CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 #:	BLA 761055
Drug Name:	Dupilumab
Indication(s):	For the treatment of atopic dermatitis in adults patients whose disease is not adequately controlled with topical prescription therapy, (b) (4) or (b) (4) not advisable.
Applicant:	Regeneron
Date(s):	Stamp date: 7/29/2016 PDUFA: 3/29/2016
Review Priority:	Priority
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Keywords:
Atopic dermatitis; superiority; monotherapy; adjunctive therapy

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1. EXECUTIVE SUMMARY

The applicant is seeking approval of dupilumab 300 mg once every 2 weeks (Q2W) for the indication of treatment of atopic dermatitis (AD) in adults patients whose disease is not adequately controlled with topical prescription therapy, (b) (4) or (b) (4) not advisable. (b) (4)

The safety and efficacy of dupilumab was evaluated in three pivotal Phase 3 trials (Trials 1334, 1416, and 1224). All trials evaluated two dose frequencies (300 mg Q2W and 300 mg QW) versus placebo. Trials 1334 and 1416 were monotherapy trials and Trial 1224 was an adjunctive therapy trial that allowed the use of topical corticosteroid (TCS).

All trials enrolled men and women, 18 years of age or older, chronic AD that had been present for at least 3 years before the screening visit, Eczema Area and Severity Index (EASI) ≥16, Investigator's Global Assessment (IGA) ≥3, ≥10% body surface area (BSA) with AD involvement, baseline pruritus numeric rating scale (NRS) average for maximum itch intensity ≥3, documented history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments were otherwise medically inadvisable (e.g. because of important side effects or safety risks). In all three trials, subjects received an initial dose of 600 mg dupilumab (two 300 mg injections) on Day 1, followed by 300 mg QW or 300 mg Q2W, or matching placebo. Dupilumab was administered by subcutaneous injection in all three trials. According to the protocol, subjects were permitted to receive rescue treatment to control intolerable symptoms, and those subjects that received rescue treatment were considered as non-responders for the efficacy analyses.

In all three trials, for the comparison of dupilumab against placebo at Week 16, the primary endpoint was the proportion of subjects achieving IGA 0 or 1. Secondary endpoints that were agreed upon with the Agency included the EASI 75 response (i.e., ≥75% reduction from baseline in EASI score), and the proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 16.

Table 1 summarizes the primary as well as the secondary efficacy endpoints for the monotherapy trials, Trials 1334 and 1416. Both dupilumab 300 mg QW and 300 mg Q2W regimens were superior to placebo at Week 16 ($p<0.0001$) for the primary endpoint of IGA success (defined as a score of 0 or 1), as well as the secondary endpoints of EASI 75, reduction of at least 4-point change from baseline in pruritus score at Week 16 in all three trials. The results of the primary and secondary endpoints are presented in Tables 1 and 2.

Table 1. Proportion of Subjects Achieving Treatment Success at Week 16 for Monotherapy Trials 1334, 1416

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
FAS	223	224	224	239	233	236
IGA 0 or 1	83 (37%)	84 (38%)	23 (10%)	86 (36%)	83 (36%)	20 (9%)
EASI 75	117 (53%)	114 (51%)	33 (15%)	113(47%)	102 (44%)	28 (12%)
Pruritus FAS (Baseline NRS≥4)	201	213	212	228	225	221
Reduction of at least 4-point change from baseline (1)	81 (40%)	86 (40%)	24(12%)	87 (38%)	79 (35%)	21 (10%)

Source: Reviewer's analysis based on the Full Analysis Set (FAS) defined as all randomized subjects. (1) Proportion of subjects with a reduction of weekly average of peak daily pruritus NRS ≥4. Missing data as well as those that received rescue medication at any time within the 16 weeks was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

Table 2 summarizes the primary as well as the secondary efficacy endpoints for the combination trial, Trial 1224.

Table 2. Proportion of Subjects Achieving Treatment Success at Week 16 for Combination Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
FAS	319	106	315
IGA 0 or 1	125 (39%)	41 (39%)	39 (12%)
EASI 75	204 (64%)	73 (69%)	73 (23%)
Pruritus FAS (Baseline NRS≥4)	295	102	299
Reduction of at least 4-point change from baseline (1)	150 (51%)	60 (59%)	59 (20%)

Source: Reviewer's results based on the Full Analysis Set (FAS) defined as all randomized subjects. (1) Proportion of subjects with a reduction of weekly average of peak daily pruritus NRS ≥4. Missing data as well as those that received rescue medication was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

2. INTRODUCTION

2.1 Overview

The applicant is seeking approval of dupilumab 300 mg every other week (Q2W) for the indication of treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, (b) (4), or (b) (4) not advisable.

The safety and efficacy of dupilumab was evaluated in three pivotal Phase 3 trials (Trials 1334, 1416, and 1224). All trials evaluated two dose frequencies (300 mg Q2W and 300 mg QW) versus placebo. Trials 1334 and 1416 were monotherapy trials and Trial 1224 was an adjunctive therapy trial that allowed the use of topical corticosteroid (TCS).

2.2 Regulatory History

The clinical development program for dupilumab was under IND 107969 which was opened on 7/12/2010, and to date, there were several meetings held between the Agency and the sponsor to discuss the development program:

- Pre-IND meeting on 5/26/2010
- Type C Guidance teleconference to discuss sponsor's Phase 2b trial (R668-AD-1021) on 1/23/2013
- CMC Type C meeting on 5/8/2014
- End of Phase 2 meeting on 5/21/2014
- Type A meeting on 8/4/2014
- Breakthrough therapy designation was granted on 11/18/2014
- Type B meeting on 6/22/2015
- Type B CMC meeting on 10/2/2015
- Type B immunogenicity meeting on 11/4/2015
- Pre-BLA meeting 12/16/2015 (cancelled by the sponsor)
- Type B CMC only meeting on 2/24/2016

During the sponsor's development phase for dupilumab for the treatment of moderate to severe atopic dermatitis, the Agency provided extensive comments concerning their Phase 3 protocols:

- Two identical, confirmatory "**Monotherapy" Trials** (**R668-AD-1334** and **R668-AD-1416**) with 16 weeks of monotherapy treatment in adult subjects with moderate-to-severe AD who are not adequately controlled with or are intolerant to topical prescription therapy (600 subjects in each trial, randomized 1:1:1 to 300 mg QW, 300 mg Q2W, placebo)
- One **Combination Trial (R668-AD-1224)** of treatment with dupilumab in combination with topical corticosteroid (TCS) of 700 subjects randomized in 3:1:3 ratio to 300 mg QW,300 mg Q2W,placebo, respectively.

Table 3 provides an overview of the sponsor's Phase 3 trials.

Table 3. Overview of the Sponsor's Phase 3 trials

	Trial 1334	Trial 1416	Trial 1224
Study design	Randomized, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab **monotherapy** in adults with moderate to severe AD and a documented history of inadequate response or intolerance to treatment with topical AD medications.		Randomized, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab administered **concomitantly with TCS** in adults with moderate to severe AD.
Dates	10/28/2014-2/12/2016	12/3/2014-1/21/2016	
Study Population	Men and women, 18 years of age or older, chronic AD that had been present for at least 3 years before the screening visit, EASI ≥16, IGA ≥3, ≥10% body surface area (BSA) with AD involvement, baseline pruritus numeric rating scale (NRS) average for maximum itch intensity ≥3, documented history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments were otherwise medically inadvisable (e.g. because of important side effects or safety risks)		
Number of Centers	131	136	160
Number of subjects in the treatment arms	671 randomized in 1:1:1 ratio: • 223 Dupilumab 300 mg QW • 224 Dupilumab 300 mg Q2W • 224 Placebo	708 randomized in 1:1:1 ratio: • 239 Dupilumab 300 mg QW • 233 Dupilumab 300 mg Q2W • 236 Placebo	740 randomized in 3:1:3 ratio: • 319 Dupilumab 300 mg QW • 106 Dupilumab 300 mg Q2W • 315 Placebo
Randomization stratification	Using an interactive voice response system (IVRS)/interactive web response system (IWRS), randomization was stratified by disease severity (IGA 3 vs. 4), and region (Asia Pacific, Eastern Europe, Western Europe, and North and South America).		

Source: Reviewer table

The sponsor's IGA instrument is shown below.

Table 4. Sponsor's IGA instrument

Score	Investigator's Global Assessment (IGA) Standard Definitions	Investigator's Global Assessment (IGA): Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

The sponsor included the following scoring index for the EASI score.

Table 5. Scoring Index for Eczema Area and Severity Index (EASI)

The definitions of the scoring signs of EASI are given below:

Erythema	**(E)**
0 – None	
1 – Mild	Faintly detectable erythema: very light pink
2 – Moderate	Dull red, clearly distinguishable
3 – Severe	Deep / dark red
Infiltration / Papulation	**(I)**
0 – None	
1 – Mild	Barely perceptible elevation
2 – Moderate	Clearly perceptible elevation but not extensive
3 – Severe	Marked and extensive elevation
Excoriations	**(Ex)**
0 – None	
1 – Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2 – Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3 – Severe	Many erosive or crusty lesions
Lichenification	**(L)**
0 – None	
1 – Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2 – Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern
3 – Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

Scoring

Line	Area	Erythema	Infiltration	Excoriations	Lichenification	Area of Involvement	Multiplier	Score
1	Head/Neck	(_____ +	_____ +	_____ +	_____)	X _____	X 0.1	
2	Trunk	(_____ +	_____ +	_____ +	_____)	X _____	X 0.3	
3	Upper Extremities	(_____ +	_____ +	_____ +	_____)	X _____	X 0.2	
4	Lower Extremities	(_____ +	_____ +	_____ +	_____)	X _____	X 0.4	

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The datasets in this review are archived at: \\cdsesub1\evsprod\bla761055\0004\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review, and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

The applicant conducted three pivotal Phase 3 trials (Trials 1334, 1416, 1224), and for enrollment criteria for all three trials, see Table 3 that provides the overview of the enrollment criteria as well as the randomization stratification factors.

3.2.1 Two Identical Monotherapy Trials (Study R668-AD-1334 and R668-AD-1416)

3.2.1.1 Study Design

Both trials were entitled "Phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis".

The primary objective of each trial was to demonstrate the efficacy of dupilumab monotherapy compared to placebo in adult patients with moderate to severe AD. The secondary objective was to assess the safety of dupilumab monotherapy compared to placebo in patients with moderate to severe AD.

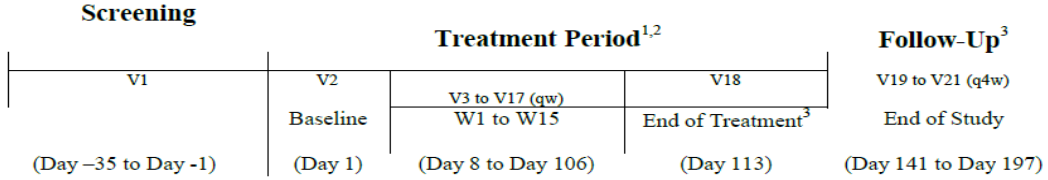
Using the IVRS/IWRS system, 671 and 708 subjects from 131 and 136 global sites (US and rest of the world) for Trial 1334 and Trial 1416, respectively, were randomized in a 1:1:1 ratio to the following groups:

- Dupilumab 600 mg loading on Day 1, followed by 300 mg weekly (QW) Dupilumab 600 mg loading on Day 1, followed by 300 mg every two weeks (Q2W) alternating with placebo Q2W
- Placebo (two injections on Day 1, then one injection QW)

Study drugs were provided in prefilled syringes for subcutaneous administration. For enrollment criteria, see Table 3.

In each trial, randomized subjects received an initial loading dose of study drug consisting of twice the nominal dose administered at subsequent dosing visits. Following the loading dose, study treatment was administered weekly for the following 15 weeks. Subjects were required to apply moisturizers twice daily for at least 7 days before randomization and continue throughout the study. Subjects received study drug by subcutaneous injections weekly for 16 consecutive weeks, and were followed up for additional 12 weeks. Visits occurred weekly until Week 16 (treatment period), then visits occurred every 4 weeks during the follow-up period (i.e., Weeks 20, 24, 28).

The sponsor's study design is shown below:



[1] Patients will receive a loading dose of study drug on day 1 and then receive dupilumab weekly or every two weeks or matching placebo during the subsequent 15 weeks. Patients in the q2w group will receive matching placebo in the weeks that dupilumab is not administered.
[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.
[3] The follow-up period will be for those patients who decline to enter the open-label extension or the maintenance study; for these patients, the end of treatment will be week 16.

Source: sponsor's protocol

3.2.1.2 Endpoints

The primary efficacy endpoint for both trials was the proportion of subjects with IGA 0 or 1 and with a reduction ≥2 points from baseline at Week 16.

The secondary endpoints for both monotherapy trials were:

- The proportion of subjects with EASI75 (≥75% improvement from baseline) at Week 16
- Proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 16
- Proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥3 from baseline to Week 16.
- Percent change from baseline to Week 16 in weekly average of peak daily pruritus NRS
- Proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 4
- Proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 2

For assessment of pruritus, the sponsor used the Pruritus NRS, and the protocol stated that subjects were instructed to use the IVRS to record their Pruritus NRS at screening and then daily through the last study visit. It should be noted that per the Advice Letter (dated 6/12/2015), the Agency considered the proportion of subjects with a reduction in peak pruritus NRS ≥4 from baseline to be an appropriate threshold, and stated that the proposed threshold of NRS ≥3 could be considered as supportive. Based on the Agency's advice, the sponsor included both in the testing hierarchy.

3.1.1.3 Statistical Methods

For both trials, the primary efficacy analyses were based on the Full Analysis Set (FAS) defined as all randomized subjects. The protocols defined the Per Protocol Set (PPS) as all FAS subjects except those with major efficacy-related protocol violations, and the protocol specified a major protocol violation as the one that may affect the interpretation of study results and listed the following criteria of major protocol violations:

- A patient who did not receive treatment as randomized
- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
- Patients who received <80% or >120% of the scheduled doses during the study treatment period.

For efficacy analyses, the protocols for both trials specified the following hypotheses for each dupilumab dose regimen:

H_0: No treatment difference between dupilumab vs. placebo.

H_1: There is a treatment difference between dupilumab vs. placebo.

The protocols specified that a hierarchical testing procedure would be used for the multiple endpoints at α=0.025 for each dose regimen independently. The sponsor used "a serial gatekeeping procedure" for the multiplicity adjustment for the secondary endpoints, and tested the endpoints in a pre-specified order.

For analysis of the binary endpoints, the CMH test adjusted by randomization strata (baseline disease severity and region) was used.

For handling missing data, the protocols for both trials specified that if a patient withdrew from the study, then this patient would be counted as non-responder for endpoints after withdrawal. In addition, if a patient received rescue medication, then the patient was specified as a non-responder from the time the rescue was used. As sensitivity analyses for handling missing data, the sponsor used the last observation carried forward (LOCF), and used all observed data analyses as a sensitivity analysis.

While the sponsor originally defined rescue treatment as having used any TCS during the trials, in an amended SAP submitted to the Agency (dated: 2/6/2016), the sponsor included a "rescue medication algorithm" that specified that subjects who used TCS during the first 14 days would not be considered using rescue treatment, and consequently, these subjects were not considered as non-responders for the efficacy analyses. It should be noted that the monotherapy trials were completed on 2/12/2016 and 1/21/2016 for Trials 1334 and 1416, respectively. Further, the protocols still specify TCS as prohibited medications, therefore, this reviewer considered those subjects that used TCS within the first 14 days as having used rescue treatment, and consequently, considered them as non-responders in the efficacy analyses.

3.2.2 Combination Study R668-AD-1224

3.2.2.1 Study Design

The primary objective of the trial was to demonstrate the efficacy of dupilumab administered concomitantly with TCS through Week 16 in adult patients with moderate to severe AD. The secondary objectives were to evaluate long-term efficacy and the long-term safety of dupilumab when administered concomitantly with TCS for up to 52 weeks.

This trial was a 64-week (52 weeks of treatment and 12 weeks of follow-up). Using the IVRS/IWRS, 740 subjects from 160 global sites were randomized in a 3:1:3 ratio to the following arms:

- Dupilumab 600 mg loading on Day 1, followed by 300 mg weekly (QW) for Weeks 1-52
- Dupilumab 600 mg loading on Day 1, followed by 300 mg every two weeks (Q2W) alternating with placebo Q2W for Weeks 1-52
- Placebo (two injections on Day 1, then one injection QW) for Weeks 1-52.

Randomization was stratified by disease severity (moderate vs. severe on the IGA), and region (Asian Pacific, East Europe, North and South America and West Europe). Enrollment criteria are summarized in Table 3 of this review.

Subjects received study drug by subcutaneous injections weekly for 16 consecutive weeks, and were followed up for additional 12 weeks. Visits occurred weekly until Week 16 (treatment period), then visits occurred every 4 weeks during the follow-up period (i.e., Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 (End of Study)).

The following figure shows the study design of Trial 1224:

Screening	**Treatment Period (Weeks, Days)[1, 2]**							**Follow-Up**
V1	V2	V3	V4	V5	V6	V7- V18 (qw)	V19-V27 (q4w)	V28-V30 (q4w)
	Baseline	W1	W2	W3	W4	W5 W16	W20-W52 End of Treatment	W56-W64 End of Study
(Day –35 to - 1)	(Day 1)	Day 8	Day 15	Day 22	Day 29	Day 36-113	Day 141-365	Day 393-449

[1] Patients will receive: 600 mg SC dupilumab loading dose on day 1 and then 300 mg dupilumab qw starting at day 8; 600 mg SC dupilumab loading dose on day 1 and then 300 mg q2w starting at day 15; or matching placebo with a placebo "loading dose" on day 1.

[2] Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug on day 1, day 8, and day 15.

Source: sponsor's protocol

All subjects were required to apply moisturizers (emollients) at least twice daily for at least 7 consecutive days immediately before randomization, and continued throughout Week 64. However, to allow adequate assessment of skin dryness, moisturizers were not to be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Starting at Day 1 (baseline), all subjects were required to initiate treatment with TCS using a standardized regimen according to the following guidelines:

- "Apply medium potency TCS once daily to areas with active lesions – low potency TCS once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium potency TCS is considered unsafe
- After lesions are under control (clear or almost clear), switch from medium potency to low potency TCS and treat once daily for 7 days, then stop
- If lesions return, reinstitute treatment with medium potency TCS, with the step-down approach described above upon lesion resolution
- For lesions persisting or worsening under once daily treatment with medium potency TCS, patients may be treated (rescued) with high or super-high potency TCS, unless higher potency TCS are considered safe
- Monitor the patient for signs of local or systemic TCS toxicity and step down or stop treatment as necessary"

The type and amount of topical products used during the study were recorded. The amount of TCS and Topical Calcineurin Inhibitor (TCI) used were determined by the weight of the tube at each visit.

The protocol specified that subjects use triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment for medium potency, and hydrocortisone 1% cream for low potency. If rescue with TCS were needed, it was recommended that subjects use mometasone 0.1% ointment for high potency and either betamethasone dipropionate 0.05% optimized ointment or clobetasol propionate 0.05% cream for super high potency TCS.

Subjects who received rescue treatment prior to Week 2 permanently discontinued study treatment. For the binary endpoints at Week 16, subjects were specified as nonresponders from the time the rescue was used.

3.2.2.2 Endpoints and Statistical Methods

The primary efficacy endpoint was the proportion of subjects with IGA 0 or 1 and with a reduction from baseline ≥2 points at Week 16.

For each dose regimen, the protocol specified that if both co-primary endpoints were statistically significant at the 2-sided 0.025 level, the following secondary endpoints were analyzed using a serial gatekeeping procedure to control the overall Type I error rate:

- The proportion of subjects with EASI 75 (≥75% improvement from baseline) at Week 16
- Proportion of subjects with improvement (reduction) of pruritus NRS ≥4 from baseline to Week 16
- Proportion of subjects with improvement (reduction) of pruritus NRS ≥3 from baseline to Week 16
- Proportion of subjects with IGA 0 or 1 and a reduction from baseline ≥2 points at Week 52
- Proportion of patients with EASI 75 response at Week 52
- Percent change from baseline to Week 16 in weekly average of peak daily pruritus NRS
- Proportion of subjects with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to Week 52
- Proportion of subjects with improvement (reduction) in weekly average of peak daily pruritus NRS ≥3 from baseline to Week 52
- Proportion of subjects with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to Week 24
- Proportion of subjects with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to Week 4
- Proportion of subjects with improvement (reduction) in weekly average of peak daily pruritus NRS ≥4 from baseline to Week 2

It should be noted that the Agency previous stated (advice letter dated: 10/27/2014), the endpoints at Week 52 (i.e., IGA at Week 52, EASI 75 at Week 52) "do not appear to add significant additional information to what has been shown by the primary endpoint and the first secondary endpoint and will therefore be unlikely to be incorporated into labeling".

For analysis of the binary endpoints, the CMH test adjusted by randomization strata (baseline disease severity and region) was used. For handling missing data, the protocol specified that if a patient withdraws from the study, then this patient was counted as non-responder for endpoints after withdrawal. In addition, if a patient received rescue medication, then the patient will be specified as a non-responder from the time the rescue was used. As sensitivity analyses for handling missing data for the binary endpoints, the sponsor used the last observation carried forward (LOCF), and also conducted sensitivity analyses by using all observed data.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 6 presents the subject disposition for the initial treatment period of the monotherapy trials (Trials 1334, 1416), and Table 7 presents the subject disposition for the initial treatment period of the combination trial (Trial 1224).

Trial 1334 enrolled a total of 671 randomized subjects from 131 centers. Trial 1416 enrolled a total of 708 randomized subjects from 136 centers. Trial 1224 enrolled a total of 740 randomized subjects from 160 centers. The discontinuation rates were generally similar between treatment arms within each trial, and between each trial. Note that with such low rates of missing data (<7%) along with the treatment effects seen in the trials, the impact of the imputation method on efficacy is minimal. In addition, subjects that received at least one rescue medication (e.g. TCS for Trials 1334, 1416) within the first 16 weeks are shown. Note that these subjects were considered as non-responders for the efficacy analyses.

In the initial treatment period of the monotherapy trials, the proportion of subjects that used at least one TCS was higher in those subjects that received placebo (26%) compared to those that received either dupilumab 300 mg QW (11%) or dupilumab 300 mg Q2W (10%). Similarly, in Trial 1224, a greater proportion of subjects that received placebo used rescue (37%) compared to those that received dupilumab (11%). Note that these subjects were considered as non-responders for the efficacy analyses. The most frequently used TCS in the initial period for Trial 1334 and Trial 1416 were betamethasone butyrate propionate (3%) and mometasone furoate (4%), respectively. In Trial 1224, most subjects that received the rescue medication used the topical medication (34%).

Table 6. Initial Treatment Period Subject Disposition for Trials 1334 and 1416

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
Discontinued	17 (8%)	11 (5%)	23 (10%)	17 (7%)	10 (4%)	15 (6%)
Reasons for discontinuation						
Adverse Events	4	2	3	1	1	3
Lack of efficacy	4	1	2	2	0	0
Lost to follow-up	0	0	0	5	3	3
Physician Decision	0	0	1	1	2	1
Protocol violation	2	1	0	1	1	2
Withdrawal by subject	5	6	14	6	2	6
Death	0	0	0	0	0	1
Other	1	1	1	0	1	0
Subjects that used at least one topical corticosteroids (TCS; dermatological preparations)[(1)]						
TCS	27 (12%)	24 (11%)	51 (23%)	24 (10%)	21 (9%)	67 (28%)

Source: Reviewer table; (1) subjects that used topical corticosteroids within the initial treatment period were considered as non-responders for the efficacy analyses.

Table 7. Initial Treatment Period Subject Disposition for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Randomized	319	106	315
Discontinued	17 (5%)	6 (6%)	25 (8%)
Reasons for discontinuation			
Adverse Events	4	0	5
Lack of efficacy	0	0	3
Lost to follow-up	2	0	1
Physician Decision	4	2	3
Protocol violation	3	1	2
Withdrawal by subject	4	3	11
Death	0	0	0
Other	0	0	0
Subjects with at least one rescue[(1)] medication			
Rescue	35 (11%)	10 (9%)	116 (37%)

Source: Applicant's table 1.1.2/3; (1) includes the dermatological (potent and very potent) as well as systemic corticosteroids, and immunosuppressants.

Tables 8 and 9 present the baseline demographics for the monotherapy trials (Trials 1334 and 1416) and the combination trial (Trial 1224), respectively. The baseline demographics were generally balanced across the treatment arms within each trial. Approximately 59% of the subjects were male, 67% were Caucasians, and 96% of subjects were <65 years of age.

Table 8. Baseline Demographics for Trials 1334 and 1416

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
Gender						
Male	142 (64%)	130 (58%)	118 (53%)	139 (58%)	137 (59%)	132 (56%)
Female	81 (36%)	94 (42%)	106 (47%)	100 (42%)	96 (42%)	104 (44%)
Age						
Mean	39.3	39.8	39.5	37.1	36.9	37.4
SD	14.4	14.7	13.9	14.5	14.0	14.1
Range	18-76	18-85	18-84	18-87	18-88	18-83
Median	39	38	39	35	34	35
<65	215 (96%)	208 (93%)	216 (96%)	226 (95%)	223 (96%)	227 (96%)
≥65	8 (4%)	16 (7%)	8 (4%)	13 (5%)	10 (4%)	9 (4%)
Race						
White	149 (67%)	155 (69%)	146 (65%)	168 (70%)	165 (71%)	156 (66%)
Black	20 (9%)	10 (5%)	16 (7%)	15 (6%)	13 (6%)	20 (9%)
Asian	51 (23%)	54 (24%)	56 (25%)	45 (19%)	44 (19%)	50 (21%)
*Other**	3 (1%)	5 (2%)	6 (3%)	11 (5%)	11 (5%)	10 (4%)

Source: Study report (Table 4.1.1/1); * Other includes not reported/missing for Trial 1416 (4, 6, 7 subjects in dupilumab 300 mg QW, Q2W, placebo, respectively).

Table 9. Baseline Demographics for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Randomized	319	106	315
Gender			
Male	191 (60%)	62 (59%)	193 (61%)
Female	128 (40%)	44 (41%)	122 (39%)
Age			
Mean	36.9	39.6	36.6
SD	13.7	14.0	13.0
Range	18-81	18-73	18-76
Median	34	41	34
<65	306 (96%)	101 (95%)	306 (97%)
≥65	13 (4%)	5 (5%)	9 (3%)
Race			
White	208 (65%)	74 (70%)	208 (66%)
Black	13 (4%)	2 (2%)	19 (6%)
Asian	89 (28%)	29 (27%)	83 (26%)
*Other**	9 (3%)	1 (1%)	5 (2%)

Source: Study report (Table 4.1.1/1).

Tables 10 and 11 presents the baseline disease severity for the monotherapy trials (Trials 1334 and 1416) and the combination trial (Trial 1224), respectively. The baseline disease characteristics of IGA, EASI scores and BSA were generally balanced across treatment groups across the trials. For all Phase 3 trials, approximately 52% of the subjects were of IGA scores 3 (moderate) at baseline, and approximately 94% of the subjects had a weekly average peak pruritus NRS score of at least 4 at baseline.

Table 10. Baseline Disease Severity for Trials 1334 and 1416

	Trial 1334			**Trial 1416**		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
IGA						
3	117 (53%)	116 (52%)	113 (50%)	127 (53%)	118 (51%)	121 (51%)
4	106 (47%)	108 (48%)	111 (50%)	112 (47%)	115 (49%)	115 (49%)
EASI score						
Mean	33.2	33.0	34.5	31.9	31.8	33.6
SD	14.0	13.6	14.5	12.7	13.1	14.3
Median	29.8	30.4	31.8	29.0	28.6	30.5
Range	16-72	16-71	16-72	9-72	12-72	16-72
Weekly Average Peak Pruritus NRS score						
Mean	7.2	7.2	7.4	7.5	7.6	7.5
SD	2.1	1.9	1.8	1.8	1.6	1.9
Median	7.7	7.6	7.7	7.8	7.8	7.7
Range	1-10	0-10	2-10	1-10	2-10	1-10
≥3	211 (95%)	220 (98%)	221 (99%)	234 (98%)	231 (99%)	226 (96%)
≥4	201 (90%)	213 (95%)	212 (95%)	228 (95%)	225 (97%)	221 (94%)
BSA						
Mean	56.1	54.7	57.5	52.2	52.7	54.3
SD	23.0	23.2	23.4	21.5	21.2	23.1
Median	54.5	53.4	57.0	50	50	53
Range	12-100	11-100	12-100	13-100	13-100	11-100

Source: Study report (Table 8)

Table 11. Baseline Disease Severity for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Randomized	319	106	315
IGA			
2	1 (1%)	N/A	N/A
3	171 (54%)	53 (50%)	168 (53%)
4	147 (46%)	53 (50%)	147 (47%)
EASI score			
Mean	32.1	33.6	32.6
SD	12.8	13.3	12.9
Median	29.0	31.0	29.6
Range	1-72	14-67	16-71
Weekly Average Peak Pruritus NRS score			
Mean	7.1	7.4	7.3
SD	1.9	1.7	1.8
Median	7.4	7.7	7.6
Range	1-10	1-10	1-10
≥3	309 (97%)	105 (99%)	306 (97%)
≥4	295 (93%)	102 (96%)	299 (95%)
BSA			
Mean	54.1	59.5	56.9
SD	21.8	20.8	21.7
Median	52.0	58.8	55.0
Range	7-100	11-100	10-100

Source: Study report (Table 10)

In Trials 1334 and 1416, subjects were required to use a moisturizer (emollient) twice daily for at least 7 days before the baseline visit and at least 7 days after the baseline visit. In Trial 1224, subjects were required to use moisturizer throughout the study duration. Table 12 below shows that the moisturizer compliance was similar across the treatment arms in all trials. Note that the lower compliance rates in Trial 1224 compared to the monotherapy trials may be due to the longer duration of the trial as well as the allowance for concomitant medication use.

Table 12. Compliance with Background Moisturizer (Emollient)

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
Compliance	75%	76%	70%	76%	74%	71%

	Trial 1224		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	**319**	**106**	**315**
Compliance	37%	37%	39%

Source: Sponsor's study reports (Section 7.1.2)

3.2.4 Results and Conclusions

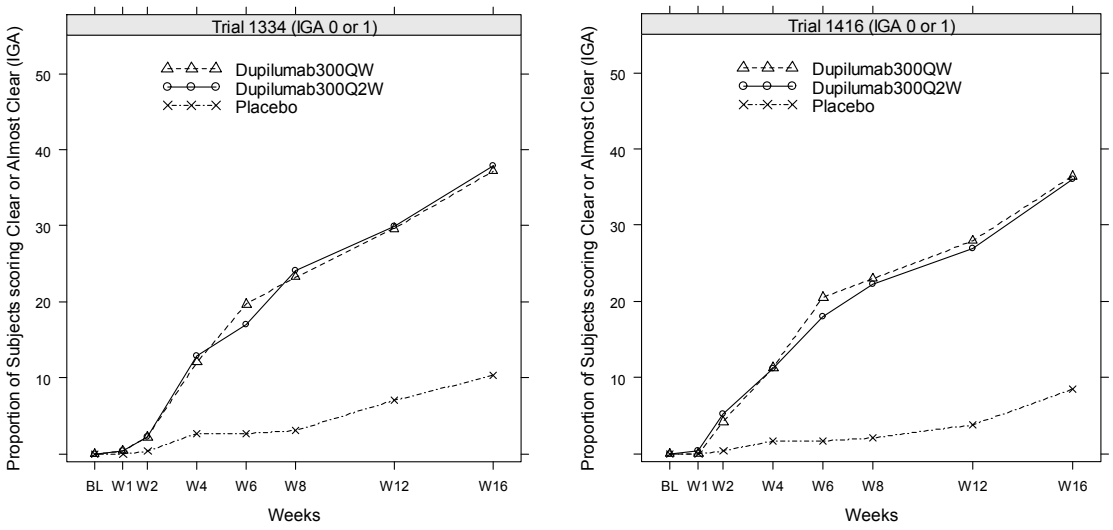
3.2.4.1 Week 16 Efficacy Results

Both dupilumab 300 mg QW and 300 mg Q2W regimens were superior to placebo at Week 16 ($p<0.0001$) for the primary endpoint of IGA success (defined as scoring 0 or 1), as well as the secondary endpoints of EASI 75 at Week 16 in all three trials. The results of the primary and secondary endpoints are presented in Tables 1 and 2. See Table A.1 (Appendix) for comparison of the sponsor's vs. reviewer's analysis. Similar results were obtained using the Per Protocol (PP) analysis set, and the results are in Table A.2 (Appendix). Note that for Trials 1334 and 1416, while the sponsor did not consider the TCS use within the first 14 days as rescue treatment, this reviewer considered those subjects as non-responders.

3.2.4.2 Efficacy Over Time

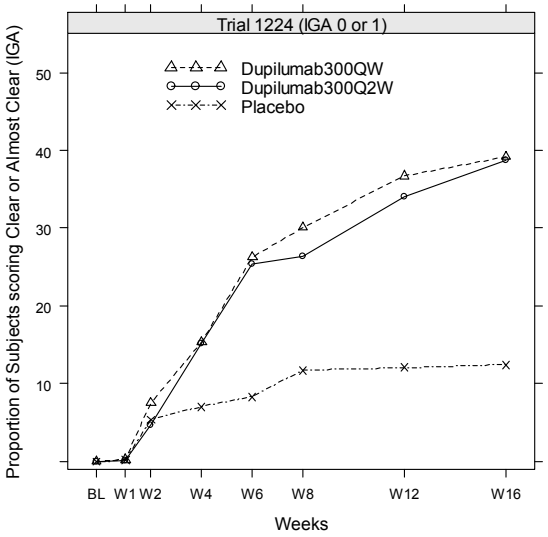
For the initial treatment period, subjects were evaluated for the IGA scores on Weeks 1, 2, 4, 6, 8, 12, and 16. Figure 1 shows the IGA response (IGA of 0 or 1) over time for the monotherapy trials (Trials 1334, 1416), and Figure 2 shows the IGA response over time for the combination trial (Trial 1224). Note that the y-axis for the figures goes up to 50%.

Figure 1. Success on the IGA(1) for the initial treatment period for Trials 1334 and 1416



Source: Reviewer's figures; note that the y-axis of the figures is limited to 50%. (1) IGA score of 0 or 1.

Figure 2. Success on the IGA[(1)] for the initial treatment period for Trial 1224



Source: Reviewer's figure; note that the y-axis of the figure is limited to 50%. (1) IGA score of 0 or 1.

3.2.4.3 Additional Analyses

In all three trials, the sponsor included secondary endpoints of the proportion of subjects achieving improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 4, and from baseline to Week 2. The Agency commented (12/9/2015) that whether or not such endpoints are acceptable for inclusion in the labeling would require clinical judgement, and also reminded the sponsor of the Agency's previous comments (5/30/2014; 10/27/2014; 10/20/2015) that secondary endpoints intended for labeling should be clinically relevant, limited in number.

Note that while all comparisons at Weeks 16, 4, 2 were statistically significant for the monotherapy trials ($p<0.0001$ for Week 16, and $p<0.01$ for Weeks 4 and 2), whether or not a treatment effect of 9-10% at Weeks 4 or 2 in Trial 1334, and a treatment effect of 9 or 16% at Weeks 2 or 4, respectively, in Trial 1416 is clinically relevant would require clinical input. Furthermore, while the sponsor proposed a secondary endpoint of the proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 52, the Agency previously commented (advice letter dated: 10/27/2014) that the endpoints at Week 52 "do not appear to add significant additional information to what has been shown by the primary endpoint and the first secondary endpoint and will therefore be unlikely to be incorporated into labeling". However, the results for the pruritus endpoint at Week 52 are provided in this review for the purpose of completion. Table 13 presents the results for the proportion of subjects achieving reduction of weekly average peak pruritus ≥ 4 from baseline at Weeks 16, 14, 2 for the monotherapy trials, and Table 14 presents the results for the pruritus endpoints at Weeks 16, 4, 2 as well as Week 52 for the combination trial.

Table 13. Proportion of Subjects with at least 4-point change from baseline (1) at Weeks 2, 4, 6 for Trials 1334, 1416

	Trial 1334			Trial 1416		
Pruritus ≥4	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
FAS	223	224	224	239	233	236
Week 2	19 (10%)	20 (9%)	7 (3%)	29 (13%)	24 (11%)	2 (1%)
Week 4	47 (23%)	34 (16%)	12 (6%)	58 (25%)	50 (22%)	14 (6%)
Week 16	81 (40%)	86 (40%)	24 (12%)	87 (38%)	79 (35%)	21 (10%)

Source: Reviewer's analysis based on the Full Analysis Set (FAS) defined as all randomized subjects. (1) Proportion of subjects with a reduction of weekly average of peak daily pruritus NRS ≥4. Missing data as well as those that received rescue medication was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

Table 14. Proportion of Subjects with at least 4-point change from baseline (1) at Weeks 2, 4, 16, 52 for Trial 1224

	Trial 1224		
Pruritus ≥4	**Dupilumab 300 mg QW + TCS**	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
FAS	319	106	315
Week 2	40 (14%)	18 (18%)	24 (8%)
Week 4	80 (27%)	38 (37%)	49 (16%)
Week 16	150 (51%)	60 (59%)	59 (20%)
Week 52	97 (39%)	44 (51%)	32 (13%)

Source: applicant's results based on the Full Analysis Set (FAS) defined as all randomized subjects. (1) Proportion of subjects with a reduction of weekly average of peak daily pruritus NRS ≥4. Missing data as well as those that received rescue medication was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

For Trial 1224, among the IGA responders at Week 16, the percentage of subjects who were IGA 0 or 1 at Week 52 was 58% (72/125), 49% (20/41) and 46% (18/39) in subjects that received dupilumab 300 mg QW +TCS, 300 mg Q2W + TCS, and placebo + TCS, respectively. However, it should be noted that the number of IGA responders at Week 16 was relatively small for the dupilumab 300 mg Q2W + TCS and the placebo + TCS arms. Table 15 presents the proportion of subjects that were IGA success (i.e., score of 0 or 1) at Week 52 among the IGA responders at Week 16 for Trial 1224.

Table 15. Proportion of Subjects with IGA success(1) at Week 52 among those that were IGA responders(1) at Week 16 for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Responders at Week 16	125	41	39
Week 52	72 (58%)	20 (49%)	18 (46%)

Source: Reviewer's analysis based on the Full Analysis Set (FAS) defined as all randomized subjects. (1) IGA score of 0 or 1. Missing data as well as those that received rescue medication was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

3.3 Evaluation of Safety

The evaluation of safety in this review is limited to the initial treatment period (16 weeks) of the three pivotal Phase 3 trials (Trials 1334, 1416, 1224). For Weeks 0-16, the treatment-emergent adverse events (TEAEs) reported by ≥2% are summarized in Table 16 for Trials 1334, 1416, and in Table 17 for Trial 1224. For details regarding the assessment of the safety outcomes, see the clinical review by Dr. Brenda Carr.

Table 16. Summary of the Treatment-Emergent Adverse Events (TEAEs) reported by ≥2% of subjects in the initial treatment period

	Trial 1334			**Trial 1416**		
TEAE	**Dupilumab 300 mg QW N=218**	**Dupilumab 300 mg Q2W N=229**	**Placebo N=222**	**Dupilumab 300 mg QW N=237**	**Dupilumab 300 mg Q2W N=236**	**Placebo N=234**
Number of subjects with at least 1 TEAE	150 (69%)	167 (72%)	145 (65%)	157 (66%)	154 (65%)	168 (72%)
Infections and infestations	74 (34%)	80 (35%)	63 (28%)	68 (29%)	65 (28%)	76 (33%)
General disorders and administrative site conditions	50 (23%)	39 (17%)	20 (9%)	41 (17%)	41 (17%)	32 (14%)
Skin and subcutaneous tissue disorders	34 (16%)	47 (21%)	78 (35%)	60 (25%)	49 (21%)	93 (40%)
Nervous system disorders	13 (6%)	30 (13%)	20 (9%)	36 (15%)	29 (12%)	23 (10%)
Eye disorders	19 (9%)	18 (8%)	4 (2%)	-	-	-
Gastro-intestinal disorders	16 (7%)	21 (9%)	9 (4%)	21 (9%)	22 (9%)	18 (8%)
Musculo-skeletal and connective tissue disorders	17 (8%)	19 (8%)	13 (6%)	16 (7%)	27 (11%)	15 (6%)
Investigations	11 (5%)	13 (6%)	9 (4%)	-	-	-
Respiratory, thoracic, and mediastinal disorders	-	-	-	13 (6%)	17 (7%)	16 (7%)
Psychiatric disorders	-	-	-	6 (3%)	6 (3%)	17 (7%)
Vascular disorders	-	-	-	4 (2%)	7 (3%)	4 (2%)

Source: sponsor's Table 53

Table 17. Summary of the Treatment-Emergent Adverse Events (TEAEs) reported by ≥2% of subjects in the initial treatment period

	Trial 1224		
TEAE	**Dupilumab 300 mg QW + TCS N=315**	**Dupilumab 300 mg Q2W + TCS N=110**	**Placebo + TCS N=315**
Number of subjects with at least 1 TEAE	227 (72%)	81 (74%)	214 (68%)
Infections and infestations	108 (34%)	39 (36%)	111 (35%)
General disorders and administrative site conditions	65 (21%)	20 (18%)	32 (10%)
Skin and subcutaneous tissue disorders	63 (20%)	20 (18%)	110 (35%)
Nervous system disorders	27 (9%)	9 (8%)	27 (9%)
Eye disorders	59 (19%)	23 (21%)	19 (6%)
Gastro-intestinal disorders	31 (10%)	11 (10%)	33 (11%)
Musculo-skeletal and connective tissue disorders	21 (7%)	10 (9%)	27 (9%)
Investigations	23 (7%)	8 (7%)	26 (8%)
Respiratory, thoracic, and mediastinal disorders	22 (7%)	8 (7%)	33 (11%)

Source: sponsor's Table 84

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the efficacy by gender, age, race, as well as country for the pivotal trials were considered.

4.1 Efficacy by Gender, Age, Race

Tables 18 and 19 present the IGA 0 or 1 success by gender, race, and age at baseline for the monotherapy and combination trials, respectively. The majority of the subjects enrolled in the trials were Caucasians (approximately 59%), and of <65 years of age (approximately 96%). Therefore, any differences in efficacy for the non-Caucasians and the older age (≥65) subgroups might be due to chance because of the small sample sizes in these subgroups. In all three trials, females generally had higher IGA response rates than those of the males; however, the majority of the subjects (59%) in the trials were male subjects. Similar results were obtained for EASI 75 response at Week 16 by subgroups of gender, age, and race (Table A.3.a-b; Appendix).

Table 18. Efficacy (IGA 0 or 1) by Baseline Demographics for Trials 1334 and 1416

	Trial 1334			**Trial 1416**		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
Gender						
Female	37/81 (46%)	42/94 (45%)	14/106 (13%)	39/100 (41%)	39/96 (41%)	13/104 (13%)
Male	46/142 (32%)	42/130 (32%)	9/118 (8%)	47/139 (34%)	44/137 (32%)	7/132 (5%)
Age						
<65	80/215 (37%)	78/208 (38%)	22/216 (10%)	81/226 (36%)	77/223 (35%)	20/227 (9%)
≥65	3/8 (38%)	6/16 (38%)	1/8 (13%)	5/13 (38%)	6/10 (60%)	0/9 (0%)
Race						
White	59/149 (40%)	63/155 (41%)	18/146 (12%)	63/168 (38%)	63/165 (38%)	16/156 (19%)
Black	8/20 (40%)	3/10 (30%)	3/16 (19%)	7/15 (47%)	2/13 (15%)	1/20 (5%)
Asian	16/51 (31%)	14/54 (26%)	2/56 (4%)	11/45 (24%)	15/44 (34%)	1/50 (2%)
*Other**	0/3 (0%)	4/5 (80%)	0/6 (0%)	5/11 (45%)	3/11 (27%)	2/10 (20%)

Source: Reviewer's table. * Other includes not reported/missing for Trial 1416 (4, 6, 7 subjects in dupilumab 300 mg QW, Q2W, placebo, respectively).

Table 19. Efficacy (IGA 0 or 1) by Baseline Demographics for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Randomized	319	106	315
Gender			
Female	55/128 (43%)	17/44 (39%)	15/122 (12%)
Male	70/191 (37%)	24/62 (39%)	24/193 (12%)
Age			
<65	120/306 (39%)	37/101 (37%)	38/306 (12%)
≥65	5/13 (38%)	3/5 (60%)	1/9 (11%)
Race			
White	87/208 (42%)	32/74 (43%)	33/208 (16%)
Black	6/13 (46%)	2/2 (100%)	4/19 (21%)
Asian	30/89 (34%)	7/29 (24%)	2/83 (2%)
*Other**	2/9 (22%)	0/1 (0%)	0/5 (0%)

Source: Study report (Table 4.1.1/1).

4.2 Efficacy by Center/Country

Trials 1334 was conducted in 10 countries (US, Germany, Japan, Estonia, Spain, Canada, Denmark, Bulgaria, Singapore, and Finland), and Trial 1416 was conducted in 10 countries (US, Canada, Poland, Germany, Korea, France, Italy, UK, Lithuania, and Hong Kong). Trial 1224 was conducted in 14 countries (US, Poland, Japan, Canada, Netherlands, Australia, UK, Hungary, Korea, Czech Republic, Italy, Spain, New Zealand, and Romania). In Trials 1334 and 1416, the country that enrolled the most subjects was the US with 238 subjects (35%), and 238 subjects (34%), respectively. In Trial 1224, the country that enrolled the most subjects was Poland with 144 subjects (19.5%) followed by US with 139 subjects (18.9%). Tables 20, 21, 22 present the results for the primary endpoint at Week 16 by country, in descending order of enrollment, for Trials 1334, 1416 and 1224, respectively. In all three trials, the treatment effects for IGA response were generally consistent across the countries. Note that some countries enrolled a small number of subjects.

Table 20. Efficacy by Country for Trial 1334

Primary Endpoint IGA 0 or 1	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Total N
FAS	**83/223 (37%)**	**84/224 (38%)**	**23/224 (10%)**	**671 (FAS)**
By Country				
USA	30/80 (38%)	28/79 (35%)	8/79 (10%)	238
Germany	15/40 (38%)	17/41 (41%)	3/43 (7%)	124
Japan	10/35 (29%)	7/36 (19%)	1/35 (3%)	106
Estonia	7/19 (37%)	8/17 (47%)	1/18 (6%)	54
Spain	9/17 (53%)	11/16 (69%)	6/16 (38%)	49
Canada	4/16 (25%)	4/16 (25%)	2/16 (13%)	48
Denmark	4/5 (80%)	3/5 (60%)	0/5 (0%)	15
Bulgaria	3/5 (60%)	3/5 (60%)	2/5 (40%)	15
Singapore	1/3 (33%)	3/6 (50%)	0/5 (0%)	14
Finland	0/3 (0%)	0/3 (0%)	0/2 (0%)	8

Source: Reviewer table

Table 21. Efficacy by Country for Trial 1416

Primary Endpoint IGA 0 or 1	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Total N
FAS	**86/239 (36%)**	**83/233 (36%)**	**20/236 (9%)**	**708**
By Country				
USA	31/80 (39%)	30/79 (38%)	6/79 (8%)	238
Canada	8/36 (22%)	12/35 (34%)	2/37 (5%)	108
Poland	9/33 (27%)	10/31 (32%)	5/33 (15%)	97
Germany	13/29 (45%)	9/29 (31%)	4/29 (14%)	87
Republic of Korea	9/27 (33%)	9/27 (33%)	0/26 (0%)	80
France	7/11 (64%)	4/9 (44%)	0/11 (0%)	31
Italy	4/8 (50%)	5/10 (50%)	2/8 (25%)	26
United Kingdom	1/7 (14%)	1/6 (17%)	0/6 (0%)	19
Lithuania	4/6 (67%)	3/6 (50%)	1/5 (20%)	17
Hong Kong	0/2 (0%)	0/1 (0%)	0/2 (0%)	5

Source: Reviewer table

Table 22. Efficacy by Country for Trial 1224

Primary Endpoint IGA 0 or 1	Dupilumab 300 mg QW + TCS	Dupilumab 300 mg Q2W + TCS	Placebo + TCS	Total N
FAS	**125/319 (39%)**	**41/106 (39%)**	**39/315 (12%)**	**740**
By Country				
Poland	27/64 (42%)	8/17 (47%)	10/63 (16%)	144
USA	23/59 (39%)	10/19 (53%)	11/61 (18%)	139
Japan	15/47 (32%)	3/16 (19%)	2/54 (4%)	117
Canada	21/51 (41%)	9/17 (53%)	5/47 (11%)	115
Netherlands	7/19 (37%)	1/7 (14%)	0/17 (0%)	43
Australia	4/17 (24%)	3/6 (50%)	3/18 (17%)	41
United Kingdom	5/15 (33%)	1/4 (25%)	1/17 (6%)	36
Hungary	8/11 (73%)	2/5 (40%)	6/11 (55%)	27
Republic of Korea	3/14/ (21%)	0/4 (0%)	0/8 (0%)	26
Czech Republic	4/6 (67%)	2/7 (29%)	1/7 (14%)	20
Italy	3/7 (43%)	0/1 (0%)	0/5 (0%)	13
Spain	2/4 (50%)	1/2 (50%)	0/4 (0%)	10
New Zealand	1/3 (33%)	1/1 (100%)	0/1 (0%)	5
Romania	2/2 (100%)	0/0 (0%)	0/2 (0%)	4

Source: Reviewer table

Because randomization of subjects to treatment arms was stratified by baseline disease severity (IGA=3, IGA=4) and by region, there were many small centers (≤2 subjects). Subjects enrolled from 131, 136, 160 centers in Trials 1334, 1416, 1224 respectively. For Trial 1334, only 12 centers enrolled ≥10 subjects across the three treatment arms. For the efficacy by center tables below, only those sites that enrolled ≥10 subjects were considered.

The applicant indicated that there was 1 site with a total of 7 Full Analysis Set (FAS) subjects (i.e., 3 placebo, 1 dupilumab 300 mg Q2W, 3 dupilumab 300 mg QW) that was closed due to "GCP-related issues". This site was included in the FAS analyses, but excluded from the Per Protocol analyses.

Table 23. Efficacy by Center (≥10 subjects) for Trial 1334

Primary Endpoint		Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Total N
IGA 0 or 1		**82/223 (37%)**	**84/224 (38%)**	**23/224 (10%)**	**671 (FAS)**
Site ID	233004	3/10 (30%)	6/10 (60%)	1/9 (11%)	29
	840004	5/7 (71%)	5/12 (42%)	0/9 (0%)	28
	840007	1/6 (17%)	2/5 (40%)	2/4 (50%)	15
	276013	0/2 (0%)	0/4 (0%)	0/8 (0%)	14
	840048	2/9 (22%)	0/1 (0%)	0/3 (0%)	13
	124009	0/5 (0%)	0/2 (0%)	0/5 (0%)	12
	840017	0/2 (0%)	0/5 (0%)	0/5 (0%)	12
	124003	1/4 (25%)	2/3 (67%)	0/3 (0%)	10
	276006	1/1 (100%)	2/4 (50%)	0/5 (0%)	10
	392010	1/5 (20%)	0/1 (0%)	0/4 (0%)	10
	840001	2/4 (50%)	1/3 (33%)	0/3 (0%)	10
	840030	0/2 (0%)	2/4 (50%)	1/4 (25%)	10

Source: Reviewer's Table

Table 24. Efficacy by Center (≥10 subjects) for Trial 1416

Primary Endpoint		Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Total N
IGA 0 or 1		**87/239 (36%)**	**84/233 (36%)**	**20/236 (9%)**	**708 (FAS)**
Site ID	840036	1/7 (14%)	1/6 (17%)	0/6 (0%)	19
	124003	1/7 (14%)	0/5 (0%)	0/6 (0%)	18
	124006	2/6 (33%)	2/6 (33%)	0/4 (0%)	16
	124014	1/7 (14%)	2/4 (50%)	0/5 (0%)	16
	250012	3/6 (50%)	3/4 (75%)	0/6 (0%)	16
	616001	2/6 (33%)	1/4 (25%)	1/6 (17%)	16
	276020	2/4 (50%)	1/6 (17%)	1/4 (25%)	14
	276021	2/3 (67%)	2/6 (33%)	2/5 (40%)	14
	276007	5/5 (100%)	2/4 (50%)	1/4 (25%)	13
	840042	1/2 (50%)	3/4 (75%)	1/6 (17%)	12
	410004	2/5 (40%)	0/2 (0%)	0/4 (0%)	11
	840010	3/7 (43%)	1/2 (50%)	1/2 (50%)	11
	840016	4/4 (100%)	1/1 (100%)	0/6 (0%)	11
	840037	1/5 (20%)	1/4 (25%)	0/2 (0%)	11
	124011	0/1 (0%)	2/5 (40%)	0/4 (0%)	10
	616003	0/4 (0%)	0/3 (0%)	0/3 (0%)	10

Source: Reviewer's Table

Table 25. Efficacy by Center (≥10 subjects) for Trial 1224

Primary Endpoint		Dupilumab 300 mg QW + TCS	Dupilumab 300 mg Q2W + TCS	Placebo + TCS	Total N
IGA 0 or 1		**125/319 (39%)**	**41/106 (39%)**	**39/315 (12%)**	**740 (FAS)**
Site ID	616025	6/6 (100%)	0	3/8 (38%)	14
	528001	1/4 (25%)	0/2 (0%)	0/5 (0%)	11
	616021	4/8 (50%)	0	0/3 (0%)	11
	840049	4/4 (100%)	1/1 (100%)	2/6 (33%)	11
	036008	1/4 (25%)	0/2 (0%)	0/4 (0%)	10
	124002	2/5 (40%)	0	0/5 (0%)	10
	124006	5/6 (83%)	1/1 (100%)	1/3 (33%)	10
	124021	0/3 (0%)	1/2 (50%)	1/5 (20%)	10
	124023	2/3 (67%)	1/2 (50%)	0/5 (0%)	10
	124024	0/5 (0%)	0/1 (0%)	0/4 (0%)	10
	528002	1/4 (25%)	0	0/6 (0%)	10
	616005	0/2 (0%)	2/3 (67%)	0/5 (0%)	10
	616007	2/5 (40%)	1/1 (100%)	0/4 (0%)	10
	616017	0/5 (0%)	0/1 (0%)	0/4 (0%)	10
	616027	0/2 (0%)	0	0/8 (0%)	10
	616028	2/5 (40%)	1/1 (100%)	0/4 (0%)	10
	826003	3/5 (60%)	0	0/5 (0%)	10
	840003	0/4 (0%)	1/1 (100%)	1/5 (20%)	10

Source: Reviewer's Table

4.3 Efficacy by Baseline Disease Severity

In all three trials, the treatment effect was generally lower for subjects with a baseline IGA score of 4 (severe) compared to those subjects with baseline IGA score of 3 (moderate). Table 26 presents the results for the IGA response at Week 16 by baseline disease severity for Trials 1334, 1416, and Table 27 presents the results for the IGA response at Week 16 by baseline disease severity for Trial 1224. For those subjects that had a baseline IGA severity of 4 (severe), the IGA responses at Week 16 were 3-6% higher than those that received the dupilumab 300 mg Q2W. For those with the baseline IGA severity of moderate (3), the IGA success rates were 3-6% higher for those that received the dupilumab 300 mg Q2W than those that received dupilumab 300 mg QW. It should be noted that such trend in efficacy was consistent across the three trials. Whether or not such treatment effect of the 300 mg QW dose for the severe subjects would be beneficial would require clinical judgment and should also take the safety profile of both dose regimens into consideration as well.

In an effort to further understand the IGA response by baseline IGA severity, this reviewer also looked at the baseline EASI scores. In all trials, the mean baseline EASI scores were generally similar across the treatment arms, and in comparing the IGA responders vs. non-responders at Week 16 (Tables A.4.a-c; Appendix), the mean baseline EASI scores were generally slightly lower in the responders compared to those of the non-responders suggesting that within the IGA category (i.e., moderate or severe), those

with a lower baseline EASI scores may have responded to the treatment than those with a higher baseline EASI score.

Table 26. IGA Responder by Baseline IGA Severity for Trials 1334 and 1416

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
IGA						
3	54/117 (46%)	61/116 (52%)	16/113 (14%)	53/127 (42%)	53/118 (45%)	17/121 (14%)
4	29/106 (27%)	23/108 (21%)	7/111 (6%)	33/112 (29%)	30/115 (26%)	3/115 (3%)

Source: Reviewer Analysis

Table 27. Success on the IGA at Week 16 by Baseline IGA Severity for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Randomized	319	106	315
IGA			
2	0/1 (0%)	N/A	N/A
3	79/171 (46%)	26/53 (49%)	31/168 (18%)
4	46/147 (31%)	15/53 (28%)	8/147 (5%)

Source: Study report (Table 10)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The safety and efficacy of dupilumab was evaluated in three pivotal Phase 3 trials (Trials 1334, 1416, and 1224). All trials evaluated two dose frequencies (300 mg Q2W and 300 mg QW) versus placebo. Trials 1334 and 1416 were monotherapy trials and Trial 1224 was an adjunctive therapy trial that allowed the use of topical corticosteroid (TCS).

In all three trials, for the comparison of dupilumab against placebo at Week 16, the primary endpoint was the proportion of subjects achieving IGA 0 or 1. Secondary endpoints that were agreed upon with the Agency included the EASI 75 response (i.e., ≥75% reduction from baseline in EASI score), and the proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 16. Both dupilumab 300 mg QW and Q2W regimens were superior to placebo at Week 16 ($p<0.0001$) for the primary endpoint of IGA success (defined as scoring 0 or 1),

as well as the secondary endpoints of EASI 75 at Week 16 in all three trials. The results of the primary and secondary endpoints are presented in Tables 1 and 2.

In addition to the secondary endpoint of the proportion of subjects with improvement (reduction) of weekly average of peak daily pruritus ≥4 from baseline to Week 16, the sponsor included this endpoint at Week 4 as well as at Week 2 for all three trials and at Week 52 for Trial 1224 as secondary endpoints. While all comparisons at Weeks 16, 4, 2 were statistically significant for the monotherapy trials ($p<0.0001$ for Week 16, and $p<0.01$ for Weeks 4 and 2), whether or not a treatment effect of 9-10% at Weeks 4 or 2 in Trial 1334, and a treatment effect of 9 or 16% at Weeks 2 or 4, respectively, in Trial 1416 is clinically meaningful would require clinical input. The sponsor also included a secondary endpoint of the percent change from baseline to Week 16 in weekly average of peak daily pruritus NRS. Note that the Agency previously commented (5/30/2014; 10/27/2014; 10/20/2015) that secondary endpoints need to be clinically relevant, and that the percent change from baseline to Week 16 in weekly average peak daily pruritus NRS might not be clinically meaningful (4/13/2015; 10/2/2015).

There were no major statistical issues affecting the overall efficacy conclusions. The treatment effects were consistent across the trials, and the amount of missing data was relative small (<7%) at Week 16.

5.2 Conclusions and Recommendations

The findings from three pivotal trials (Trials 1334, 1416, and 1224) support the efficacy of dupilumab 300 mg Q2W for the treatment of adults with atopic dermatitis (AD) in adults patients whose disease is not adequately controlled with topical prescription therapy, (b) (4), or (b) (4) not advisable.

6. Appendix

6.1 Investigating the Impact of Handling Subjects with TCS use

The sponsor did not consider those subjects that used the TCS within the first 14 days as rescue, and consequently, did not consider these subjects as non-responders. As specified in the protocol, this reviewer considered those subjects that used TCS as non-responders. Table A.1 compares the sponsor's analysis vs. reviewer's analysis and provides the subjects numbers in the footnote for the type of TCS and the duration of TCS use. In addition to the primary and secondary endpoints, this reviewer also provides the proportion of subjects that achieved EASI 90 at Week 16 which was one of the "other secondary endpoints", and not part of the testing hierarchy.

Table A.1. Proportion of Subjects Achieving Treatment Success at Week 16 for Trials 1334, 1416

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
FAS	223	224	224	239	233	236
IGA 0 or 1 at Week 16 (Primary)						
Sponsor's	83 (37%)	85 (38%)	23 (10%)	87 (37%)	84 (36%)	20 (8%)
Reviewer's	83 (37%)	84[(1)] (38%)	23 (10%)	86[(2)] (36%)	83[(3)] (36%)	20 (9%)
EASI 75 at Week 16 (Key secondary)						
Sponsor's	117 (53%)	115 (51%)	33 (15%)	115 (48%)	103 (44%)	28 (12%)
Reviewer's	117 (53%)	114[(1)] (51%)	33 (15%)	113[(2), (4)] (47%)	102[(3)] (44%)	28 (12%)
Pruritus Endpoints (Secondary)						
Baseline NRS,≥4	201	213	212	228	225	221
Sponsor's	81 (40%)	87(41%)	26 (12%)	89 (39%)	81 (36%)	21 (10%)
Reviewer's	81 (40%)	86[(1)] (40%)	24[(5)] (12%)	87[(6)] (38%)	79[(7)] (35%)	21 (10%)
Baseline NRS,≥3	211	220	221	234	231	226
Sponsor's	109 (52%)	103 (47%)	38 (17%)	115 (49%)	117 (51%)	29 (13%)
Reviewer's	108[(9)] (51%)	102[(1)] (46%)	36[(5)] (16%)	113[(6)] (48%)	114[(7)(8)] (49%)	29 (13%)
EASI 90 at Week 16 (other secondary)						
Sponsor's	74 (33%)	80 (36%)	17 (8%)	73 (31%)	70 (30%)	17 (7%)
Reviewer's	74 (33%)	79[(1)] (35%)	17 (8%)	72[(2)] (30%)	69[(3)] (30%)	17 (7%)

Source: applicant's results based on the Full Analysis Set (FAS) defined as all randomized subjects. Missing data as well as those that received rescue medication was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

(1) R668-AD-1334-233005005 should be excluded due to the use of TCS in the first 14 days.
(2) R668-AD-1416-124014013 used bethamethasone valerate for 3 days
(3) R668-AD-1416-616021006 used mometasone fluroate for 3 days during the trial.
(4) R668-AD-1416-840074001 used triamcinolone for 2 days during the 16 weeks. IGA not success, but EASI success.
(5) R668-AD-1334-276013012 used prednicarbate for 2 days ; R668-AD-1334-276019009 used mometasone furoate for 4 days
(6) R668-AD-1416-27602005 used prednisolone for 2 days; R668-AD-1416-616001009 used hydrocortisone for 8 days
(7) R668-AD-1416-276021009 used mometasone fluorate for 1 day; R668-AD-1416-616021006 used momeasone fluorate for 3 days
(8) R668-AD-1416-616001010 used clobetasol propionate for 10 days.
(9) R668-AD-1334-124007007 used mometasone for 22 days

6.2 Comparison of Intent to Treat (ITT) analysis vs. Per Protocol (PP) analysis

Tables A.2.a-b provide the IGA response at Week 16 using the Per Protocol (PP) analysis set as a supportive analysis.

Table A.2a. Proportion of Subjects Achieving Treatment Success at Week 16 for Trials 1334, 1416 (Per Protocol Analysis)

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
IGA 0 or 1 (FAS)	83/223 (37%)	84/224 (38%)	23/224 (10%)	86/239 (36%)	83/233 (36%)	20/236 (9%)
IGA 0 or 1 (PP)	81/215 (38%)	82/216 (38%)	21/215 (10%)	83/231 (36%)	80/224 (36%)	20/225 (9%)

Source: Reviewer's table

Table A.2b. Proportion of Subjects Achieving Treatment Success at Week 16 for Trials 1224 (Per Protocol Analysis)

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
IGA 0 or 1 (FAS)	125/319 (39%)	41/106 (39%)	39/315 (12%)
IGA 0 or 1 (PP)	121/308 (39%)	40/100 (40%)	38/301 (13%)

Source: Reviewer's table

6.3 Investigating EASI 75 by baseline demographics

The following tables provide the EASI 75 response by baseline demographics for the monotherapy trials (Trials 1334, 1416), and the combination trial (Trial 1224)

Table A.3.a Efficacy (EASI 75) by Baseline Demographics for Trials 1334 and 1416

	Trial 1334			Trial 1416		
	Dupilumab 300 mg QW	**Dupilumab 300 mg Q2W**	**Placebo**	**Dupilumab 300 mg QW**	**Dupilumab 300 mg Q2W**	**Placebo**
Randomized	223	224	224	239	233	236
Gender						
Female	50/81 (62%)	57/94 (60%)	18/106 (17%)	49/100 (49%)	47/96 (49%)	18/104 (17%)
Male	67/142 (47%)	57/130 (44%)	15/118 (13%)	64/139 (46%)	55/137 (40%)	10/132 (8%)
Age						
<65	113/215 (53%)	104/208 (50%)	32/216 (15%)	108/226 (48%)	96/223 (43%)	28/227 (12%)
≥65	4/8 (50%)	10/16 (63%)	1/8 (13%)	5/13 (38%)	6/10 (60%)	0/9 (0%)
Race						
White	78/149 (52%)	86/155 (55%)	22/146 (15%)	81/168 (48%)	74/165 (45%)	19/156 (12%)
Black	11/20 (55%)	5/10 (50%)	5/16 (31%)	9/15 (60%)	5/13 (38%)	3/20 (15%)
Asian	26/51 (51%)	19/54 (35%)	6/56 (11%)	15/45 (33%)	16/44 (36%)	3/50 (6%)
*Other**	2/3 (67%)	4/5 (80%)	0/6 (0%)	8/11 (73%)	7/11 (64%)	3/10 (30%)

Source: Reviewer's table.

Table A.3.b Efficacy (EASI 75) by Baseline Demographics for Trial 1224

	Trial 1224		
	Dupilumab 300 mg QW + TCS	**Dupilumab 300 mg Q2W + TCS**	**Placebo + TCS**
Randomized	319	106	315
Gender			
Female	85/128 (66%)	31/44 (70%)	35/122 (29%)
Male	119/191 (62%)	42/62 (68%)	38/193 (20%)
Age			
<65	197/306 (64%)	69/101 (68%)	70/306 (23%)
≥65	7/13 (54%)	4/5 (80%)	3/9 (33%)
Race			
White	135/208 (65%)	52/74 (70%)	53/208 (25%)
Black	7/13 (54%)	2/2 (100%)	5/19 (26%)
Asian	57/89 (64%)	18/29 (62%)	14/83 (17%)
*Other**	5/9 (56%)	1/1 (100%)	1/5 (20%)

Source: Reviewer's table

6.4 Investigating the differential treatment effect based on baseline EASI scores by IGA responders vs. IGA non-responders

The following Tables A.4.a, A.4.b, A.4.c display the mean baseline EASI scores by baseline IGA disease severity for the IGA responders vs. non-responders at Week 16 for Trials 1334, 1416, and 1224, respectively. The tables show that the mean baseline EASI scores were generally similar across the treatment arms, and in comparing the IGA responders vs. non-responders at Week 16, the mean baseline EASI scores were generally slightly lower in the responders compared to those of the non-responders.

Table A.4.a Comparison of the Mean (SD) Baseline EASI scores by Baseline IGA Severity for Responders vs. Non-responders in Trials 1334

	IGA responders			**IGA non-responders**		
Treatment ($N_{IGA=3}$, $N_{IGA=4}$)	**Dupilumab 300 mg QW (54, 29)**	**Dupilumab 300 mg Q2W (61, 23)**	**Placebo (16, 7)**	**Dupilumab 300 mg QW (63, 77)**	**Dupilumab 300 mg Q2W (55, 85)**	**Placebo (97, 104)**
IGA						
3	26.1 (10.3)	23.9 (7.5)	25.8(10.1)	27.6 (9.8)	26.1 (8.6)	26.0 (8.9)
4	34.7 (11.4)	38.7 (12.3)	42.9(14.8)	42.2 (15.0)	42.5 (13.0)	43.3(13.7)

Source: Reviewer Analysis

Table A.4.b Comparison of the Mean (SD) Baseline EASI scores by Baseline IGA Severity for Responders vs. Non-responders in Trials 1416

	IGA responders			**IGA non-responders**		
Treatment ($N_{IGA=3}$, $N_{IGA=4}$)	**Dupilumab 300 mg QW (53, 33)**	**Dupilumab 300 mg Q2W (53, 30)**	**Placebo (17, 3)**	**Dupilumab 300 mg QW (74, 79)**	**Dupilumab 300 mg Q2W (65, 85)**	**Placebo (104, 112)**
IGA						
3	24.4 (7.6)	24.2 (7.8)	25.9(10.9)	26.7 (10.0)	26.0 (8.4)	25.3 (7.4)
4	36.8 (11.2)	32.4(11.6)	46.6(23.3)	39.6 (13.3)	40.7 (13.9)	42.1 (14.3)

Source: Reviewer Analysis

Table A.4.c Comparison of the Mean (SD) Baseline EASI scores by Baseline IGA Severity for Responders vs. Non-responders in Trials 1224

	IGA responders			**IGA non-responders**		
Treatment ($N_{IGA=3}$, $N_{IGA=4}$)	**Dupilumab 300 mg QW (79, 46)**	**Dupilumab 300 mg Q2W (26, 15)**	**Placebo (31, 8)**	**Dupilumab 300 mg QW (92, 101)**	**Dupilumab 300 mg Q2W (27, 38)**	**Placebo (137, 139)**
IGA						
3	24.1 (7.7)	25.2 (7.1)	25.8 (7.7)	27.2 (8.6)	27.2 (9.4)	25.1 (8.5)
4	35.2 (12.9)	38.0 (11.3)	35.1 (8.0)	41.5 (12.4)	42.2 (13.9)	41.3 (12.2)

Source: Reviewer Analysis

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/s/

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12/07/2016

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