# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206088Orig1s000

# STATISTICAL REVIEW(S)

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

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | 206088 |
| **Drug Name:** | OTEZLA (apremilast) Tablets, 10 mg, 20 mg, and 30 mg |
| **Indication(s):** | Plaque Psoriasis |
| **Applicant:** | Celgene Corporation |
| **Date(s):** | Letter Date: 12/5/2013 |
| | PDUFA Date: 9/23/2014 |
| **Review Priority:** | Standard |
| | |
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| | |
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**Keywords:** Plaque psoriasis, superiority trial, multiple imputation

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# 1 EXECUTIVE SUMMARY

The applicant, Celgene, is seeking approval of OTEZLA® (apremilast) tablets, 30 mg twice daily for the indication of treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On March 21, 2014, OTEZLA® tablets, 30 mg were approved for the indication of treatment of adult patients with active psoriatic arthritis.

The applicant submitted data from two randomized, multicenter, placebo-controlled, parallel-group, pivotal Phase 3 trials (CC-10004-PSOR-008 and CC-10004-PSOR-009). The trials evaluated the safety and efficacy of OTEZLA® tablets, 30 mg compared to placebo. The trials enrolled adult subjects (18 years of age and older) with a clinical diagnosis of moderate to severe plaque psoriasis, defined as at least 10% body surface area (BSA) involvement, a Psoriasis Area and Severity Index (PASI) score ≥ 12 and a static Physician Global Assessment (sPGA) score ≥ 3 (moderate), and be candidates for systemic or phototherapy. The protocol-specified primary efficacy endpoint was the proportion of subjects who achieved at least a 75% reduction in PASI (PASI-75) at Week 16 from baseline. The protocol specified the major secondary efficacy endpoint of the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (almost clear) at Week 16. It should be noted that the Agency has repeatedly stated that demonstrating success on the sPGA is a key component in establishing the efficacy of the proposed product; therefore, the Agency recommended this endpoint either be included into a composite endpoint (success on both the sPGA and PASI-75) or as a co-primary endpoint with PASI-75. Both endpoints were statistically significant and the results are presented in Table 1.

**Table 1: Primary and Major Secondary Efficacy Results at Week 16 (FAS[3], LOCF[4])**

| | Study 008 | | | Study 009 | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **OTEZLA (N=562)** | **Placebo (N=282)** | **P-value[2]** | **OTEZLA (N=274)** | **Placebo (N=137)** | **P-value[2]** |
| PASI-75 | 186 (33.1%) | 15 (5.3%) | <0.001 | 79 (28.8%) | 8 (5.8%) | <0.001 |
| Success[1] on sPGA | 122 (21.7%) | 11 (3.9%) | <0.001 | 56 (20.4%) | 6 (4.4%) | <0.001 |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.
(2) P-value is based on the 2-sided Chi-square test.
(3) Full Analysis Set (FAS): all subjects who were randomized and dispensed medication.
(4) LOCF: last observation carried forward

# 2 INTRODUCTION

## 2.1 Overview

The applicant, Celgene, is seeking approval of OTEZLA® (apremilast) tablets, 30 mg twice daily for the indication of treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On March 21, 2014, OTEZLA® tablets, 30 mg were approved for the indication of treatment of adult patients with active psoriatic arthritis [NDA 205437].

### 2.1.1 Regulatory History

The IND for the proposed product and indication was opened in 2004 under IND 70270. The following meetings were held with the sponsor:

- Guidance Meeting (August 25, 2004) to discuss safety
- Guidance Meeting (August 27, 2004) to discuss the sponsor's facsimile that address the Agency's comments from the guidance meeting on August 25, 2004
- Guidance Meeting (July 27, 2005)
- Guidance Meeting (December 10, 2007)
- End of Phase 2 Meeting (May 12, 2010)
- Pre-Phase 3 Meeting (December 8, 2010)
- CMC Guidance Meeting (March 15, 2012)
- Pre-NDA Meeting (May 15, 2013)

#### 2.1.1.1 End of Phase 2 Meeting (May 12, 2010)

For this End of Phase 2 (EOP2) meeting, the sponsor submitted protocol concept sheets for their Phase 3 development program. The sponsor proposed the primary endpoint as the proportion of subjects who achieved PASI-75 at Week 16. During the meeting, the Agency recommended defining success in Phase 3 clinical trials on the PGA as well as PASI-75 for assessing treatment effect, and recommended use of a composite endpoint based on both endpoints, that is, a treatment success to be defined as (i) success on the PGA and (ii) success on PASI-75. The Agency noted that the protocol concept sheets listed a large number of secondary endpoints (49 endpoints). The Agency stated that the set of secondary endpoints intended to support efficacy should be clinically relevant and limited in number, and the analysis of the secondary endpoints should be adjusted for multiplicity. For handling of missing data, the Agency recommended that the protocols should include a few alternate methods as sensitivity analyses to ensure that the conclusions are not driven by the method of imputation. In addition, the Agency recommended that the sensitivity analyses should include methods that use alternate assumptions (e.g., multiple imputation, etc.).

#### 2.1.1.2 Advice Letter (June 3, 2011)

On January 6 and 10, 2011, the sponsor submitted two Phase 3 protocols. An advice letter was sent to the sponsor on June 3, 2011.

In the advice letter, the Agency stated that demonstrating success on the sPGA will be a key component to establishing the efficacy of the proposed product. The Agency reiterated the recommendation from the EOP2 meeting to use a composite endpoint, treatment success, where treatment success is defined as success on both the sPGA and PASI-75. The Agency stated that if the sponsor elects to keep PASI-75 as a component of the primary endpoint assessment but does not use the composite definition, then the Agency recommended designing the study to establish efficacy on both the sPGA and PASI endpoints (i.e., co-primary) rather than relegating sPGA to a key secondary.

In the Phase 3 trials, the sponsor proposed a treatment withdrawal phase (Weeks 32 to 52) where "responders" originally randomized to OTEZLA will be re-randomized to either continue on OTEZLA or switch to placebo. The sponsor proposed to use different criteria for response and relapse in each study (PASI-75 in Study 008 and PASI-50 in Study 009). The Agency recommended selecting criteria for the eligibility of treatment withdrawal and treatment re-initiation based on the same endpoint(s) used for the Week 16 primary analysis, and recommended the definition of relapse should account for sufficient worsening of disease. The Agency noted that a sufficient threshold to distinguish the categories for response and relapse should be defined; and defining response and relapse using a sPGA with adequately distinct categories could address the above issues. In addition, the Agency noted that by using different cutoffs for each study, the studies lack replicability. The Agency also commented that it is unclear that a product achieving a PASI score of 50 would demonstrate a different clinical benefit than a product achieving a PASI-75 score.

The Agency noted that the proposed randomization and analysis plan does not allow for meaningful investigation of the site-to-site variability. Since this is an important aspect of a study evaluation, the Agency recommended that the studies be designed so that centers enroll sufficient number of active and placebo subjects to adequately assess treatment effects within centers and treatment by center interactions. In addition, the Agency recommended using a randomization scheme that eithers stratified by center or allocated complete blocks to centers rather than using a study-wide randomization scheme, as the latter may lead to substantial imbalance in the treatment allocations at some centers. For the analysis of the primary and secondary binary endpoints, the Agency recommended using a method that incorporated the effect of center, such as the Cochran-Mantel-Haenszel (CMH) test stratified by center, rather than the chi-square test.

In addition to the major secondary endpoints (PASI-75 at Week 16), the sponsor proposed 8 additional secondary endpoints. For secondary endpoints intended to support efficacy claims, the Agency recommended limiting the set of secondary endpoints to a small set of clinically relevant endpoints that are adjusted for multiplicity. Although the protocol proposed to test the endpoints sequentially to control the Type I error rate, the Agency noted that the utility of this

method depends on whether the endpoints have been appropriately ordered, as later endpoints can only be assessed if all previous endpoints demonstrated statistical significance.

For the handling of missing data, the sponsor proposed using the last observation carried forward (LOCF) as the primary imputation method and 'missing as failure' as the sensitivity analysis. The Agency noted that these two methods are likely to lead to similar results, as many subjects who discontinue the study early will not discontinue as responders. In addition, the Agency noted that it is difficult to scientifically justify the underlying assumptions of LOCF. The Agency reiterated the recommendation from the EOP2 meeting that the protocols should include a few alternate methods of handling missing data as sensitivity analyses to ensure that the conclusions are not driven by the method of imputation and these methods should include methods that use alternate assumptions (e.g., multiple imputation, modeling, etc.).

#### 2.1.1.3 Pre-NDA Meeting (May 15, 2013)

During this meeting, the sponsor asked if the proposed the two pivotal studies are sufficient for NDA submission and Agency filing. The Agency stated that the Pre-NDA meeting is not the appropriate venue for discussing SAPs for the individual studies as any discussions and agreements should have been made at the protocol stage prior to the study, not after the studies has been completed and the study data have been analyzed. The Agency noted that SAPs should be based on the analyses specified in the protocol. The Agency stated that the submission should adequately address the issues from the advice letter (dated June 3, 2011) such as assessment of site-to-site variability and sensitivity analyses for handling of missing data.

The Agency provided general comments on how the data should be submitted (data tabulation datasets, data definition files, annotated case report forms, and analysis datasets).

### 2.1.2 Clinical Studies Overview

The applicant submitted data from two Phase 3 trials (CC-10004-PSOR-008 and CC-10004-PSOR-009). An overview of the trials is presented in Table 2.

**Table 2: Clinical Study Overview**

| Trial | Location | Study Population | Treatment Arms | Number of Subjects | Dates |
|---|---|---|---|---|---|
| 008 | US (34 sites), Canada (17 sites), Europe (15 sites), Australia (6 sites) | Males and females, ≥ 18 years of age who are candidates for phototherapy and/or systemic therapy with PASI score ≥ 12, BSA ≥ 10%, and sPGA ≥ 3 (moderate) | OTEZLA 30 mg BID | 562 | 9/22/2010 – 12/21/2012 |
| | | | Placebo BID | 282 | |
| 009 | US (19 sites), Canada (7 sites), Europe (19 sites) | | OTEZLA 30 mg BID | 275 | 11/30/2010 – 12/21/2012 |
| | | | Placebo BID | 138 | |

### 2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The datasets in this review are archived at the following locations:
\\cdsesub1\evsprod\NDA206088\0000\m5\datasets\cc-10004-psor-008\
\\cdsesub1\evsprod\NDA206088\0000\m5\datasets\cc-10004-psor-009\

# 3 STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

The databases for the study required minimal data management prior to performing analyses. In the Filing Communication sent on December 5, 2013, the Agency reiterated the recommendation that the applicant should include methods that use alternative assumptions as sensitivity analysis for handling of missing data (e.g., multiple imputation or modeling approach), and the Agency requested that the applicant provide the results using the recommended analysis methods. The applicant submitted the requested results.

## 3.2 Evaluation of Efficacy

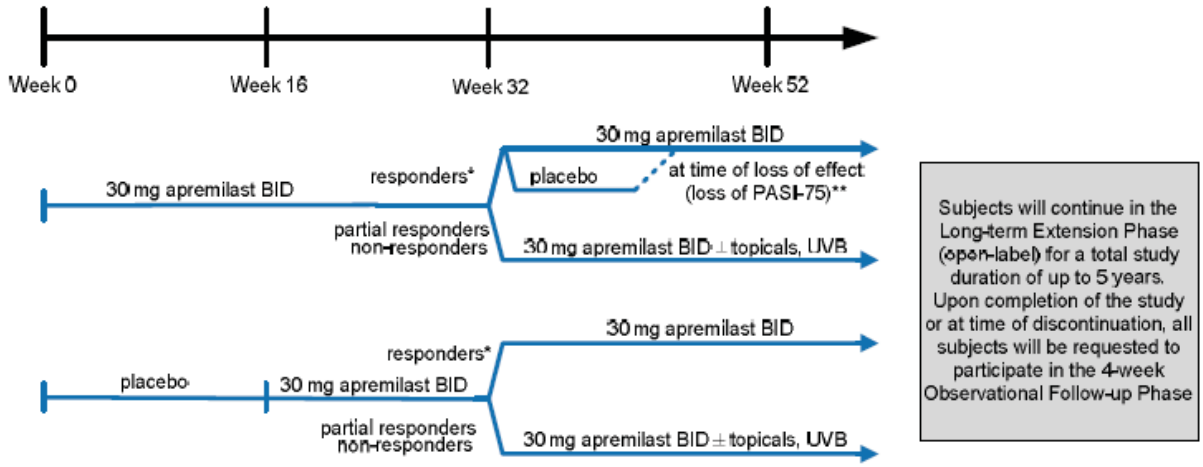
### 3.2.1 Study Design

The applicant conducted two pivotal Phase 3 trials (CC-10004-PSOR-008 and CC-10004-PSOR-009). Figure 1 displays the overall trial design for the trials. Both were randomized, multicenter, double-blind trials that consisted of the following periods:

- Placebo-controlled Period (Weeks 0 to 16): subjects were randomized in a 2:1 ratio to either OTEZLA 30 mg BID or placebo BID for 16 weeks. Study 008 planned to randomize approximately 825 subjects and Study 009 planned to randomize approximately 405 subjects. The primary timepoint for establishing efficacy was Week 16.
- Maintenance Period (Weeks 16 to 32): at Week 16, placebo subjects were switched to receive OTEZLA 30 mg BID and OTEZLA subjects remained on OTEZLA 30 mg BID. All subjects were to remain on OTEZLA 30 mg BID through Week 32.
- Randomized Withdrawal Period (Weeks 32 to 52):
  - Subjects originally randomized to OTEZLA at baseline that were responders (≥PASI-75 in Study 008 and ≥PASI-50 in Study 009) at Week 32 were re-randomized in a 1:1 ratio to either maintain OTEZLA 30 mg BID or switch to placebo BID. If these subjects experienced a loss of response, they were to resume OTEZLA 30 mg BID. Non-responders at Week 32 had the option of adding topical therapies and/or phototherapy to their treatment regimen.
  - Subjects originally randomized to placebo BID maintained the OTEZLA regimen. Non-responders at Week 32 had the option to add topical therapies and/or phototherapy to their treatment regimen.

- Long-term Extension Period (Weeks 52 to 260): subjects are being followed and evaluated for safety and efficacy for up to an additional 4 year.

**Figure 1: Overall Study Design**




Source: pg. 28 of the protocol for Study 008.
*In Study 008, "response" is defined as PASI-75 and in Study 009 "response" is defined as PASI-50.

For enrollment, the protocol specified the following key inclusion criteria:

- Male or female, ≥ 18 years of age at the time of signing the informed consent document
- Have moderate to severe plaque psoriasis at screening and baseline defined by
  - Psoriasis Area Severity Index (PASI) score ≥ 12, see Section 3.2.2 for details on the calculation of PASI
  - Body Surface Area (BSA) ≥ 10%
  - Static Physician's Global Assessment (sPGA) ≥ 3 (moderate), see Section 3.2.2 for details on the sPGA scale
- Must be a candidate for phototherapy and/or systemic therapy

Subjects were evaluated at screening, baseline, and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 34, 36, 40, 44, 48, and 52. Subjects were scheduled to be evaluated every 13 week in the long-term extension period through Week 260.

In order to minimize potential gastrointestinal (GI) side effects, dose titration over a period of 6 days was implemented during Week 1 (Days 1-7) and Week 16 (when placebo subjects were switched to receive OTEZLA). The schemas for dose titration during Week 1 and Week 16 are presented in Figures 2 and 3, respectively.

**Figure 2: Treatment Schema for Dose Titration at Baseline**

| Dose | Day 1 | | Day 2 | | Day 3 | | Day 4 | | Day 5 | | Days 6 through 28 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| 30 mg apremilast | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg apremilast + 30 mg placebo | 20 mg apremilast + 30 mg placebo | 20 mg apremilast + 30 mg placebo | 20 mg apremilast + 30 mg placebo | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast |
| placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 20 mg placebo + 30 mg placebo | 20 mg placebo + 30 mg placebo | 20 mg placebo + 30 mg placebo | 20 mg placebo + 30 mg placebo | 20 mg placebo + 30 mg placebo | 20 mg placebo + 30 mg placebo |

Source: pg. 47 of the protocols for Studies 008 and 009.

**Figure 3: Treatment Schema for Dose Titration at Week 16**

| Dose | Day 1 | | Day 2 | | Day 3 | | Day 4 | | Day 5 | | Days 6 through 28 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| Placebo to 30 mg apremilast | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg placebo + 30 mg placebo | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg apremilast + 20 mg placebo + 30 mg placebo | 10 mg placebo + 20 mg apremilast + 30 mg placebo | 20 mg apremilast + 30 mg placebo | 20 mg apremilast + 30 mg placebo | 20 mg apremilast + 30 mg placebo | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast |
| 30 mg apremilast | 10 mg placebo + 20 mg placebo + 30 mg apremilast | 10 mg placebo + 20 mg placebo + 30 mg apremilast | 10 mg placebo + 20 mg placebo + 30 mg apremilast | 10 mg placebo + 20 mg placebo + 30 mg apremilast | 10 mg placebo + 20 mg placebo + 30 mg apremilast | 10 mg placebo + 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast | 20 mg placebo + 30 mg apremilast |

Source: pg. 47 of the protocols for Studies 008 and 009.

### 3.2.2 Endpoints

The protocol-specified primary efficacy endpoint was the proportion of subjects who achieve at least a 75% reduction in PASI (PASI-75) at Week 16 from baseline.

The protocol specified the "major" secondary efficacy endpoint as the proportion of subjects with a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline at Week 16. The protocol also specified the following 8 secondary efficacy endpoints:

- Percent change from baseline in percent of affected BSA at Week 16
- Percent change in the PASI score from the baseline at Week 16
- Proportion of subjects who achieve PASI-50 at Week 16
- Change from baseline in Pruritus VAS at Week 16
- Change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 16
- Change from baseline in Mental Component Summary (MCS) score of SF-36 at Week 16
- Proportion of subjects who achieve both PASI-75 and sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline at Week 16
- Time to loss of effect (PASI-75 in Study 008 and PASI-50 in Study 009) during the Randomized Treatment Withdrawal Phase

It should be noted that the above list of secondary endpoints is the same list reviewed for the advice letter dated June 3, 2011. In the advice letter, the Agency recommended that secondary endpoints intended to support efficacy should be limited to a small set of clinically relevant endpoints.

The protocol specified the following as "exploratory" efficacy endpoints:

- PASI
  - Time to achieve PASI-50 and PASI-75 during Placebo-controlled Phase (Weeks 0-16)
  - Proportion of subjects who achieve PASI-75 at Weeks 24, 32, and 52
  - Proportion of subjects who achieve PASI-50 at Weeks 24, 32, and 52
  - Proportion of subjects who achieve PASI-90 at Weeks 16, 24, 32, and 52
  - Percent change in the PASI score from the Baseline Visit at Weeks 24, 32, and 52
- Proportion of subjects with a sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Weeks 24, 32, and 52
- Percent change from baseline in the psoriasis affected BSA (%) at Weeks 24, 32, and 52
- DLQI
  - Proportion of subjects who achieve a decrease of at least 5 points in DLQI total score at Weeks 16, 24, 32, and 52
  - Proportion of subjects who achieve PASI-50 with a decrease of at least 5 points in DLQI total score at Weeks 16, 24, 32, and 52
  - Change from baseline in the DLQI total score at Weeks 24, 32, and 52
- VAS
  - Change from baseline in the Pruritus VAS at Weeks 24, 32, and 52
  - Proportion of subjects who achieve at least a 10 mm decrease in the Pruritus VAS score at Weeks 16, 24, 32, and 52
  - Change from baseline in the Psoriatic Arthritis (PsA) Disease Activity Pain VAS at Weeks 16, 24, 32, and 52 in subjects with joint involvement
  - Change from baseline in the Skin Discomfort/Pain VAS at Weeks 16, 24, 32, and 52
  - Change from baseline in the Subject's Global Assessment of Psoriasis Disease Activity VAS at Weeks 16, 24, 32, and 52
- Health-related Quality of Life (HRQoL)
  - Change from Baseline in SF-36 scores at Weeks 16, 24, 32, and 52
  - Change from Baseline in PHQ-8 scores at Weeks 16, 24, 32, and 52
  - Change from baseline in EQ-5D scores at Weeks16, 32 and 52
  - Change from baseline in WLO-25 scores at Weeks 16, 32 and 52

(b) (4)

(b) (4)

**Table 3: Static Physician's Global Assessment (sPGA)**

| Score | Category | Description |
|---|---|---|
| 0 | Clear | Plaque elevation = 0 (no elevation over normal skin)<br>Scaling = 0 (no evidence of scaling)<br>Erythema = 0 (except for residual hyperpigmentation/hypopigmentation) |
| 1 | Almost Clear | Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin)<br>Scaling = ± (surface dryness with some desquamation)<br>Erythema = ± (faint, diffuse pink or slight red coloration) |
| 2 | Mild | Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped)<br>Scaling = fine (fine scale partially or mostly covering lesions)<br>Erythema = mild (light red coloration) |
| 3 | Moderate | Plaque elevation = marked (marked definite elevation with rough or sloped edges)<br>Scaling = coarser (coarser scale covering most or all of the lesions)<br>Erythema = moderate (definite red coloration) |
| 4 | Severe | Plaque elevation = marked (marked elevation typically with hard or sharp edges)<br>Scaling = coarser (coarse, non tenacious scale predominates covering most or all of the lesions)<br>Erythema = severe (very bright red coloration) |

**Psoriasis Area Severity Index (PASI):**

PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The index ranges from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

### 3.2.3 Statistical Methodologies

In addition to the protocols, the applicant wrote Statistical Analysis Plans (SAPs) as separate documents. The SAP for Study 008 was finalized and signed on December 11, 2012, and the SAP for Study 009 was finalized and signed on December 12, 2012. The applicant did not submit the SAPs until the Pre-NDA meeting (May 15, 2013). During the meeting, the applicant asked if the SAPs are sufficient for NDA submission and Agency filing. The Agency commented the Pre-NDA meeting is not the appropriate venue for discussing SAPs for the individual studies as any discussions and agreements should be made at the protocol stage prior to the study, and not after the studies have been completed and the study data have been analyzed. In addition, the Agency stated that SAPs should be based on the analyses specified in the protocol. It should be noted that the definition of the analysis populations, the multiplicity testing strategy, and the sensitivity analyses for handling missing data are different between the SAPs and the protocols, which are discussed below.

The primary analysis population was the full analysis set (FAS). In the protocols, FAS was defined as all randomized subjects. In the SAPs, the applicant specified that subjects who are randomized in error and do not receive any dose of study product will be excluded from FAS. Supportive analyses were specified to be conducted using the per-protocol (PP) population. In the protocols, the PP population was defined as all randomized subjects who have received at least one dose of study product, have at least one post-treatment PASI evaluation, and no protocol violation. In the SAPs, the definition of the PP population requires that subjects have at least one post-treatment PASI or sPGA evaluation.

For binary endpoints, the protocol-specified analysis method was the Chi-square test. For continuous endpoints, the protocol-specified analysis method was the analysis of covariance (ANCOVA) method with a term for treatment and baseline score as a covariate. For the time to loss of effect analysis within the re-randomize population (from Week 32), the protocol specified that the Kaplan-Meier method will be used to estimate the median time to loss of effect and the log-rank test will be used to compare the treatment groups.

To control the Type I error rate for testing multiple secondary endpoints, the protocols specified to test the secondary endpoints sequentially in the order listed in Section 3.2.2. However, the lists of endpoints in the SAPs differ from the list of endpoints in the protocols. The applicant changed the list by including several “exploratory” efficacy endpoints (4 were added to the list for Study 008 and 3 were added to the list for Study 009). These endpoints were inserted in the protocols’ list of secondary endpoints. In the study reports, the applicant used the list presented in the SAP. Table 4 presents the list and sequential testing order for both the protocols and SAPs.

**Table 4: Multiplicity Testing Strategy in the Protocols and SAPs for Studies 008 and 009**

| Endpoint | Type of Endpoint | Order in Protocols | Order in SAPs |
|---|---|---|---|
| Proportion of subjects with a sPGA score of clear (0) or almost clear (1) with at least 2 points reduction from baseline at Week 16 | Major Secondary | 1 | 1 |
| Percent change from baseline in the psoriasis affected BSA (%) at Week 16 | Secondary | 2 | 2 |
| Percent change in the PASI score from the Baseline Visit at Week 16 | Secondary | 3 | 3 |
| Proportion of subjects who achieve PASI-50 at Week 16 | Secondary | 4 | 4 |
| Change from baseline in the Pruritus VAS at Week 16 | Secondary | 5 | 5 |
| Change from baseline in the DLQI total score at Week 16 | Secondary | 6 | 6 |
| (b) (4) | | | |
| Change from baseline in the MCS score of SF-36 at Week 16 | Secondary | 7 | 10 |
| (b) (4) | | | |
| Proportion of subjects who achieve both PASI-75 and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction from baseline at Week 16 | Secondary | 8 | 12 |
| Time to loss of 50% of the improvement in PASI score (loss of effect) during the Randomized Treatment Withdrawal Phase | Secondary | 9 | 13 |

For the handling of missing data, the primary imputation method specified in the protocols was the last observation carried forward (LOCF). For continuous endpoints, it should be noted that LOCF was used only if the subjects had at least one post-baseline measure; otherwise, the subject was not included in the analysis. For the primary and major secondary endpoints (both binary endpoints), the protocols specified a sensitivity analysis for missing data where missing data is imputed as failures. In the SAPs, an additional sensitivity analysis for the primary and major secondary endpoint was specified where dropouts due to adverse events or lack of efficacy are imputed as failures and all other missing data is imputed using LOCF. In the Filing Communication sent on December 5, 2013, the Agency reiterated the recommendation that the applicant should include methods that use alternative assumptions as sensitivity analysis for handling of missing data (e.g., multiple imputation or modeling approach), and the Agency requested that the applicant provide the results using the recommended analysis methods. In

response, the applicant conducted an additional sensitivity analysis where missing data was imputed using multiple imputation (MI). For MI, the applicant generated 15 complete data sets using the Markov Chain Monte Carlo (MCMC) approach to impute the missing data.

### 3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Study 008 enrolled and randomized a total of 844 subjects (562 to OTEZLA and 282 to placebo) from 72 centers (34 in US, 17 in Canada, 15 in Europe, and 6 in Australia) and Study 009 enrolled and randomized a total of 413 subjects (275 to OTEZLA and 138 to placebo) from 45 centers (19 in US, 7 in Canada, and 19 in Europe). In Study 009, 1 subject randomized to OTEZLA and 1 subject randomized to placebo were randomized in error and did not have investigation product dispensed. Thus, neither subject was included in the FAS.

The proportion of subject who discontinued during the placebo-controlled phase in Study 008 was similar between the two treatment arms (10.5% for OTEZLA arm and 11.7% for placebo arm). In Study 009, a higher proportion of subjects in the placebo arm (18.2%) discontinued during the placebo-controlled period compared to the OTEZLA arm (12.8%). The reasons for discontinuations are presented in Table 5.

**Table 5: Disposition of Subjects during Placebo-Controlled Phase (Randomized Subjects)**

| | **Study 008** | | **Study 009** | |
|---|---|---|---|---|
| | **OTEZLA (N=562)** | **Placebo (N=282)** | **OTEZLA (N=275)** | **Placebo (N=138)** |
| **Randomized** | 562 | 282 | 275 | 138 |
| **FAS[(1)]** | 562 | 282 | 274 | 137 |
| **Discontinued[(2)]** | 59 (10.5%) | 33 (11.7%) | 35 (12.8%) | 25 (18.2%) |
| *Adverse Event* | 23 | 5 | 12 | 8 |
| *Death* | 0 | 1 | 0 | 0 |
| *Lack of Efficacy* | 2 | 7 | 3 | 2 |
| *Lost to Follow-Up* | 7 | 9 | 6 | 6 |
| *Non-Compliance with Study Drug* | 7 | 0 | 1 | 0 |
| *Other* | 1 | 1 | 2 | 1 |
| *Protocol Violation* | 7 | 1 | 2 | 1 |
| *Withdrawal by Subject* | 12 | 9 | 9 | 7 |

Source: Reviewer's Analysis
(1) Subjects who were randomized in error and did not have study product dispensed were excluded from FAS.
(2) Subjects who discontinued in the placebo-controlled phase on a date earlier than the visit window for Week 16/Visit 7 (16 weeks minus 4 days).

Baseline demographics were generally balanced across the treatment arms in both studies. The mean age was about 46 years and approximately 9% of the subjects were 65 or older. Approximately 68% of the subjects were male and approximately 90% of the subjects were white. Approximately 35% of subject in Study 008 were from US sites, while approximately 50% of subjects in Study 009 were from US sites. The demographics are summarized in Table 6.

**Table 6: Demographics (FAS)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| | **OTEZLA (N=562)** | **Placebo (N=282)** | **OTEZLA (N=274)** | **Placebo (N=137)** |
| **Age** | | | | |
| Mean (SD) | 45.8 (13.1) | 46.5 (12.7) | 45.3 (13.1) | 45.6 (13.4) |
| Median | 46 | 46 | 45.5 | 46 |
| Range | 18 - 80 | 20 - 82 | 18 - 83 | 22 - 73 |
| < 65 | 514 (91.5%) | 258 (91.5%) | 252 (92.0%) | 123 (89.8%) |
| ≥ 65 | 48 (8.5%) | 24 (8.5%) | 22 (8.0%) | 14 (10.2%) |
| **Gender** | | | | |
| Male | 379 (67.4%) | 194 (68.8%) | 176 (64.2%) | 100 (73.0%) |
| Female | 183 (32.6%) | 88 (31.2%) | 98 (35.8%) | 37 (27.0%) |
| **Race** | | | | |
| White | 507 (90.2%) | 250 (88.7%) | 250 (91.2%) | 128 (93.4%) |
| Black | 18 (3.2%) | 10 (3.5%) | 13 (4.7%) | 2 (1.5%) |
| Asian | 28 (5.0%) | 16 (5.7%) | 8 (2.9%) | 6 (4.4%) |
| Other | 9 (1.6%) | 6 (2.1%) | 3 (1.1%) | 1 (0.7%) |
| **Ethnicity** | | | | |
| Hispanic or Latino | 32 (5.7%) | 13 (4.6%) | 37 (13.5%) | 20 (14.6%) |
| Not Hispanic or Latino | 530 (94.3%) | 269 (95.4%) | 237 (86.5%) | 117 (85.4%) |
| **Region** | | | | |
| US | 196 (34.9%) | 98 (34.8%) | 141 (51.5%) | 65 (47.4%) |
| Canada | 211 (37.5%) | 106 (37.6%) | 62 (22.6%) | 30 (21.9%) |
| Europe | 80 (14.2%) | 37 (13.1%) | 71 (25.9%) | 42 (30.7%) |
| Australia | 75 (13.4%) | 41 (14.5%) | 0 | 0 |
| **BMI** | | | | |
| Mean (SD) | 31.2 (6.7) | 31.3 (7.4) | 30.9 (6.7) | 30.7 (7.1) |
| Range | 17.2 - 65.3 | 16.8 - 64.3 | 17.7 - 54.3 | 18.4 - 60.2 |

Source: Reviewer's Analysis
SD: Standard Deviation

The baseline disease characteristics are presented in Table 7. For Study 008, the baseline disease characteristics were generally balanced across the treatment arms. Approximately 70% of the subjects in Study 008 had a sPGA score of 3 (moderate). For Study 009, the baseline disease characteristics were higher in the placebo arm compared to the OTEZLA arm. Approximately 27% of the subjects in the OTEZLA arm and 36% of the subjects in the placebo arm had a sPGA score of 4 (severe).

For enrollment, the protocol specified that subjects must have a PASI score ≥ 12, BSA ≥ 10%, and sPGA ≥ 3 (moderate); however, several subjects did not meet these key inclusion criteria. In Study 008, 1 subject (randomized to OTEZLA) had a BSA of 9% at baseline and 1 subject (randomized to placebo) had a sPGA of 2 (mild). In Study 009, 1 subject (randomized to OTEZLA) had a sPGA of 2 (mild) and 1 subject (randomized to placebo) had a PASI score of 11.2.

**Table 7: Baseline Disease Characteristics (FAS)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| | OTEZLA (N=562) | Placebo (N=282) | OTEZLA (N=274) | Placebo (N=137) |
| **Total PASI Score** | | | | |
| Mean (SD) | 18.7 (7.2) | 19.4 (7.4) | 18.9 (7.1) | 20.0 (8.0) |
| Range | 12 - 60 | 12 - 59.3 | 12 - 57.8 | 11.2 - 53.3 |
| **BSA (%)** | | | | |
| Mean (SD) | 24.4 (14.7) | 25.3 (14.6) | 25.5 (15.4) | 27.6 (15.8) |
| Range | 9 - 86 | 10 - 84 | 10 - 86 | 10 - 78 |
| **sPGA** | | | | |
| 2 - Mild | 0 | 1 (0.4%) | 1 (0.4%) | 0 |
| 3 - Moderate | 401 (71.4%) | 192 (68.1%) | 198 (72.3%) | 88 (64.2%) |
| 4 - Severe | 161 (28.6%) | 89 (31.6%) | 75 (27.4%) | 49 (35.8%) |

Source: Reviewer's Analysis
SD: Standard Deviation

### 3.2.5 Primary and Major Secondary Efficacy Results

OTEZLA was statistically superior (p<0.001) to placebo on the primary efficacy endpoint (proportion of subjects with PASI-75 at Week 16) and the major secondary efficacy endpoint (proportion of subjects with a sPGA score of 0 or 1 with at least 2 points reduction from baseline at Week 16) in both studies. The results from the FAS and PP analyses were similar. The FAS and PP results are presented in Tables 8 and 9, respectively.

**Table 8: Primary and Major Secondary Efficacy Results at Week 16 (FAS, LOCF)**

| | Study 008 | | | Study 009 | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **OTEZLA (N=562)** | **Placebo (N=282)** | **P-value(2)** | **OTEZLA (N=274)** | **Placebo (N=137)** | **P-value(2)** |
| PASI-75 | 186 (33.1%) | 15 (5.3%) | <0.001 | 79 (28.8%) | 8 (5.8%) | <0.001 |
| Success(1) on sPGA | 122 (21.7%) | 11 (3.9%) | <0.001 | 56 (20.4%) | 6 (4.4%) | <0.001 |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.
(2) P-value is based on the 2-sided Chi-square test.

**Table 9: Primary and Major Secondary Efficacy Results at Week 16 (PP)**

| | Study 008 | | | Study 009 | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **OTEZLA (N=555)** | **Placebo (N=276)** | **P-value(2)** | **OTEZLA (N=266)** | **Placebo (N=134)** | **P-value(2)** |
| PASI-75 | 185 (33.3%) | 15 (5.4%) | <0.001 | 79 (29.7%) | 8 (6.0%) | <0.001 |
| Success(1) on sPGA | 121 (21.8%) | 11 (4.0%) | <0.001 | 56 (21.1%) | 6 (4.5%) | <0.001 |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.
(2) P-value is based on the 2-sided Chi-square test.

The endpoints in Tables 8 and 9 were analyzed using a two-sided Chi-square test. A *post hoc* analysis of these endpoints using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center produced very similar results (p<0.001).

### 3.2.6 Handling of Missing Data

Table 10 provides the number of subjects with missing data for PASI and sPGA at Weeks 16 by treatment arm and study. For Study 008, the proportion of subjects with missing data in each treatment arm was approximately the same. Two subjects in the OTEZLA arm had values for sPGA at Week 16 but did not have values for PASI. For Study 009, the placebo arm had a higher proportion of subjects with missing data than the OTEZLA arm.

**Table 10: Number of Subjects with Missing Data for the Primary and Major Secondary Endpoints at Week 16 (FAS)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| **Endpoint** | **OTEZLA (N=562)** | **Placebo (N=282)** | **OTEZLA (N=274)** | **Placebo (N=137)** |
| **PASI** | 61 (10.9%) | 35 (12.4%) | 37 (13.5%) | 26 (19.0%) |
| **sPGA** | 63 (11.2%) | | | |

Source: Reviewer's Analysis

For the primary and major secondary endpoints (both binary endpoints), the applicant conducted three sensitivity analyses for handling missing data: imputing missing as failures, imputing dropouts due to AE or lack of efficacy as failures and all others using LOCF, and multiple imputation (MI-MCMC). The results of the sensitivity analyses are presented in Table 11 for Study 008 and Table 12 for Study 009. In both studies, the results were very similar across the different sensitivity analyses.

**Table 11: Comparison of the Primary and Major Secondary Efficacy Results at Week 16 with Different Approaches for Handling Missing Data for Study 008 (FAS)**

| | PASI-75 | | | Success[1] on sPGA | | |
|---|---|---|---|---|---|---|
| **Imputation Method** | **OTEZLA (N=562)** | **Placebo (N=282)** | **P-value[2]** | **OTEZLA (N=562)** | **Placebo (N=282)** | **P-value[2]** |
| LOCF (Primary) | 186 (33.1%) | 15 (5.3%) | <0.001 | 122 (21.7%) | 11 (3.9%) | <0.001 |
| Failures | 183 (32.6%) | 14 (5.0%) | <0.001 | 118 (21.0%) | 11 (3.9%) | <0.001 |
| Dropouts due to AE or lack of Efficacy as Failures and all others as LOCF | 185 (32.9%) | 14 (5.0%) | <0.001 | 122 (21.7%) | 11 (3.9%) | <0.001 |
| MI-MCMC[3] | 196.2 (34.9%) | 15.6 (5.5%) | <0.001 | 126.2 (22.4%) | 11.1 (4.0%) | <0.001 |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.
(2) P-value is based on the 2-sided Chi-square test.
(3) The rates displayed are the averages over the 15 imputed datasets.

**Table 12: Comparison of the Primary and Major Secondary Efficacy Results at Week 16 with Different Approaches for Handling Missing Data for Study 009 (FAS)**

| Imputation Method | PASI-75 | | | Success[1] on sPGA | | |
|---|---|---|---|---|---|---|
| | OTEZLA (N=274) | Placebo (N=137) | P-value[2] | OTEZLA (N=274) | Placebo (N=137) | P-value[2] |
| LOCF (Primary) | 79 (28.8%) | 8 (5.8%) | <0.001 | 56 (20.4%) | 6 (4.4%) | <0.001 |
| Failures | 77 (28.1%) | 7 (5.1%) | <0.001 | 54 (19.7%) | 5 (3.6%) | <0.001 |
| Dropouts due to AE or lack of Efficacy as Failures and all others as LOCF | 79 (28.8%) | 7 (5.1%) | <0.001 | 56 (20.4%) | 5 (3.6%) | <0.001 |
| MI-MCMC | 84.4 (30.8%) | 8.9 (6.5%) | <0.001 | 59.7 (21.8%) | 6.4 (4.7%) | <0.001 |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.
(2) P-value is based on the 2-sided Chi-square test.
(3) The rates displayed are the averages over the 15 imputed datasets.

### 3.2.7 Secondary Efficacy Results

Tables 13 and 14 present the results of the secondary efficacy endpoints. As noted in Section 3.2.3, the multiplicity testing strategy to control the Type I error rate was different between the protocols and the SAPs. Both strategies involved sequentially testing a list of endpoints; however, the lists in the SAPs included "exploratory" efficacy endpoints (4 were added to the list for Study 008 and 3 were added to the list for Study 009). In the study reports, the applicant used the strategy specified in the SAPs. Using the strategy specified in the protocols, all of the secondary endpoints in Tables 13 and 14 would be statistically significant ($\alpha = 0.05$). However, for the strategy specified in the SAPs, the last two secondary endpoints in Table 13 and the secondary endpoint in Table 14 would not have been tested because one of the exploratory endpoints (the proportion of subjects with improvement of PPPGA scores to clear (0) or almost clear (1) with at least 2 points reduction from baseline at Weeks 16 [Pooled data from Studies 008 and 009] for subjects with baseline PPPGA score moderate (3) or above) was not statistically significant (the exploratory endpoints were inserted into the list ahead of those three secondary endpoints). See Section 3.2.8 for the results of the exploratory efficacy endpoints.

While the results presented in Tables 13 and 14 are statistically significant (using the strategy specified in the protocols), it does not mean they are clinically significant. During the EOP2 meeting (May 12, 2010) and in an advice letter (dated June 3, 2011), the Agency provided several recommendations and comments regarding secondary efficacy endpoints, which the applicant did not implement. The Agency has consistently stated that secondary endpoints intended to support efficacy claims should be limited to a small set of clinically relevant endpoints. In the advice letter, the Agency commented that the applicant should consider how relative changes in PASI score are clinically meaningful and that changes in PASI should have adequate clinical correlation. The Agency noted that it is unclear that a product achieving a PASI score of 50 would demonstrate a different clinical benefit than a product achieving a PASI-75 score. The Agency recommended selecting criteria for the eligibility for treatment withdrawal and treatment re-initiation based on the same endpoint(s) used for the Week 16 primary analysis and the definition of relapse should account for sufficient worsening of disease.

The Agency noted that a sufficient threshold to distinguish the categories for response and relapse should be defined; and defining response and relapse using a sPGA with adequately distinct categories could address the above issues. In addition, the Agency noted that by using different cutoffs for each study, the studies lack replicability.

**Table 13: Secondary Efficacy Results at Week 16 (FAS, LOCF[1])**

| | Study 008 | | | Study 009 | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **OTEZLA (N=562)** | **Placebo (N=282)** | **P-value[3]** | **OTEZLA (N=274)** | **Placebo (N=137)** | **P-value[3]** |
| Percent Change in BSA | -47.8 (38.5) | -6.9 (38.9) | <0.001 | -48.5 (40.8) | -6.1 (47.6) | <0.001 |
| Percent Change in PASI Score | -52.1 (32.8) | -16.7 (31.5) | <0.001 | -50.9 (34.0) | -15.8 (41.3) | <0.001 |
| PASI-50 | 330 (58.7%) | 48 (17.0%) | <0.001 | 152 (55.5%) | 27 (19.7%) | <0.001 |
| Absolute Change in VAS Score | -31.5 (32.4) | -7.3 (27.1) | <0.001 | -33.5 (35.5) | -12.2 (30.9) | <0.001 |
| Absolute Change in DLQI Total Score | -6.6 (6.7) | -2.1 (5.7) | <0.001 | -6.7 (6.9) | -2.8 (7.2) | <0.001 |
| Absolute Change in MAS Score of SF-36 | 2.4 (9.5) | -1.0 (9.2) | <0.001 | 2.6 (10.1) | 0 (10.5) | 0.008 |
| Achieved PASI-75 and Success on sPGA | 114 (20.3%) | 10 (3.5%) | <0.001 | 51 (18.6%) | 6 (4.4%) | <0.001 |

Source: Reviewer's Analysis
(1) For continuous endpoints, LOCF was used only if the subjects had at least one post-baseline measure; otherwise, the subject was not included in the analysis. The results presented were very similar to the results when the last observation was carried forward even if it was the baseline value.
(2) P-value for continuous endpoint is based on an ANCOVA model with treatment as a factor and baseline value as a covariate. P-value for binary endpoint is based on the 2-sided Chi-square test.

**Table 14: Time to Loss of the Improvement of PASI Score for Subjects Who Were Re-randomized During the Randomized Treatment Withdrawal Period (Weeks 32 to 52)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| | **Re-randomized to OTEZLA (N=77)** | **Re-randomized to Placebo (N=77)** | **Re-randomized to OTEZLA (N=62)** | **Re-randomized to Placebo (N=61)** |
| Number of Subjects who Lost Response (PASI-75 for Study 008 and PASI-50 for Study 009) | 40 | 63 | 7 | 35 |
| Number of Censored Subjects | 37 | 14 | 54 | 27 |
| Median Time to First Loss of Response[2] | 17.7 | 5.1 | 21.9 | 12.4 |
| Hazard Ratio[3] | 2.65 | | 7.70 | |
| P-value[4] | <0.001 | | <0.001 | |

Source: pg. 146 of Study Report for Study 008, pg. 142 of Study Report for Study 009.
(1) Medians are based on the Kaplan-Meier estimates.
(2) Hazard ratios are based on a Cox model with treatment as the independent variable.
(3) P-values are based on the log-rank test.

### 3.2.8 Exploratory Efficacy Results

As noted in Section 3.2.3, the multiplicity testing strategy was different between the SAPs and the protocols. In the SAPs, the applicant included several exploratory endpoints (4 were added to the list for Study 008 and 3 were added to the list for Study 009). The applicant did not submit the SAPs for review until the Pre-NDA meeting (May 15, 2013), which was after the studies were unblinded and analyzed.

Tables 15, 16, and 17 present the results of the three exploratory endpoints included in the multiplicity strategy specified in the SAP and reported in the study reports. (b) (4)

(b) (4)

(b) (4)

(b) (4)

[redacted]

## 3.3 Evaluation of Safety

### 3.3.1 Extend of Exposure

The extent of exposure to study product is presented in Table 18. The planned duration of exposure for the placebo-controlled phase in both studies was 16 weeks. For Study 008, the duration of exposure was similar between the two treatment arms. For Study 009, the duration of exposure was slightly higher in the OTEZLA arm compared to the placebo arm. The duration of exposure in Study 008 was slightly higher compared to Study 009.

**Table 18: Extent of Exposure During the Placebo-Controlled Phase (Weeks 0 to 16) in Studies 008 and 009 (Safety Population)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| | **OTEZLA (N=560)** | **Placebo (N=282)** | **OTEZLA (N=272)** | **Placebo (N=136)** |
| **Duration of Exposure (weeks)** | | | | |
| Mean (SD) | 15.0 (3.44) | 14.8 (3.58) | 14.6 (4.12) | 14.0 (4.55) |
| Median | 16.0 | 16.0 | 16.0 | 16.0 |
| Range | 0.1 - 18.4 | 0.1 - 18.0 | 0.1 - 18.3 | 0.1 - 17.9 |
| **Duration of Exposure Category** | | | | |
| < 4 Weeks | 23 (4.1%) | 9 (3.2%) | 17 (6.3%) | 12 (8.8%) |
| ≥ 4 to < 8 Weeks | 18 (3.2%) | 14 (5.0%) | 8 (2.9%) | 6 (4.4%) |
| ≥ 8 to < 12 Weeks | 7 (1.3%) | 9 (3.2%) | 7 (2.6%) | 5 (3.7%) |
| ≥ 12 to < 16 Weeks | 141 (25.2%) | 67 (23.8%) | 43 (15.8%) | 26 (19.1%) |
| ≥ 16 Weeks | 371 (66.3%) | 183 (64.9%) | 197 (72.4%) | 87 (64.0%) |

Source: pg. 188 of Study Report for Study 008, pg. 188 of Study Report for Study 009.

### 3.3.2 Adverse Events

Approximately 68-69% of OTEZLA and 56-60% of placebo subjects experienced at least one adverse event, and approximately 2% of OTEZLA and 2-3% of placebo subjects experienced a serious adverse event. Approximately 5-6% of OTEZLA and 3-5% of placebo subjects discontinued treatment due to adverse events. Table 19 presents an overview of adverse events reported during the placebo-controlled phase. The adverse events observed in at least 2% of subjects in either treatment arm during the placebo-controlled phase in Studies 008 and 009 are presented in Table 20.

**Table 19: Overview of Adverse Events Reported During the Placebo-Controlled Phase (Weeks 0 to 16) in Studies 008 and 009 (Safety Population)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| **Subjects With:** | **OTEZLA (N=560)** | **Placebo (N=282)** | **OTEZLA (N=272)** | **Placebo (N=136)** |
| Any AEs | 388 (69.3%) | 157 (55.7%) | 185 (68.0%) | 82 (60.3%) |
| Any Drug-related[(1)] AEs | 224 (40.0%) | 58 (20.6%) | 106 (39.0%) | 29 (21.3%) |
| Any Severe AEs | 20 (3.6%) | 9 (3.2%) | 12 (4.4%) | 6 (4.4%) |
| Any Serious AEs | 12 (2.1%) | 8 (2.8%) | 5 (1.8%) | 3 (2.2%) |
| Any Serious Drug-related AEs | 4 (0.7%) | 0 | 0 | 0 |
| Any AEs Leading to Drug Interruption | 37 (6.6%) | 13 (4.6%) | 16 (5.9%) | 4 (2.9%) |
| Any AEs Leading to Drug Withdrawal | 29 (5.2%) | 9 (3.2%) | 15 (5.5%) | 7 (5.1%) |
| Any AEs Leading to Death | 1 (0.2) | 1 (0.4%) | 0 | 0 |

Source: pg. 191 of Study Report for Study 008, pg. 192 of Study Report for Study 009.
(1) Drug-related as assessed by the investigator.

**Table 20: Adverse Events in >2% of Subjects in any Treatment Group During the Placebo-Controlled Phase (Weeks 0 to 16) by System Organ Class and Preferred Term in Studies 008 and 009 (Safety Population)**

| | | Study 008 | | Study 009 | |
|---|---|---|---|---|---|
| **System Organ Class** | **Preferred Term** | **OTEZLA (N=560)** | **Placebo (N=282)** | **OTEZLA (N=272)** | **Placebo (N=136)** |
| **Infections and infestations** | Upper respiratory tract infection | 57 (10.2%) | 21 (7.4%) | 13 (4.8%) | 6 (4.4%) |
| | Nasopharyngitis | 41 (7.3%) | 23 (8.2%) | 20 (7.4%) | 6 (4.4%) |
| | Sinusitis | 16 (2.9%) | 5 (1.8%) | 2 (0.7%) | 1 (0.7%) |
| | Urinary Tract Infection | 10 (1.8%) | 9 (3.2%) | 5 (1.8%) | 0 |
| | Gastroenteritis | 10 (1.8%) | 6 (2.1%) | 3 (1.1%) | 3 (2.2%) |
| | Influenza | 4 (0.7%) | 6 (2.1%) | 3 (1.1%) | 1 (0.7%) |
| **Metabolism and nutrition disorders** | Decreased appetite | 16 (2.9%) | 2 (0.7%) | 7 (2.6%) | 2 (1.5%) |
| **Psychiatric disorders** | Insomnia | 15 (2.7%) | 2 (0.7%) | 5 (1.8%) | 2 (1.5%) |
| **Nervous system disorders** | Tension headache | 41 (7.3%) | 12 (4.3%) | 20 (7.4%) | 2 (1.5%) |
| | Headache | 31 (5.5%) | 13 (4.6%) | 17 (6.3%) | 1 (0.7%) |
| | Migraine | 13 (2.3%) | 3 (1.1%) | 4 (1.5%) | 1 (0.7%) |
| **Vascular disorders** | Hypertension | 10 (1.8%) | 7 (2.5%) | 4 (1.5%) | 3 (2.2%) |
| **Respiratory, thoracic and mediastinal disorders** | Cough | 10 (1.8%) | 4 (1.4%) | 4 (1.5%) | 3 (2.2%) |
| **Gastrointestinal disorders** | Diarrhea | 105 (18.8%) | 20 (7.1%) | 43 (15.8%) | 8 (5.9%) |
| | Nausea | 88 (15.7%) | 19 (6.7%) | 50 (18.4%) | 9 (6.6%) |
| | Vomiting | 17 (3.0%) | 2 (0.7%) | 14 (5.1%) | 5 (3.7%) |
| | Dyspepsia | 17 (3.0%) | 1 (0.4%) | 8 (2.9%) | 3 (2.2%) |
| | Abdominal Discomfort | 14 (2.5%) | 5 (1.8%) | 4 (1.5%) | 1 (0.7%) |
| | Frequent Bowel Movements | 14 (2.5%) | 1 (0.4%) | 3 (1.1%) | 0 |
| | Gastrooesophageal Reflux Disease | 11 (2.0%) | 3 (1.1%) | 4 (1.5%) | 1 (0.7%) |
| | Abdominal pain upper | 10 (1.8%) | 3 (1.1%) | 8 (2.9%) | 1 (0.7%) |
| | Abdominal pain | 8 (1.4%) | 3 (1.1%) | 9 (3.3%) | 3 (2.2%) |
| **Skin and subcutaneous tissue disorders** | Psoriasis | 4 (0.7%) | 6 (2.1%) | 4 (1.5%) | 7 (5.1%) |
| | Pruritus | 4 (0.7%) | 3 (1.1%) | 3 (1.1%) | 3 (2.2%) |
| **Musculoskeletal and connective tissue disorders** | Back Pain | 14 (2.5%) | 2 (0.7%) | 6 (2.2%) | 2 (1.5%) |
| | Myalgia | 5 (0.9%) | 3 (1.1%) | 4 (1.5%) | 3 (2.2%) |
| | Pain in extremity | 5 (0.9%) | 1 (0.4%) | 6 (2.2%) | 2 (1.5%) |
| **General disorders and administration site conditions** | Fatigue | 17 (3.0%) | 3 (1.1%) | 8 (2.9%) | 3 (2.2%) |
| | Oedema peripheral | 0 | 2 (0.7%) | 2 (0.7%) | 4 (2.9%) |
| | Influenza like illness | 1 (0.2%) | 1 (0.4%) | 1 (0.4%) | 3 (2.2%) |
| | Pyrexia | 2 (0.4%) | 2 (0.7%) | 1 (0.4%) | 3 (2.2%) |

Source: pg. 1521-1534 of Study Report for Study 008, pg. 1459-1468 of Study Report for Study 009.

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race, Age, and Baseline Disease Severity

Treatment effects were generally consistent across gender, race (white and non-white), age (18-64 and 65+), and baseline disease severity (sPGA) subgroups in Studies 008 and 009. See Tables 21 and 22.

**Table 21: Primary and Major Secondary Efficacy Results at Week 16 by Gender, Race, Age, and Baseline Disease Severity (sPGA) for Study 008 (FAS, LOCF)**

| | PASI-75 at Week 16 | | Success[1] on sPGA at Week 16 | |
|---|---|---|---|---|
| | OTEZLA (N=562) | Placebo (N=282) | OTEZLA (N=562) | Placebo (N=282) |
| **Gender** | | | | |
| Male | 110/379 (29.0%) | 8/194 (4.1%) | 68/379 (17.9%) | 8/194 (4.1%) |
| Female | 76/183 (41.5%) | 7/88 (8.0%) | 54/183 (29.5%) | 3/88 (3.4%) |
| **Race** | | | | |
| Non-White | 14/55 (25.5%) | 2/32 (6.3%) | 11/55 (20.0%) | 0/32 (0%) |
| White | 172/507 (33.9%) | 13/250 (5.2%) | 111/507 (21.9%) | 11/250 (4.4%) |
| **Age** | | | | |
| 18-64 | 168/514 (32.7%) | 14/258 (5.4%) | 110/514 (21.4%) | 10/258 (3.9%) |
| 65+ | 18/48 (37.5%) | 1/24 (4.2%) | 12/48 (25.0%) | 1/24 (4.2%) |
| **Baseline Disease Severity (sPGA)** | | | | |
| 2 - Mild | * | 0/1 (0%) | * | 0/1 (0%) |
| 3 - Moderate | 142/401 (35.4%) | 12/192 (6.3%) | 94/401 (23.4%) | 10/192 (5.2%) |
| 4 - Severe | 44/161 (27.3%) | 3/89 (3.4%) | 28/161 (17.4%) | 1/89 (1.1%) |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.

**Table 22: Primary and Major Secondary Efficacy Results at Week 16 by Gender, Race, Age, and Baseline Disease Severity (sPGA) for Study 009 (FAS, LOCF)**

| | PASI-75 at Week 16 | | Success[1] on sPGA at Week 16 | |
|---|---|---|---|---|
| | OTEZLA (N=274) | Placebo (N=137) | OTEZLA (N=274) | Placebo (N=137) |
| **Gender** | | | | |
| Male | 44/176 (25.0%) | 4/100 (4.0%) | 27/176 (15.3%) | 2/100 (2%) |
| Female | 35/98 (35.7%) | 4/37 (10.8%) | 29/98 (29.6%) | 4/37 (10.8%) |
| **Race** | | | | |
| Non-White | 7/24 (29.2%) | 0/9 (0%) | 4/24 (16.7%) | 0/9 (0%) |
| White | 7/250 (28.8%) | 8/128 (6.3%) | 52/250 (20.8%) | 6/128 (4.7%) |
| **Age** | | | | |
| 18-64 | 69/252 (27.4%) | 6/123 (4.9%) | 51/252 (20.2%) | 5/123 (4.1%) |
| 65+ | 10/22 (45.5%) | 2/14 (14.3%) | 5/22 (22.7%) | 1/14 (7.1%) |
| **Baseline Disease Severity (sPGA)** | | | | |
| 2 - Mild | 0/1 (0%) | * | 0/1 (0%) | * |
| 3 - Moderate | 60/198 (30.3%) | 7/88 (8.0%) | 47/198 (23.7%) | 5/88 (5.7%) |
| 4 - Severe | 19/75 (25.3%) | 1/49 (2.0%) | 9/75 (12.0%) | 1/49 (2.0%) |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.

## 4.2 Center and Geographic Region

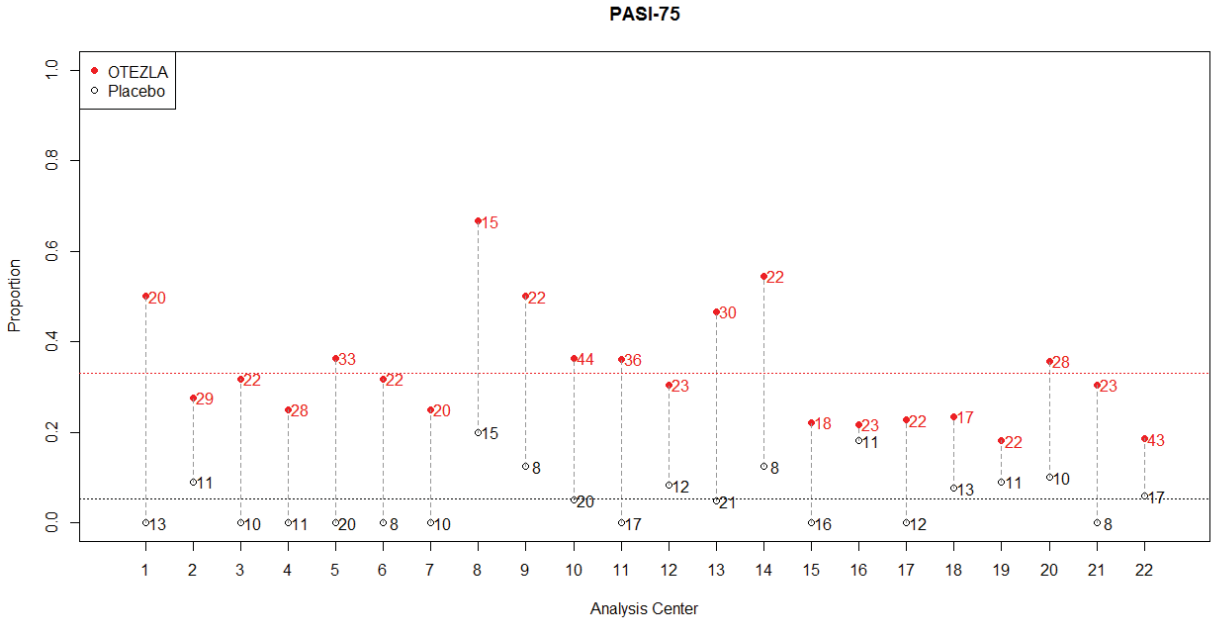
The Agency recommended (Advice Letter dated 6/3/2011) that the studies be designed so that centers enroll sufficient numbers of active and placebo subjects to adequately assess treatment effects within centers and treatment by center interactions. In addition, the Agency recommended using a randomization scheme that either stratifies by center or allocates complete blocks to centers rather than using a study-wide randomization scheme. However, the applicant did not implement the Agency's advice when conducting the randomization, which resulted in substantial imbalance in treatment allocation in several centers. See Section A.4 in Appendix.

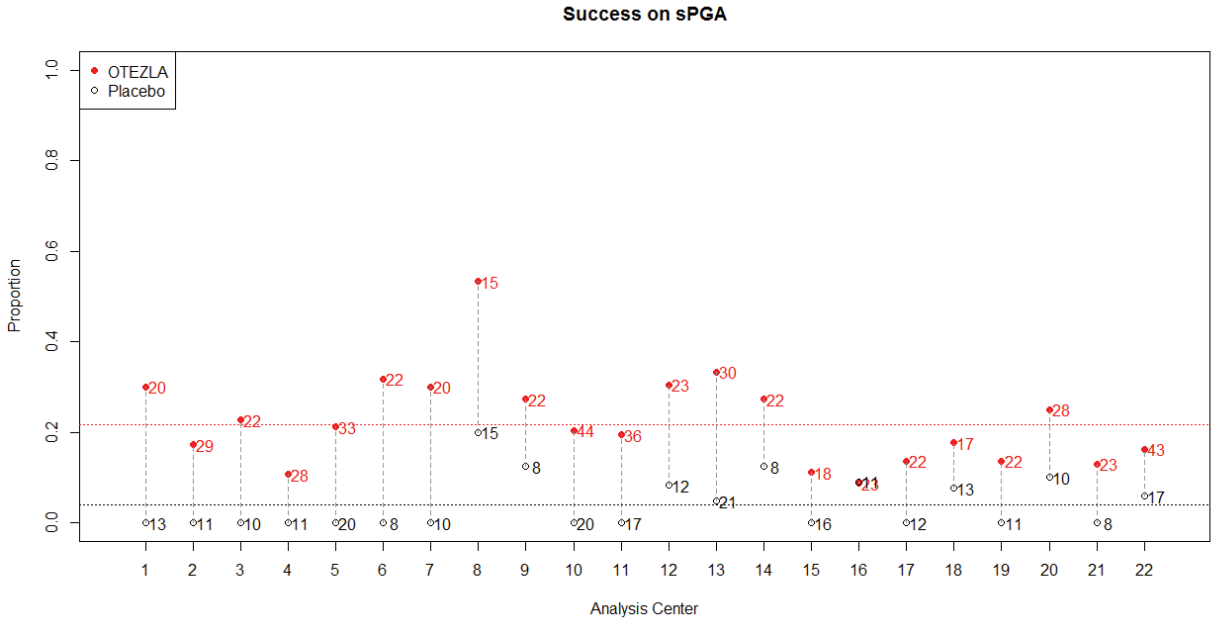
Study 008 enrolled and randomized subjects from 72 centers (34 in US, 17 in Canada, 15 in Europe, and 6 in Australia). Study 009 enrolled and randomized subjects from 45 centers (19 in US, 7 in Canada, and 19 in Europe). The applicant pooled centers to have at least 30 subjects in each analysis center. The SAPs pre-specified that centers were to be first pooled within each country according to their rank, starting with the smallest centers (i.e., within a country, the smallest centers were first pooled until the pooled center had a minimum size of 30). Countries within a region (US, Canada, and Europe) with fewer than 30 subjects were pooled similarly from small to large. After pooling, Study 008 had 22 analysis centers and Study 009 had 10 analysis centers. It should be noted that pooling process could mask center effects. Therefore, a more meaningful assessment of the center-to-center variability would be to evaluate the treatment effects prior to pulling. Among the centers that enrolled a reasonable number of subjects, the treatment effect was generally consistent and no center was overly influential on the overall results; however, a couple of these centers showed no treatment effect. See Tables A.4.1 and A.4.2 in Appendix.

Figures 4 and 5 display the primary and major secondary efficacy results at Week 16 by analysis center for Studies 008 and 009, respectively. For Study 008, all but one analysis center (16) had success rates for both endpoints higher in the OTEZLA arm compared to the placebo arm. For Study 009, all analysis centers had success rates for both endpoints higher in the OTEZLA arm compared to the placebo arm; however, two of the analysis centers (3 and 6) had small treatment effects for the major secondary endpoint of success on sPGA.

Figure 6 displays the primary and major secondary efficacy results at Week 16 by region for Studies 008 and 009. In general, the treatment effects were consistent across the regions in both studies.

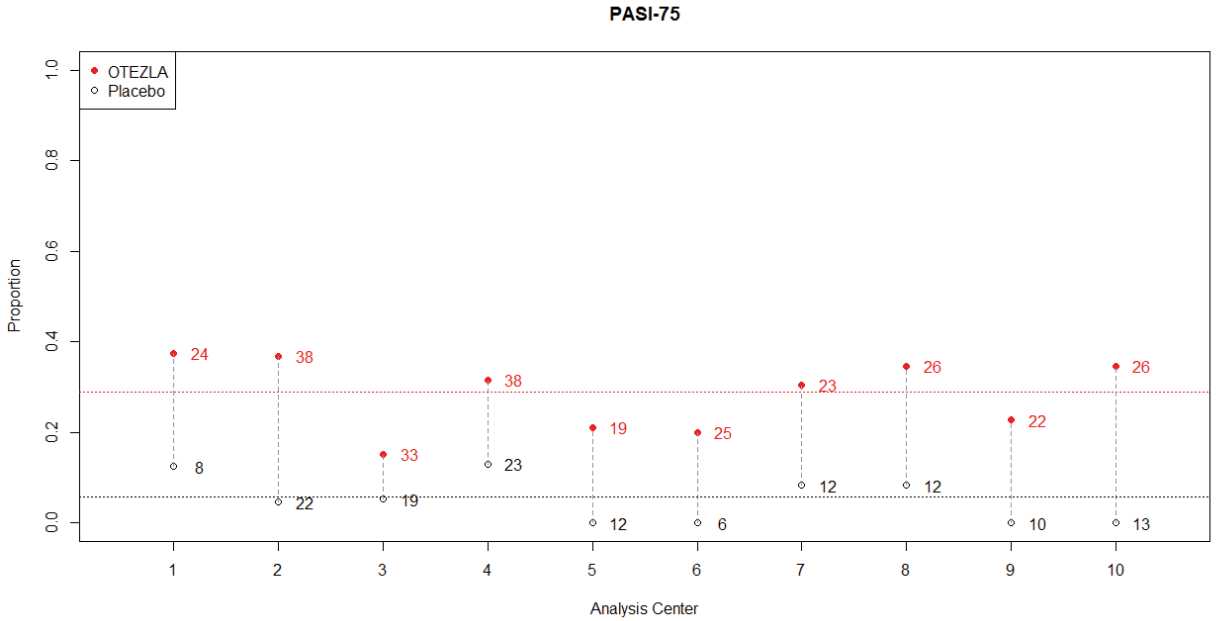
**Figure 4: Primary and Major Secondary Efficacy Results at Week 16 by Analysis Center in Study 008 (FAS, LOCF)**

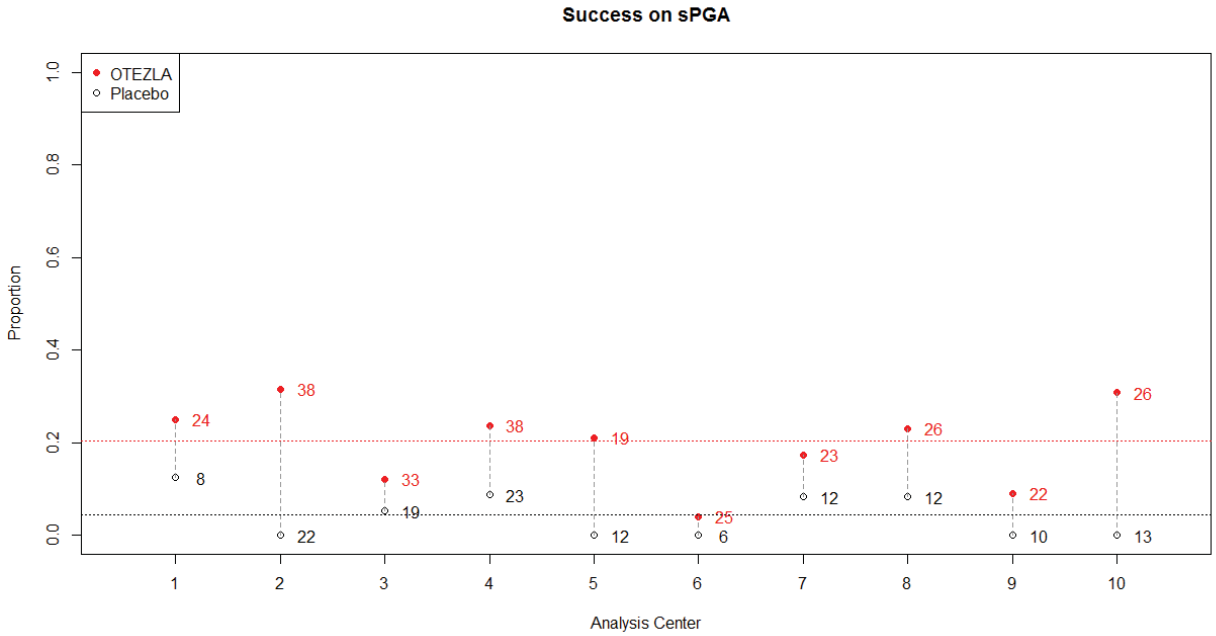



Source: Reviewer's Analysis

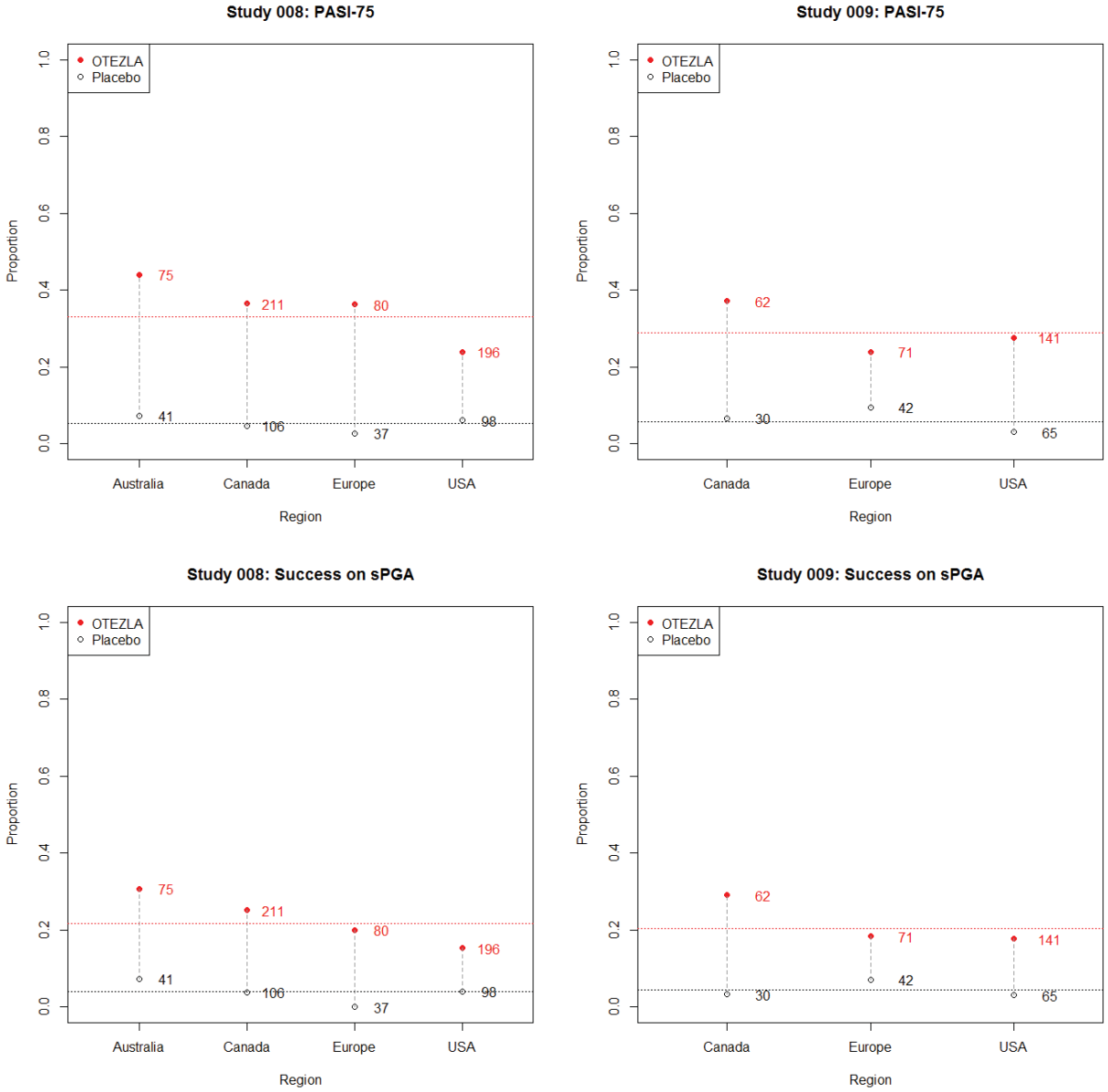
**Figure 5: Primary and Major Secondary Efficacy Results at Week 16 by Analysis Center in Study 009 (FAS, LOCF)**




Source: Reviewer's Analysis

**Figure 6: Primary and Major Secondary Efficacy Results at Week 16 by Region in Studies 008 and 009 (FAS, LOCF)**




Source: Reviewer's Analysis

## 4.3 Other Special/Subgroup Populations

The protocols permitted the following concomitant medications/therapy:

- Low-potency or weak corticosteroids (eg, Class 6 or 7 in US, such as hydrocortisone, desonide, alclometasone dipropionate) will be allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study
- Subjects with scalp psoriasis will be permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions
- An unmedicated skin moisturizer (eg, Eucerin) will be also permitted for body lesions only

A subgroup analysis was conducted to investigate the potential impact of concomitant medications. Subjects were classified as whether or not they used concomitant medications (known to treat psoriasis indications) during the placebo-controlled phase. For Study 008, the rate of concomitant medication use was similar between the two treatment arms. For Study 009, the rate of concomitant medication use was higher in the placebo arm compared to the OTEZLA arm. The treatment effect was similar between the two subgroups in Study 008. For Study 009, the treatment effect was higher in the subgroup that used concomitant medication; however, the number of subjects using concomitant medication was very small in Study 009. See Table 23.

**Table 23: Efficacy Results at Week 16 by Concomitant Medication(1) Use (FAS, LOCF)**

| | Study 008 | | Study 009 | |
|---|---|---|---|---|
| | **OTEZLA (N=562)** | **Placebo (N=282)** | **OTEZLA (N=274)** | **Placebo (N=137)** |
| **Concomitant Medication** | | | | |
| Yes | 48 (8.5%) | 25 (8.9%) | 15 (5.5%) | 24 (17.5%) |
| No | 514 (91.5%) | 257 (91.1%) | 259 (94.5%) | 113 (82.5%) |
| **PASI-75** | | | | |
| Concomitant -Yes | 13/48 (27.1%) | 0/25 (0%) | 8/15 (53.3%) | 1/24 (4.2%) |
| Concomitant -No | 173/514 (33.7%) | 15/257 (5.8%) | 71/259 (27.4%) | 7/113 (6.2%) |
| **Success(2) on sPGA** | | | | |
| Concomitant -Yes | 10/48 (20.8%) | 0/25 (0%) | 5/15 (33.3%) | 1/24 (4.2%) |
| Concomitant -No | 112/554 (21.8%) | 11/257 (4.3%) | 51/259 (19.7%) | 5/113 (4.3%) |

Source: Reviewer's Analysis
(1) Medications known to treat psoriasis indications.
(2) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

There were no major statistical issues affecting overall conclusions. The Agency recommended (Advice Letter dated 6/3/2011) that the studies be designed so that centers enroll sufficient numbers of active and placebo subjects to adequately assess treatment effects within centers and treatment by center interactions. In addition, the Agency recommended using a randomization scheme that either stratifies by center or allocates complete blocks to centers rather than using a study-wide randomization scheme. However, the applicant did not implement the Agency's advice when conducting the randomization, which resulted in substantial imbalance in treatment allocation in several centers. Among the centers that enrolled a reasonable number of subjects, the treatment effect was generally consistent and no center was overly influential on the overall results; however, a couple of these centers showed no treatment effect.

The Agency has consistently stated (EOP2 meeting on May 12, 2010 and in the advice letter sent on June 3, 2011) that secondary endpoints intended to support efficacy claims should be limited to a small set of clinically relevant endpoints that are adjusted for multiplicity. Instead of reducing the number of secondary endpoints (the protocols specified 8 secondary endpoints), the applicant added several exploratory endpoints (4 were added to the list for Study 008 and 3 were added to the list for Study 009) to the multiplicity testing strategy in the SAPs. The addition of the exploratory endpoints into the multiplicity testing strategy occurred after the studies started and the SAPs were not submitted to the Agency until the Pre-NDA meeting on May 15, 2013.

For the handling of missing data, the primary imputation method specified in the protocol was LOCF. In the study reports, the applicant conducted two sensitivity analyses for handling missing data: imputing missing as failures and imputing dropouts due to AE or lack of efficacy as failures and all others using LOCF. In the Filing Communication sent on December 5, 2013, the Agency reiterated the recommendation that the applicant should include methods that use alternative assumptions as sensitivity analysis for handling of missing data (e.g., multiple imputation or modeling approach), and the Agency requested that the applicant provide the results using the recommended analysis methods. In response, the applicant conducted an additional sensitivity analysis where missing data was imputed using multiple imputation (MI). In both studies, the results were very similar across the different sensitivity analyses.

## 5.2 Collective Evidence

The applicant evaluated the efficacy of OTEZLA tablets, 30 mg in two placebo-controlled trials for the treatment of plaque psoriasis. The trials enrolled adult subjects (18 years of age and older) with a clinical diagnosis of moderate to severe plaque psoriasis, defined as at least 10% body surface area (BSA) involvement, a Psoriasis Area and Severity Index (PASI) score ≥ 12 and a static Physician Global Assessment (sPGA) score ≥ 3 (moderate), and be candidates for systemic or phototherapy. The protocol-specified primary efficacy endpoint was the proportion of subjects who achieved at least a 75% reduction in PASI (PASI-75) at Week 16 from baseline.

The protocol specified the major secondary efficacy endpoint of the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (almost clear) at Week 16. Both endpoints were statistically significant and the results are presented in Table 24.

**Table 24: Primary and Major Secondary Efficacy Results at Week 16 (FAS, LOCF)**

| | Study 008 | | | Study 009 | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **OTEZLA (N=562)** | **Placebo (N=282)** | **P-value[2]** | **OTEZLA (N=274)** | **Placebo (N=137)** | **P-value[2]** |
| PASI-75 | 186 (33.1%) | 15 (5.3%) | <0.001 | 79 (28.8%) | 8 (5.8%) | <0.001 |
| Success[1] on sPGA | 122 (21.7%) | 11 (3.9%) | <0.001 | 56 (20.4%) | 6 (4.4%) | <0.001 |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.
(2) P-value based on the 2-sided Chi-square test.

## 5.3 Conclusions and Recommendations

Efficacy findings from the two pivotal trials (Studies 008 and 009) established that OTEZLA tablets, 30 mg twice daily was superior to placebo for the treatment of moderate to severe plaque psoriasis in adults 18 years of age and older.

# APPENDIX

(b) (4)

(b) (4)

## A.4 Detailed Center Information

**Table A.4.1: Primary and Major Secondary Efficacy Results at Week 16 by Center for Study 008 (FAS, LOCF)**

| | Number of Subjects | | | PASI-75 at Week 16 | | Success[1] on sPGA at Week 16 | |
|---|---|---|---|---|---|---|---|
| SITEID | Total | OTEZLA | Placebo | OTEZLA | Placebo | OTEZLA | Placebo |
| 101 | 30 | 22 | 8 | 31.8% | 0% | 31.8% | 0% |
| 103 | 30 | 20 | 10 | 25.0% | 0% | 30.0% | 0% |
| 105 | 30 | 15 | 15 | 66.7% | 20.0% | 53.3% | 20.0% |
| 106 | 30 | 22 | 8 | 50.0% | 12.5% | 27.3% | 12.5% |
| 406 | 30 | 22 | 8 | 54.5% | 12.5% | 27.3% | 12.5% |
| 104 | 28 | 19 | 9 | 42.1% | 0% | 21.1% | 0% |
| 405 | 28 | 18 | 10 | 61.1% | 0% | 38.9% | 0% |
| 4 | 26 | 18 | 8 | 27.8% | 12.5% | 33.3% | 12.5% |
| 114 | 25 | 14 | 11 | 28.6% | 0% | 21.4% | 0% |
| 401 | 23 | 12 | 11 | 25.0% | 9% | 25.0% | 9.1% |
| 202 | 21 | 18 | 3 | 55.6% | 0% | 33.3% | 0% |
| 111 | 20 | 15 | 5 | 40.0% | 0% | 20.0% | 0% |
| 404 | 20 | 12 | 8 | 0.0% | 0% | 0% | 0% |
| 113 | 19 | 13 | 6 | 7.7% | 0% | 0% | 0% |
| 301 | 18 | 15 | 3 | 53.3% | 0% | 20.0% | 0% |
| 303 | 18 | 10 | 8 | 40.0% | 0% | 30.0% | 0% |
| 2 | 17 | 13 | 4 | 23.1% | 0% | 7.7% | 0% |
| 5 | 17 | 13 | 4 | 15.4% | 0% | 7.7% | 0% |
| 26 | 17 | 12 | 5 | 8.3% | 0% | 0% | 0% |
| 117 | 17 | 14 | 3 | 28.6% | 0% | 21.4% | 0% |
| 304 | 17 | 11 | 6 | 27.3% | 0% | 18.2% | 0% |
| 107 | 15 | 8 | 7 | 37.5% | 0% | 25.0% | 0% |
| 49 | 14 | 10 | 4 | 40.0% | 0% | 20.0% | 0% |
| 108 | 14 | 12 | 2 | 8.3% | 0% | 0% | 0% |
| 112 | 14 | 9 | 5 | 33.3% | 0% | 22.2% | 0% |
| 8 | 13 | 11 | 2 | 63.6% | 0% | 45.5% | 0% |
| 19 | 13 | 10 | 3 | 30.0% | 33.3% | 20.0% | 33.3% |
| 6 | 12 | 7 | 5 | 0% | 0% | 0% | 0% |
| 102 | 12 | 8 | 4 | 50.0% | 25.0% | 37.5% | 0% |
| 16 | 11 | 5 | 6 | 40.0% | 0% | 20.0% | 0% |
| 18 | 11 | 9 | 2 | 0% | 0% | 11.1% | 0% |
| 47 | 11 | 8 | 3 | 25.0% | 33.3% | 12.5% | 0% |
| 110 | 11 | 4 | 7 | 50.0% | 0% | 25.0% | 0% |
| 801 | 11 | 8 | 3 | 37.5% | 0% | 12.5% | 0% |
| 3 | 10 | 7 | 3 | 14.3% | 0% | 0% | 0% |
| 25 | 10 | 5 | 5 | 0% | 0% | 0% | 0% |
| 30 | 10 | 5 | 5 | 60.0% | 20.0% | 60.0% | 20.0% |
| 109 | 10 | 8 | 2 | 75.0% | 0% | 37.5% | 0% |
| 116 | 10 | 6 | 4 | 33.3% | 0% | 33.3% | 0% |
| 403 | 10 | 8 | 2 | 87.5% | 50.0% | 87.5% | 50.0% |
| 32 | 9 | 6 | 3 | 33.3% | 0% | 33.3% | 0% |
| 48 | 9 | 8 | 1 | 25.0% | 0% | 12.5% | 0% |
| 204 | 9 | 3 | 6 | 0% | 0% | 0% | 0% |
| 10 | 8 | 4 | 4 | 25.0% | 50.0% | 25.0% | 25.0% |
| 21 | 8 | 3 | 5 | 33.3% | 0% | 0% | 0% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 31 | 8 | 5 | 3 | 0% | 0% | 0% | 0% |
| 11 | 7 | 6 | 1 | 50.0% | 0% | 16.7% | 0% |
| 22 | 7 | 5 | 2 | 0% | 0% | 0% | 0% |
| 15 | 6 | 5 | 1 | 0% | 0% | 0% | 0% |
| 34 | 6 | 3 | 3 | 33.3% | 0% | 0% | 0% |
| 305 | 6 | 3 | 3 | 0% | 33.3% | 0% | 0% |
| 23 | 5 | 3 | 2 | 0% | 0% | 0% | 0% |
| 27 | 5 | 2 | 3 | 50.0% | 0% | 50.0% | 0% |
| 302 | 5 | 5 | 0 | 20.0% | * | 20.0% | * |
| 402 | 5 | 3 | 2 | 0% | 0% | 0% | 0% |
| 1 | 4 | 2 | 2 | 0% | 0% | 0% | 0% |
| 12 | 4 | 2 | 2 | 50.0% | 0% | 0% | 0% |
| 14 | 4 | 2 | 2 | 50.0% | 0% | 0% | 0% |
| 33 | 4 | 1 | 3 | 0% | 0% | 0% | 0% |
| 501 | 3 | 1 | 2 | 0% | 0% | 0% | 0% |
| 502 | 3 | 3 | 0 | 0% | * | 0% | * |
| 28 | 2 | 1 | 1 | 0% | 0% | 0% | 0% |
| 35 | 2 | 2 | 0 | 0% | * | 0% | * |
| 58 | 2 | 1 | 1 | 0% | 0% | 0% | 0% |
| 115 | 2 | 2 | 0 | 0% | * | 0% | * |
| 802 | 2 | 1 | 1 | 0% | 0% | 0% | 0% |
| 13 | 1 | 1 | 0 | 0% | * | 0% | * |
| 59 | 1 | 1 | 0 | 100% | * | 100% | * |
| 201 | 1 | 0 | 1 | * | 0% | * | 0% |
| 503 | 1 | 0 | 1 | * | 0% | * | 0% |
| 701 | 1 | 1 | 0 | 0% | * | 0% | * |
| 703 | 1 | 1 | 0 | 0% | * | 0% | * |

Source: Reviewer's Analysis
(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.

**Table A.4.2: Primary and Major Secondary Efficacy Results at Week 16 by Center for Study 009 (FAS, LOCF)**

| | Number of Subjects | | | PASI-75 at Week 16 | | Success[1] on sPGA at Week 16 | |
|---|---|---|---|---|---|---|---|
| SITEID | Total | OTEZLA | Placebo | OTEZLA | Placebo | OTEZLA | Placebo |
| 37 | 20 | 13 | 7 | 38.5% | 0% | 38.5% | 0% |
| 118 | 20 | 12 | 8 | 16.7% | 0% | 41.7% | 0% |
| 119 | 20 | 14 | 6 | 35.7% | 16.7% | 14.3% | 0% |
| 122 | 20 | 12 | 8 | 58.3% | 0% | 41.7% | 0% |
| 45 | 19 | 13 | 6 | 30.8% | 0% | 23.1% | 0% |
| 120 | 18 | 14 | 4 | 50.0% | 0% | 35.7% | 0% |
| 220 | 18 | 10 | 8 | 20.0% | 0% | 0% | 0% |
| 57 | 17 | 12 | 5 | 41.7% | 0% | 16.7% | 0% |
| 60 | 15 | 10 | 5 | 0% | 0% | 0% | 0% |
| 323 | 15 | 10 | 5 | 30.0% | 0% | 30.0% | 0% |
| 36 | 13 | 6 | 7 | 33.3% | 0% | 33.3% | 0% |
| 51 | 13 | 11 | 2 | 36.4% | 50.0% | 27.3% | 50.0% |
| 324 | 13 | 9 | 4 | 11.1% | 0% | 0% | 0% |
| 40 | 12 | 9 | 3 | 22.2% | 0% | 0% | 0% |
| 43 | 12 | 8 | 4 | 25.0% | 25.0% | 12.5% | 25.0% |
| 56 | 12 | 9 | 3 | 33.3% | 0% | 11.1% | 0% |
| 38 | 11 | 8 | 3 | 12.5% | 0% | 12.5% | 0% |
| 50 | 11 | 9 | 2 | 0% | 0% | 0% | 0% |
| 52 | 11 | 6 | 5 | 50.0% | 0% | 50.0% | 0% |
| 320 | 10 | 6 | 4 | 0% | 25.0% | 0% | 25.0% |
| 321 | 10 | 5 | 5 | 0% | 0% | 0% | 0% |
| 42 | 9 | 8 | 1 | 50.0% | 0% | 0% | 0% |
| 123 | 8 | 6 | 2 | 16.7% | 50.0% | 16.7% | 50.0% |
| 41 | 7 | 6 | 1 | 33.3% | 0% | 33.3% | 0% |
| 44 | 7 | 5 | 2 | 0% | 0% | 20.0% | 0% |
| 251 | 6 | 3 | 3 | 33.3% | 33.3% | 33.3% | 33.3% |
| 450 | 6 | 5 | 1 | 20.0% | 0% | 0% | 0% |
| 39 | 5 | 3 | 2 | 33.3% | 0% | 0% | 0% |
| 46 | 5 | 3 | 2 | 0% | 0% | 0% | 0% |
| 53 | 4 | 0 | 4 | * | 0% | * | 0% |
| 121 | 4 | 3 | 1 | 0% | 0% | 0% | 0% |
| 322 | 4 | 3 | 1 | 33.3% | 0% | 33.3% | 0% |
| 350 | 4 | 3 | 1 | 0% | 0% | 0% | 0% |
| 920 | 4 | 1 | 3 | 0% | 66.7% | 0% | 33.3% |
| 921 | 4 | 3 | 1 | 33.3% | 0% | 33.3% | 0% |
| 922 | 4 | 2 | 2 | 100% | 0% | 100% | 0% |
| 54 | 3 | 2 | 1 | 50.0% | 0% | 50.0% | 0% |
| 221 | 3 | 3 | 0 | 66.7% | * | 33.3% | * |
| 822 | 3 | 1 | 2 | 100% | 0% | 100% | 0% |
| 923 | 3 | 2 | 1 | 100% | 0% | 100% | 0% |
| 124 | 2 | 1 | 1 | 100% | 0% | 0% | 0% |
| 820 | 2 | 2 | 0 | 0% | * | 0% | * |
| 924 | 2 | 1 | 1 | 0% | 0% | 100% | 0% |
| 222 | 1 | 1 | 0 | 0% | * | 0% | * |
| 250 | 1 | 1 | 0 | 0% | * | 0% | * |

Source: Reviewer's Analysis

(1) Success is defined as a sPGA score of 0 (clear) or 1 (almost clear) with at least 2 points reduction from baseline.

## SIGNATURES/DISTRIBUTION LIST

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