CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761,055
Link to EDR	\\CDSESUB1\evsprod\BLA761055\761055.enx (SDN 4, eCTD 0004)
Submission Date	July 29, 2016
Submission Type	Priority
Brand Name	DUPIXENT®
Generic Name	Dupilumab
Dosage Form and Strength	Single-use prefilled syringe: 300 mg of dupilumab in 2 mL solution
Route of Administration	Subcutaneous injection
Proposed Indication	For the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
Applicant	Regeneron Pharmaceuticals, Inc.
Associated IND	IND 107,969
OCP Review Team	Jie Wang, PhD Luke Oh, PhD Luning Zhuang, PhD Jeffry Florian, PhD Yow-Ming Wang, PhD
OCP Final Signatory	Hae Young Ahn, PhD Division Deputy Director Division of Clinical Pharmacology 3

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1. EXECUTIVE SUMMARY

The Applicant is seeking the approval of DUPIXENT® (dupilumab) for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab is administered by subcutaneous injection. The proposed dosing regimen is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week (Q2W). (b) (4) . Three pivotal Phase 3 studies in adult AD patients were conducted to support the efficacy and safety of dupilumab 300 mg Q2W and 300 mg QW with or without topical therapy. The 300 mg Q2W and 300 mg QW dosing regimens were selected for Phase 3 studies based on a Phase 2 dose ranging study. The Applicant additionally submitted results of 12 clinical pharmacology studies in healthy subjects and subjects with AD to support the pharmacokinetics (PK) and pharmacodynamics (PD) of dupilumab.

1.1 Recommendations

The Divisions of Clinical Pharmacology 3 and Pharmacometrics have reviewed the information contained in BLA 761,055. The review team recommends approval of this BLA from a clinical pharmacology perspective. The key review issues with specific recommendations and/or comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Two Phase 3 monotherapy Studies R668-AD-1334 and R668-AD-1416 and one Phase 3 concomitant treatment with TCS Study R668-AD-1224 provide the primary evidence of effectiveness. The Phase 2 dose ranging Study R668-AD-1021 also provides supportive evidence. In addition, supportive evidence comes from exploratory pharmacodynamic (PD) evaluations on the reduction from baseline in serum concentrations of thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE, and lactate dehydrogenase (LDH) following dupilumab treatment.
General dosing instructions	The dose-response relationship for efficacy in Phase 3 overall supports a recommendation of the 300 mg Q2W dosing regimen

	(with an initial 600 mg dose). We do not recommend including an option to increase the dose to 300 mg QW based on individual therapeutic response, because the available data do not support such dose adjustment. Specifically, the available data did not show a preferential treatment benefit with 300 mg QW compared to 300 mg Q2W in any particular subset of patients. In addition, a switch from 300 mg Q2W to 300 mg QW based on individual therapeutic response was not evaluated as part of the trial.
Dosing in patient subgroups	No dose individualization is recommended based on intrinsic or extrinsic factors. Body weight based dosing is not needed.
Drug interactions	Dupilumab could modulate cytokine levels and consequently have disease-drug-drug interaction potential in subjects with AD. – *See Section 1.2 PMC recommendations;* – *See Section 2.4 Labeling recommendations*
Immunogenicity	Immunogenicity has a negative impact on systemic exposure of dupilumab. Adverse reactions of serum sickness reaction and serum sickness-like reaction were observed in AD clinical trials. These adverse reactions were associated with development of high titer anti-drug antibodies to dupilumab. – *See Section 2.4 Labeling recommendations*
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. The to-be-marketed formulation was used in Phase 3 clinical trials.
Labeling	Generally acceptable. The review team has recommendations for specific content and formatting changes.

1.2 Post-Marketing Requirements and Commitments

PMC: We recommend that the Applicant conduct a clinical trial to determine the potential for dupilumab to alter the pharmacokinetics of CYP substrates in AD patients.

The Applicant is currently conducting a clinical drug interaction study (R668-AD-1433) to evaluate the potential effects of dupilumab on the PK of CYP450 substrates in adult patients with moderate-to-severe atopic dermatitis (AD). The PMC recommendation will request that the Applicant complete this ongoing drug interaction study.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Dupilumab is a recombinant human IgG4 mAb that binds to the IL-4 receptor alpha (IL-4Rα) subunit which is a component of Type I and Type II receptor complexes; Type I receptor only binds to IL-4, whereas Type II receptor binds to both IL-4 and IL-13. Consequently, dupilumab inhibits activities of both IL-4 and IL-13 which are key Type 2 cytokines involved in inflammatory responses in AD.

The following is a summary of clinical pharmacokinetics of dupilumab:

The PK of dupilumab was described by a 2-compartment model with parallel linear and non-linear elimination and first order absorption following subcutaneous administration. Dupilumab exposure increased in a greater than dose-proportional manner; the systemic exposure increased by 30-fold when the dose increased 8-fold from 75 mg to 600 mg.

Absorption: Following a single subcutaneous (SC) dose of 300 mg, dupilumab reached peak mean±SD concentrations (C_{max}) of 34.8±17.5 mcg/mL by approximately 1 week post-dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly or every 2 weeks. Across clinical trials, the mean±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9 ±41.4 mcg/mL for 300 mg administered every 2 weeks and from 173±75.9 mcg/mL to 193 ±77.0 mcg/mL for 300 mg administered weekly. Dupilumab trough concentrtions were lower in subjects with higher body weight.

The bioavailability of dupilumab following an SC dose was estimated to be 64%.

Distribution: The estimated toal volume of distribution was approximately 4.6 L.

Eliminaiton: The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. The mean systemic clearance for the linear elimination pathway was 0.13 L/day. The clearance for the nonlinear elimination pathway is concentration-dependent and plays a role in the studied SC dose range of 75 mg to 300 mg.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week (Q2W). (b) (4)

(b) (4)

The dose-response relationship for efficacy in Phase 3 overall supports the recommended 300 mg Q2W dosing regimen (with an initial 600 mg dose). We do not recommend including an option to increase the dose to 300 mg QW based on individual therapeutic response, because the available data do not support such dose adjustment. Specifically, the available data did not show a preferential treatment benefit with 300 mg QW compared to 300 mg Q2W in any particular subset of patients. In addition, a switch from 300 mg Q2W to 300 mg QW based on individual therapeutic response was not evaluated as part of the trial. See *Section 3.3.2* for more information.

2.2.2 Therapeutic individualization

Therapeutic individualization is not recommended based on intrinsic or extrinsic factors. The only factor of interest from a dose individulizaiton perspective was the impact of body weight because body weight was identified as a significant covariate on dupilumab PK. Dupilumab trough concentrtions were lower in subjects with higher body weight. However, subgroup analyses of the Phase 3 efficacy data did not demonstrate remarkable differences in IGA 0/1 response rate across the body weight subgroups. The response rate for EASI-75 was similar across the body weight quartiles for both 300 mg Q2W and 300 mg QW dosing regimens. Therefore, body weight based dosing is not needed. See *Section 3.3.3* for more information.

2.3 Outstanding Issues

None from a Clinical Pharmacology's perspective.

2.4 Summary of Labeling Recommendations

In general the Applicant has provided adequate clinical pharmacology information to support the product labeling. We recommend including the following labeling concepts in the product labeling:

- **2.1 Dosage.** The Applicant proposed that (b) (4) We recommend removing this sentence from the product labeling.
- **6.2 Immunogenicity**:
    a. In addition to reporting the immunogenicity incidences of anti-drug antibodies (ADA) and neutralizing ADA, we recommend including the immunogenicity impact on PK in this section of labeling; specifically, immunogenicity is associated with reduced dupilumab serum concentrations. See *Secion 4.5* for more information.

b. Two cases of adverse reactions of serum sickness reaction and serum sickness-like reaction were observed in AD clinical trials. These two adverse reactions were associated with development ADA to dupilumab with high antibodies titer values of 122,880 and 15,360, respectively. We recommend reporting the observed apparent association of serum sickness reaction and serum sickness-like reaction adverse reactions with immunogenicity in this section. See *Secion 4.5* for more information.

- **7.3 Drug Interactions**: As information on clinical drug interaction for dupilumab in AD patients is not available at this time, we recommend including the following labeling language: "The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-4, IL-6, IL-10, IL-13, TNFα, and IFN) during chronic inflammation. Thus, DUPIXENT, an antagonist of IL-4 receptor alpha, could modulate the formation of CYP450 enzymes. Therefore, upon initiation or discontinuation of DUPIXENT in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate." This recommendation is consistent with the labeling of other biological products that modulate cytokine levels associated with an inflammatory disease condition. See *Section 3.3.4* for more information.

- **12.2 Pharmacodynamics**: We recommend including the results from a small exploratory study showing serum levels of IL-4 and IL-13 were increased following dupilumab treatment. See *Section 4.4* for more information.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

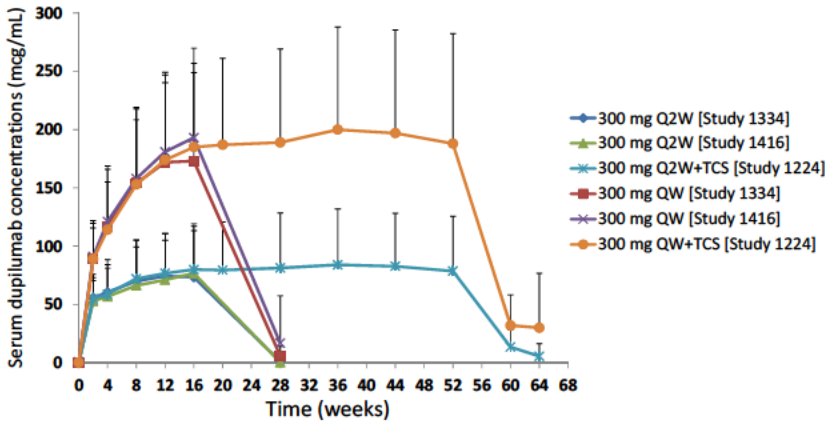
Dupilumab is a human monoclonal antibody of the IgG4 subclass and has an approximate molecular weight of 147 kDa. Dupilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. DUPIXENT is supplied as a single-dose prefilled syringe with or without needle shield in a 2.25 mL syringe. Each prefilled syringe delivers 300 mg dupilumab in 2-mL solution.

Moderate-to-severe atopic dermatitis (AD) is a serious chronic inflammatory skin disease. Available treatments for AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and systemic non-selective immunosuppressants. Currently there are no approved biologic products for the treatment of AD.

In 2014, the FDA granted dupilumab the Breakthrough Therapy designation for the treatment of moderateto-severe AD in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy or when those treatments are not advisable.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. Blocking IL-4Rα inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines and chemokines.
Pharmacodynamics	Results from a small exploratory study showed that serum levels of IL-4 and IL-13 were increased following dupilumab treatment. The relationship between the pharmacodynamic activity and the mechanism(s) by which dupilumab exerts its clinical effects is unknown.
General Information	
Bioanalysis	Dupilumab concentrations in human serum were quantified by a validated enzyme-linked immunosorbent assay (ELISA) using human IL-4Rα as the capture reagent. The captured dupilumab is detected using a biotinylated mouse anti-human IgG4 monoclonal antibody, followed by NeutriAvidin conjugated to horseradish peroxidase. The ELISA

	method measures the concentration of dupilumab with 1 or both binding sites available for target IL-4Rα. The lower limit of quantification (LLOQ) was 0.078 mcg/mL in undiluted human serum. See *Section 4.1* for more information.
PK model	A two-compartment model with parallel linear and nonlinear elimination and first order absorption following SC administration described the PK of dupilumab well.
Heathy subjects vs AD patients	Population PK analysis indicated no significant differences in PK between AD patients and healthy subjects when body weight has been accounted for.
Drug exposure at steady state	Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly or every 2 weeks. Across three Phase 3 clinical trials, the mean ±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9 ±41.4 mcg/mL for 300 mg administered every 2 weeks and from 173±75.9 mcg/mL to 193 ±77.0 mcg/mL for 300 mg administered weekly. The figure below shows the mean±SD dupilumab concentration-time profiles in subjects with AD in Phase 3 trials. Note that Study 1334 and Study 1416 each had a 16-week treatment period whereas Study 1224 had a 52-week treatment period (see *Section 3.3.1, Table 3.3.1.b*). 
Dose Linearity	Dupilumab exhibited nonlinear pharmacokinetics with exposures that increased in a greater than dose-proportional manner. The systemic exposure (AUC) increased by 30-fold when the SC dose increased 8-fold from 75 mg to 600 mg. The exposure (AUC) increased by 38-fold when the IV dose incrased 12-fold from 1 mg/kg to 12 mg/kg.

Body weight	Dupilumab trough concentrtions were lower in subjects with higher body weight.
Renal or Hepatic Impairment	No formal trial was conducted to evaluate the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab.
ADME	
Absorption	Following a single subcutaneous (SC) dose of 300 mg, dupilumab reached peak mean ±SD concentrations (C_{max}) of 34.8±17.5 mcg/mL by approximately 1 week (range of 3 to 14 days) post-dose. The bioavailability of dupilumab following an SC dose was estimated to be 64%.
Distribution	Based on population PK analysis, the estimated toal volume of distribution was approximately 4.6 L. The central volume of distribution was 2.7 L and peripheral volume of distribution was 1.9 L.
Elimination	The mean systemic clearance for the linear elimination pathway was 0.13 L/day. The clearance for the nonlinear elimination pathway is concentration-dependent and plays a role in the studied SC dose range of 75 mg to 300 mg.
Metabolism	The metabolic pathway of dupilumab has not been characterized. As a human monoclonal antibody dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
Excretion	The excretion of dupilumab has not been studied. Dupilumab is a human monoclonal antibody of the IgG4 subclass and has a molecular weight of approximately 147 kDa; therefore, intact dupilumab are unlikely to be filtered by kidney or excreted in urine.
Immunogenicity	
Incidence	In the combined Phase 3 monotherapy Studies AD-1334 and AD-1416, approximately 13.6% (61/447) and 7.2% (31/429) of subjects had anti-drug antibodies to dupilumab following 16 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the subjects who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 18% (11/61) and 13% (4/31), respectively, had neutralizing antibodies.

	In the Phase 3 concomitant treatment with TCS Study R668-AD-1224, approximately 9.5% (10/105) and 10.7% (33/308) of subjects had anti-drug antibodies to dupilumab following 52 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the subjects who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 10% (11/10) and 0% (0/33), respectively, had neutralizing antibodies.
Impact on PK	Development of ADA was associated with reduced serum dupilumab concentrations.
Impact on efficacy	Overall, no consistent evidence of reduced efficacy was observed in subjects who developed ADA or NAb in Phase 3 trials. However, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on the clinical efficacy measures because of the small number of subjects with ADA.
Impact on safety	Two cases of adverse reactions of serum sickness reaction and serum sickness-like reaction were observed in AD clinical trials. These two adverse reactions were associated with development ADA to dupilumab with high antibodies titer values of 122,880 and 15,360, respectively.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Primary efficacy results in Phase 3 trials

The primary efficacy results in each of the three pivotal Phase 3 studies showed that a significantly greater proportion of subjects randomized to dupilumab (300 mg Q2W or 300 mg QW) achieved an IGA 0 or 1 and EASI-75 responses at Week 16 (Table 3.3.1.a), in comparison to subjects randomized to placebo.

The Applicant conducted three pivotal randomized, double-blind, placebo-controlled Phase 3 studies to evaluate efficacy and safety of dupilumab in adult subjects with moderate-to-severe AD: Studies R668-AD-1334 (SOLO1) and R668-AD-1416 (SOLO2) evaluated dupilumab as monotherapy and Study R668-AD-1224 (CHRONOS) evaluated dupilumab as an adjunct therapy with concomitant topical corticosteroids (TCS) treatment (Table 3.3.1.b). In all three studies, patients were randomized to receive (1) Placebo, (2) dupilumab 300 mg Q2W with an initial dose of 600 mg, or (3) dupilumab 300 mg QW with an initial dose of 600 mg.

Table 3.3.1.a. Primary efficacy results in Phase 3 trials. Primary efficacy endpoints were the proportion of patients with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale and the proportion of patients with improvement of at least 75% in EASI (EASI-75) at Week 16. p-value<0.0001 between all dupilumab treatment groups and matching placebo. Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment. (*Source of data: Applicant's summary of clinical efficacy*)

Studies	Monotherapy						With concomitant TCS		
	R668-AD-1334 (SOLO 1)			R668-AD-1416 (SOLO 2)			R668-AD-1224 (CHRONOS)		
Treatment	**Placebo**	**300 mg Q2W**	**300 mg QW**	**Placebo**	**300 mg Q2W**	**300 mg QW**	**Placebo**	**300 mg Q2W**	**300 mg QW**
N	224	224	223	236	233	239	315	106	319
IGA 0/1	10.3 %	37.9 %	37.2 %	8.5 %	36.1 %	36.4 %	12.4 %	38.7 %	39.2 %
EASI-75	14.7 %	51.3 %	52.5 %	11.9 %	44.2 %	48.1 %	23.2 %	68.9 %	63.9 %

Table 3.3.1.b. Phase 3 trials design. Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; TCS, topical corticosteroids (*Source of data: FDA reviewer's summary*)

	Monotherapy		Concomitant TCS
	R668-AD-1334 (SOLO 1)	**R668-AD-1416 (SOLO 2)**	**R668-AD-1224 (CHRONOS)**
Study Design	Randomized, double-blind, placebo-controlled, parallel group	Randomized, double-blind, placebo-controlled, parallel group	Randomized, double-blind, placebo-controlled, parallel group
Treatment duration	16 weeks	16 weeks	52 weeks
Initial treatment period (16 weeks)	– 300 mg Q2W (N=224) – 300 mg QW (N=223) – Placebo (N=224)	– 300 mg Q2W (N=233) – 300 mg QW (N=239) – Placebo (N=236)	– 300 mg Q2W (N=106) – 300 mg QW (N=319) – Placebo (N=315)
Maintenance (up to 52 weeks)	n/a	n/a	– 300 mg Q2W (N=89) – 300 mg QW (N=270) – Placebo (N=264)
Primary Efficacy Endpoints	– IGA 0/1 at Week 16 – EASI-75 at Week 16	– IGA 0/1 at Week 16 – EASI-75 at Week 16	– IGA 0/1 at Week 16 – EASI-75 at Week 16

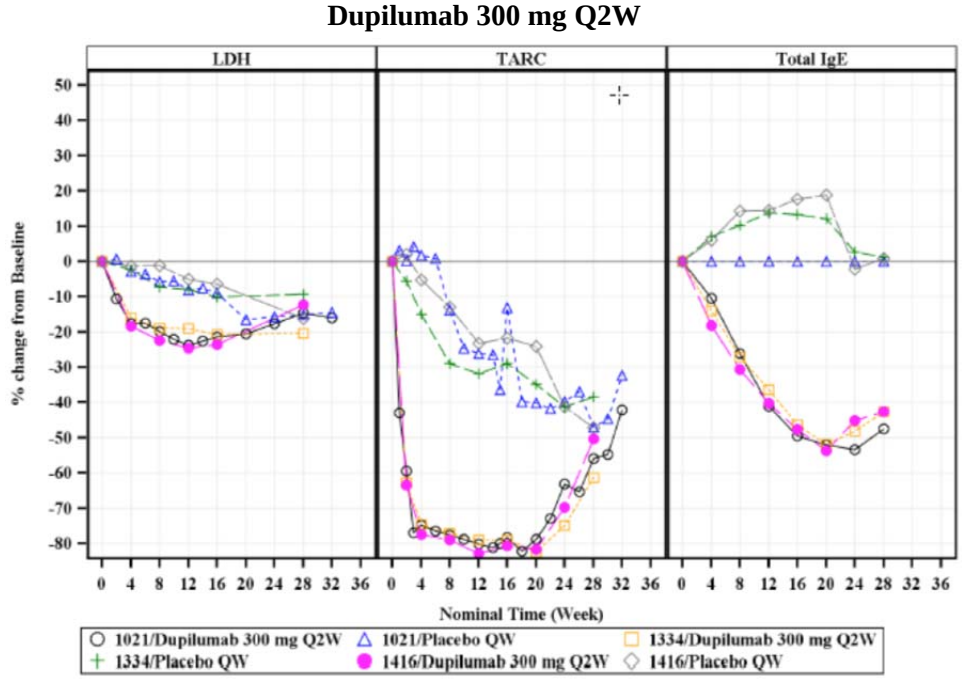
Efficacy results in Phase 2 trials

The results of Phase 2 dose-ranging study R668-AD-1021 also supported the effectiveness of dupilumab 300 mg Q2W and 300 mg QW dosing regimens for the treatment of AD. See *Sections 3.3.2* and *4.7.3* for more information.

Pharmacodynamics

Treatment with dupilumab (300 mg Q2W or 300 mg QW) was associated with decreases from baseline in serum concentrations of thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE, and lactate dehydrogenase (LDH) (Figure 3.3.1.a). Table 3.3.1.c shows proportion of patients achieving normalized status of TARC, IgE, and LDH following treatment

with dupilumab in Phase 3 studies. TARC, IgE, and LDH are biomarkers associated with AD disease activity and severity.



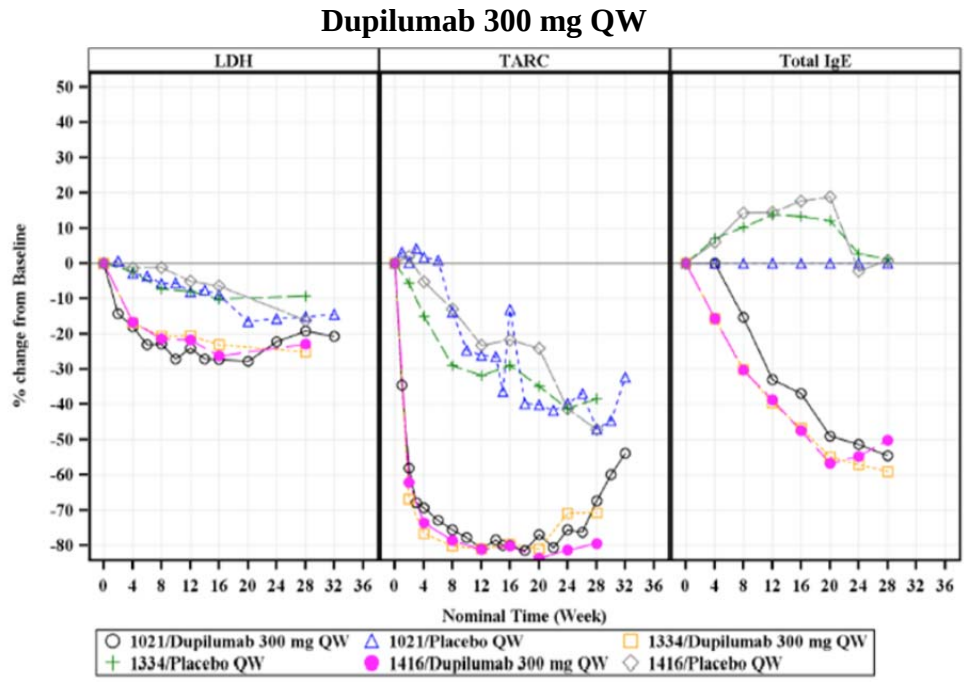


Figure 3.3.1.a. Median %change in serum concentrations of lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC/CCL17), and total serum IgE following 16 Weeks of treatment with SC dupilumab 300 mg Q2W (upper panel), 300 mg QW (lower panel) versus placebo in subjects with AD in Studies R668-AD-1021, R668-AD-1334 and R668-AD-1416. (*Source of data: Figure 16 and Figure 17, Summary of Clinical Pharmacology Studies*)

Table 3.3.1.c. Proporation of subjects achieving normalized status for TARC, total IgE and LDH in Phase 3 studies. Upper limit of normal TARC and total IgE concentration were defined as 1081.5 pg/mL and 119 kU/L, respectively. The normal range for LDH was 135 to 330 U/L for female patients and 135 to 281 U/L for male patients. (*Source of data: Table 7, Summary of Clinical Pharmacology Studies*)

	Week 16						Week 52	
Study	R668-AD-1334		R668-AD-1416		R668-AD-1224		R668-AD-1224	
	N	%	N	%	N	%	N	%
TARC								
300 QW	109/148	73.6	120/148	81.1	189/226	83.6	157/185	84.9
300 Q2W	103/137	75.2	129/164	78.7	62/80	77.5	60/69	87.0
Placebo	17/148	11.5	22/165	13.3	47/235	20.0	38/190	20.0
IgE								
300 QW	20/182	11.0	13/206	6.3	23/280	8.2	37/232	15.9
300 Q2W	10/179	5.6	9/202	4.5	6/90	6.7	9/77	11.7
Placebo	2/181	1.1	2/201	1.0	4/276	1.4	10/229	4.4
LDH								
300 QW	52/57	91.2	56/60	93.3	129/143	90.2	105/113	92.9
300 Q2W	47/51	92.2	57/63	90.5	45/56	80.4	40/43	93.0
Placebo	32/58	55.2	24/51	47.1	59/143	41.3	51/95	53.7

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The dose-response relationship for efficacy overall supports that the proposed dosing regimen of dupilumab 300 mg Q2W with an initial dose of 600 mg is appropriate for the general adult AD patient population.

All Phase 3 trials included the administration of the initial loading dose of 600 mg dupilumab which may potentially reduce the time to achieve steady-state; therefore, it is appropriate to include an intial loading in the recommended dosing regimen. However, the design of the Phase 3 studies did not allow an evaluation of whether the loading dose is essential for the initial response or the overall efficacy. See *Section 4.7* for more information

We do not recommend the increase of dosage to 300 mg QW based on individual therapeutic response, nor do we recommend initating treatment in any subgroup of patients with 300 mg QW for the following reasons:

- Dose adjustment from 300 mg Q2W to 300 mg QW has not been evaluated in clinical studies; therefore, the evidence of benefit has not been demonstrated.
- There is almost no identifiable difference (<1%) in the proportion of patients achieving IGA 0/1 response at Week 16 between 300 mg Q2W and 300 mg QW dosing regimens across the Phase 3 trials (Table 3.3.1.a).

- The 300 mg Q2W and 300 mg QW dosing regimens showed similar time-course of IGA 0/1 response rate from Week 0 to Week 16, which indicated that the more frequent dosing regimen of 300 mg QW did not offer a benefit of a faster onset of disease improvement (Figure 3.3.2.a).
- The 300 mg QW dosing regimen only showed <4% higher EASI-75 response rates than the 300 mg Q2W dosing regimen at Week 16 across the two monotherapy Phase 3 studies. In contrast, the 300 mg Q2W dosing regimen showed a 5% higher EASI-75 response rate than the 300 mg QW dosing regimen at Week 16 in the concomitant TCS Phase 3 study (Table 3.3.1.a).
- In the Phase 2 dose-ranging study (AD-1201), the 300 mg QW dosing regimen achieved only 3.6% higher IGA 0/1 response rate at Week 16 than the 300 mg Q2W dosing regimen (Figure 3.3.2.a).
- By Week 52 in the maintanence treatment period, the 300 mg QW dosing regimen achieved only 4% higher IGA 0/1 response rate but 1% lower EASI-75 response rate than the 300 mg Q2W dosing regimen in Study R668-AD-1224 (Table 3.3.2.a).
- The available data did not show a preferential treatment benefit with 300 mg QW compared to 300 mg Q2W in any particular subset of patients (Table 4.7.1.5 - 4.7.1.8)

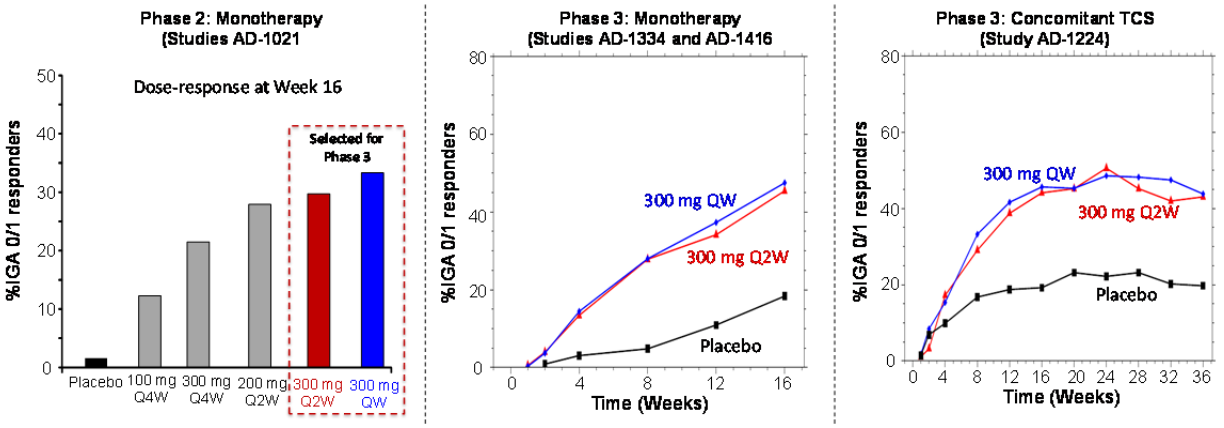


Figure 3.3.2.a. Dose-response for IGA 0/1 in AD Phase 2 and Phase 3 trials. (*Source of data: CSR for AD-1021; Figure 17 and Figure 18, E-R analysis report REGN668-MX-16102-CP-01V1*)

Table 3.3.2.a. Week 52 efficacy results in Phase 3 study R668-AD-1224. *Abbreviations*: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment. (*Source of data: Applicant's summary of clinical efficacy*)

	Placebo + TCS	**Dupilumab 300 mg Q2W + TCS**	**Dupiluamb 300 mg QW + TCS**
N	264	89	270
IGA 0 or 1, % responders	12.5 %	36.0 %	40.0 %
EASI-75, % responders	21.6 %	65.2 %	64.1 %

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. There is no need for alternative dosing regimen for subpopulations based on the intrinsic factors. The fixed 300 mg Q2W dosing regimen (with an initial 600 mg dose) is appropriate for the general population.

Body weight

Body weight had an effect on dupilumab concentrations (Figure 3.3.3.a), with lower trough concentrations in higher body weight subgroups. See *section 4.7* for more information. However, the following subgroup analysis for efficacy did not indicate the need for body weight stratified dosing:

- Subgroup analyses of the Phase 3 efficacy data did not demonstrate remarkable differences in IGA 0/1 response rate across the three body weight subgroups at Week 16 (Table 3.3.3.a).
- The response rate for EASI-75 was similar across the body weight quartiles for both 300 mg Q2W and 300 mg QW dosing regimens in the two monotherapy Phase 3 studies (Table 3.3.3.b).

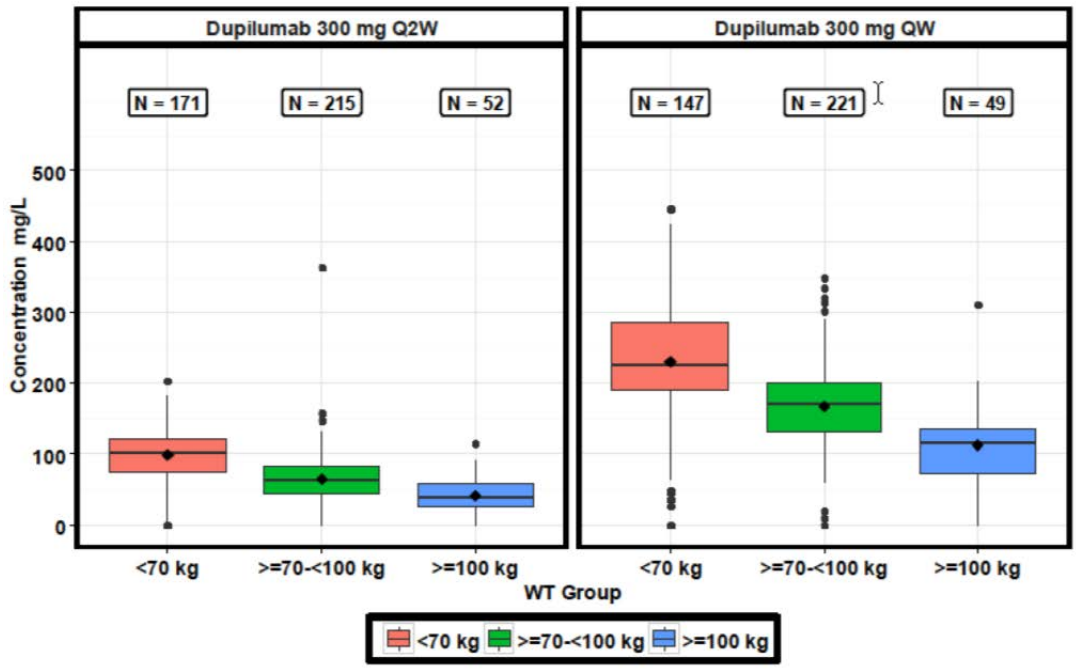


Figure 3.3.3.a. Dupilumab trough concentrations at Week 16 by body weight subgroups in Studies R668-AD-1334 and R668-AD-1416. Ctrough values at Week 16 decrease with increasing body weight. (*Source of data: Figure 9, Summary of Clinical Pharmacology*)

Table 3.3.3.a. Effect of body weight on IGA 0/1 response rates at Week 16 in Phase 3 studies. (*Source of data: CSR for Studies AD-1334, AD-1416 and AD-1224*)

Study	Body weight	IGA 0/1 response at Week 16, % (n)		
		Placebo	Dupilumab	
			300 mg Q2W	300 mg QW
AD-1334	<70 kg	9% (100)	36.5% (85)	42.3% (71)
	≥70 kg to <100 kg	10.9% (101)	38.0% (121)	36.6% (123)
	≥100 kg	13.6% (22)	44.4% (18)	27.6% (29)
AD-1416	<70 kg	10.6% (85)	36.2% (94)	39.6% (91)
	≥70 kg to <100 kg	6.4% (125)	37.5% (104)	31.4% (121)
	≥100 kg	11.5% (26)	31.4% (35)	48.1% (27)
AD-1224	<70 kg	10.6% (141)	32.7% (49)	40.8% (147)
	≥70 kg to <100 kg	15% (147)	45.1% (51)	38.6% (140)
	≥100 kg	7.4% (27)	33.3% (6)	34.4% (32)
Pooled	<70 kg	10.1% (326))	35.5% (228)	40.8% (309)
	≥70 kg to <100 kg	11.0% (373)	39.1% (276)	35.7% (384)
	≥100 kg	10.7% (75)	35.6% (59)	36.4% (88)
	All BW groups	10.6% (774)	37.3% (563)	37.8% (781)

Table 3.3.3.a. Effect of body weight on dupilumab exposure and EASI-75 response rates at Week 16. (*Source of data: FDA reviewer's analysis. See Section 4.7 for more information*)

Body weight (kg) Quantile (min-max)	No. of Subjects	AUCss over two weeks (mg·day/L) Median (min-max)	EASI-75 response rate
300 mg Q2W			
1st quartile (42.3-64)	113	1680 (488-2962)	0.47
2nd quartile (>64-75)	112	1379 (502-2334)	0.46
3rd quartile (>75-89)	113	1027 (407-1892)	0.55
4th quartile (>89-175.4)	111	766 (195-1512)	0.49
300 mg QW			
1st quartile (42.3-65)	110	3417 (819-6931)	0.52
2nd quartile (>65-75)	111	2951 (780-4861)	0.57
3rd quartile (>75-87)	109	2488 (615-4332)	0.54
4th quartile (>87-157.5)	109	1994 (544-4174)	0.48

Age

Based on population PK *post hoc* estimates of exposure for the 300 mg Q2W and 300 mg QW dosing regimens, age did not affect dupilumab PK. The age range for subjects in the population PK analyses was 18 to 88 years (N=1298); with 61 (4.7%) subjects ≥65 years.

Sex

Based on population PK *post hoc* estimates of exposure for the 300 mg Q2W and 300 mg QW dosing regimens, sex (N=1298; 40% female and 60% male) did not affect dupilumab PK.

Race

Based on population PK *post hoc* estimates of exposure for the 300 mg Q2W and 300 mg QW dosing regimens, race (N=1298; 24% Asian, 68% White, and 8% others) did not affect dupilumab PK.

Renal and hepatic impairment

There were no dedicated studies conducted in patients with renal or hepatic impairment since PK of monoclonal antibodies are not known to be affected by renal or hepatic impairment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug interactions are not applicable as dupilumab is administered by SC injection.

There is a potential for AD disease-drug-drug interaction based on the current understanding that AD patients have elevated proinflammatory cytokines. The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-4, IL-6, IL-10, IL-13, TNFα, and IFN) during chronic inflammation. Thus, dupiluamb, an antagonist of IL-4Rα, could modulate the formation of CYP450 enzymes.

We recommend that the Applicant conduct a clinical drug-drug interaction (DDI) study to evaluate the potential for dupilumab to alter the pharmacokinetics of CYP substrates in subjects with AD who are treated with dupilumab. We note that a clinical study (R668-AD-1433) designed to evaluate the effects of dupilumab on the PK of CYP substrates in subjects with AD was on-going at the time of the BLA submission. Therefore, we will recommend a PMC for completing the ongoing study and submitting the results for review.

See Section 1.2 Postmarketing Requirements and Commitments.

See Section 2.4 Summary of Labeling Recommendations.

4. APPENDICES

4.1 Summary of Bioanalytical Methods

4.1.1 Dupilumab assay

The dupilumab serum concentrations were analyzed using an enzyme linked immunosorbent assay (ELISA). The ELISA procedure employs a microtiter plate coated with recombinant human IL-4Rα. Dupilumab binds to IL-4Rα on the plate. The captured dupilumab is detected using a biotinylated mouse anti-human IgG4 monoclonal antibody, followed by NeutriAvidin conjugated to horseradish peroxidase, and a luminal-based substrate specific for peroxidase is then added to achieve a signal intensity that is proportional to the concentration of dupilumab (Figure 4.1.1.a). The assay detect dupilumab with 1 or both binding sites available for binding to IL-4Rα, which means that the ELISA assay does not detect dupilumab that are fully bound with two IL-4Rα molecules.

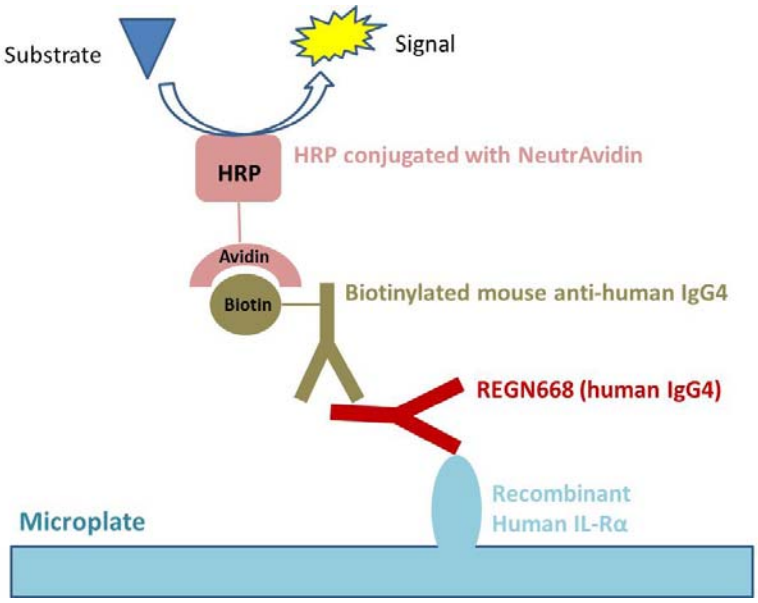


Figure 4.1.1.a. The ELISA method for dupilumab detection. (*Source of data*: *Graph created by the FDA Reviewer to help understand the assay procedure*).

The Applicant conducted two versions of assay validation for measuring serum dupilumab concentration in AD clinical trials. The first version of the assay validation (*R668-AV-09095-VA-01V2*) utilized a triplicate format for sample analysis. The second version of the assay validation (*R668-AV-13074-VA-01V1*) utilized a duplicate format for sample analysis. An overview of the clinical studies associated with the assay validations are summarized in Table 4.1.1.a.

Table 4.1.1.a. Summary of bioanalytical assays for measurement of dupilumab serum concentrations in AD clinical studies. *Abbreviations*: AR, analyte recovery; Cal., calibration; LLOQ, lower limit of quantification. Long-term stability was conducted under conditions of -80 or -20 ^{o}C. (*Source of data: Table 4, Appendix 1, Summary of Biopharmaceutics and Associated Analytical Methods*)

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Assay validations	Matrix (MRD)	Cal. curve	LLOQ (mcg/mL)	Accuracy (%AR)	Within-run precision (CV%)	Between-run precision (CV%)	Long-term stability	Clinical Studies
REGN668-AV-09095-VA-01V2	Human serum (1:50)	1.56-100	0.078	93-109	≤12	≤16	24 months	PKM12350 HV-1108 AD-0914 AD-1026 AD-1117 AD-1121
REGN668-AV-13074-VA-01V1	Human serum (1:50)	1.56-100	0.078	96-105	≤9	≤9	24 months	AD-1021 AD-1307 AD-1314 AD-1334 AD-1416 AD-1224 AD-1224 PKM14161 PKM14271

Standard Curve

The dupilumab ELISA assay has an 8-point standard curve consisting of 7 standards ranging from 1.56 ng/mL to 100 ng/mL, a standard with zero concentration, and 7 validation QCs, all prepared in 2% human serum (Table 4.1.1.b).

Table 4.1.1.b. Nominal concentrations of dupilumab standards and quality controls. *Abbreviations*: ULOQ, Upper Limit of Quantitation; EHQC, Extra High QC; HQC, High QC; MQC, Mid QC; LQC, low QC; ULQC, Ultra Low QC; LLOQ, the Lower Limit of Quantitation.

Standard #	Dupilumab conc. (ng/mL)	Validation QCs	Dupilumab conc. (ng/mL)
1	100	ULOQ	100
2	50	EHQC	85
3	25	HQC	75
4	12.5	MQC	20
5	6.25	LQC	4.5
6	3.13	ULQC	3.0
7	1.56	LLOQ	1.56
8	0	n/a	

Detailed assay validation results

The Table 4.1.1.c summarizes the assay validation results for *REGN668-AV-13074-VA-01V1*.
The Table 4.1.1.d summarizes the assay validation results for *REGN668-AV-09095-VA-01V2*.
The ELISA assay has an upper limit of quantification (ULOQ) and lower limit of quantification (LLOQ) of 100 ng/mL and 1.56 ng/mL, respectively, which translates to an ULOQ of 5 mcg/mL and a LLOQ of 0.078 mcg/mL in undiluted human serum. The assay validations are considered acceptable.

Table 4.1.1.c. Validation summary of bioanalytical assay *REGN668-AV-13074-VA-01V1.* *Abbrievations*: AR, analyte recovery; LLOQ, lower limit of quantification; BLQ, below the limit of quantification; CV, coefficient of variation; MRD, minimum required dilution; REGN668, dupilumab; ULOQ, upper limit of quantification. *(Source of Data: Section 3, Validation summary, Bioanalytical validation report REGN668-AV-13074-VA-01V1; The assay valiation report has been previously reviewed under IND 107969, SDN 174.)*

Validation Parameters ***acceptance criteria***	**Results**
Assay Range: Undiluted human serum (ULOQ-LLOQ) 2% human serum (assay MRD=1:50)	 5-0.078 mcg/mL 100-1.56 ng/mL
Inter assay-Accuracy *%AR 80 - 120% (ULOQ and LLOQ 75 - 125%)*	 96 - 105%
Inter assay-Precision *CV%≤ 20% (ULOQ and LLOQ ≤ 25%)*	 4 - 9%
Inter assay-Linearity *%AR 80 - 120% (Standard 1 and 7: 75 - 125%)* *CV%≤ 20% (Standard 1 and 7: ≤ 25%)*	 96 - 105% 1 - 2%
Intra assay-Accuracy *%AR 80 - 120%*	 97 - 106%
Intra assay-Precision *CV% ≤ 20%*	 3 - 9%
Intra assay-Linearity *%AR 80 - 120% (Standard 1 and 7: 75 - 125%)* *CV% ≤ 20% (Standard 1 and 7: ≤ 25%)*	 98 - 103% 0 - 3%
Matrix Interference *80% of the samples must be < LLOQ (BLQ)* 1) Normal individuals 2) Normal individuals with hemoglobin (2 mg/mL) 3) Individuals with high LDL levels (>130 mg/mL)	 10 of 10 samples BLQ 10 of 10 samples BLQ 10 of 10 samples BLQ
Selectivity at LLOQ *%AR 75 - 125%;* *CV%≤ 25% for 80% of LLOQ-spiked samples* 1) Normal individuals 2) Normal individuals with hemoglobin (2 mg/mL) 3) High LDL samples (>130 mg/mL)	 1) 87 - 106%; 0 - 11% (10 of 10 samples) 2) 86 - 109%; 1 - 6% (10 of 10 samples) 3) 82 - 105%; 0 - 9% (10 of 10 samples)
Dilution Recovery (High Level QCs) *%AR 80 - 120%* *CV%≤ 20%* (400 mcg/mL) (100 mcg/mL) (20 mcg/mL)	 91 - 118%; 0 - 9% (91-107%; 2-7%) (103-114%; 0-3%) (94-118%; 1-9%)
Robustness (impact of non-critical agents: human serum, NeutrAvidin-HRP, and substrate) *%AR 80 - 120% (ULOQ and LLOQ 75 - 125%)* *CV% ≤ 20% (ULOQ and LLOQ ≤ 25%)*	 84 - 101% 0 - 19%
Ruggedness (impact of analysts and laboratories) *%AR 80 - 120% (ULOQ and LLOQ 75 - 125%)* *CV%≤ 20% (ULOQ and LLOQ ≤ 25%)*	 97 - 108% 1 - 12%
Specificity *%AR 80-120%;*	

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%CV≤20% for free REGN668 *BLQ for hIL-4Rα only* 1) Free REGN668 (positive control) 2) hIL-4Rα only (negative control) 3) 5:1 hIL-4Rα:REGN668 molar ratio 4) 1:1 hIL-4Rα:REGN668 molar ratio 5) 1:5 hIL-4Rα:REGN668 molar ratio	 1) 95 -113%; 1 - 5% 2) BLQ 3) 3 - 5%; 0 - 1% 4) 44 - 58 %; 0 - 5% 5) 109 - 113%; 1 - 5%

Table 4.1.1.d. Validation summary of bioanalytical assay *REGN668-AV-09095-VA-01V2*. *Abbrievations*: AR, analyte recovery; LLOQ, lower limit of quantification; BLQ, below the limit of quantification; CV, coefficient of variation; MRD, minimum required dilution; REGN668, dupilumab; ULOQ, upper limit of quantification. *(Source of Data: Section 3, Validation summary, Bioanalytical validation report REGN668-AV-09095-VA-01V2)*

Validation Parameters ***acceptance criteria***	**Results**
Assay Range: Undiluted human serum (ULOQ-LLOQ) 2% human serum (assay MRD=1:50)	 5-0.078 mcg/mL 100-1.56 ng/mL
Inter assay-Accuracy *%AR: 75 - 125%*	 93-109%
Inter assay-Precision *CV%≤ 25%*	 10-16%
Inter assay-Linearity *%AR: 75 - 125%* *CV%≤ 25%*	 96-104% 2-5%
Intra assay-Accuracy *%AR 75 - 125%*	 99-110%
Intra assay-Precision *CV% ≤ 25%*	 6-12%
Intra assay-Linearity *%AR 75 - 125% (Standard 1 and 7: 75 - 125%)* *CV% ≤ 25% (Standard 1 and 7: ≤ 25%)*	 97 - 103% 0 - 6%
Matrix Interference *80% of the samples must be < LLOQ (BLQ)*	10 of 10 samples BLQ
Selectivity at LLOQ *%AR 75 - 125% of LLOQ* *CV%≤ 25%* *for at least 80% of LLOQ-spiked samples* ***at 0.156 mcg/mL*** *%AR 75 - 125% of 0.156 mcg/mL* *CV%≤ 25%* *for at least 80% of LLOQ-spiked samples*	 80-121% 4-23% for 9 of 10 samples 75-119% 1-22% for 8 of 10 samples
Dilution Recovery (High Level QCs) *%AR 75 - 125%* *CV%≤ 25%*	 103-124%; 3-19%
Robustness (impact of non-critical agents: human serum, NeutrAvidin-HRP, and substrate) *%AR 80 - 120% (ULOQ and LLOQ 75 - 125%)* *CV% ≤ 20% (ULOQ and LLOQ ≤ 25%)*	 95-113% 3-23%

Ruggedness (impact of analysts and laboratories) *%AR 80 - 120% (ULOQ and LLOQ 75 - 125%)* *CV%≤ 20% (ULOQ and LLOQ ≤ 25%)*	 96-119% 0-17%
Specificity *%AR 80-120%;* *%CV≤20% for free REGN668* *BLQ for hIL-4Rα only* 1) Free REGN668 (positive control) 2) hIL-4Rα only (negative control) 3) 5:1 hIL-4Rα:REGN668 molar ratio 4) 1:1 hIL-4Rα:REGN668 molar ratio 5) 1:2 hIL-4Rα:REGN668 molar ratio 6) 1:5 hIL-4Rα:REGN668 molar ratio	 97-109%; 5-12% BLQ 3-4%; 5-11% 58-62 %; 12-23% 80-91%; 10-12% 97-109%; 12-20%
Short-term stability: 4°C overnight, 4 hours room temperature, 10 times freeze/thaw cycles %AR 75-125% CV%≤25%	 94-116% 1-9%
Long-term stability: -80 or -20°C, 24-month storage %AR 75-125% CV%≤25%	 76-125% 1-23%

Incurred sample reanalysis (ISR)

For assay validation version 2 (*REGN668-AV-09095-VA-01V2*), incurred sample reanalysis (ISR) was performed on samples from 4 clinical studies (*R668-AD-0914, R668-AD-1026, R668-AD-1121 and R668-AD-1108*). For assay validation version 1 (*REGN668-AV-13074-VA-01V1*), ISR was performed on samples from study R668-AD-1021. All of these ISRs met acceptance criteria of 66.7% of the reanalysis results within ±30% variability of the original results (Table 4.1.1.e).

Table 4.1.1.e. Incurred sample reanalysis (ISR) results. (*Source of data: Sample Analysis Reports of individual clinical studies*)

Assay	Clinical Studies	Total # of ISR samples	% of ISR samples pass the acceptance criteria
REGN668-AV-09095-VA-01V2	R668-AD-1108	50	88% (44/50)
	R668-AD-1026	50	90% (45/50)
	R668-AD-1121	27	78% (21/27)
	R668-AD-0914	50	94% (47/50)
REGN668-AV-13074-VA-01V1	R668-AD-1021	435	89% (386/435)

4.1.2 Bioanalytical assays for immunogenicity assessment

Anti-drug antibodies (ADA) were assessed in all dupilumab clinical studies and ADA positive immunogenicity samples were further tested for neutralizing ADA (NAb). The Applicant developed and validated the immunogenicity assays *R668-AV-09106-VA-01V2* and *R668-AV-*

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13089-VA-01V2 for detection of binding ADA and the immunogenicity assay *R668-AV-13112-VA-01V1* for detection of neutralizing ADA (NAb). The initial ADA binding assay *R668-AV-09106-VA-01V2* was modified by including acid treatment of serum samples prior to analysis to improve the drug tolerance level. The improved ADA binding assay *R668-AV-13089-VA-01V2* was further validated using AD patient sample with a different assay cutpoint. A summary of assay sensitivity and tolerance is provided in Table 4.1.2.a. The drug toleranace levels for the improved ADA assay and NAb assay are higher than the mean trough serum dupilumab concentrations in Phase 3 studies and are considered acceptable for immunogenicity assessment in AD Phase 3 studies. *See Product Quality Review (immunogenicity section) for more detailed information regarding the immunogenicity assay validations.*

Table 4.1.2.a. Sensitivity and drug tolerance of the immunogencity assays for detecting binding and neutralizing anti-drug antibodies (ADA) in dupilumab clinical studies. Assay sensitivity was determined in neat serum in the absence of duplilumab. (*Source of Data: Summary of Biopharmaceutics and Associated Analytical Methods*)

Immunogenicity Assays	***Validation Report***	**Sensitivity**		**Drug tolerance**	
		Monoclonal positive control	**Polyclonal positive control**	**Monoclonal positive control (0.5 mcg/mL)**	**Polyclonal positive control (0.5 mcg/mL)**
ADA Assay-1	*R668-AV-09106-VA-01V2*	35.6 ng/mL	n/a	122 mcg/mL	227 mcg/mL
ADA Assay-2	*R668-AV-13089-VA-01V2*	6.9 ng/mL	1.0 ng/mL	316 mcg/mL	763 mcg/mL
ADA Assay-2 (for AD patients)	*R668-AV-13089-VA-01V2*	9.9 ng/mL	1.6 ng/mL	251 mcg/mL	635 mcg/mL
NAb assay	*R668-AV-13112-VA-01V1*	144 ng/mL	135 ng/mL	276 mcg/mL	498 mcg/mL
Reference: *dupilumab steady state trough concentrations in Phase 3 studies*		The mean±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9 ±41.4 mcg/mL for 300 mg Q2W and from 173±75.9 mcg/mL to 193 ±77.0 mcg/mL for 300 mg QW.			

Bindign ADA Assay-1: R668-AV-09106-VA-01V2

ADA Assay-1 is a non-quantitative, titer-based, electrochemiluminescence bridging immunoassay. The immunoassay employs a mouse anti-dupilumab monoclonal antibody as the positive control and biotinylated dupilumab (Bio-dupilumab) and ruthenium-labeled dupilumab (Ru-dupilumab) as bridging components.

Samples and controls are diluted in a solution containing Bio-dupilumab and Ru-dupilumab. Upon incubation, a bridge is formed when the positive control or any ADA present in the sample binds to both Bio-dupilumab and Ru-dupilumab, forming a complex. Samples and controls are then added to a streptavidin coated microplate, which captures the Bio-dupilumab, binding the complex (Bio-dupilumab: ADA: Ru-dupilumab), to the microplate surface. The ruthenium label generates an electrochemiluminescent signals when voltage is applied to the plate. The measured

electrochemiluminescence (i.e., counts) is proportional to the amount of positive control/ADA present in the sample.

Binding ADA Assay-2: R668-AV-13089-VA-01V2

The Applicant modified the Binding ADA Assay-1 to improve the sensitivity and drug tolerance level. The modified ADA assay is also a nonquantitative, titer-based, electrochemiluminescent bridging immunoassay which employs a mouse anti-REGN668 monoclonal antibody as the positive control and Bio-dupilumab and Ru-dupilumab as bridging components. This method includes acid treatment of serum samples prior to analysis. The acid treatment dissociates antibody:drug complexes present in serum samples and allows improved detection of ADA in the presence of dupilumab.

Both ADA assays involve 3 tiers in determination of a sample immunogenicity status: an initial screening assay to identify samples that are potentially positive for ADA; a confirmation assay to determine if any positive response in the screening assay can be competed with unlabeled dupilumab; and a titer assay to assess levels of ADA in samples positive in the confirmation assay.

Neutralizing anti-drug antibody (NAb) assay: R668-AV-13112-VA-01V1

The NAb assay uses an electrochemiluminescence-based competitive ligand binding (CLB) assay format to detect anti-dupilumab NAbs in human serum samples. The CLB procedure employed a mouse anti-dupilumab monoclonal antibody as the positive control, bio-dupilumab as the capture reagent, and ruthenium-labeled target IL-4Rα (Ru-REGN560) as the detection reagent. Samples and controls are diluted in acetic acid and then neutralized using a Tris-base solution containing Bio-dupilumab and REGN675. The acid treatment results in the dissociation of NAb: drug and drug: target complexes present in serum samples. In order to mitigate target interference, the anti-IL-4Rα monoclonal antibody (REGN675) is used to bind free target potentially released by the acid treatment.

Upon incubation, the positive control (REGN2266) or any NAb present in patient serum samples binds to the Bio-dupilumab. The acid treated samples are then added to the high bind avidin-coated microplate, where the avidin captures the Bio-dupilumab along with any NAb that is bound to it. Ru-REGN560 is then added to the microplate as the detection agent. In the absence of NAb in the sample, the Bio-dupilumab binds to the Ru-REGN560 forming a Bio-dupilumab: Ru-REGN560 complex generating an electrochemiluminescent signal. In the presence of NAb in the sample, the NAb binds to the Bio-dupilumab preventing the formation of the Bio-dupilumab: Ru-REGN560 complex. This reduces the electrochemiluminescent signal. Hence, the measured electrochemiluminescence (i.e., counts) is inversely proportional to the amount of positive control/NAb present in the sample.

4.2 Biopharmaceutics: Comparative PK Studies

In the clinical development program of dupilumab, the Applicant made several manufacturing changes related to drug substance and drug product. The manufacturing process changes during the AD clinical program included the following:

Drug Substance: Dupilumab drug substance (DS) was initially manufactured with recombinant Chinese hamster ovary (CHO) cells Cell Line 1 and Process 1 (C1P1). The Applicant made the following DS manufacturing changes:

(b) (4)

Drug product: Multiple dupilumab drug products (DP) differing in DS, formulation (b) (4) , and presentation (vial *vs.* PFS) were used in AD clinical program (See *Table 3.2.a of the Clinical Pharmacology Filing Review*).

The Applicant conducted comparative PK studies to evaluate the PK of the before-change product and the after-change product. This section summarizes two studies; one study compared drug product #2 to drug product #6 (Study PKM12350) and one study compared drug product #6 in vial presentation to drug product #7 in PFS presentation (Study PKM14161).

Table 4.2.a contains product information for Products #2, #6 and #7. Table 4.2.b contains the study design information for Study PKM12350 and Study PKM14161. Table 4.2.c contains the C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ data and the statistical comparisons of these parameters between the test product and the reference product for both studies. Figure 4.2.a shows the PK profiles.

Below is a summary of the results of the comparative PK studies:

- The comparative PK data showed that the before-change product and the after-change product had similar PK in each of the studies because geometric mean ratios of C_{max} and AUC parameters were close to the value of 1. While the 90% CI were not within 80%-125%, it is not unexpected because of the small sample size.
- Results from Study PKM14161 supported the Phase 3 study dose selection based on data from the Phase 2 dose finding study which used drug product #2.
- Results from Study PKM12350 supported a major manufacturing process change (b) (4)

Table 4.2.a. Summary of product information of Products #2, #6 and #7 that were used in comparative PK studies: Study PKM 12350 and Study PKM14161.

Drug Product	Product #2	Product #6	Product #7
Drug substance	C1P2	C2P1	C2P1
Formulation	150 mg/mL	150 mg/mL	150 mg/mL
			(b) (4)
Presentation	5 mL glass vial	5 mL glass vial	PFS
DP used in PK comparative studies	PKM12350	PKM12350 PKM14161	PKM14161
DP used in other clinical study	R668-HV-1108 R668-AD-0914 R668-AD-1026 R668-AD-1117 R668-AD-1121	TDU12265 R668-AD-1021 R668-AD-1224 R668-AD-1314	Phase 3 studies R668-AD-1225 R668-AD-1224 R668-AD-1334 R668-AD-1416

Table 4.2.b. Summary of study design information for comparative PK Studies PKM 12350 and PKM14161.

Study number	PKM12350		PKM14161	
Pruducts compared	*Reference*: Product #2 *Test*: Product #6		*Reference*: Product #6 *Test*: Product #7	
Study design	Parallel group, double-blind		Parallel group, double-blind	
Study population	Healthy Subjects (18-45 yo)		Healthy Subjects (18-65 yo)	
Number of subjects	*Ref*: 13	*Test*: 15	*Ref*: 19	*Test*: 19
Dupilumab dose	300 mg single dose		300 mg single dose	
Administration route	SC		SC	
Primary endpoints	AUC_{0-t}, AUC_{0-inf}, C_{max}		AUC_{0-t}, C_{max}	
PK sampling timepoints	Days 0 (predose), 1, 2, 3, 8, 11, 15, 22, 29, 36, 43, 50, and 57		Days 0 (predose), 2, 4, 8, 11, 15, 29, 36, 43, 50, and 57	
Study period	2/20/2012 – 07/06/2012		11/03/2014 – 01/26/2015	

Table 4.2.c. Geometric mean ratios and 90% confidence interval (CI). All PK parameter values are presented as mean ± SD. *(Source of Data: Table 16 in CSR PKM12350 and Table 17 in CSR PKM14161)*

Study number	Comparison	Test	Reference	Geometric Mean Ratio	90% CI
PKM12350	N	13	16	--	--
	C_{max} (mcg/mL)	28.9 ± 9.11	27.2 ± 9.95	1.10	(0.89 to **1.35**)
	AUC_{0-t} (mg*d/L)	488 ± 200	500 ± 179	0.90	(**0.71** to 1.16)
	AUC_{0-inf} (mg*d/L)	554 ± 163	521 ± 199	1.05	(0.86 to **1.29**)
PKM14161	N	19	19	--	--
	C_{max} (mcg/mL)	34.8 ± 17.5	34.3 ± 11.6	0.96	(**0.74** to 1.25)
	AUC_{0-t} (mg*d/L)	587 ± 302	575 ± 235	0.98	(**0.71** to **1.37**)

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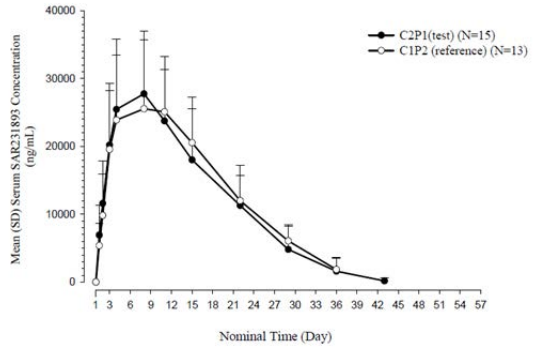
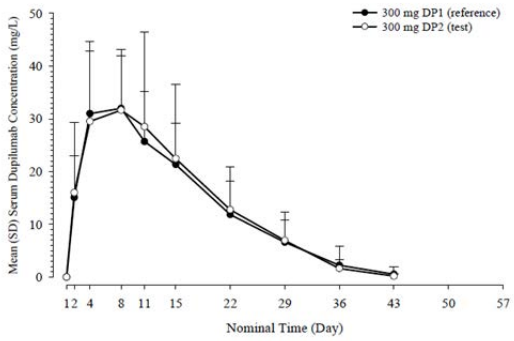
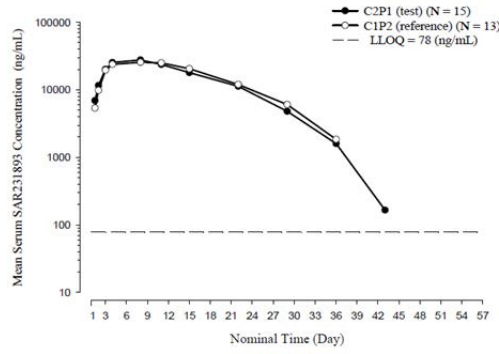
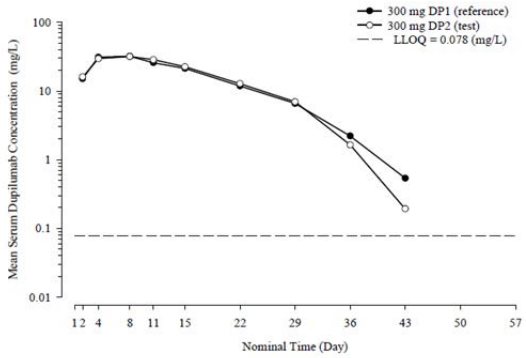
Study PKM12350	Study PKM14161
	
	

Figure 4.2.a. Mean (SD) serum dupilumab concentration-time profiles following single SC doses from two comparative PK studies of dupilumab *(Source: Figure 2 in CSR PKM12350 and Figure 2 in CSR PKM14161)*

Reference ID: 4030358

4.3 Pharmacokinetics: Individual Study Summary

Table 4.3. provides a summary of dupilumab exposure and PK parameters following different dosing regimens across clinical trials. A brief description of the study design and PK results for each study are summarized in this section. See *Section 4.2. Biopharmaceutics* for comparative PK study summaries. See *Section 3.2* for integrated PK summary.

Single Dose (SC) Studies – Healthy Subjects

PK Parameter	TDU12265			R668-AS-0907		R668-HV-1108	
	Dose (mg)			Dose (mg)		Dose (mg)	
	150	300	600	150	300	300 Slow	300 Fast
Cmax (mg/L)	10.4	38.3	70.1	13.5	32.4	35.0	34.4
t_{max} (d) median	7.01	7.01	7.00	6.42	5.69	5.19	6.25
AUC_{last} (mg.d/L)	150	700	1780	168	594	530	630

	PKM12350		PKM14161		PKM14271	
	Dose (mg) DP		Dose (mg) DP		Dose (mg) DP	
	300 C2P1	300 C1P2	300 C2P1 (PS20, vial)	300 C2P1 (PS80, PFS)	200 C2P1 (PS20, vial)	200 C2P1 (PS80, PFS)
Cmax (mg/L)	28.9	27.2	34.8	34.3	23.2	22.8
t_{max} (d) median	7	7	7	7	3.14	3.00
AUC_{last} (mg.d/L)	487.5	500.0	587	575	339	323

Repeat Dose (SC) Studies Phase 1 and 2 – AD Patients

PK Parameter	R668-AD-0914			R668-AD-1026		R668-AD-1121	R668-AD-1117	R668-AD-1021		R668-AD-1307
	Dose (mg) x4W			Dose (mg) x4W		Dose (mg) x4W	Dose (mg) x12W	Dose x 16W	Dose x 16W	Dose x 16W
	75 QW	150 QW	300 QW	150 QW	300 QW	300 QW	300 QW	300 Q2W	300 QW	200 QW
C_{trough} (mg/L)	6.74	19.2	69.3	34.0	86.4	95.6	158	61.5	168	118
C_{max} (mg/L)	11.4	26.6	94.8	39.2	102	99.8	NA	NA	NA	NA

Repeat Dose (SC) Studies Phase 3 – AD Patients

PK Parameter	R668-AD-1334		R668-AD-1416		R668-AD-1224		R668-AD-1225
	Dose (mg) x 16W		Dose (mg) x 16W		Dose (mg) x 52W		Dose (mg) x 68W
	300 Q2W	300 QW	300Q2W	300 QW	300Q2W	300QW	300 QW
C_{trough} (mg/L)	73.3	173	76.6	193	78.6	188	204
C_{max} (mg/L)	NA	NA	NA	NA	NA	NA	NA

Table 4.3. Summary of dupilumab exposure and PK parameters across clinical trials. (*Source of Data: Table 13, Appendix, Summary of Clinical Pharmacology Studies*).

Reference ID: 4030358

4.3.1. Study R668-AS-0907

Study R668-AS-0907 was a randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study conducted in 48 healthy volunteers. Subjects received dupilumab IV (1, 3, 8, and 12 mg/kg infused over 2 hours) or dupilumab SC (150 mg and 300 mg).

The dupilumab concentration-time profiles by treatment groups are shown in Figure 4.3.1. The exposure (AUC) of dupilumab increased in a greater than dose-proportional manner, indicating the concentration-dependent nature of drug clearance.

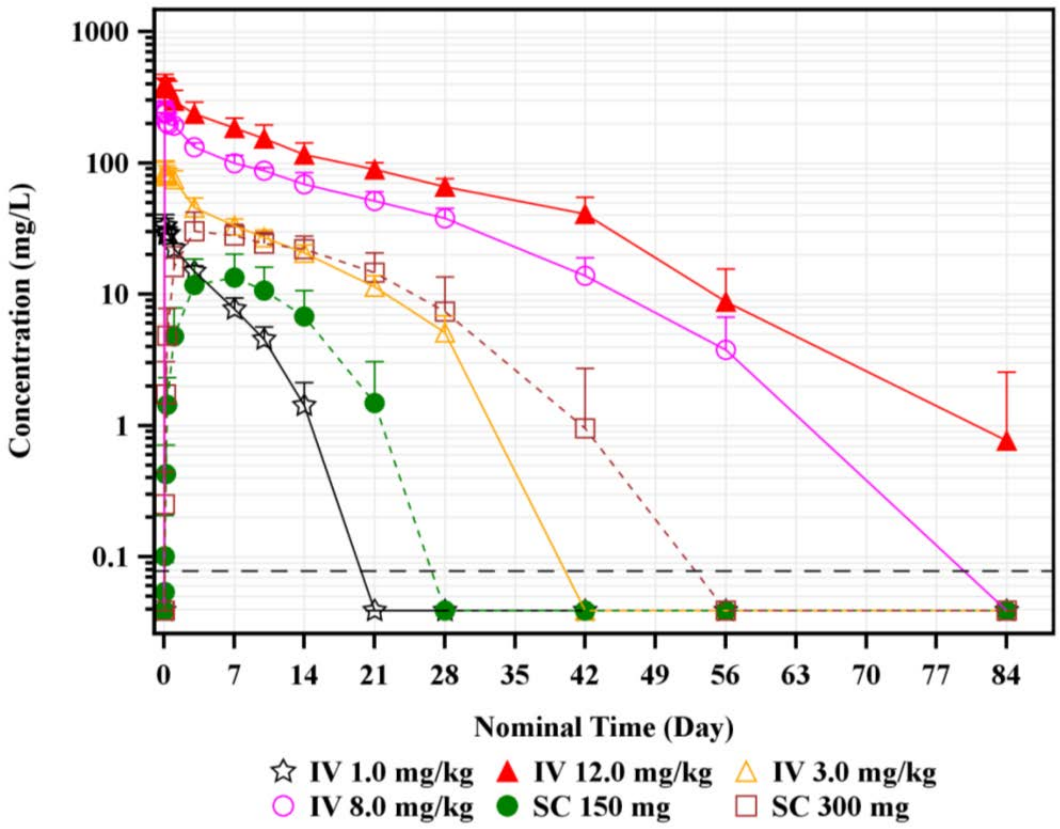


Figure 4.3.1. Dupilumb concentration-time profiles following single IV or SC doses in healthy subjects.
Concentrations below the lower limit of quantitation (LLOQ, 0.078 mcg/mL) are imputed as LLOQ/2.
(*Source of data: Figure 3, Summary of Clinical Pharmacology Studies*)

4.3.2. Study R668-HV-1108

Study R668-HV-1108 was an open-label, randomized, parallel-group, single-dose study to assess the safety, tolerability, and PK of a single 300 mg in 2 mL dose of dupilumab administered SC at 2 different rates (30 seconds "Fast" *vs* 10 minutes "Slow") in 36 healthy subjects.

The dupilumab concentration-time profiles are shown in Figure 4.3.2. The injection rates did not appear to affect the concentration-time profiles of dupilumab up to Day 21 following a single 300 mg SC dose administration.

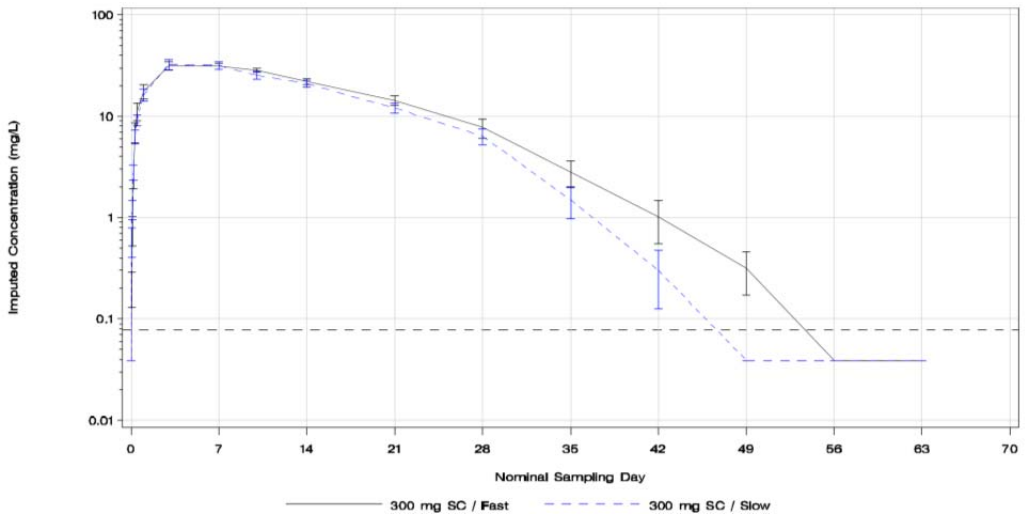


Figure 4.3.2. Dupilumb mean±SE concentration-time profiles following single 300 mg SC dose at two different injection rates in healthy subjects. Concentrations below the lower limit of quantitation (LLOQ, 0.078 mg/L) are imputed as LLOQ/2. (*Source of data: Figure 7, CSR R668-HV-1108*)

4.3.3. Study TDU12265

Study TDU12265 was a randomized, double-blinded, placebo-controlled, sequential ascending single-dose study to assess safety, tolerability, and PK of dupilumab in healthy Japanese male subjects. A total of 32 subjects were randomized, 6 subjects to each of 4 dupilumab treatment groups (75 mg, 150 mg, 300 mg, and 600 mg) and 8 subjects to the placebo group.

The dupilumab concentration-time profiles are shown in Figure 4.3.3. Mean systemic exposure to dupilumab increased in a greater than dose proportional manner, with an 8-fold increase in dose from 75 mg to 600 mg resulting in a 13.1-, and 30.4-fold increase in geometric mean C_{max} and AUC_{last}, respectively (Table 4.3).

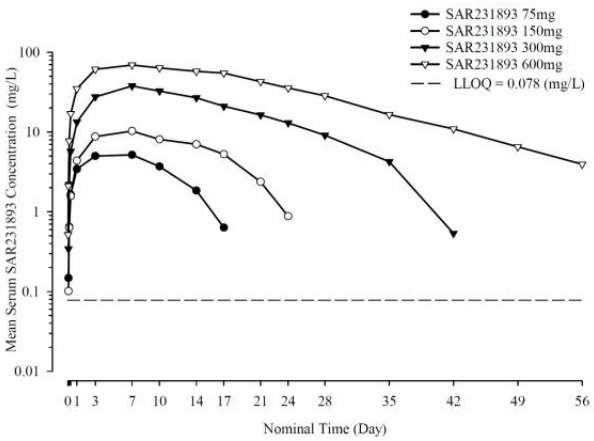


Figure 4.3.3. Dupilumb concentration-time profiles following single SC dose administrations in healthy Japanese subjects. (*Source of data: Figure 4, CSR TDU12265*)

Reference ID: 4030358

4.3.4. Study R668-AD-0914

Study R668-AD-0914 was a 12-week multicenter, randomized, double-blind, placebo-controlled, sequential ascending dose study to assess the safety and PK profile of dupilumab following multiple SC doses in 30 adult patients with moderate-to-severe AD. Study drug was administered weekly for 4 consecutive weeks.

A summary of serum dupilumab exposure data by dupilumab treatment groups (75 mg, 150 mg, and 300 mg) are presented in Table 4.3.4. The serum concentration-time propfies are presented in Figure 4.3.4.

Dose (mg)	Parameter (Unit)	N	Mean	SD	SE	CV%	Min	Median	Max	Range
75	C_{max} (mg/L)	8	11.4	8.86	3.13	77.7	3.42	8.57	29.1	25.7
	C_{last} (mg/L)	8	0.989	0.644	0.228	65.1	0.288	0.904	2.01	1.72
	t_{last} (day)	8	35.5	8.74	3.09	24.6	28.0	32.5	49.2	21.2
150	C_{max} (mg/L)	8	26.6	16.0	5.67	60.2	7.19	25.1	53.9	46.7
	C_{last} (mg/L)	8	4.10	6.67	2.36	163	0.104	1.70	20.2	20.1
	t_{last} (day)	8	40.6	14.4	5.10	35.6	22.0	38.5	63.0	41.0
300	C_{max} (mg/L)	8	94.8	11.1	3.91	11.7	82.2	91.6	112	29.8
	C_{last} (mg/L)	8	5.07	4.40	1.56	86.8	1.59	3.21	13.0	11.4
	t_{last} (day)	8	70.2	13.4	4.75	19.1	50.1	70.0	91.0	40.9

C_{last} = last measureable concentration; C_{max} = maximum concentration following the fourth (last) dose; CV = coefficient of variation; Max = Maximum; Min = Minimum; SD = standard deviation; SE = standard error; t_{last} = time of last measureable concentration in actual days ([actual date] = [date/time of event] – [date/time of the first dose])

Table 4.3.4. Summary of dupilumab exposure following 4 SC doses at 75 mg, 150 mg, or 300 mg of dupilumab once Weekly in subjects with AD. (*Source of Data: Table 20, CSR R668-AD-0914*)

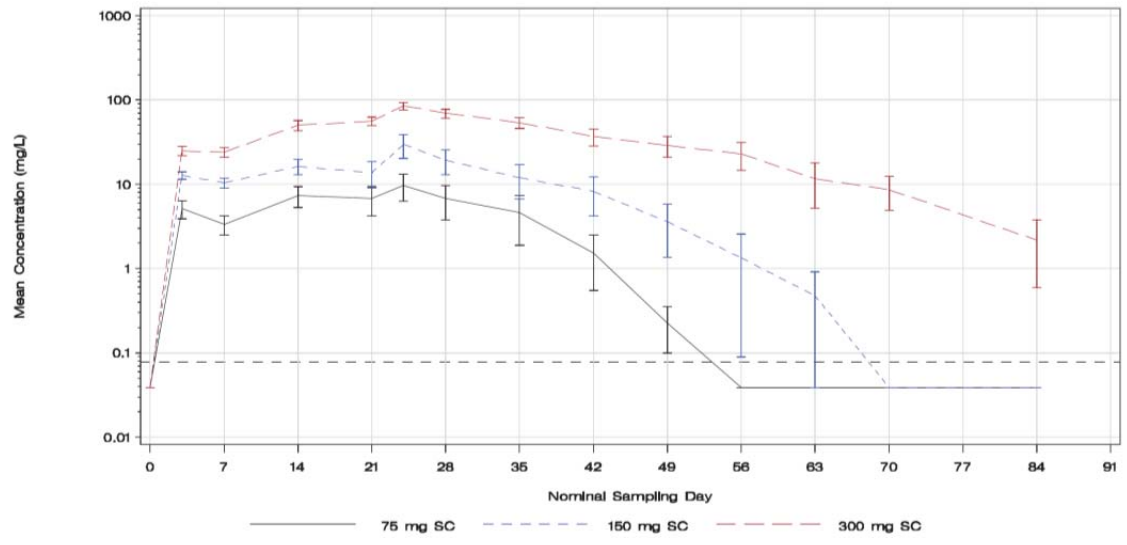


Figure 4.3.4. Dupilumab mean±SE serum concentration-time profiles following 4 Weekly 75 mg, 150 mg, and 300 mg SC doses of dupilumab in subjects with AD. (*Source of Data: Figure 2, CSR R668-AD-0914*)

Reference ID: 4030358

4.3.5. Study R668-AD-1026

R668-AD-1026 was a 12-week, randomized, double-blind, placebo-controlled, sequential ascending, repeated dose study to assess the safety and PK profile of SC treatment with dupilumab in 37 adult patients with moderate-to-severe AD. Study drug was administered weekly for 4 consecutive weeks via SC injections.

A summary of serum dupilumab exposure by dupilumab treatment groups (75 mg, 150 mg, and 300 mg) are presented in Table 4.3.5. The serum concentration-time propfies are presented in Figure 4.3.5.

Dose (mg)	Parameter (Unit)	N	Mean	SD	SE	CV%	Min	Median	Max	Range
150	C_{max} (mg/L)[a]	12	39.2	16.1	4.64	41.1	5.63	47.1	53.2	47.6
	C_{last} (mg/L)	12	2.55	1.55	0.449	60.9	0.182	2.51	4.89	4.71
	t_{last} (day)[b]	12	53.5	13.7	3.96	25.6	27.8	55.0	70.0	42.2
300	C_{max} (mg/L)[a]	13	102	44.7	12.4	43.7	41.8	101	182	140
	C_{last} (mg/L)	13	7.80	9.72	2.70	125	1.68	3.57	32.7	31.0
	t_{last} (day)[b]	13	74.3	13.1	3.62	17.6	49.0	78.2	87.1	38.1

CV = coefficient of variation; SD = standard deviation; SE = standard error
a Maximum concentration of functional REGN668 following the fourth (last) dose.
b t_{last} = Mean time of last measurable concentration in actual days.

Table 4.3.5. Summary of dupilumab exposure following 4 weekly SC doses at 150 mg or 300 mg of dupilumab in subjects with AD. (*Source of Data: Table 18, CSR R668-AD-1026*)

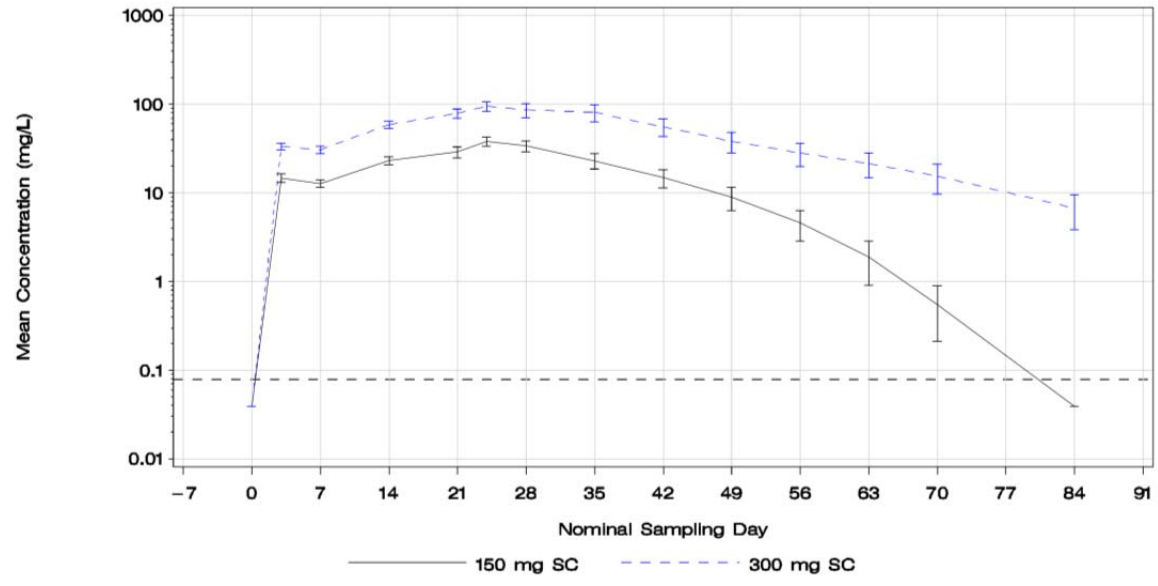


Figure 4.3.5. Dupilumab mean±SE serum concentration-time profiles following 4 Weekly 150 mg and 300 mg SC doses of dupilumab in subjects with AD. (*Source of Data: Figure 3, PK report, CSR R668-AD-0914*)

4.3.6. Study R668-AD-1121

Study R668-AD-1121 was an 11-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study conducted in Europe to assess the safety of repeated SC doses of dupilumab 300 mg administered concomitantly with TCS to patients with moderate-to-severe AD. Study drug was administered weekly, beginning at Day 1 (baseline) for 4 consecutive weeks via SC injections. A summary of serum dupilumab exposure data are presented in Table 4.3.6. The serum concentration-time propfie are presented in Figure 4.3.6.

Dose	Parameter (Unit)	N	Mean	SD	SE	CV%	Min	Median	Max
300 mg	C_{max} (mg/L)	21	99.8	28.1	6.14	28.2	47.7	101	145
	t_{max} (day)	21	25.5	5.67	1.24	22.2	13.9	28.0	32.9
	C_{last} (mg/L)	21	11.6	8.87	1.93	76.7	0.897	9.67	31.9
	t_{last} (day)	21	69.9	10.6	2.31	15.2	48.9	76.9	83.9

Note: For the purposes of this report, C_{max} is defined as the highest observed trough concentration.
C_{last} = Last observed concentration; N = Number of samples; t_{last} = Time of last observed concentration

Table 4.3.6. Summary of dupilumab exposure following 4 weekly SC 300 mg of dupilumab in subjects with AD. (*Source of Data: Table 26, CSR R668-AD-1121*)

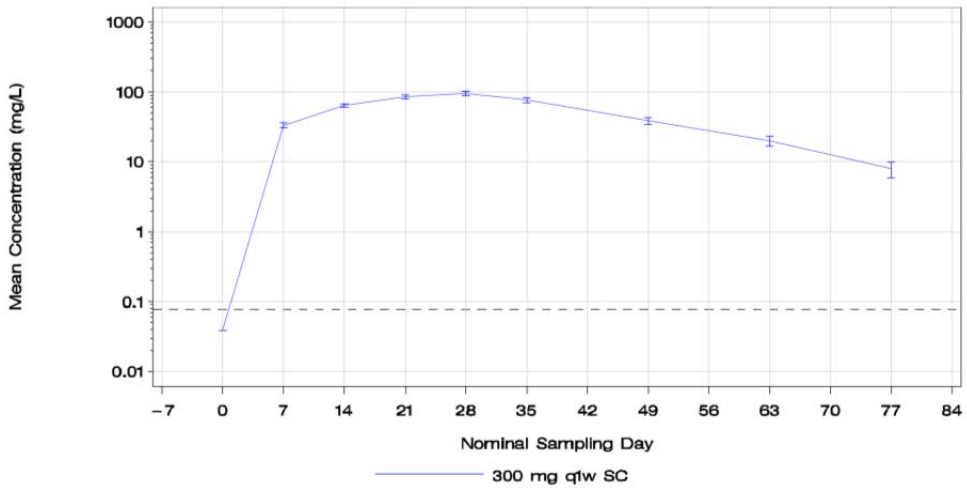
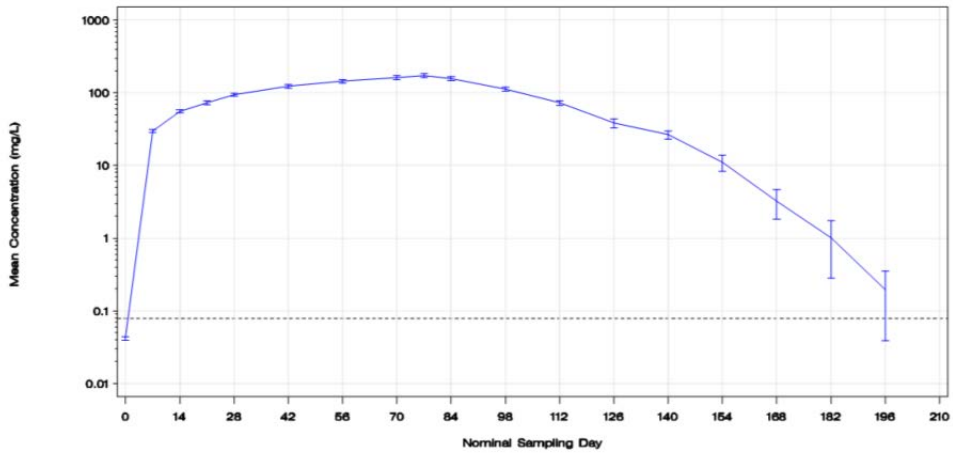


Figure 4.3.5. Dupilumab mean±SE serum concentration-time profile following 4 Weekly 300 mg SC doses of dupilumab in subjects with AD. (*Source of Data: Figure 9, CSR R668-AD-1121*)

4.3.7. Study R668-AD-1117

R668-AD-1117 was a phase 2a, 28-week, multicenter, double-blind, randomized, placebo-controlled, proof-of-concept study conducted in Europe to assess the efficacy, safety and tolerability, and PD of SC dupilumab treatment in 109 adults (55 dupilumab, 54 placebo) with moderate to severe AD. Study drug (300 mg) was administered weekly, beginning at day 1 (baseline) for 12 consecutive weeks via SC injections.

The concentration-time profile of dupilumab is shown in Figure 4.3.7. Following weekly SC administrations of dupilumab, the mean Ctrough values increased with each subsequent dose administration up to the 11th dose, indicating that the mean concentrations are approaching steady state.



Notes: One standard error around the mean is presented. Individual concentrations below the lower limit of quantification (LLOQ, horizontal dotted line = 0.0780) are imputed as LLOQ/2 = 0.0390.

Figure 4.3.7. Dupilumab mean±SE serum concentration-time profile following 12 Weekly 300 mg SC doses of dupilumab in subjects with AD. (*Source of Data: Figure 46, CSR R668-AD-1117*)

4.3.8. Study R668-AD-1021

Study R668-AD-1021 was a 32-week (16-week treatment period and 16-week follow-up period), multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the dose-response profile of SC doses of dupilumab in 380 adult patients with moderate-to-severe AD. The treatment groups were dupilumab 100 mg Q4W, 300 mg Q4W, 200 mg Q2W, 300 mg Q2W, and 300 mg QW and placebo.

Across all dose regimens studied, exposure to dupilumab increased in a greater than dose-proportional manner. The mean dupilumab Ctrough values at Week 16 (steady-state) for the 100 mg and 300 mg Q4W dose groups were 0.398 mcg/mL and 13.8 mcg/mL, respectively. This represents a 34.7-fold increase in Ctrough with a 3-fold increase in total monthly dose.

The mean dupilumab Ctrough values at Week 16 for the 200 mg and 300 mg Q2W dose groups were 35.9 mcg/mL and 61.5 mcg/mL, respectively. This represents a 1.71-fold increase in Ctrough with a 1.5-fold increase in total monthly dose, which is a small deviation from dose proportionality.

The mean dupilumab Ctrough values at Week 16 for the 300 mg QW dose group was 168 mcg/mL, which is a 2.73-fold increase over the Ctrough value of 61.5 mcg/mL for 300 mg Q2W. A 2.73-fold increase in Ctrough for a 2-fold increase in dosing frequency provides evidence that the target-mediated pathway appears to be approaching saturation.

Visit	Nominal Time	Functional Dupilumab (mg/L)																
		Placebo			100 mg Q4W			300 mg Q4W			200 mg Q2W			300 mg Q2W			300 mg QW	
		N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
2	Day 1	61	0	0	65	0	0	64	0	0	61	0	0	63	0	0	63	0.483	3.83
3	Day 8	60	0	0	63	41.7	17.3	64	74.9	26.1	59	41.6	15.1	62	72.5	26.3	61	67.0	23.1
4	Day 15	58	0	0	64	30.8	13.9	62	55.6	21.5	59	31.1	12.9	62	54.3	20.7	61	90.5	32.1
5	Day 22	57	0	0	62	18.7	11.6	65	36.6	17.6	56	45.7	21.0	61	73.6	26.7	61	95.4	36.9
6	Day 29	52	0	0	59	11.3	9.55	64	24.8	16.1	55	33.0	18.7	62	52.4	19.8	59	113	43.3
8	Day 43	52	0	0	60	9.99	10.9	65	36.8	21.6	53	35.4	23.2	61	54.7	24.6	59	133	58.4
10	Day 57	52	0	0	58	2.76	4.94	62	16.4	13.1	49	34.5	23.0	61	56.8	25.9	58	143	67.3
12	Day 71	50	1.08	7.67	56	4.68	6.33	64	31.8	19.0	50	35.5	21.7	59	55.1	30.0	57	156	71.8
14	Day 85	50	0	0	56	1.27	3.99	61	15.4	12.7	50	36.6	22.9	60	57.3	32.0	60	169	71.5
16	Day 99	49	0	0	55	3.84	5.21	61	30.4	19.1	49	36.8	21.7	58	60.0	32.7	58	178	69.0
17	Day 106	49	0	0	57	1.32	2.77	61	21.3	15.3	46	49.8	27.5	56	74.9	37.7	58	177	72.3
18	Day 113	54	0	0	60	0.398	1.20	63	13.8	12.1	52	35.9	24.6	61	61.5	36.7	62	168	80.8
19	Day 127	47	0.00277	0.0190	52	0	0	57	4.40	5.70	48	17.2	15.8	61	33.2	26.9	57	119	55.3
20	Day 141	49	0.00214	0.0150	52	0	0	62	0.765	2.13	46	8.69	10.7	59	17.7	18.2	56	74.0	43.0
21	Day 155	47	0	0	51	0	0	60	0.0243	0.142	45	3.00	6.19	58	6.58	10.8	57	46.0	29.1
22	Day 169	45	0	0	47	0	0	56	0	0	41	0.646	2.59	56	2.26	4.88	56	27.3	23.6
23	Day 183	44	0	0	45	0	0	56	0	0	39	0.245	1.47	52	0.653	1.71	57	16.1	19.0
24	Day 197	44	0	0	41	0	0	54	0	0	36	0.0844	0.507	53	0.00438	0.0319	53	8.04	11.0
25	Day 211	41	0.00334	0.0214	40	0	0	52	0	0	33	0.00288	0.0165	50	0	0	49	2.94	6.09
26	EOS (Day 225)	44	0.00541	0.0259	41	0	0	54	0	0	33	0	0	51	0.00908	0.0648	52	1.04	3.35

SC = Subcutaneous; N = Number of Patients; SD = Standard deviation; EOS = End of study

Note: Placebo patients 606-001 had a concentration of 54.2 mg/L at day 71; 104-002 had concentrations of 0.130 mg/L and 0.105 mg/L at day 127 and 141, respectively; 007-002 had a concentration of 0.0890 mg/L at day 225; 604-004 had concentrations of 0.137 and 0.149 mg/L at Day 211 and 225, respectively.

Table 4.3.8. Summary of dupilumab exposure by treatment groups in subjects with AD. (*Source of Data: Table 52, CSR R668-AD-1021*)

4.3.9. Study R668-AD-1307

R668-AD-1307 was a 32-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of SC dupilumab 200 mg QW for 15 weeks (with an initial 400 mg loading dose) in patients with moderate-to-severe AD (27 dupilumab, 27 placebo).

The concentration-time profile of dupilumab following SC 200 mg QW (with an initial 400 mg loading dose) is shown in Figure 4.3.9. Steady-state concentrations of dupilumab were achieved at approximately Week 12 and the mean steady-state concentration was 119 mcg/mL.

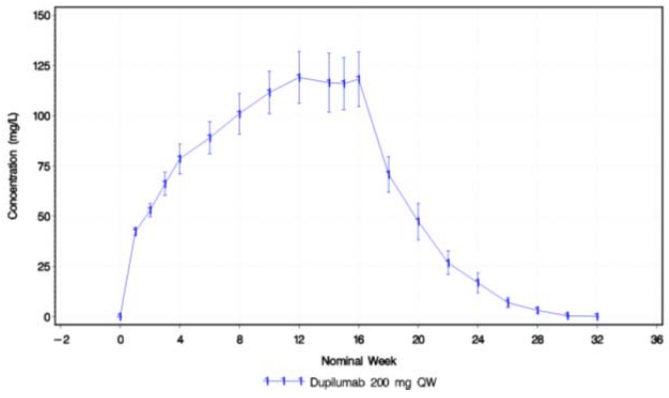


Figure 4.3.9. Mean (±SE) dupilumab concentrations following SC administration of dupilumab 200 mg QW with an initial 400 mg loading dose in subjects with AD. (*Source of Data: Figure 49, CSR R668-AD-1307***)**

4.3.10. Study R668-AD-1314

R668-AD-1314 was a 32-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study to assess T-cell-dependent and T-cell-independent immunization responses in adults with moderate-to-severe AD who were treated with SC dupilumab. Patients were randomized in a 1:1 ratio to receive a 600 mg SC dupilumab loading dose or placebo on Day 1, and then 300 mg SC dupilumab or placebo once a week for 16 weeks, starting on Day 8 (Week 1). At Week 12, patients were vaccinated with Adacel ([Tdap] IM) and Menomune (SC), 1 vaccination in each arm, preferably in an area without AD lesions.

The dupilumab concentration-time profile is shown in Figure 4.3.10. Following a 600 mg SC loading dose and 300 mg SC weekly dosing, the mean dupilumab concentration of 179 mcg/mL was attained by Week 16.

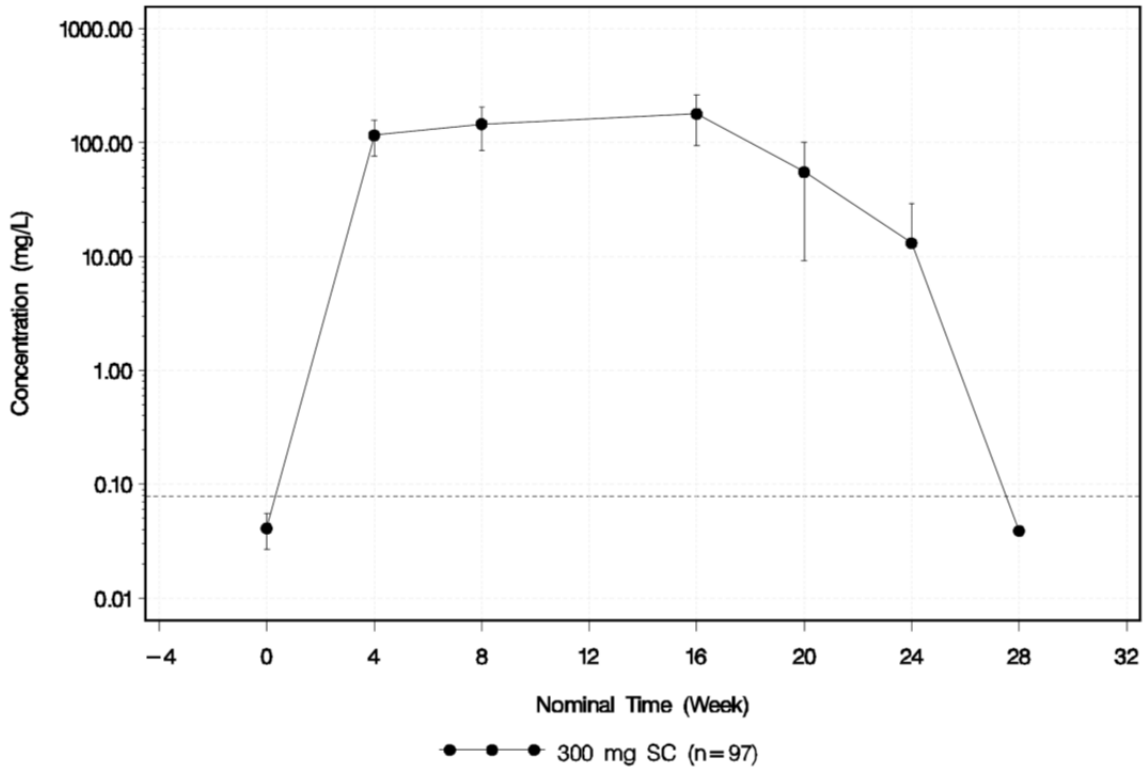


Figure 4.3.10. Mean (±SD) dupilumab concentration-time profile following an initial 600 mg SC loading dose followed by weekly 300 mg SC dupilumab in subjects with AD. (*Source of data, Figure 1, Clinical Pharmacology Report, R668-AD-1314-CP-01V1*)

4.4 Pharmacodynamics

Plasma concentrations of IL-4 and IL-13 following dupilumab treatment were assessed in Study R668-AD-1307. In the study, subjects with moderate-to-severe AD were treated with SC dupilumab 200 mg QW for 16 weeks (with an initial 400 mg loading dose). The PK profile of dupilumab is summarized in section 4.3.9.

The time courses of plasma IL-4 and IL-13 levels are shown in Figure 4.4.a. and Figure 4.4.b, respectively. The results showed the following:

- Baseline median IL-4 level was 0 pg/mL. The plasma IL-4 level was increased by ~ 1 pg/mL from baseline during the entire dupilumab treatment period (i.e., from Week 2 through Week 16) and returned to the baseline level at the next assessment timepoint (Week 32) after the dupilumab treatment was stopped at Week 16.

- Baseline median IL-13 level was 2 pg/mL. The plasma IL-13 levels were increased at Weeks 2 and 4 following dupilumab treatment and returned to the baseline level by Week 8 while the subjects were still receiving the dupilumab treatment.

The increased plasma IL-4 and IL-13 levels could be a result of the blockade of the IL-4Rα by dupilumab leading to a decrease in clearance of both cytokines.

The increased plasma IL-13 lelvel occurred only at Weeks 2 and 4 for the dupilumab 200 mg QW dosing regimen. The transient increase in IL-13 may be resulting from the interaction of IL-13 with IL-13Rα2 which dupilumab does not block. The PD effect on IL-13 levels for the 300 mg QW or 300 mg Q2W dosing regimens are unknown.

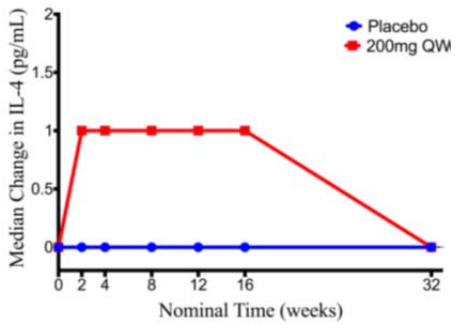


Figure 4.4.a. Median absolute change of plasma IL-4 levels (pg/mL) following 16 weeks of treatment with dupilumab or placebo 200 mg QW in subjects with AD in Study R668-AD-1307. Dupilumab group is shown in red line and the placebo group is shown in blue line. Median baseline values were 0 pg/mL for both the placebo and dupilumab groups. (*Source of data: Figure 14, Summary of Clinical Pharmacology*)

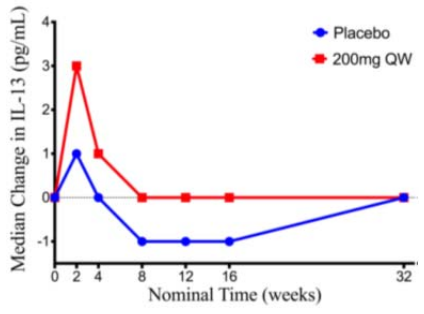


Figure 4.4.b Median absolute change of plasma IL-13 levels (pg/mL) following 16 weeks of treatment with dupilumab or placebo 200 mg QW in subjectst with AD in Study R668-AD-1307. Dupilumab group is shown in red line and the placebo group is shown in blue line. Median baseline values were 2 pg/mL for both the placebo and dupilumab groups. (*Source of data: Figure 15, Summary of Clinical Pharmacology*)

4.5 Immunogenicity

This section summarizes the immunogenicity incidences for developing anti-drug antibodies (ADA) and neutralizing ADA (NAb) and the impact of immunogenicity on PK, efficacy and safety in dupilumab AD Phase 3 trials.

4.5.1. Immunogenicity incidences of ADA and NAb

The overall immunogenicity incidences for developing ADA, treatment-emergent ADA, and NAb are summarized in Table 4.5.1.a by treatment groups across the three Phase 3 trials.

In the combined Phase 3 monotherapy Studies AD-1334 and AD-1416, approximately 13.6% (61/447) and 7.2% (31/429) of subjects had anti-drug antibodies to dupilumab following 16 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the subjects who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 18% (11/61) and 13% (4/31), respectively, had neutralizing antibodies.

In the Phase 3 concomitant treatment with TCS Study R668-AD-1224, approximately 9.5% (10/105) and 10.7% (33/308) of subjects had anti-drug antibodies to dupilumab following 52 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the subjects who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 10% (11/10) and 0% (0/33), respectively, had neutralizing antibodies.

Table 4.5.1.a. Summary of incidences of anti-drug antibodies (ADA), treatment-emergent ADA (TE-ADA) and neutralizing ADA (NAb) in AD Phase 3 studies. ADA positive (ADA+) subjects were defined as subjects with a positive ADA response at any time. TE-ADA+ subjects were defined as subjects with no positive ADA response at baseline but with any positive response after receiving the treatment. Incidene of NAb is calculated to refect the percentage among ADA+ subjects because NAb was only measured in ADA+ samples. Monotherapy data represent pooled data for studies AD-1334 and AD-1416. *(Source of Data: CSR of Phase 3 studies R668-AD-1334, R668-AD-1416, and R668-AD-1224)*

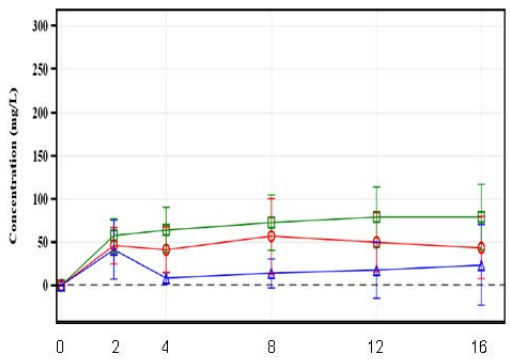
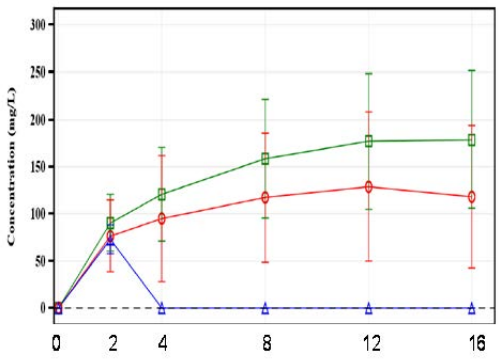
Studies	ADA status	ADA incidence, % (n/N)			
		Placebo	Dupilumab		
			300 mg Q2W	300 mg QW	Combined
AD-1334 (16 weeks)	ADA+	3.8% (8/209)	14.4% (32/222)	7.3% (15/206)	11.0% (47/428)
	T-E ADA+	0.96% (2/209)	6.8% (15/222)	2.9% (6/206)	4.9% (21/428)
	NAb+	0% (0/8)	15.6% (5/32)	13.3% (2/15)	14.9% (7/47)
AD-1416 (16 weeks)	ADA+	7.3% (16/218)	12.9% (29/225)	7.2% (16/223)	10.0% (45/448)
	T-E ADA+	1.8% (4/218)	8.00% (18/225)	2.7% (6/223)	5.4% (24/448)
	NAb+	12.5% (2/16)	20.7% (6/29)	12.5% (2/16)	1.8% (8/45)

Combined AD-1334 and AD-1416 (Monotherapy) (16 Weeks)	ADA+	5.6% (24/427)	13.6% (61/447)	7.2% (31/429)	10.5% (92/876)
	T-E ADA+	1.4% (6/427)	7.4% (33/447)	2.8% (12/429)	5.1% (45/876)
	NAb+	8.3% (2/24)	18.0% (11/61)	12.9% (4/31)	16.3% (15/92)
AD-1224 (52 weeks)	ADA+	12.8% (39/305)	9.5% (10/105)	10.7% (33/308)	10.4% (43/413)
	T-E ADA+	6.6% (20/305)	5.7% (6/105)	4.6% (14/308)	4.8% (20/413)
	NAb+	5.1% (2/39)	10% (1/10)	0% (0/33)	2.3% (1/43)

4.5.2. Impact of ADA on PK profile

Overall, development of ADA was associated with reduced serum dupilumab concentrations. The impacts of immunogenicity on dupilumab PK are summarized below:

- The dupilumab concentration-time profiles showed a trend that subjects who developed ADA or NAb were associated with lower serum dupilumab concentrations in AD Phase 3 studies (Figure 4.5.2.a).
- In Phase 3 studies, the mean steady state dupilumab concentrations at Week 16 were lower in ADA+ subjects compared to those in ADA- subjects for both dupilumab 300 mg Q2W and 300 mg QW treatment groups (Table 4.5.2.a).
- Two subjects in the 300 mg QW cohort in Study AD-1334 exhibited high ADA titer at Week 16 and were positive in the NAb assay. In these 2 subjects, dupilumab concentrations were below LLOQ starting at Week 4 through Week 16 indicating a remarkable impact of ADA on dupilumab PK (Figure 4.5.2.b).

Studies	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**
AD-1334	Green rectangle: ADA- (n=190) Red circle:ADA+ (n=27) Blue triangle:NAb+ (n=5) 	Green rectangle: ADA- (n=191) Red circle:ADA+ (n=13) Blue triangle:NAb+ (n=2) 

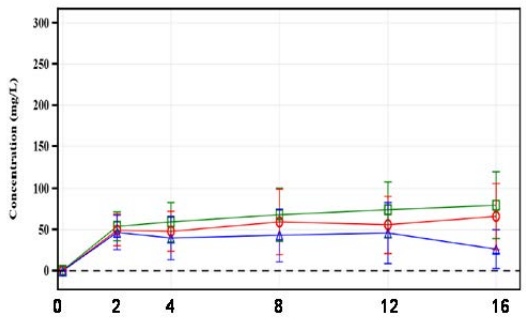
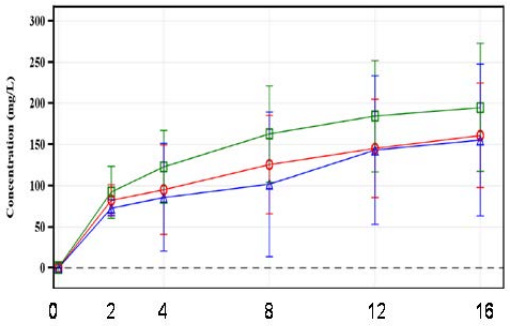
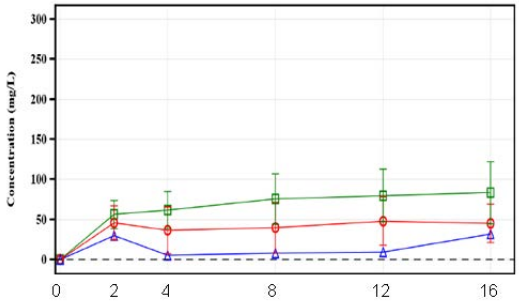
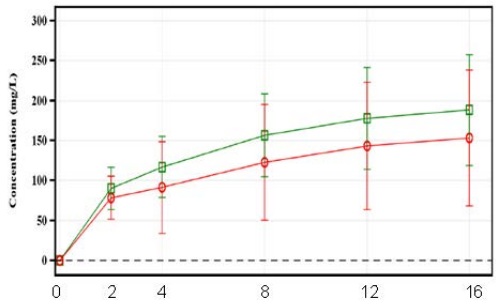
AD-1416	Green rectangle: ADA- (n=194) Red circle:ADA+ (n=23), Blue triangle:NAb+ (n=6) 	Green rectangle: ADA- (n=205) Red circle:ADA+ (n=14) Blue triangle:NAb+ (n=2) 
AD-1224	Green rectangle: ADA- (n=95), Red circle:ADA+ (n=9), Blue triangle:NAb+ (n=1) 	Green rectangle: ADA- (n=275), Red circle: ADA+ (n=33) 

Figure 4.5.2.a Impact of immunogenicity on dupilumab concentration in subjects with AD in Phase 3 studies. *(Source of Data: CSR of Phase 3 studies AD-1334, AD-1416, and AD-1224)*

Table 4.5.2.a. Dupilumab trough concentrations at Week 16 by subjects ADA and NAb status.
Percentage values represent the ratio of dupilumab concentration in ADA positive subjects compared to that in ADA negative subjects. Values in **red/bold text** indicate redues dupilumab concentrations in ADA or NAb positive subjects in comparison to ADA negative subjects. *(Source of Data: CSR of Phase 3 studies AD-1334, AD-1416, and AD-1224)**

Studies	Dupilumab dosing regimen	Mean Dupilumab concentration (mcg/mL) by subject immunogenicity status (% represents the relative exposure in comparison to ADA- subjects)			
			ADA-	ADA+	NAb+
AD-1334	300 mg Q2W	N	153	19	4
		Concentration (%)	80.7	**44.6 (55.3%)**	**28 (34.7%)**
	300 mg QW	N	147	8	1
		Concentration (%)	185	**141 (76.2%)**	0
AD-1416	300 mg Q2W	N	164	21	4
		Concentration (%)	77.1	**65.5 (85.0%)**	**18.1 (23.5%)**
	300 mg QW	N	164	11	1
		Concentration (%)	196	**140 (71.4%)**	**221 (112.8%)**

AD-1224	300 mg Q2W	N	84	8	1
		Concentration (%)	84.2	**45.3 (53.8%)**	**32 (38.0%)**
	300 mg QW	N	236	**28**	0
		Concentration (%)	190	**151 (79.5%)**	NA
Combined	300 mg Q2W	N	401	48	9
		Concentration (%)	80.7	**51.8 (64.2%)**	**26.0 (32.3%)**
	300 mg QW	N	547	47	2
		Concentration (%)	190.3	**144 (75.7%)**	**110.5 (58.1%)**

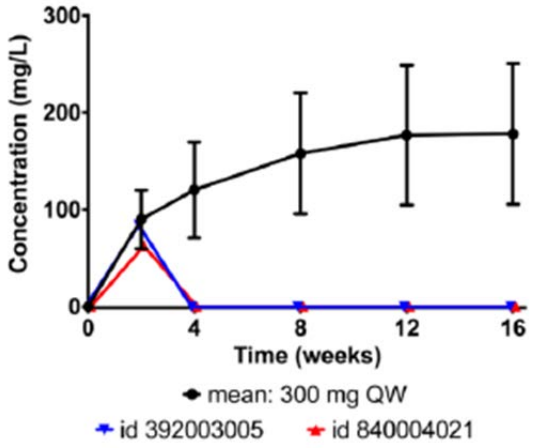
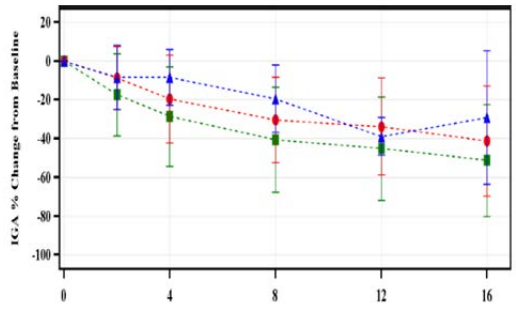
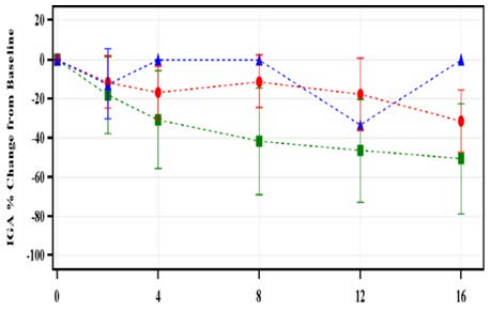
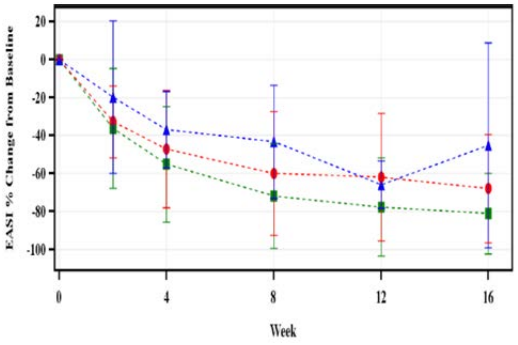
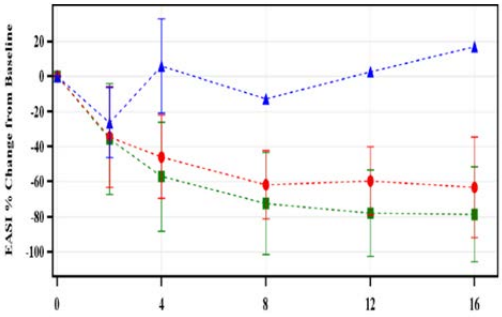
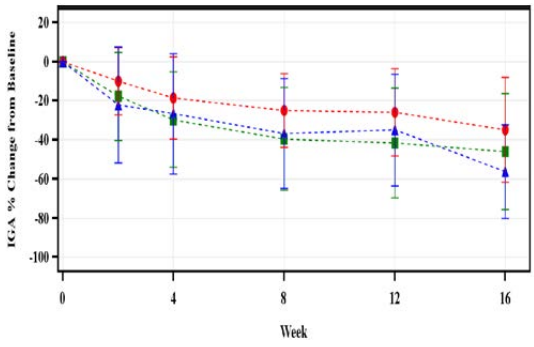
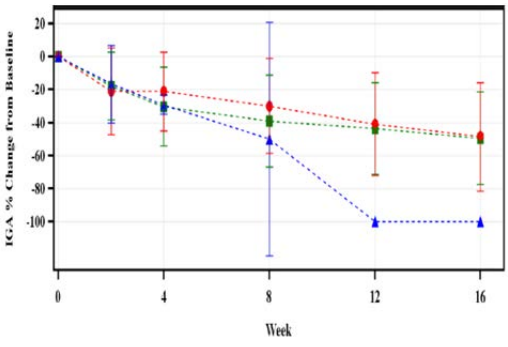
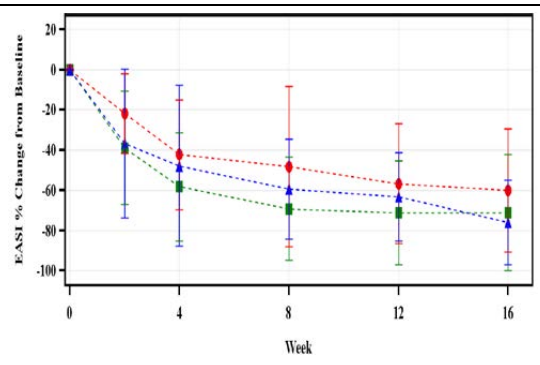
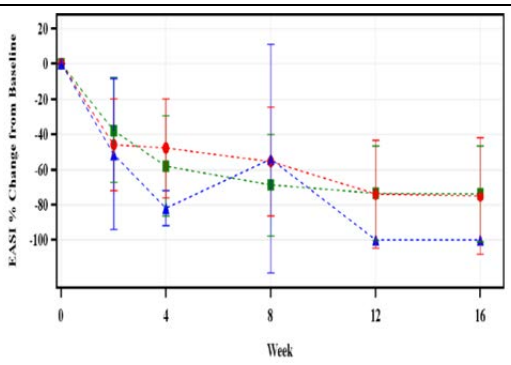


Figure 4.5.2.b. Dupilumab concentration-time profiles in the 2 subjects who had a high ADA titer and were positive for neutralizing ADA in Study AD-1334. The two subjects received 300 mg QW. The black line shows the mean concentrations for the 300 mg QW dosing regimen in Study AD-1334. *(Source of Data: Figure 25 in 2.7.2 Summary of Clinical Pharmacology Studies)*

4.5.3. Impact of ADA on efficacy

Overall, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on the clinical efficacy measures because of the small number of subjects with ADA. The impacts of immunogenicity on efficacy are summarized below:

- No consistent evidence of reduced efficacy was observed in subjects who developed ADA or NAb when evaluating the time-course of IGA% or EASI% reduction from baseline in AD Phase 3 trials (Figure 4.5.3.a). NAb+ subjects in Study AD-1334 had reduced efficacy whereas NAb+ subjects in Study AD-1416 and Study AD-1224 did not.
- No clear pattern of reduced efficacy was observed when evaluating the percentage change in EASI at Week 16 by comparing ADA+ subjects with different ADA titers with ADA- subjects (Figure 4.5.3.b).

	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
AD-1334	Green rectangle: ADA- (n=190) Red circle: ADA+ (n=27) Blue triangle: NAb+ (n=5)	Green rectangle: ADA- (n=191) Red circle: ADA+ (n=13) Blue triangle: NAb+ (n=2)
		
		
AD-1416	Green rectangle: ADA- (n=194) Red circle: ADA+ (n=23) Blue triangle: NAb(n=6)	Green rectangle: ADA- (n=205) Red circle: ADA+ (n=14) Blue triangle: NAb(n=2)
		
		

AD-1224	Green rectangle: ADA- (n=95) Red circle: ADA+ (n=9) Blue triangle:NAb+ (n=1)	Green rectangle: ADA- (n=275) Red circle: ADA+ (n=33)

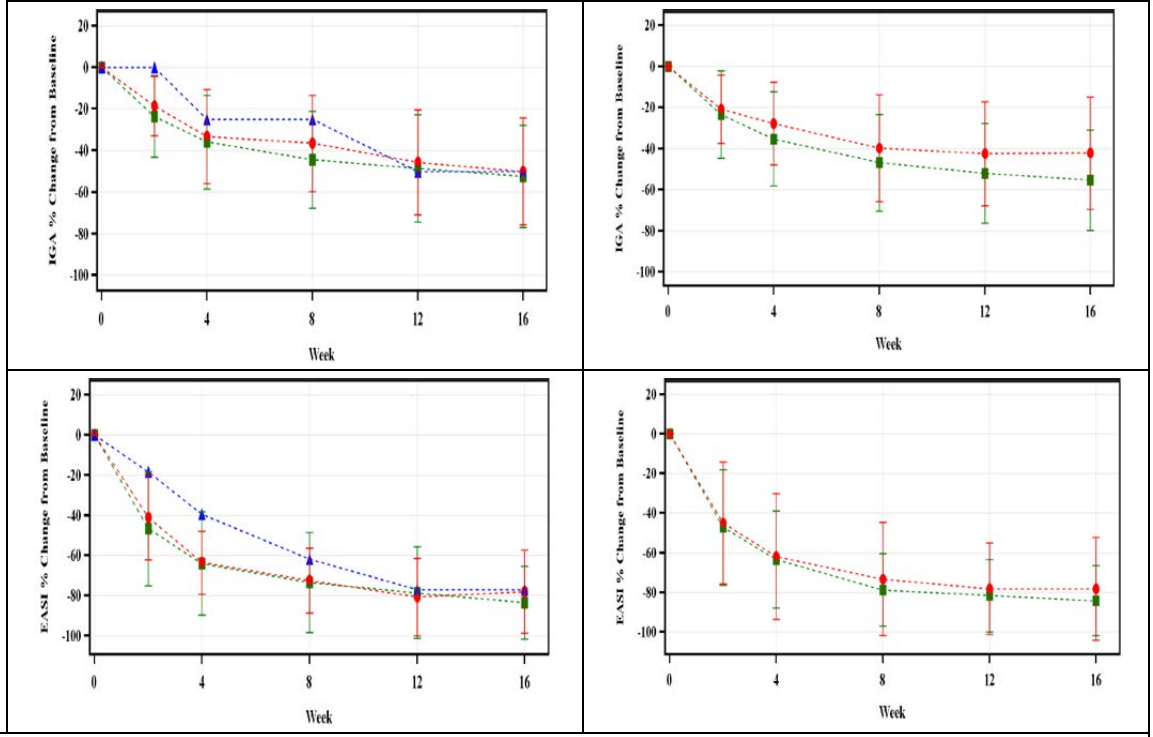
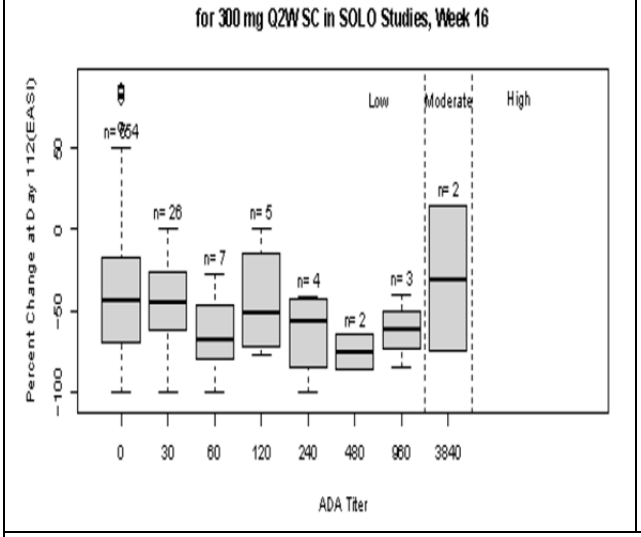


Figure 4.5.3.a. Impact of immunogenicity on efficacy in AD Phase 3 studies. *(Source of Data: CSR of Phase 3 studies AD-1334, AD-1416, and AD-1224)*



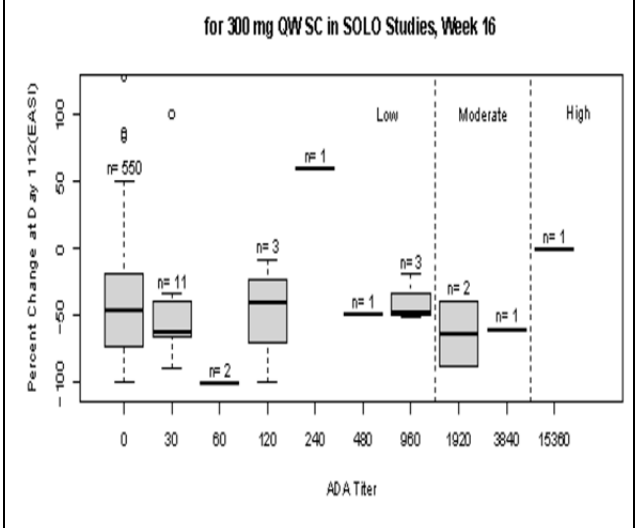


Figure 4.5.3.b. Percent change in EASI at Week 16 by ADA titers in pooled Studies R668-AD-1334 and R668-AD-1416). *(Data source: Figures 10 and 11 in 2.7.2 Summary of Clinical Pharmacology Studies)*

4.5.4 Impact of ADA on safety

Two adverse reactions, one patient with serum sickness reaction and one patient with serum sickness-like reaction were reported in dupilumab clinical studies. These two adverse reactions were associated with development of ADA with high ADA titers, as described below.

- Subject 840011001 (38-year-old female) in the dupilumab 300 mg QW group in Study R668-AD-1314 experienced a treatment-emergent SAE of serum sickness-like reaction. The patient received a total of 3 doses of study drug prior to the onset of the treatment-emergent SAE: Day 1/baseline, Day 8, and Day 15. This patient was ADA positive at Day 15 and at the early termination visit (Day 22), with a peak titer of 122,880 at the early termination visit.

- Subject 137007 (30-year-old female) had a serious event of serum sickness in Study AD-1224 (Open-label Extension Study). This subject had previously received placebo treatment in study R668-AD-1334 (1334-840007002). This subject experienced serum sickness on Day 18 after receiving 2 doses of dupilumab 300 mg QW following a 600 mg loading dose at Week 0. At Week 0, the patient exhibited a low titer ADA. No additional titers were measured until the end of treatment (approximately 79 days) at which time the patient had a ADA titer of 15,360.

In the primary safety pool including studies AD-1334, AD-1416 and AD-1021 (16-week monotherapy, the overall incidence of treatment-emergent adverse events (TEAE) was 78.8% in subjects who had treatment-emergent or boosted ADA compared to 70.9% in subjects who did not have treatment-emergent or boosted ADA (Table 4.5.4).

Table 4.5.4. TEAEs with ≥5% incidence by subjects immunogenicity status of whether the subject developed treatment-emergent or boosted ADA in the primary safety pool including studies AD-1334, AD-1416 and AD-1021 (16-week monotherapy). (*Source of data: Table 72 in Summary of clinical safety)*

	Placebo		Dupilumab 300 mg Q2W		Dupilumab 300 mg QW		Dupilumab Combined	
Primary System Organ Class Preferred term	**Treatment-Emergent or Boosted ADA (N=8)**	**Neither Treatment-Emergent nor Boosted ADA (N=480)**	**Treatment-Emergent or Boosted ADA (N=45)**	**Neither Treatment-Emergent nor Boosted ADA (N=466)**	**Treatment-Emergent or Boosted ADA (N=21)**	**Neither Treatment-Emergent nor Boosted ADA (N=471)**	**Treatment-Emergent or Boosted ADA (N=66)**	**Neither Treatment-Emergent nor Boosted ADA (N=937)**
Number of patients with at least 1 TEAE, n (%)	8 (100)	346 (72.1)	34 (75.6)	335 (71.9)	18 (85.7)	329 (69.9)	52 (78.8)	664 (70.9)
Infections and infestations	4 (50.0)	180 (37.5)	20 (44.4)	173 (37.1)	11 (52.4)	170 (36.1)	31 (47.0)	343 (36.6)
Nasopharyngitis	0	61 (12.7)	12 (26.7)	55 (11.8)	5 (23.8)	60 (12.7)	17 (25.8)	115 (12.3)
Upper respiratory tract infection	1 (12.5)	25 (5.2)	10(22.2)	23 (4.9)	3 (14.3)	24 (5.1)	13 (19.7)	47 (5.0)
Eczema impetiginous	1 (12.5)	1 (0.2)	0	3 (0.6)	0	2 (0.4)	0	5 (0.5)
Skin bacterial infection	1 (12.5)	2 (0.4)	0	0	0	0	0	0
Conjunctivitis	0	4 (0.8)	2 (4.4)	21 (4.5)	2 (9.5)	19 (4.0)	4 (6.1)	40 (4.3)
Oral herpes	1 (12.5)	7 (1.5)	0	21 (4.5)	1 (4.8)	12 (2.5)	1 (1.5)	33 (3.5)
Skin infection	1 (12.5)	6 (1.3)	1 (2.2)	4 (0.9)	0	1 (0.2)	1 (1.5)	5 (0.5)
Viral upper respiratory tract infection	1(12.5)	4 (0.8)	0	3 (0.6)	0	2 (0.4)	0	5 (0.5)
Skin and subcutaneous tissue disorders	5 (62.5)	182 (37.9)	12 (26.7)	116 (24.9)	6 (28.6)	103 (21.9)	18 (27.3)	219 (23.4)
Dermatitis atopic	4 (50.0)	154 (32.1)	8 (17.8)	76 (16.3)	5 (23.8)	63 (13.4)	13 (19.7)	139 (14.8)
General disorders and administration site conditions	2 (25.0)	55 (11.5)	11 (24.4)	75 (16.1)	6 (28.6)	91 (19.3)	17 (25.8)	166 (17.7)
Injection site reaction	2 (25.0)	25 (5.2)	5 (11.1)	45 (9.7)	4 (19.0)	66 (14.0)	9 (13.6)	111 (11.8)
Injection site erythema	0	2 (0.4)	3 (6.7)	3 (0.6)	0	7 (1.5)	3 (4.5)	10 (1.1)
Nervous system disorders	0	48 (10.0)	7 (15.6)	59 (12.7)	3 (14.3)	57 (12.1)	10 (15.2)	116 (12.4)
Headache	0	25 (5.2)	4 (8.9)	40 (8.6)	1 (4.8)	39 (8.3)	5 (7.6)	79 (8.4)
Musculoskeletal and connective tissue disorders	0	36 (7.5)	7 (15.6)	50 (10.7)	3 (14.3)	38 (8.1)	10 (15.2)	88 (9.4)
Arthralgia	0	10 (2.1)	3 (6.7)	13 (2.8)	0	5 (1.1)	3 (4.5)	18 (1.9)

4.6 Population PK Analyses

A population PK analysis was conducted by the Applicant to characterize the pharmacokinetics of dupilumab administered IV or SC in healthy volunteers and patients with atopic dermatitis (AD). The objectives of this analysis were to identify clinically relevant covariates which may explain variability in the PK parameters and to compute the individual exposure estimates for subsequent exposure-response analyses.

Overall, 16 PK studies were pooled for population PK analysis including 13 phase 1 and phase 2 studies, 2 pivotal phase 3 studies (SOLO1 and SOLO2), and data from patients in the ongoing long term treatment (LTT) study (2115 subjects including 202 healthy subjects and 1913 AD patients). Population PK of dupilumab was characterized by nonlinear mixed-effects modeling using NONMEM 7.3. A standard two-compartment population PK model with parallel linear and nonlinear elimination was implemented based on phase 1 and phase 2 data and was further applied to the phase 3 data. A transit compartment model was used to describe the absorption of dupilumab. A step-wise approach was utilized to develop the model due to the highly nonlinear PK of dupilumab and sparse samplings in Phase 3 data.

Most of the parameters were estimated using rich data from early clinical studies and subsequently fixed. As it is well established that weight is an important and statistically significant covariate of volume of distribution for monoclonal antibodies (mAbs), body weight was included as a covariate in all models including the primary base model. The following were tested as potential model covariates: body mass index (BMI), anti-drug antibodies (ADA) (Subjects who developed high or moderate ADA titers were excluded from population PK analysis), dupilumab assay, sex, age, race, populations – healthy subjects vs. AD patients, predicted creatinine clearance, AST, ALT, ALP, albumin, and EASI score as shown in Table 4.6.1-3. The validation of the final model was performed using bootstrap and visual predictive check (VPC).

Table 4.6.1 Summary of Baseline Values of Continuous Covariates in Subjects on Active Treatment - Phase 3 Studies Only

Covariate	N	Mean	SD	Min	P5	Q1	Median	Q3	P95	Max
Age (yr)	897	37.3	14.0	18.0	19.0	26.0	35.0	47.0	64.0	88.0
Weight (kg)	897	75.7	18.6	41.0	50.5	62.3	73.0	85.0	109	175
BMI (kg/m^2)	897	26.0	5.65	16.3	19.2	22.0	24.9	28.4	37.0	57.3
CrCL (mL/min)	897	111	27.5	21.6	66.6	91.3	109	136	150	150
AST (IU/L)	897	23.9	10.2	5.00	14.0	18.0	22.0	27.0	38.0	184
ALT (IU/L)	897	23.9	14.7	5.00	10.0	15.0	20.0	27.0	51.0	185
ALP (IU/L)	897	73.6	21.5	29.0	44.0	60.0	71.0	85.0	111	259
Albumin (g/L)	897	44.6	3.69	22.0	39.0	42.0	45.0	47.0	50.0	57.0
EASI (Unitless)	897	32.1	12.9	0.600	16.8	21.3	29.3	40.9	56.4	72.0

Source: Applicant's population PK report, Page 37, Table 5

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Table 4.6.2 Summary of Baseline Values of Categorical Covariates in Subjects on Active Treatment - Phase 3 Studies Only

Sex				Population		Assay		All Subjects	
F		M		Atopic Dermatitis Patients		PCL3277			
n	%	n	%	n	%	n	%	n	%
369	41.1	528	58.9	897	100.0	897	100.0	897	100.0

Source: Applicant's population PK report, Page 38, Table 8

Table 4.6.3 Race of subjects on active treatment - Phase 3 Studies Only

Race								All Subjects	
Asian		Black Or African American		Caucasian/White		Other			
n	%	n	%	n	%	n	%	n	%
207	23.1	43	4.8	615	68.6	32	3.6	897	100.0

Source: Applicant's population PK report, Page 38, Table 9

Reviewer's comments: The baseline of ADA was not listed in the demographic table from the Applicant's population PK report. The reviewer looked into the Phase 3 data, which excluded outlier, BLQ observations, that the majority of the patients do not have ADA while round 10% patients have low ADA titers. The Applicant did not include the patients with high and moderate ADA titers in the population PK analysis, which account for less than 1% of the whole population. Excluding the patients with high and moderate ADA titers would be one of the limitations for the pop PK analysis. Since the ADA titers may have significant impact on PK, but it would not be identified with this exclusion criterion.

Table 4.6.4 ADA titers of subject on active treatment-Phase 3 studies only

	High ADA titers	*Moderate ADA titers*	*Low ADA titers*	*No ADA*	*All subject*
N	*2*	*6*	*87*	*803*	*898*
%	*0.2%*	*0.7%*	*9.7%*	*89.4%*	*100%*

Source: Reviewer's independent analysis on population PK data (k_1L.xpt)

The initial base structural model (Model 1) was developed based on four studies with rich sampling schedules, the FIH study R668-AS-0907 (the only study with IV administration), the SC studies TDU12265 and PKM14161 (Wide range of SC doses), and multiple-dose study R668-AD-1117. The transit-compartment model was explored by comparing the influence of the number of compartments on the objective function value (OFV). The number of transit

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compartments was varied from 0 to 9 (Table 4.6.5). Based on the values of OFV, three transit compartments were selected.

Table 4.6.5 Relationship between Number of Transit Compartments and Objective Function

Outcome Measures	Number of Transit Compartments									
	0	1	2	3	4	5	6	7	8	9
MTT (d)	---	0.243	0.132	0.106	0.0912	0.0838	0.0795	0.0759	0.0738	0.0704
ka (1/d)	0.355	0.282	0.269	0.263	0.256	0.258	0.251	0.252	0.249	0.248
Objective Function	8650.56	7797.15	7659.70	7624.46	7621.02	7625.04	7627.69	7625.56	7626.77	7630.30

Source: Applicant's population PK report, Page 42, Table 10

Different versions of the model persistently estimated the Michaelis-Menten (MM) constant (Km) at values below ~0.01 mg/L with large relative standard errors. This can be explained by a very steep target-mediated phase with few observations available at concentrations that would permit accurate characterization of this phase. As such, Km was fixed at 0.01 mg/L to ensure model stability. The parameters of Model 1 are presented in Table 4.6.6 (columns 1 and 2). The median bootstrap estimates were close to the population PK estimates and the bootstrap confidence intervals were acceptable to proceed with the estimated parameters.

Table 4.6.6 Population PK Parameters and Bootstrap Confidence Intervals for Initial Models Based on Rich and Sparse Data (Model 1 and Model 2)

Parameter	Model 1. Estimates Bioavailability, Intercompartmental Rates, and MTT		Model 2. Estimates/Confirms Target-Mediated Rate of Elimination	
	Population Estimate (SE)b	Bootstrap Median (2.5th, 97.5th percentiles)	Population Estimate (SE)	Bootstrap Median (2.5th, 97.5th percentiles)
PK Parameter				
V2 (L)	2.48 (0.0481)	2.43 (2.29, 2.60)	2.54 (0.0230)	2.54 (2.49, 2.60)
ke (1/d)	0.0534 (0.000387)	0.0513 (0.0466, 0.0560)	0.0550 (0.000831)	0.0545 (0.0521, 0.0572)
k23 (1/d)	0.213 (0.0286)	0.214 (0.151, 0.283)	0.211 (fixed)	---
k32 (1/d)	---	---	0.310 (fixed)	---
M32 (1/d)	0.686 (0.00986)	0.704 (0.603, 0.821)	---	---
ka (1/d)	0.256 (0.00696)	0.262 (0.231, 0.295)	0.309 (0.00942)	0.310 (0.292, 0.331)
MTT (d)	0.105 (0.0100)	0.104 (0.0850, 0.141)	0.105 (fixed)	---
Vm (mg/L/d)	1.07 (0.0279)	1.10 (0.984, 1.20)	1.07 (0.0162)	1.06 (1.02, 1.10)
Km (mg/L)	0.01 (fixed)	---	0.01 (fixed)	---
F (unitless)	0.643 (0.00914)	0.637 (0.582, 0.685)	0.642 (fixed)	---
Covariates				
V2 ~ weight	0.711 (0.0161)	0.677 (0.481, 0.825)	0.803 (0.0322)	0.788 (0.665, 0.894)
Omega[a]				
σ (η(V2))	0.192 (0.00554)	0.187 (0.136, 0.237)	0.199 (0.00354)	0.195 (0.180, 0.218)
σ (η(ke))	0.285 (0.0146)	0.264 (0.198, 0.331)	0.327 (0.00961)	0.324 (0.298, 0.367)
σ (η(ka))	0.438 (0.0379)	0.473 (0.382, 0.543)	0.467 (0.0227)	0.462 (0.411, 0.523)
σ (η(Vm))	0.285 (0.0133)	0.257 (0.196, 0.313)	0.268 (0.00785)	0.262 (0.227, 0.321)
σ (η(MTT))	0.525 (0.114)	0.503 (0.377, 0.854)	---	---
Residual SD				
σ prop. (CV%)	15.0 (0.00340)	14.8 (0.133, 0.160)	17.2 (0.194)	17.2 (16.5, 18.2)
σ add. (mg/L)	0.03 (fixed)	0.03 (fixed)	0.403 (0.0364)	0.400 (0.241, 0.525)
Derived				
CL (L/d)	0.132	---	0.140	---
Q (L/d)	0.528	---	0.536	---
V3 (L)	1.70	---	1.73	---
k32	0.310	---	---	---

Source: Applicant's population PK report, Page 45, Table 12

MM elimination was parameterized in such a way that the unit of maximum target-mediated elimination rate (Vm) was mg/L/d, which can be interpreted as an assumption of a proportional relationship between the production rate of the target and the volume of the central compartment. In addition, the model was parameterized so that the calculated individual volume of the

peripheral compartment was proportional to the volume of the central compartment, because inter-compartmental rates were used instead of the inter-compartmental clearance and volume of the peripheral compartment. Another reason to use rates instead of clearances was that the linear clearance (CL) and inter-compartmental clearance (Q) are products of rates and volumes of distribution, and are therefore correlated with each other and also with weight. The selected parameterization strategy appeared useful not only to avoid uninformative covariates, but also to interpret the results.

The Applicant's next model (Model 2) was a minor modification of Model 1. In this model k23, k32, F and MTT were fixed based on the estimates of Model 1. BLQ values were excluded from the analysis. Twelve studies, Phase 1 through Phase 2b, were analyzed (R668-AS-0907, PKM12350, PKM14161, PKM14271, PKM14161, R668-AD-0914, R668-AD-1026, R668-AD-1117, R668-AD-1121, R668-AD-1021, R668-AD-1307, and R668-AD-1314). Overall, parameter estimates for Model 2 were similar to the estimates obtained with Model 1 (Table 4.6.6) and demonstrated excellent convergence to the same values.

Using this model structure, the Applicant conducted another modeling exercise (Model 3) using only data from Phase 3 studies (R668-AD-1334 (SOLO1), R668-AD-1416 (SOLO2), and R668-AD-1224 (LTT)) with the following parameters fixed: k23, k32, ka, MTT, Vm, Km, and F. As only trough concentration were available in the Phase 3 studies, only the V2 and ke parameters were estimated to ensure the stability of the model. These results are presented in the Table 4.6.7. The bootstrap medians were very similar to the population predicted values. The bootstrap confidence intervals of most PK parameters were narrow.

The next modeling step tested all the covariates listed in Tables 4.6.1-3 (Model 4). Covariates were incorporated into the model or rejected based on the following selection criteria:

- Forward inclusion. A parameter remains in the model when the addition of the covariate results in alpha of ≤ 0.01.
- Backward elimination. A parameter remains in the primary model when removal of the covariate results in alpha ≤ 0.001.

The population PK parameters for Model 4 are presented in Table 4.6.7. Among all covariates, the most pronounced impact was caused by weight in V2. Nevertheless, this association did not warrant a dose adjustment based on weight because therapeutic index of dupilumab is wide and because weight only partially explains variability in V2. The diagnostic plots and VPC presented in Figures 4.6.1 and 4.6.2 demonstrating good predictability between the model and observations.

Table 4.6.7 Population PK Parameters and Bootstrap Confidence Intervals for Base and Covariate Model

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Parameter Name	Parameter Estimate (Bootstrap 5th, 95th percentiles)			
	Model 3 Primary Base model		Model 4 Primary Covariate model	
	Population Estimate (SE)	Bootstrap Median (2.5th, 97.5th percentiles)	Population Estimate (SE)	Bootstrap Median (2.5th, 97.5th percentiles)
PK parameter				
V_2 (L)	2.76 (0.021)	2.76 (2.70, 2.80)	2.74 (0.021)	2.72 (2.67, 2.78)
k_e (1/d)	0.0448 (0.000490)	0.0448 (0.0436, 0.0461)	0.0477 (0.00078)	0.0477 (0.0457, 0.0498)
Covariates				
V_2 ~ weight	0.919 (0.027)	0.918 (0.864, 0.969)	0.817 (0.031)	0.805 (0.740, 0.891)
V_2 ~ albumin	---	---	-0.653 (0.072)	-0.679 (-0.829, -0.536)
k_e ~ BMI	---	---	0.368 (0.053)	0.378 (0.225, 0.521)
k_e ~ ADA	---	---	0.164 (0.029)	0.168 (0.103, 0.248)
k_e ~ EASI	---	---	0.143 (0.021)	0.147 (0.104, 0.198)
k_e ~ race (white)	---	---	-0.123 (0.018)	-0.116 (-0.168, -0.0749)
Omega Matrix				
σ (η(V_2))[a]	0.216 (0.0065)	0.217 (0.200, 0.241)	0.206 (0.0068)	0.213 (0.198, 0.231)
σ (η(k_e))	0.301 (0.0098)	0.311 (0.287, 0.349)	0.293 (0.010)	0.306 (0.280, 0.332)
Corr(k_e,V_2)	-0.373 (0.036)	-0.413 (-0.669, -0.201)	-0.450 (0.035)	-0.502 (-0.757, -0.335)
Residual SD				
σ prop. (CV%)	12.4 (0.18)	12.4 (11.6, 13.0)	12.5 (0.18)	12.3 (0.117, 0.132)
σ add. (mg/L)	6.17 (0.23)	6.18 (5.18, 7.14)	6.06 (0.23)	6.04 (4.85, 7.03)
Fixed Parameters				
k_{23} (1/d)	0.211	---	0.211	---
k_{32} (1/d)	0.310	---	0.310	---
k_a (1/d)	0.306	---	0.306	---
MTT (d)	0.105	---	0.105	---
V_m (mg/L/d)	1.07	---	1.07	---
K_m (mg/L)	0.01	---	0.01	---
F (unitless)	0.642	---	0.642	---
Derived Parameters[b]				
CL (L/d)[b,c]	0.131	---	0.131	---
Q (L/d)	0.578	---	0.578	---
V_3 (L)	1.86	---	1.86	---

[a] V_2 is adjusted for body weight.
[b] Linear clearance calculated as $V_2 \cdot k_e$.
[c] As the kinetics are substantially nonlinear, the beta half-life and linear clearance cannot be used to calculate time to the LLOQ concentration or another concentration of interest. No attempts should be made to do this to predict when patients reach clinically insignificant concentrations. Instead, model-based predictions should be used, which are proved to be precise.

Source: Applicant's population PK report, Page 62, Table 15

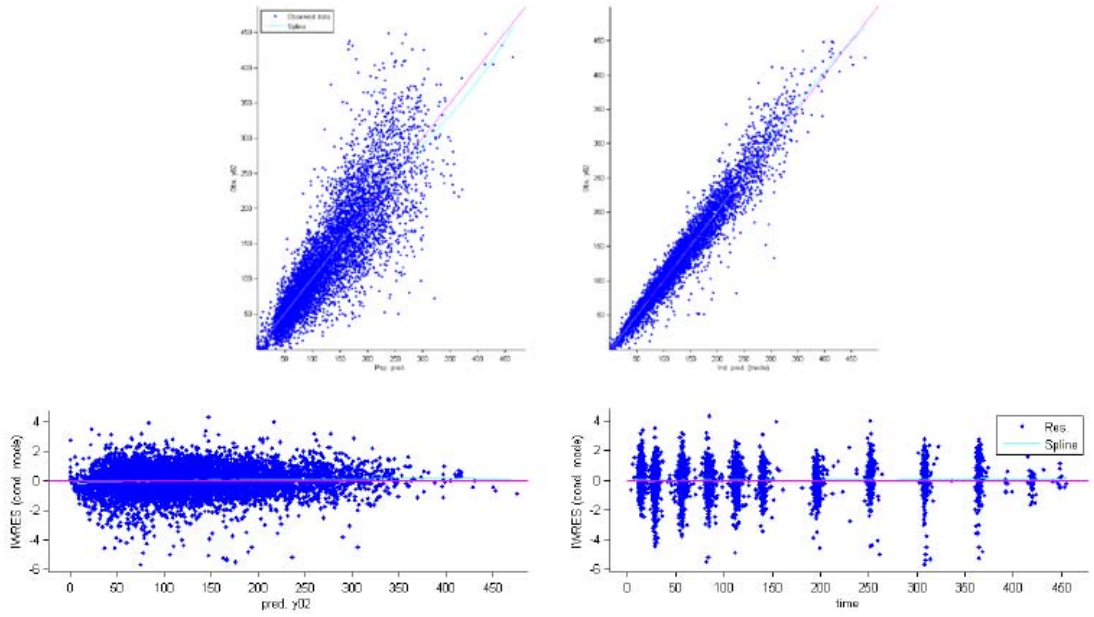

Figure 4.6.1 Diagnostic Plot for the Primary Covariate Model (Model 4)

Source: Applicant's population PK report, Page 116, Figures 43 and 45

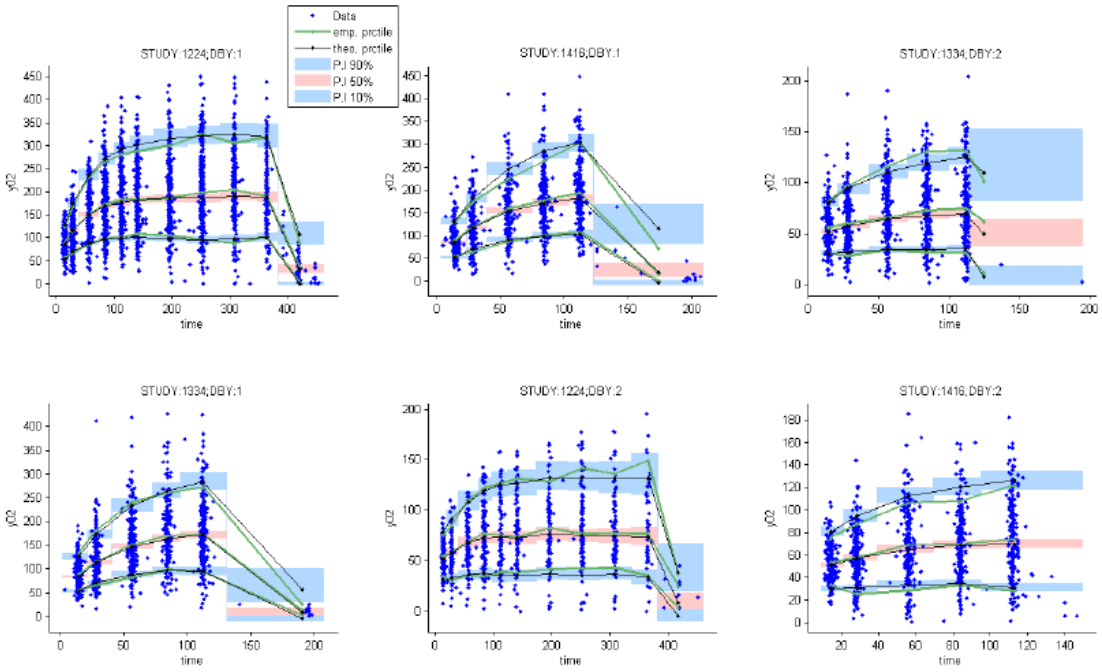

Figure 4.6.2: VPC for Primary Base Model by Study and Treatment Interval versus Actual Day (Model 4)

Note: DBY = 1 refers to 300mg QW and DBY = 2 refers to 300 mg Q2W.

Source: Applicant's population PK report, Page 117, Figure 46

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To estimate the effect of covariates of dupilumab exposure, Model 4 was used to simulate plasma concentration-time profiles for each patient receiving either 300mg Q2W or 300mg QW in the phase 3 studies. The results of these individual predictions were summarized based on the significant covariates included in the model. Table 4.6.8 summarizes the result of these simulations.

Table 4.6.8 Summary (Mean ±SE) of Individual Post-Hoc Estimates of Exposure at Steady State (AUCtau and Ctrough), Categorized by Covariate (Studies R668-AD-1334, R668-1416 and R668-AD-1224)

Covariate	Population Pharmacokinetic Post Hoc Estimates of Exposure					
	300 mg Q2W			300 mg QW		
	N	$AUC_{tau(ss)}$	$C_{trough(ss)}$	N	$AUC_{tau(ss)}$	$C_{trough(ss)}$
		mg*day/L	mg/L		mg*day/L	mg/L
Weight (kg)						
<70	223	1670(30.1)	101(2.01)	296	1780(28.3)	242(3.93)
≥70 to <100	270	1130(22.9)	67.1(1.52)	369	1310(19.3)	177(2.68)
≥100	59	729(42.2)	41.8(2.77)	81	872(35.0)	117(4.84)
BMI (kg/m^2)						
≥15 to <25	262	1600(28.0)	97.5(1.85)	359	1720(25.1)	234(3.48)
≥25 to <30	182	1150(29.8)	68.4(1.97)	232	1320(25.9)	179(3.59)
≥30	108	830(31.9)	48.0(2.09)	155	1010(27.2)	135(3.76)
BASELINE EASI score						
<21	131	1370(47.9)	82.9(3.12)	160	1590(41.5)	217(5.74)
≥21 to <50	352	1310(26.7)	78.5(1.75)	495	1430(22.9)	194(3.17)
≥50	69	1150(60.0)	67.8(3.91)	90	1280(45.9)	173(6.37)
ALBUMIN (g/L)						
≥30 to <40	35	1020(63.7)	60.5(4.18)	41	1240(73.0)	168(10.1)
≥40 to <50	462	1300(24.4)	77.9(1.59)	634	1440(20.1)	195(2.78)
≥50	55	1520(56.4)	92.7(3.71)	71	1690(60.8)	229(8.38)
RACE						
Asian	128	1340(45.9)	80.0(3.02)	182	1490(33.8)	201(4.68)
White	382	1310(26.1)	78.9(1.71)	499	1450(23.2)	197(3.21)
Other	42	1120(80.0)	66.6(5.21)	65	1320(72.8)	178(10.1)
ADA						
Negative	486	1340(22.8)	81.0(1.49)	689	1470(19.3)	199(2.66)
Positive	66	1000(62.2)	57.8(4.03)	57	1230(72.5)	167(10.0)

Note:
1. Data included up to week 24.
2. Steady state $AUC_{tau} = AUC_{[week\ 22\text{-}week\ 24]}$ for 300 mg Q2W;
3. Steady state $AUC_{tau} = AUC_{[week\ 23\text{-}week\ 24]}$ for 300 mg QW;
4. Treatment allocation in the simulation was based on the original randomization.
5. Simulation assumed all patients received all planned doses, up to week 24, including a loading dose of 600 mg on day 1.

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Covariate	Population Pharmacokinetic Post Hoc Estimates of Exposure					
	300 mg Q2W			300 mg QW		
	N	$AUC_{tau(ss)}$	$C_{trough(ss)}$	N	$AUC_{tau(ss)}$	$C_{trough(ss)}$
		mg*day/L	mg/L		mg*day/L	mg/L
Age (years)						
≥18 to <40	314	1370(30.6)	82.3(2.00)	432	1520(24.4)	206(3.37)
≥40 to <65	208	1230(33.1)	73.4(2.18)	283	1360(30.3)	185(4.20)
≥65	30	1150(68.3)	68.9(4.44)	31	1280(81.5)	173(11.3)
Gender						
Female	227	1440(37.2)	87.2(2.44)	294	1580(33.8)	215(4.68)
Male	325	1200(25.4)	72.0(1.66)	452	1360(20.8)	185(2.88)
Site (Country)						
ASIA (Japan, Korea, Hong Kong, Singapore)	90	1380(55.1)	82.1(3.63)	127	1470(40.3)	199(5.58)
Rest of World sites	462	1290(23.9)	77.5(1.56)	619	1450(21.0)	196(2.91)
Renal Function (Creatinine Clearance, mL/min)						
<50	8	1080(175)	64.3(11.4)	7	1760(272)	240(37.5)
≥50 to <80	69	1190(56.3)	71.1(3.73)	98	1420(51.0)	192(7.06)
≥80	474	1320(23.9)	79.4(1.56)	639	1450(20.2)	197(2.79)

Note:
1. Simulation up to week 24.
2. Steady state AUC_{tau} = $AUC_{[week\ 22\text{-}week\ 24]}$ for 300 mg Q2W;
3. Steady state AUC_{tau} = $AUC_{[week\ 23\text{-}week\ 24]}$ for 300 mg QW;
4. Treatment allocation in the simulation was based on the original randomization.
5. Simulation assumed all patients received all planned doses, up to week 24, including a loading dose of 600 mg on day 1.

Source: Applicant's population PK report, Page 93, Table 20

Reviewer's comments: The Applicant used predicted AUCtau in Table 4.6.8, which is misleading that AUCtau values of two dosing regimen seems to be similar. It would be more reasonable to use steady state AUC over same dosing interval in the post-hoc analysis.

To conclude, the PK of dupilumab was described by a 2-compartment model with parallel linear and nonlinear elimination and first order absorption. A transit compartment model was used to describe the lag time in the absorption of subcutaneously administered dupilumab. The inter-

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compartmental rates (k23 and k32) were used to characterize the inter-compartmental distribution. Elimination was characterized by a first order process described by ke and a non-linear process described by Michaelis-Menten parameters (maximal rate of clearance (Vm) and the Michaelis-Menten constant (Km)). While ADA, albumin, race, and baseline EASI score were statistically significant covariates, only weight on central volume and BMI on ke had a notable effect with around 50% increase.

Reviewer's comments: The reviewer verified the Applicant's population PK model for dupilumab. The goodness-of-fit plots indicate that the model reasonably describes the data. The impact of body weight, BMI, race, gender, albumin, ADA, and EASI score on exposure were all predicted to result in a less than 2-fold exposure change between groups or between the first and fourth quartiles for continuous covariates.

The Applicant proposed the following language in the label:

The (b) (4) ***bioavailability of dupilumab following a SC dose is estimated to be 64%*** (b) (4)

(b) (4)

The reviewer performed independent analysis to assess the accuracy of the labeling language derived from population PK model. The result is consistent with what was proposed by the Applicant. The proposed labeling language based on population PK analyses is acceptable from a pharmacometrics perspective.

As the elimination of dupilumab is non-linear process, the AUCtau (for 300 mg Q2W, AUCtau is AUC over two weeks; for 300 mg QW, AUCtau is AUC over one week), which was further used in Applicant's ER analysis, was generated by simulation based on population PK model. However, the dosing intervals for 300 mg Q2W and 300 mg QW are different; thus, AUCtau is an inappropriate exposure parameter to compare two dosing regimens. The steady state AUC (AUCss) over two weeks was used in the Reviewer's analysis.

4.7 Exposure-Response Analyses

4.7.1 E-R for efficacy

Exposure-response analyses for efficacy were conducted by the Applicant using both descriptive analyses and empirical ER model developed using dupilumab data from their clinical development program.

The analyses set for the descriptive E-R assessment consisted of patients from the two phase 3 studies (SOLO1 and SOLO2) administered either 300 mg QW or 300 mg Q2W who:

- completed the study through at least week 16
- had functional dupilumab concentration at week 16
- had non-missing efficacy response variables (EASI, IGA, and pruritus NRS) at baseline and week 16.

Patients who discontinued treatment or were rescued before week 16 were excluded from these analyses. A total of 967 patients were included in these analyses (Table 4.7.1.1).

Table 4.7.1.1 Summary of Patients by Study, Treatment Group, and Overall for Descriptive E-R Analyses of Efficacy Response Variables

Study Number	Dupilumab Treatment group		Placebo	Overall
	300 mg Q2W	300 mg QW		
R668-AD-1334 (SOLO1)	181	166	112	459
R668-AD-1416 (SOLO2)	200	189	119	508
Overall	381	355	231	967

Note: Patients who did not complete week 16 (Day 112) assessment were not included.

Source: Applicant's exposure-response analyses report, Page 25, Table 1

The time course of the efficacy response variables was plotted. Efficacy variables evaluated included mean changes from baseline in EASI, peak pruritus NRS scores, and proportion of patients achieving IGA 0 or 1. The distribution of trough concentrations (or AUC0-112) at each time point were divided into 4 quarters; Q1 (< 25 percentile), Q2 (25 to <50 percentile), Q3 (50 to 75 percentile), and Q4 (>75 percentile) at each time point. It is anticipated that if there is an exposure-response relationship, time-course efficacy should be aligned in the same rank order as the quarter concentrations (or AUC0-112) of functional dupilumab at each time point across the treatment period. In order to assess the impacts of body weight on E-R relationships, a similar analysis was applied to patient body weight distribution, i.e. from low body weight quarter (Q1), to high body weight quarter (Q4). The time-course for continuous efficacy variables (percent change from baseline in EASI and NRS score) were plotted by dose regimen and by quarter-concentration (or quarter-AUC0-112). For the categorical efficacy endpoint (IGA), the time-course of percentage of patients achieving IGA 0 or 1 at each time point were plotted by dose regimen and by quartile-concentration (or quarter-AUC0-112).

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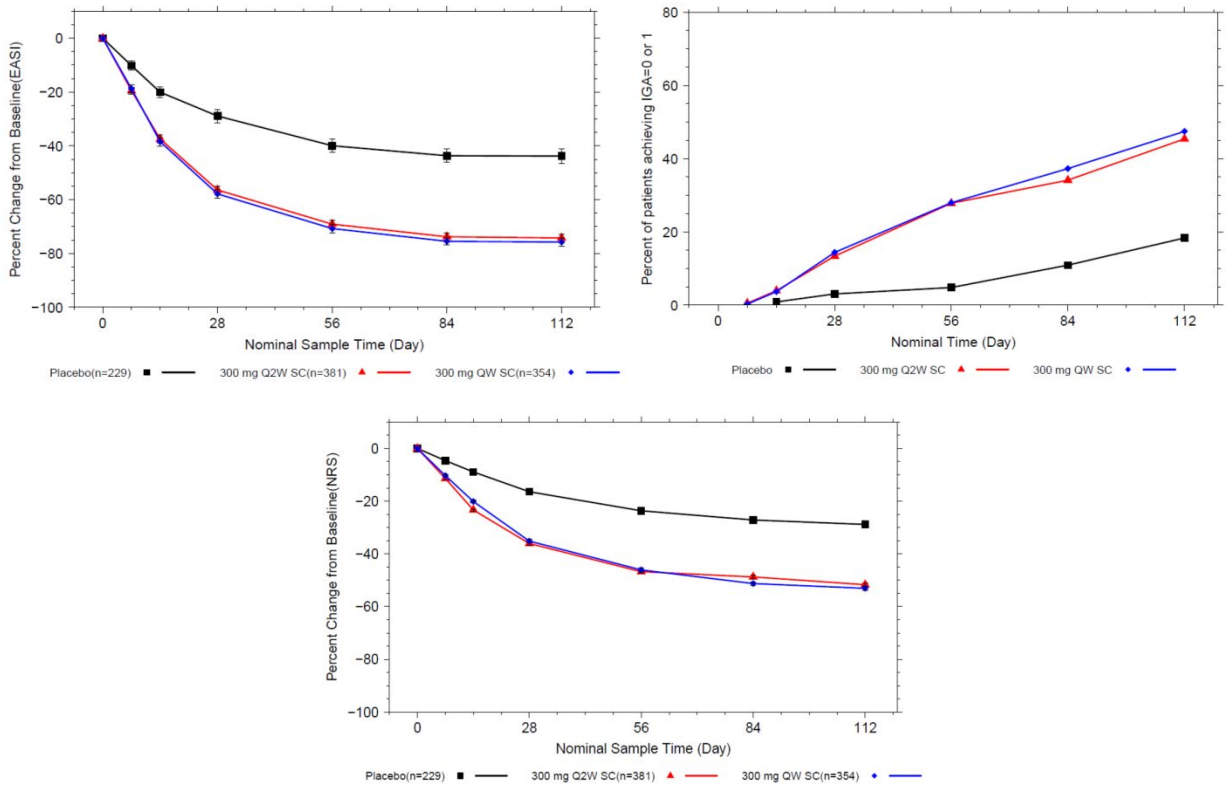

Figure 4.7.1.1 Efficacy Responses (EASI (Upper left), IGA (Upper right) and NRS scores (Bottom)) versus Time by Dupilumab Dose Regimen or Placebo.

Source: Applicant's exposure-response analyses report, Page 40, Figure 1; Page 71, Figure 17; Page 94, Figure 29

The results show no notable difference is observed when comparing mean percent change from baseline EASI score, proportion of patients achieving IGA 0-1, and mean percent change from baseline in peak pruritus NRS for the 300 mg Q2W and 300 mg QW treatment regimens. Despite this apparent lack of a dose-response relationship, in an analysis of the pooled dupilumab treatment groups of the two mono-therapy phase 3 studies by quartile of exposure, a shallow but pronounced E-R relationship is observed for all three efficacy responses (show below are the plots using Ctrough; plots for AUC are not shown but followed the same trend).

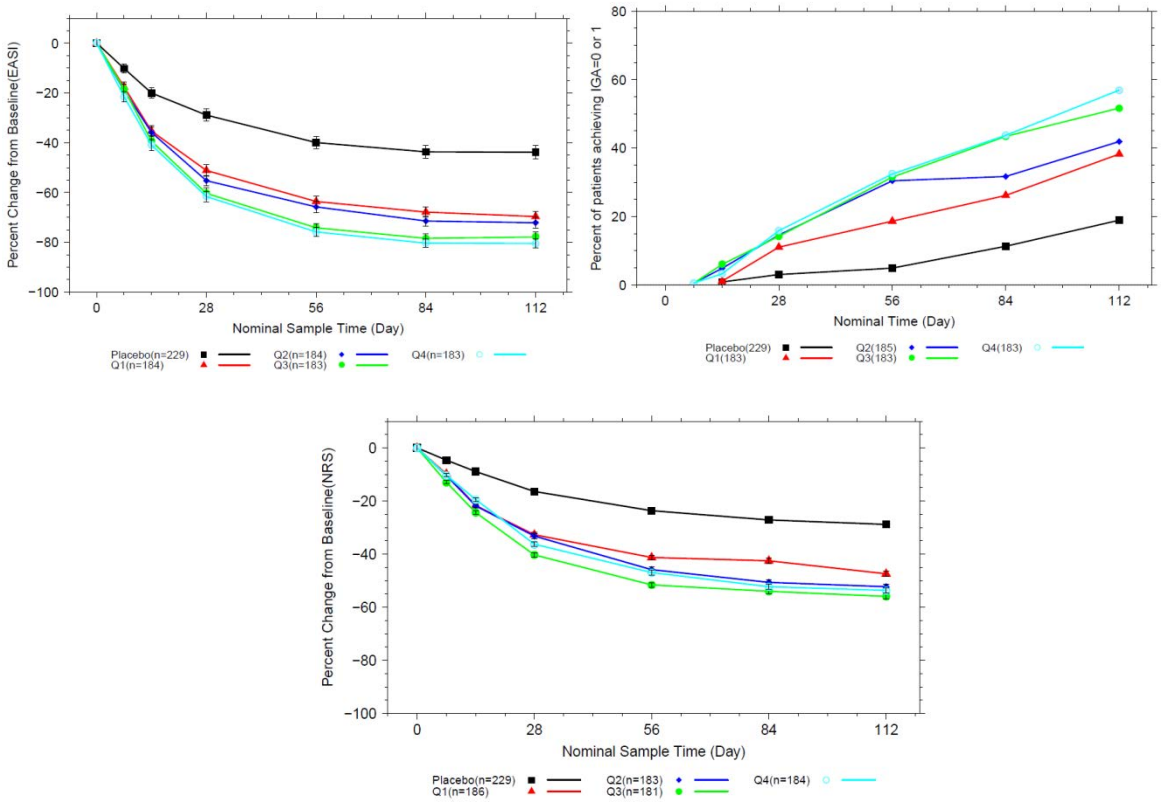

Figure 4.7.1.2 Efficacy Responses (EASI (Upper left), IGA (Upper right) and NRS scores (Bottom)) versus Time by Quartile of Dupilumab Concentration at Each Time Point or Placebo.

Source: Applicant's exposure-response analyses report, Page 46, Figure 6; Page 75, Figure 20; Page 98, Figure 32

To evaluate the effect of body weight on the E/R relationship of dupilumab and the selected efficacy response variables, the active treatment groups (300 mg Q2W and 300 mg QW) from the combined SOLO 1 and SOLO 2 studies were examined by quartile of body weight.

Table 4.7.1.2 Inter-Quartile Comparison by Day 112 Dupilumab Ctrough Concentrations and Body Weight on Selected Efficacy Response Variables

Quartile	EASI (% change from baseline)		IGA 0-1 (Proportion of patients)		NRS (% change from baseline)	
	Quartile by body weight	Quartile by exposure	Quartile by body weight	Quartile by exposure	Quartile by body weight	Quartile by exposure
Q1	-76.2%	-69.5%	51.9%	37.1%	-54.3%	-49.4%
Q2	-76.4%	-73.1%	48.0%	45.5%	-52.2%	-52.4%
Q3	-76.5%	-78.2%	48.6%	51.1%	-53.3%	-53.6%
Q4	-70.7%	-80.6%	39.8%	56.6%	-49.6%	-54.1%
Q4-Q1	-5.5%	-11.1%	12.1%	19.5%	-4.7%	-4.7%
Q3-Q1	-0.3%	-8.7%	3.3%	14.0%	-1.0%	-4.2%

Source: Applicant's exposure-response analyses report, Page 102, Table 35

For both EASI and IGA, a greater improvement was observed in the lowest quartile of body weight than in the highest quartile. When assessed across the 3 remaining quartiles (Q3 to Q1), the impact of body weight on response is far less. While the impact of exposure on response is also narrowed over these 3 quartiles, the difference between the effects of body weight on response compared to the effect of exposure widens, further indicating that the impact of body weight accounts for only a portion of the E-R relationship.

Exposure-response modeling analyses were also conducted using observed trough concentration (Ctrough) of functional dupilumab and AUC up to week 16 calculated using trapezoidal rule based on observed data from studies R668-AD-1334 and R668-AD-1416. The E-R model analysis was used only to characterize the percentage change in EASI. IGA score was not modeled due to its categorical nature; and peak pruritus NRS were not considered due to lack of the identifiable E/R relationship. Four base E-R models (Emax, Sigmoidal Emax (sigEmax), logistic and linear), were compared to select the model that best fit available patient data as assessed by goodness of fit criterion (AIC). Based on these results, as well as the visual inspection of the E-R relationship, a simple Emax model was selected as the structural model.

Table 4.7.1.3 Summary of Base Model Selection Using AIC as Criteria

Model	AIC (model with AUC_{0-112})	AIC (model with concentration at week 16)
Emax	12921.89	12935.76
sigEmax	12923.58	12938.62
logistic	12925.58	12944.21
linear	13039.76	13066.37

Source: Applicant's exposure-response analyses report, Page 110, Table 39

Continuous covariates on fixed effects were tested as a power function normalized with their median value. Evaluated continuous covariates include age, weight, height, BSA, BMI, baseline EASI and NRS score, on E0 and EC50. Categorical covariates including gender, ADA positivity, baseline IGA, study ID, were tested on E0 and EC50 as a fractional change on the fixed effect. Forward addition and backward elimination were used to identify significant covariate effects. The covariates that were found to significantly ($p<0.01$) affect the E-R model parameters (E0 and EC50) were BMI, baseline NRS score and IGA score, creatinine clearance (mL/min), and albumin levels. The most influential covariate was BMI (or body weight) on baseline response (E0); other parameter effects were considered to be small in magnitude and are not to be clinically meaningful. The parameter estimates are listed in Table 4.7.1.4.

Table 4.7.1.4 Final Model Structural Parameter Estimates

Parameters	Estimate (Trough Conc)	%RSE	95% CI	Estimate (AUC_{0-112})	%RSE	95% CI
THETA						
GAMMA	1	---	---	1	---	---
EC50	30.96	139.41	[28.45, 362.95]	5770.82	55.17	[4760.8,76909]
E0	-40	-1.62	[-93.93, -0.49]	-40	-1.49	[-86.33, -0.31]
EMAX	-64.16	---	---	-71.92	---	---
IGA_BL_E0	-0.04	---	---	0	---	---
BMIBL_NOR_E0	0	---	---	0.4	---	---
NRS_BL_NOR_E0	0	---	---	0.04	---	---
PCC_NOR_E0	0	---	---	0.03	---	---
ALB_NOR_E0	0	---	---	-0.04	---	---
OMEGA						
EC50-EC50	1.49	---	---	5.16	---	---
E0-E0	2.07	---	---	3.6	---	---
SIGMA						
Proportional Error	5.38	---	---	10.36	---	---
Additional Error	0.11	---	---	0.11	---	---

Source: Applicant's exposure-response analyses report, Page 119, Table 41

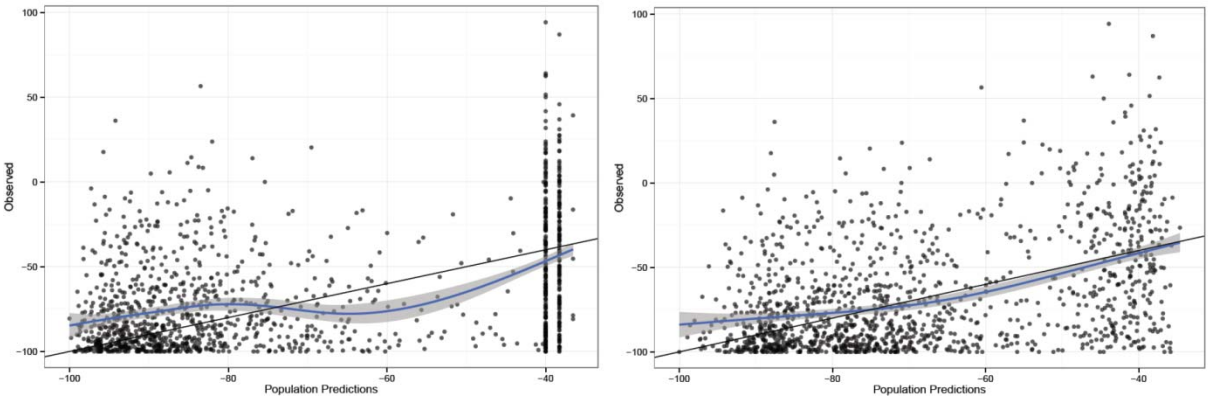

Figure 4.7.1.3 Population Predicted (PRED) versus Observed (DV) Percent Change from Baseline in EASI Obtained from the Final Model (Left: Ctrough, Right: AUC0-112)

Source: *Applicant's exposure-response analyses report, Page 115, Table 42; and Page 117, Table 44*

In conclusion, no clear identifiable dose-response with the efficacy response variables was observed for 300 mg QW or 300 mg Q2W. However, the descriptive and empirical model based exposure-response analysis presented for the overall randomized treatment group provides clear evidence of a concentration and AUC exposure-response relationship.

The exposure-response relationships for the efficacy response variables suggests there is a patient subpopulation that may benefit from the increased exposure associated with the more intense 300 mg QW. However, this analysis cannot determine a priori the patient type most likely to benefit from this more intensive treatment regimen.

Reviewer's comments: The review performed an independent analysis using the full dataset of SOLO1 and SOLO2 studies including the patients with missing efficacy endpoint at week 16. A significant exposure-efficacy relationship was identified by using EASI-75 as the efficacy endpoint and predicted steady state AUCss over two weeks as the independent variable. The logistic regression analysis shows there is a trend of increasing EASI-75 as AUCss over two weeks increases (Figure 4.7.1.4). Covariate analysis shows that other than exposure, the EASI baseline also has a significant impact on the response rate. This indicates that the probability of achieving EASI-75 is dependent on disease severity prior to treatment. Based on the exposure-response relationship by doses, it would be concluded that the probability of EASI-75 would increase as exposure increase under both dosing regimens. As expected, around 75% patients administered 300 mg QW have higher exposure (AUCss over two weeks) compared to the patients administered 300 mg Q2W. It is worth noting that the overall response rate under dosing of 300 mg Q2W is driven by the highest exposure quantile and that except for that quartile the response rates are aligned by exposure.

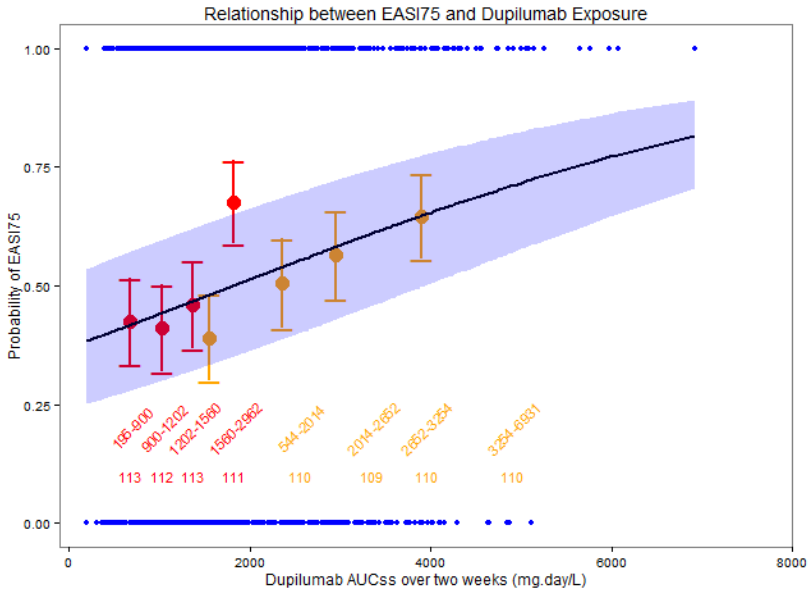

Figure 4.7.1.4 Exposure-response analyses for dupilumab using efficacy endpoint of EASI-75

Blue points represent observations of all the subjects in studies of SOLO1 and SOLO2; black line and blue shade represent the logistic model-predicted relationship and 90% CI based on all the data; red bars represent the four quantiles of exposure under treatment of 300 mg Q2W and orange bars represent the four quantiles of exposure under treatment of 300 mg QW.

Source: Reviewer's independent analysis.

The study results from SOLO1 and SOLO2 show there was no treatment difference between the two dosing regimens, 300 mg QW and 300 mg Q2W, which differs from the results of the exposure-response analysis. The underlying reason may be there are confounding covariates which affect dupilumab exposure as well as the response. Thus, the exposure-response relationship is artificial. Based on known information, the EASI baseline is a potential confounding covariate that affects both exposure and efficacy as suggested by the pop PK model (Table 4.6.7) and the covariate analysis for the ER relationship. The subgroup analysis results confirm both AUC and response decrease when EASI baseline score increased as listed in Table 4.7.1.5. The result also demonstrates that response rates are comparable between 300 mg Q2W and 300 mg QW in based on EASI baseline with a potential exception of those subjects with the highest baseline EASI score (>50), which may be caused by relatively small sample size. There may be other confounding covariates that have not been identified from this analysis.

Table 4.7.1.5 AUCss over two weeks and response rate of EASI-75 by dosing regimens and EASI baseline quantile

EASI baseline	300 mg Q2W			300 mg QW		
	N	Median AUCss (mg·day/L)	EASI-75 %	N	Median AUCss (mg·day/L)	EASI-75 %
1st Quantile (16-21)	111	1300	0.61	98	2851	0.61
2nd Quantile (>21-50)	284	1197	0.50	290	2604	0.53
3rd Quantile (>50)	54	1001	0.20	51	2125	0.31
Overall	449	1439	0.53	439	1236	0.49

Source: Reviewer's independent analysis on ER dataset (auc-easi-sigmoid.xpt and ADSL.xpt of ISE pool 1)

The review also did subgroup analysis for body weight and ADA titers. Although body weight is a significant covariate on exposure, the response rate (take EASI-75 as an example) is similar across the body weight range in the two Phase 3 studies, SOLO1 and SOLO2 (Table 4.7.1.6). Thus no dose adjustment is necessary. A similar result was observed for ADA titers that the response rate is not expected to be correlated with ADA titers (Table 4.7.1.7), although the sample size for patients with moderate ADA titer is relative small. The impact of ADA titer on exposure is observed while it was not identified by the population PK analysis where the patients with high and moderate ADA titer were excluded. Also, as compared to two dosing regimens, 300 mg Q2W and 300 mg QW, the AUC values under same dosing interval would be roughly 2-fold difference, but associated to the similar response rates. Thus, covariate having impact on PK less than 2-fold is not expected to have clinical significant impact on efficacy and no dose adjustment is necessary.

Table 4.7.1.6 Response rate comparisons across body weight ranges separated by dose based on SOLO1 and SOLO2 studies

Reference ID: 4030358

Body weight (kg) Quantile (min-max)	*No. of patients*	*AUCss over two weeks (mg·day/L) Median (min-max)*	*EASI-75*
300 mg Q2W			
1st quantile (42.3-64)	*113*	*1680 (488-2962)*	*0.47*
2nd quantile (>64-75)	*112*	*1379 (502-2334)*	*0.46*
3rd quantile (>75-89)	*113*	*1027 (407-1892)*	*0.55*
4th quantile (>89-175.4)	*111*	*766 (195-1512)*	*0.49*
300 mg QW			
1st quantile (42.3-65)	*110*	*3417 (819-6931)*	*0.52*
2nd quantile (>65-75)	*111*	*2951 (780-4861)*	*0.57*
3rd quantile (>75-87)	*109*	*2488 (615-4332)*	*0.54*
4th quantile (>87-157.5)	*109*	*1994 (544-4174)*	*0.48*

Source: Reviewer's independent analysis on ER dataset (auc-easi-sigmoid.xpt and ADSL.xpt of ISE pool 1)

Table 4.7.1.7 Response rate comparisons across different categories of ADA titers separated by dose based on SOLO1 and SOLO2 studies

ADA titer	*No. of patients*	*AUCss over two weeks (mg·day/L) Median (min-max)*	*EASI-75*
300 mg Q2W			
No ADA	*393*	*1243 (195-2962)*	*0.51*
Low	*54*	*898 (199-2432)*	*0.33*
Moderate	*2*	*495 (439-551)*	*0.50*
High	*0*	*-*	*-*
300 mg QW			
No ADA	*411*	*2678 (615-6931)*	*0.53*
Low	*26*	*2288 (737-3674)*	*0.54*
Moderate	*2*	*1003 (544-1463)*	*0.5*
High	*0*	*-*	*-*

** The less subject in Table 4.7.1.7 compared to Table 4.6.4 is due to exclude the patients without AUC prediction.*

Source: Reviewer's independent analysis on ER dataset (auc-easi-sigmoid.xpt and ADSL.xpt/ADISADA.xpt of ISE pool 1)

Other subgroups similarly show no preferential benefit for 300 mg QW compared to 300 mg Q2W as listed in Table 4.7.1.8.

Table 4.7.1.8 Response rate comparisons across different categories of age, sex, and IGA baseline separated by dose based on SOLO1 and SOLO2 studies

Covariates	*No. of patients*	*AUCss over two weeks (mg·day/L) Median (min-max)*	*EASI-75*
Age (years)			

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300 mg Q2W			
18≤, <40	*264*	*1284 (195-2668)*	*0.51*
40≤, <65	*159*	*1072 (441-2962)*	*0.46*
≥65	*26*	*1003 (510-1918)*	*0.62*
300 mg QW			
18≤, <40	*246*	*2760 (544-6931)*	*0.52*
40≤, <65	*175*	*2553 (697-6075)*	*0.54*
≥65	*18*	*2686 (1073-5250)*	*0.5*
Sex			
300 mg Q2W			
Male	*264*	*1107 (199-2334)*	*0.43*
Female	*185*	*1391 (195-2962)*	*0.57*
300 mg QW			
Male	*267*	*2526 (544-5763)*	*0.49*
Female	*172*	*2935 (697-6931)*	*0.58*
IGA baseline			
300 mg Q2W			
3	*231*	*1250 (314-2962)*	*0.61*
4	*218*	*1139 (195-2538)*	*0.37*
300 mg QW			
3	*228*	*2800 (614-6931)*	*0.60*
4	*221*	*2457 (544-6075)*	*0.45*

Source: Reviewer's independent analysis on ER dataset (auc-easi-sigmoid.xpt and ADSL.xpt/ADISADA.xpt of ISE pool 1)

Overall, the data suggests that no specific subgroup showed preferentially benefit on 300 mg QW compared to 300 mg Q2W. (b) (4)

One thing that needs to be noted is that the exposure-response analyses dataset utilized by Applicant only included 84% and 78% of on-treatment patients inform the two Phase 3 studies for the 300 mg Q2W and 300 mg QW arms, respectively (Table 4.7.1.9). The patients who had missing efficacy endpoint data at week 16 were excluded from the Applicant's exposure-response analyses while these patients were considered as non-responders in the efficacy evaluation. This exclusion criterion resulted in an imbalance in the number of patients included from the two treatment arms (300 mg QW and 300 mg Q2W). In addition, this exclusion altered the EASI-75 response rates for the two treatment arms. The overall EASI-75 response rate for 300 mg Q2W in SOLO1 and SOLO2 changed from 49% to 59%. Likewise, the overall EASI-75 response rate for 300 mg QW in SOLO1 and SOLO2 changed from 53% to 68%. A greater increase was observed for the 300 mg QW arm as more patients were missing the efficacy endpoint in that arm.

Table 4.7.1.9 Subject number comparison between ER dataset and efficacy dataset

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	300 mg Q2W		300 mg QW		Placebo	
	N	Response rate	N	Response rate	N	Response rate
ER dataset	377	0.59	343	0.68	222	0.27
efficacy dataset	449	0.49	439	0.53	456	0.13
Percentage	84%	-	78%	-	49%	-

**Four patients in 300 mg Q2W arm and 2 patients in 300 mg QW arm do not have PK information*

Source: Reviewer's independent analysis on ER dataset (auc-easi-sigmoid.xpt and ADSL.xpt of ISE pool 1)

4.7.2. E-R for safety

Exposure-response analysis for safety was conducted by Applicant. The most notable TEAEs observed in the phase 3 program (conjunctivitis, herpes simplex, and oral herpes) were assessed against the quartile of the exposure through week 16 (AUC0-112) calculated by trapezoidal rul based on studies of R668-AD-1334 and R668-AD-1416.

The descriptive exposure-response analysis for safety illustrated that the adverse drug reactions (ADRs) identified in the AD phase 3 studies (conjunctivitis, herpes simplex, and oral herpes) were balanced across the quartiles of exposure and that no exposure-response relationship could be identified. While the overall number of events was small, the analysis did not suggest an increased incidence of these ADRs across the various exposure quartiles (Table 4.7.2.1).

Table 4.7.2.1 Summary of TEAEs related to Herpes Infections/Conjunctivitis through Week 16 by AUC

		Dupilumab			
Preferred Term/MedDRA 18.0	Placebo (N=456)	AUC1 (N=219)	AUC2 (N=219)	AUC3 (N=218)	AUC4 (N=218)
Oral Herpes	8 (1.8%)	8 (3.7%)	7 (3.2%)	7 (3.2%)	8 (3.7%)
Herpes Simplex	4 (0.9%)	2 (0.9%)	4 (1.8%)	1 (0.5%)	3 (1.4%)
Conjunctivitis	10 (2.2%)	24 (11.0%)	20 (9.1%)	17 (7.8%)	15 (6.9%)
Conjunctivitis	3 (0.7%)	12 (5.5%)	7 (3.2%)	8 (3.7%)	7 (3.2%)
Conjunctivitis bacterial	2 (0.4%)	5 (2.3%)	4 (1.8%)	4 (1.8%)	1 (0.5%)
Conjunctivitis viral	1 (0.2%)	2 (0.9%)	1 (0.5%)	1 (0.5%)	0
Conjunctivitis allergic	4 (0.9%)	5 (2.3%)	7 (3.2%)	5 (2.3%)	7 (3.2%)
Atopic keratoconjunctivitis	0	0	1 (0.5%)	0	0

Source: *Applicant's exposure-response analyses report, Page 209, Table 86*

Reviewer's comments: The reviewer performed a cumulative event analysis with regard to conjunctivitis, herpes simplex and oral herpes. The AUCss over two weeks was divided into four quantiles of AUC from low values to high values plus placebo group. Although there seems to be a trend across the AUCss quantiles, the event rate is very low for all the safety endpoint. The analysis showed that the hazard ratio was not statistically significant for all three safety endpoints, which is aligned with the sponsor's conclusion that no exposure-safety relationship was identified for the ADRs based on the phase 3 data (Figure 4.7.2.1). The summary of safety event by AUCss quantile and dosing regimen is listed in Table 4.7.2.2. Although there is slightly different in number compared to Applicant's summary (Table 4.7.2.1), a similar result can be

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observed that no exposure-response relationship was identified for safety event across different dosing regimen.

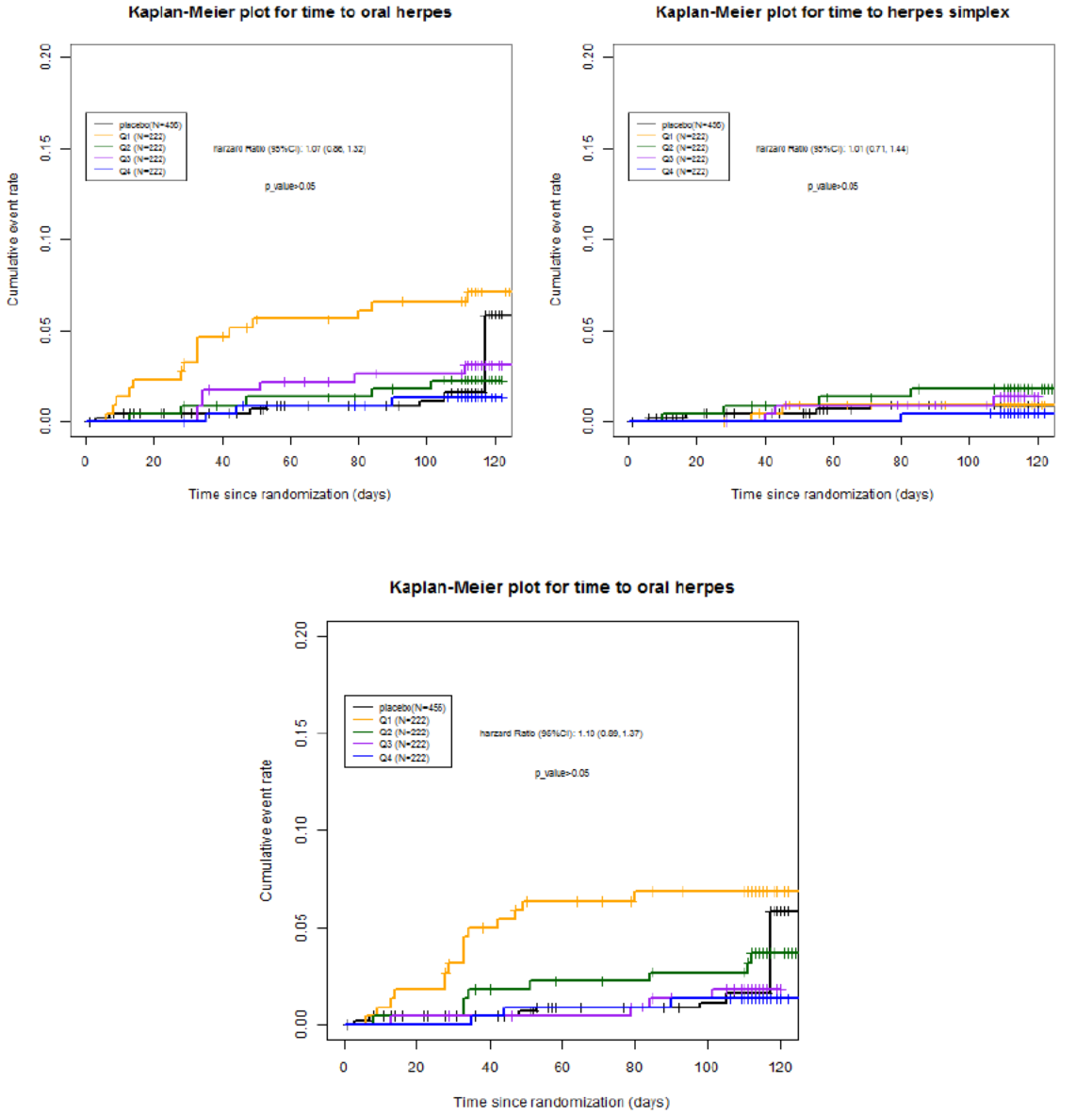

Figure 4.7.2.1 Cumulative event analysis for three safety endpoints (Upper left: conjunctivitis; Upper right: Herpes simplex; bottom: Oral herpes)

Source: Reviewer's independent analysis on dataset of pktte.xpt

Table 4.7.2.2 Summary of AE events by AUCss over two weeks and dosing regimen

AUCss (mg·day/L) (min-max)	N	Conjunctivitis, N (%)	Herpes simplex, N (%)	Oral herpes, N (%)
Placebo	456	10 (2.2%)	4 (0.9%)	8 (1.8%)
300 mg Q2W				
1st quantile (195-900)	113	18 (15.9%)	2 (1.8%)	8 (7.2%)
2nd quantile (900-1202)	112	11 (9.8%)	4 (3.6%)	6 (5.4%)
3rd quantile (1202-1560)	112	11 (9.8%)	1 (0.9%)	2 (1.7%)
4th quantile (1560-2962)	112	5 (4.5%)	0	1 (0.9%)
300 mg QW				
1st quantile (544-2014)	110	19 (17.3%)	0	7 (6.3%)
2nd quantile (2014-2652)	110	5 (4.5%)	0	3 (2.7%)
3rd quantile (2652-3254)	109	7 (6.4%)	2 (1.8%)	0
4th quantile (3254-6931)	110	1 (0.9%)	1 (0.9%)	3 (2.7%)

Source: Reviewer's independent analysis on dataset of pktte.xpt

4.7.3 Dose selection for Phase 3

Loading dose:

Loading dose was evaluated by comparing the results from Phase 2a proof-of-concept study (R668-AD-1117, without loading dose) and phase 2b dose-ranging study (R668-AD-1021, with loading dose).

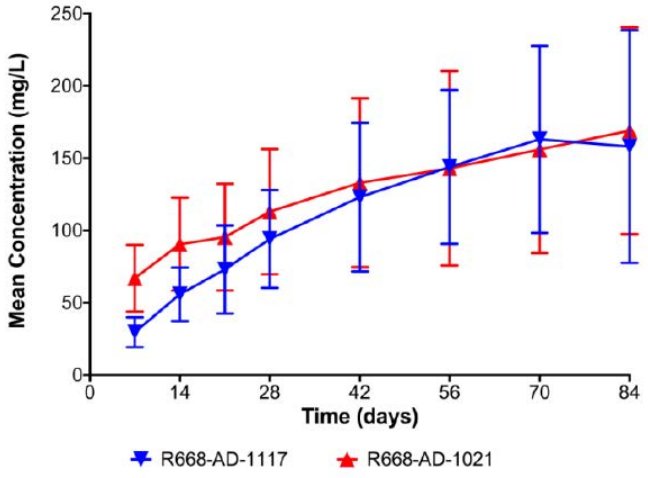

Figure 4.7.3.1 Comparison of Mean Trough Concentration-Time Profiles for 300 mg QW Dosing Regimen, Given for 12 Weeks With (R668-AD-1021) and Without (R668-AD-1117) a 600 mg Loading Dose

Source: Applicant summary of clinical pharmacology studies, Page 47, Figure 8

The administration of the loading dose of dupilumab allowed more rapid attainment of target-saturating concentrations, reaching steady-state faster, and thus potentially reducing the time to onset of clinical effect. Figure 4.7.2.1 compares mean trough concentration-time profiles for the

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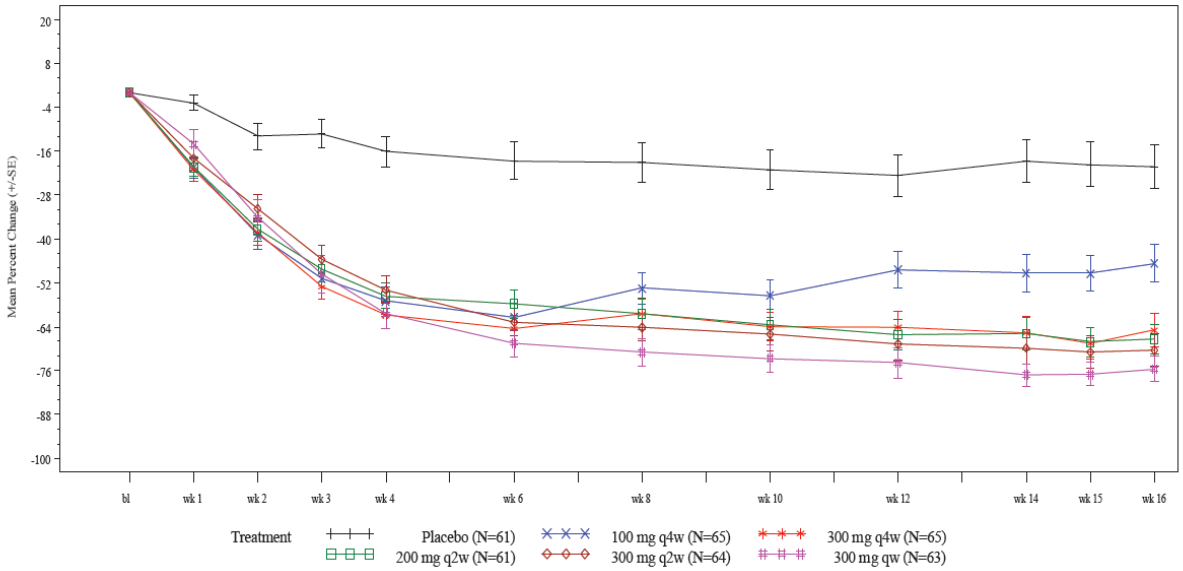
300 mg QW dosing regimen, given for 12 weeks with and without a 600 mg loading dose (study R668-AD-1021 and study R668-AD-1117, respectively). As expected, the regimen that includes a loading dose achieves concentrations about 2 weeks faster than without a loading dose, but after 8 weeks, the mean concentrations are similar for both regimens. Thus, loading dose was used for Phase 3 studies.

Reviewer's comments: From PK perspective, the loading dose may shorten the time to achieve steady state dupilumab exposure. However, achieving steady state concentrations faster did not appear to translate to a better initial or overall efficacy response. As shown in Figure 4.7.3.2, the EASI changes from base line at day 8 and day 15 are similar between study R668-AD-1021 and study R668-AD-1117. The observations suggest that the dupilumab loading dose may not be meaningfully contributing to the overall treatment effect. However, as the Phase 3 studies all used the loading dose and there was no safety signal associated with its use, the reviewer considers the loading dose appropriate for labeling.



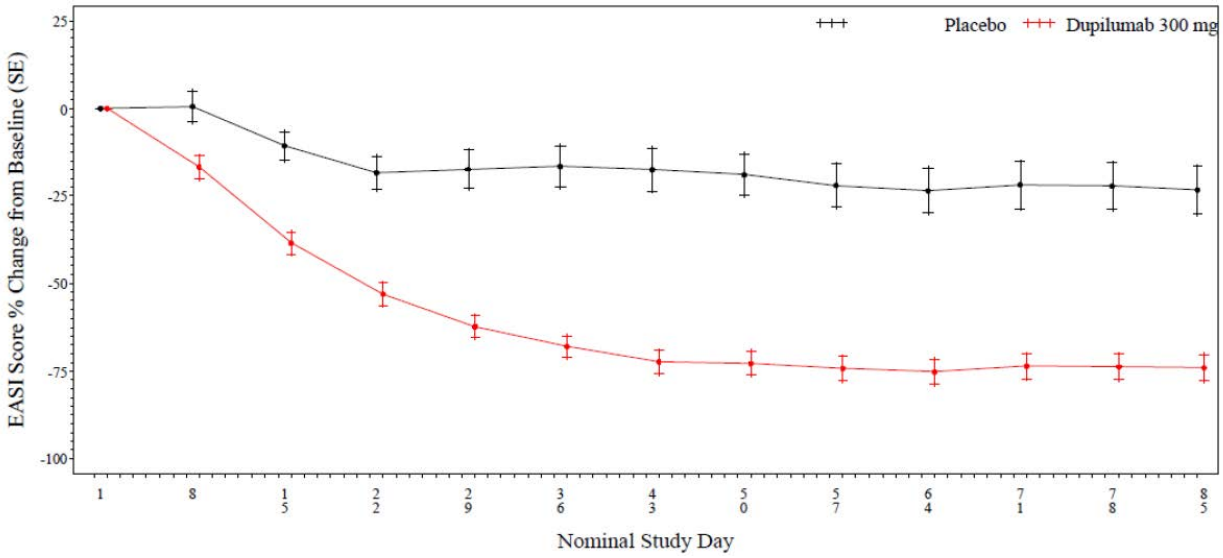


Figure 4.7.3.2 Mean Percent Change in EASI from Baseline to Week 16 – FAS (LOCF) for study R668-AD-1021 (top) and study R668-AD-1117 (bottom)

Dose regimen

The dose regimens were selected based largely on the efficacy and safety results of the R668-AD-1021 dose-ranging study, which evaluated dupilumab dose regimens of 300 mg QW, 300 mg Q2W, 300 mg Q4W, 200 mg Q2W, and 100 mg Q4W versus placebo administered weekly for 16 weeks. All 5 doses were efficacious, although the efficacy of the 100 mg Q4W dose regimen appeared to be sub-optimal, trending towards a lower percentage change in EASI than the other doses. Efficacy data suggested a dose-response pattern with evidence of numerical superiority at the highest dose (300 mg QW) (Table 4.7.3.2) compared to placebo. However, differences in mean efficacy between the highest two dosing regimens (300 mg QW and 300 mg Q2W) were relatively small. The consistency of the results for the 300 mg QW dose with those observed in the R668-AD-1117 study (Table 4.7.3.3), as well as the dose-dependent efficacy response at the lower doses from earlier phase 1b studies (R668- AD-0914 and R668-AD-1026) were all utilized to inform dose selection for the phase 3 program (Table 4.7.3.4-5). Both the 300 mg QW and 300 mg Q2W doses were selected for further evaluation in phase 3.

Table 4.7.3.2 Percent Change in EASI score from Baseline to Week 16 in Study R668-AD-1021

N	Placebo QW	100 mg Q4W	300 mg Q4W	200 mg Q2W	300 mg Q2W	300 mg QW
	61	65	65	61	64	63
Baseline (SD)	32.9 (13.77)	32.2 (13.49)	29.4 (11.48)	32.9 (15.50)	33.8 (14.52)	30.1 (11.23)
Week 16 (SD)	-20.2 (46.15)	-46.7 (41.96)	-64.9 (37.21)	-67.4 (31.97)	-70.5 (35.09)	-75.5 (26.86)
Min:Max	-92:107	-100:59	-100:66	-100:26	-100:106	-100:44

Source: Applicant's clinical report for R668-AD-1021, Page 94, Table 17

Table 4.7.3.3 Percent Change in EASI score from Baseline to Week 12 in Study R668-AD-1117

N	Placebo QW	300 mg QW
	54	55
Baseline (SD)	30.8 (13.63)	28.4 (13.57)
Week 12 (SD)	-23.3 (49.26)	-74.0 (26.94)
Min:Max	-97:100	-100:515

Source: Applicant's clinical report for R668-AD-1117, Page 78, Table 17

Table 4.7.3.4 Percent Change in EASI score from Baseline to Week 12 in Study R668-AD-0914

N	Placebo QW	75 mg QW	150 mg QW	300 mg QW
	6	8	8	8
Baseline (SD)	18.1 (7.17)	36.9 (11.75)	25.6 (13.84)	29.8 (6.44)
Week 12 (SD)	-46.9 (31.31)	- 28.3 (29.69)	-51.5 (27.74)	-53.4 (25.38)
Min:Max	-100:-12	-77:2	-83:-6	-83:-2

Source: Applicant's clinical report for R668-AD-0914, Post-text, Page 131, Table 5-3

Table 4.7.3.5 Percent Change in EASI score from Baseline to Week 12 in Study 1026

N	Placebo SD	150 mg SD	300 mg SD
	10	14	13
Baseline (SD)	25.6 (13.73)	32.6 (18.56)	25.9 (13.38)
Week 12 (SD)	10.9 (98.09)	-46.2 (44.50)	-68.8 (23.94)
Min:Max	-83:233	-100:43	-100:-28

Source: Applicant's clinical report for R668-AD-0914, post-text, Page 81, Table 5-3

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/s/

JIE WANG
12/19/2016

LUKE Y OH
12/19/2016

LUNING ZHUANG
12/19/2016

JEFFRY FLORIAN
12/19/2016

YOW-MING C WANG
12/19/2016

HAE YOUNG AHN
12/19/2016