Deaths

De Novo Study 3002

A total of 16 deaths (8 in each group) occurred during the first 12 months of Study 3002. Eleven of the 16 deaths occurred either when the patient was receiving the study drug or within 30 days of last dose of the study drug, hence classified as “treatment emergent” by the applicant. In addition to these 16 deaths, two more deaths in the Prograf group and one more death in the LCP-Tacro group occurred outside the 12 month study period making the total number of deaths in the study 19. During the 12 month study period, the most common cause of death was cardiovascular AEs (3/8) in the LCP-Tacro group compared to infections (7/8) in the Prograf group. There was one malignancy-related death in an LCP-Tacro patient who died due to post-transplant lymphoproliferative disorder (PTLD). Overall, the numbers of deaths in the two study groups were balanced and the reported causes of death were compatible with the generally encountered causes of death in the transplant patient population.

Conversion Study 3001

A total of four patients died in Study 3001, three in the LCP-Tacro group and one in the Prograf group. One of the three deaths in the LCP-Tacro group occurred outside the 12 month study period. In the Clinical Reviewer’s assessment none of the four deaths seem to be attributable to the study drugs. No graft losses were reported during the study period in Study 3001.

Phase 2 Study 2017

There were no deaths reported in this study.

Graft Losses

De Novo Study 3002

In Study 3001, 9 patients in the LCP-Tacro group and 11 patients in the Prograf group lost their grafts during the 12 month study period. One patient in each group lost their grafts without ever receiving the study drug.

Conversion Study 3001

There were no graft losses in this study.

Phase 2 Study 2017

There were no graft losses in this study

Other Serious Treatment Emergent events

De Novo Study 3002

Treatment-emergent adverse event was defined as any adverse event that started after the first dose and within 30 days after the final dose of study drug. More than half of all patients (53.4% in the LCP-Tacro group and 58.9% in the Prograf group) experienced at least 1 serious treatment-emergent adverse event. The most common of these were urinary tract infection, kidney transplant rejection and other transplant-related complication, CMV infection and increased creatinine. Polyomavirus-associated nephropathy (PVAN) as an SAE was only reported in the LCP-Tacro group (n=2) and resulted in treatment discontinuation in these two patients.

Conversion Study 3001

SAEs were reported for 36 (22.2%) patients in the LCP-Tacro group and 26 (16.0%) patients in the Prograf group. The most frequently reported SAE was UTI (2.2% overall), and this event occurred in both treatment groups in Study 3001. Since Study 3001 is a study conducted in stable transplant patients the rates of SAEs in both groups are much lower compared to Study 3002 conducted in de novo transplant recipients. Overall SAEs are balanced across the two treatment groups.

Phase 2 Study 2017

SAEs were reported for 15 (46.9%) patients in the LCP-Tacro group and 21 (67.7%) patients in the Prograf group in this de novo Phase 2 study. The most frequently reported SAE were in the Infections and Infestations group.

Discontinuations

De Novo Study 3002

The numbers of patients who experienced TEAEs resulting in discontinuation from study drug and/or withdrawal from the study were similar in the two treatment groups (12.3% and 12.4% in the LCP-Tacro and Prograf groups, respectively).

The most common adverse reactions leading to discontinuation in Envarsus XR-treated patients were related to infections (1.1%), injury/procedural (2.2%), renal and urinary disorders (1.5%), and investigations (0.4%). The incidence of TEAEs was similar between the two treatment groups.

Conversion Study 3001

TEAEs leading to discontinuation of the study drug and/or withdrawal from the study were more frequent in the LCP-Tacro group compared to the Prograf group (8% vs. 1.2%).

The most common adverse reactions leading to discontinuation in Envarsus XR-treated patients were related to infections (1.2%), neoplasms benign/malignant (1.2%), cardiac disorders (1.2%), and investigations (1.2%). The incidence of TEAEs was similar between the two treatment groups.

Phase 2 De Novo Study 2017

In both the LCP-Tacro and the Prograf groups, 2 patients in each group withdrew early from the study due to adverse events.

Common Adverse Reactions

The adverse reactions reported in the two Phase 3 studies are presented in Table 5. As can be seen, similar types of adverse reactions are reported, and the rates are lower in the stable population, as would generally be expected.

Table 5. Adverse Reactions Occurring in ≥10% of LCP Tacro-Treated Kidney Transplant Patients in Study 3002 and Study 3001 through 12 Months

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

Source: Statistical Review, page 40. * A patient reporting more than 1 adverse event within a system organ class or preferred term is counted only once at that level of summarization.

In Study 300, 326 patients were randomized to the two treatment groups with 163 patients in each treatment group. One patient in each treatment group did not receive study drug, therefore, there were 162 in LCP-Tacro group and 162 in Prograf group included in the analysis of efficacy.

The clinical reviewer noted that in Studies 3002, 3001 and 2017, no imbalances were observed between the LCP-Tacro groups and the Prograf groups with regards to deaths, graft losses, serious adverse events (SAEs), AEs, opportunistic infections, malignancies and other adverse events of interest, except for a higher number of patients with higher tacrolimus trough concentrations (tacrolimus toxicity) and BK virus associated nephropathy (BKVAN) events in the LCP-Tacro group of Study 3002, but not the other two studies (3001, and 2017).

The overall incidence of infections and infections with identified etiology in the de novo kidney transplant recipients treated with Envarsus XR or tacrolimus immediate-release product

in Study 3002 are shown in Table 6.

Table 6. Percentage of Patients with Infections through One Year Post-Kidney Transplant in Study 3002

	ENVARUSUS XR N=268	Prograf (tacrolimus) N=275
All infections	70%	65%
Urinary Tract Infections	29%	27%
Respiratory Infections	28%	24%
Bacterial Infections	13%	18%
Cytomegalovirus Infections	11%	9%
Fungal Infections	9%	8%
Gastrointestinal Infections	6%	4%
BK virus*	6%	9%
Serious Infections	26%	24%

*BK virus associated nephropathy (BKVAN) occurred in 1.5% (4/268) and 0.7% (2/275) in the Envarsus and tacrolimus immediate-release treatment groups, respectively.

Source: derived from the clinical review.

Subgroup Analysis

The statistical reviewer examined outcome by demographic subgroups in Study 3002 and noted no significant differences. There were very few events in Study 3001 to allow meaningful subgroup analyses.

The efficacy failure rates among males were slightly higher (21.3%) in the LCP-Tacro group than the failure rate (19.3%) in the Prograf group. Among females, the efficacy failure rate in the LCP-Tacro arm was lower (13.8%) than the failure rate in the Prograf arm (20.2%). The difference was not statistically significant. Among patients younger than 65 years of age, the efficacy failure rates were the same (19.4%) for the two treatment groups. Among older than 65 years patients, the efficacy failure rate was lower in the LCP-Tacro test arm (1/16=6.3%) than in the Prograf control arm (6/28=21.4%). The difference was not statistically significant. Race (black vs non-black) was one of the stratification factors at randomization. The majority of the patients in the study were white (417/543=76.8%). The results between the two treatment groups appear to be similar for white and other groups of patients. For black patients, the failure rate was lower (3/10=30%) in the LCP Tacro arm than in the Prograf arm (6/15=40%). The difference was not statistically significant.

Elevated Tacrolimus Trough Concentrations

As summarized in the medical officer review, there were 26 LCP-Tacro patients reported to have tacrolimus overdosing or tacrolimus toxicity, compared to 3 Prograf patients in Study 3002. This coding was used for patients whose tacrolimus trough concentrations were noticeably higher than the target concentrations. In the LCP-Tacro arm, values up to 52 ng/mL were reported. A similar imbalance was not observed in either Study 3001 or Study 2017.

Information relating to adverse reaction findings in the submission and class labeling will be reflected in the warnings, precautions, and adverse reactions sections of the labeling, as appropriate.

Comment: The clinical and the statistical reviewers concluded that benefits outweigh the risk and recommend approval of this application.

9. Advisory Committee Meeting

The review of this NDA submission for the indication of kidney transplant indication did not raise new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

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.

PREA requirements do not apply to the current NDA submission since it has been granted orphan designation by the FDA.

11. Other Relevant Regulatory Issues

11.1 Office of Compliance Facility Inspections

The Office of Compliance has issued an overall recommendation of ‘Acceptable’ based on the satisfactory cGMP status of the manufacturing facilities.

11.2 Office of Scientific Investigation (OSI) Audits

Inspections were performed at one domestic site (UCLA Medical Center) and two international sites (Poland and Germany) by the Office of Scientific Investigations (OSI). No issues were identified in any of these three sites and NAI letters will be issued.

11.3 Debarment certification

Veloxis Pharmaceuticals certified 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.

11.4 Financial Disclosure

As part of the NDA submission the Applicant included the FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and FDA Form 3455 (Disclosure Statement). Sixty-eight investigators participated in Study 3002, forty-seven participated in Study 3001, and nine in Study 2017; 2 of these 124 investigators had disclosable financial arrangements. The reviewer determined that these arrangements did not

affect the reliability on the study results because these were only 2 investigators, the Phase 3 trials were blinded, and the primary and secondary endpoints were objective leaving no room for investigator bias.

11.5 Other Regulatory Issues

This is a 505(b)(2) application – the 505(b)(2) assessment committee has cleared this application from their perspective. Veloxis is relying on Prograf for non-clinical safety data. Clinical trials to support approval were conducted by Veloxis and are required for approval of this application.

The applicant (b) (4) (see Section 2.2).

The application received orphan designation on December 20, 2013 and the applicant is requesting orphan exclusivity (see Section 2.3).

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPP and OBP. OMP/DMPP and labeling recommendations were discussed. Final carton container labels were submitted on October 16, 2014, PI and Medication Guide were submitted on October 29, 2014.

- **Package insert (PI):** The PI is written in PLR format. Labeling recommendations from reviewers have been incorporated.
- **Medication Guide:** Revisions recommended from various reviewers including OMP and OPDP have been incorporated.
- **Carton and Container Labels:** The labels have been reviewed by the Division, CMC and DMEPA and agreement was reached.
- **Proprietary Name:** The trade name Envarsus XR was considered acceptable from a promotional and safety perspective on April, 15 2014 and a letter to Veloxis accepting the name Envarsus XR was signed by Todd D Bridges on behalf of Kellie A Taylor on April 18, 2014.

(b) (4)

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The NDA will be issued a *Tentative Approval* letter given that there is currently 3-year marketing exclusivity listed in the orange book for Astagraf XL, and the Office of Regulatory Policy has provided a Memorandum summarizing the issues related to the exclusivity and language to communicate this decision to the applicant. The applicant will be advised that,

As noted in the “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”), the listed drug product Astagraf XL (NDA 204096), with which you share conditions of approval for which new clinical studies were essential, is subject to a period of exclusivity protection under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until that product’s exclusivity period has expired.

Otherwise, the application is ready for approval, all disciplines recommend approval, two large controlled Phase 3 trials and one Phase 2 trial demonstrated Envarsus XR is safe and effective for the prophylaxis of organ rejection in kidney transplant recipients. The facilities are acceptable and investigator site inspections recommend the clinical trial data are reliable. Labeling has been finalized.

13.2 Risk Benefit Assessment

End-stage kidney disease is a life-threatening condition with limited treatment options: dialysis or kidney transplantation. Long-term outcome and survival has been shown to be greater after transplantation than dialysis. The recipients of the kidney allograft need to receive immunosuppressants to prevent the recipient’s immune system from rejecting the allograft.

There are a number of immunosuppressants available. Because transplant recipients are generally on multiple drugs including immunosuppressants and drugs for managing other medical conditions, Astellas developed a once-daily formulation of tacrolimus as an extended release capsule.

Managing transplant patients is a balance in terms of providing sufficient immunosuppression to keep the recipient from rejecting the organ, but adjusting doses and immunosuppressants to minimize toxicity. The increased survival, reduced graft loss and reduced rates of acute rejection achieved with these products, is weighed against the toxicity associated with their use. The goal of management is achieve adequate immunosuppression and to minimize the toxicity through dose reduction, changing drugs, or treating the toxicity (e.g., infection, hypertension, NODAT, etc.).

The efficacy of the extended release tablet was evaluated in two Phase 3 studies: Study 3002 evaluated Envarsus XR in de novo kidney transplant patients and Study 3001 evaluated patients converted from Prograf to Envarsus XR. In addition, Study 2017 was relevant in the selection of the initial Envarsus XR starting dose of 0.14 mg/kg/day. In Study 3002, Envarsus was shown to be non-inferior to Prograf, and the outcome met the pre-defined non-inferiority margin. In Study 3001, comparable efficacy was shown between the two arms.

In Study 3002, LCP-Tacro patients had comparatively more frequent and higher recordings of tacrolimus trough levels above the protocol specified target range, mainly occurring during the initial two weeks after transplantation which was as high as 52 ng/mL. Conversely patients in the Prograf group experienced less frequent and of smaller magnitude elevations of trough levels above the target range throughout the study. This difference is likely due to the higher

starting dose in Study 3002. Such differences were not seen in the other two studies. As a result, a caution identified in the medical officer review is that due to protocol-specified cardiac exclusion criteria only low cardiac risk patients were enrolled into Study 3002. Patients with electrocardiograms (ECG) demonstrating clinically relevant abnormalities (including QTc prolongation, reversible ischemia), clinically symptomatic congestive heart failure or documented ejection fraction of less than 45% were excluded from the trial. Therefore it is not known whether or not patients with high cardiac risk factors exposed to such high tacrolimus levels early on in the study would have experienced serious adverse reactions.

For the evaluation of adverse events in the Phase 3 studies, there were no significant differences reported between LCP-Tacro and Prograf. Specifically, the difference in tremors reported in the one-way crossover Study 3003 was not reproduced in the Phase 3 trials, where tremors were reported in a small number of patients and there was no significant difference between the treatment arms.

Dosing of Envarsus XR, as well as Astagraf XL, Prograf and several of the other immunosuppressants, is based on therapeutic drug monitoring (TDM). For this application, as for other products that are dosed using TDM, the labeling includes information not only on the recommended starting dosing and target trough concentrations over time, but also provides information on the actual doses and/or trough concentrations used in the clinical trials. One of the key issues identified during the review of the application is that the starting dose of 0.17 mg/kg/day used in Study 3002 resulted in patients having levels above the target trough concentrations up to 52 ng/mL for the first 2 weeks post transplantation, whereas in Study 2017, the starting dose of 0.14 mg/kg/day was not associated with trough concentrations significantly outside the target range.

Overall, the reviewers concluded that the benefits of Envarsus XR outweigh its risk in the prophylaxis of organ rejection in kidney transplant recipients; Envarsus XR represents another treatment option.

13.3 Recommendation for other Postmarketing Requirements and Commitments

For complete details of the five CMC-related PMCs, see the PMR/PMC development template forms for product quality (CMC) dated October 24, 2014, the CMC review dated October 28, 2014. The PMCs are not included in the TA letter; they will be included when the Approval Letter is issued.

The purpose of the CMC PMCs is to:

- Develop and validate a regulatory X-ray powder diffraction (XRPD) test with LOD \leq (b) (4) for determination of crystalline tacrolimus content in tacrolimus extended-release tablets. (PMC #1).
- Develop and validate an XRPD test with a LOD of $<$ (b) (4) (PMC #2).
- Evaluate the crystalline content of available legacy batches of tacrolimus (b) (4) and of drug product stability batches by XRPD. (PMC #3).

- Evaluate conditions that might be expected to promote crystallization of tacrolimus in (b) (4) tablets, such as elevated (b) (4) and exposure to accelerated and stress conditions (PMC #4).
- Evaluate the effect of MeltDose manufacturing process parameters on the crystalline content of (b) (4) tablets (PMC #5).

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/s/

OZLEM A BELEN
10/30/2014

RENATA ALBRECHT
10/30/2014

Cross Discipline Team Leader Review
NDA 206406, Envarsus XR (tacrolimus extended-release tablets)
Prophylaxis of organ rejection in kidney transplant patients

Memorandum - Cross-Discipline Team Leader Review

Date	See stamp date
From	Ozlem Belen, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA # Supplement#	NDA 206406
Applicant	Veloxis Pharmaceuticals, Inc.
Date of Submission	December 28, 2013
PDUFA Goal Date	October 30, 2014
Proprietary Name / Established (USAN) name	Envarsus XR tacrolimus extended-release tablets
Dosage forms / Strength	0.75, 1, and 4 mg oral tablets
Proposed Indication(s)	Prophylaxis of organ rejection in kidney transplants patients
Therapeutic Class	Calcineurin Inhibitor
Action	CDTL Review and Summary Review will be combined in a joint review, co-authored by Ozlem Belen, MD, MPH and Renata Albrecht, MD

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/s/

OZLEM A BELEN
10/15/2014