CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761032Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	STN 761,032
Link to EDR	*\\CDSESUB1\EVSPROD\BLA761032\761032.enx*
Submission Date	11/16/2015
Submission Type (Priority or standard)	Original BLA, New Molecular Entity (Standard)
Brand Name	SILIQ
Generic Name	Brodalumab (AMG 827)
Dosage Form and Strength	Single-use prefilled syringe (PFS): 210 mg of brodalumab in 1.5 mL solution (140 mg/mL)
Route of Administration	Subcutaneous injection
Proposed Dosing Regimen	The proposed dose is 210 mg administered by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks
Proposed Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Applicant	Valeant Pharmaceuticals North America LLC
Associated IND	IND 104,671
OCP Review Team	Jie Wang, Ph.D. Dhananjay Marathe, Ph.D. Anuradha Ramamoorthy, Ph.D. Christian Grimstein, Ph.D. Jeffry Florian, Ph.D. Yow-Ming Wang, Ph.D.
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1. EXECUTIVE SUMMARY

The Applicant submitted original BLA 761,032 for SILIQ (brodalumab, also known as AMG 827) for the treatment of moderate to severe psoriasis. Brodalumab is a human monoclonal IG2κ antibody that binds to interleukin-17 receptor A (IL-17RA).

- *Proposed indication:* For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
- *Proposed dosing regimens*: 210 mg administered by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks (Q2W)
- *Proposed brodalumab dosage forms/presentations:* Single-use prefilled syringe: 210 mg of brodalumab in 1.5 mL solution (140 mg/mL)

1.1 Recommendations

From a Clinical Pharmacology standpoint, the BLA is acceptable to support the approval of SILIQ (brodalumab) for the treatment moderate to severe plaque psoriasis in adult patients provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

A required OCP office level briefing was held on June 30, 2016.

The key review findings with specific recommendations/comments are summarized below:

Review issues	Recommendations/comments
Evidence of effectiveness	• Primary evidence: efficacy results of three pivotal Phase 3 trials • Additional evidence: dose- and exposure-response relationships for efficacy.
Safety: completed suicide; suicidal ideation and behavior (SIB)	The limited available clinical data did not suggest a direct correlation between brodalumab exposure or up-regulation of serum IL-17A levels and completed suicide or SIB. – *See section 2.3 Outstanding Issues*
General dosing instructions	The 210 mg Q2W dosing regimen as proposed by the Applicant is acceptable.
Pharmacodynamics	Brodalumab treatment resulted in an increase in serum IL-17A levels in subjects with psoriasis. – *See section 2.4 Labeling Recommendations.*
Disease-drug-drug interactions (Disease-DDI)	Brodalumab co-administration increased the exposure of midazolam (CYP3A4 substrate) in subjects with psoriasis. – *See section 2.4 for Labeling Recommendations.*
Immunogenicity	The antidrug antibody (or binding antibody) assay performance was acceptable, whereas the neutralizing antibody assay has limitations in detecting neutralizing antibodies in the presence of brodalumab. The final determination of whether the Applicant needs to improve the assay performance in a PMR/PMC study is deferred to OBP.
PK bridge supporting "to-be-marketed" presentation	Study 20130307 has demonstrated the PK comparability between the to-be-marketed [1.5 mL PFS] and Phase 3 [1.0 mL PFS +0.5mL PFS] presentations.

1.2 Post-Marketing Requirements and Commitments

There are no Clinical Pharmacology-specific PMC or PMR recommendations.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of action (MOA) and pharmacodynamics

- *MOA*: Brodalumab is a human monoclonal IG2κ antibody that binds to interleukin-17 receptor A (IL-17RA). Blocking IL-17RA prevents its interaction with IL-17A which is a naturally occurring cytokine involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis. Because IL-17RA is a component of the heterodimer receptors for several cytokines, brodalumab inhibits the biological activities of IL-17A, IL-17F, IL-17A/F heterodimer, IL-25 (also known as IL-17E), and IL-17C.
- *Brodalumab treatment resulted in an increase in serum IL-17A levels*: Serum levels of IL-17A were increased after receiving 140 mg or 210 mg brodalumab treatment compared to the pre-treatment levels in subjects with moderate to severe plaque psoriasis. The increase in trough serum IL-17A levels at steady state appeared to be dose-dependent: 210 mg every 2 weeks (Q2W) dosing was associated with a greater increase in trough serum levels of IL-17A than 140 mg Q2W dosing.

  Beyond the IL-17A levels, there are no data available for evaluating the impact of brodalumab treatment on serum levels of other cytokines. Theoretically, increased serum levels of IL-17A may modulate serum level of other cytokines, including IL-6. The relationship between these pharmacodynamic activities and the mechanism(s) by which brodalumab exerts its clinical effects is unknown.

Pharmacokinetics (PK) of brodalumab in subjects with psoriasis

- *Bioavailability:* Following subcutaneous administration, the estimated brodalumab bioavailability was approximately 55% based on population PK modeling.
- *Non-linear PK*: Brodalumab exhibited non-linear PK with brodalumab exposures increasing in a greater than dose-proportional manner and the clearance of brodalumab decreasing with increasing dose.

  Following a single subcutaneous administration, brodalumab reached peak serum concentrations (C_{max}) of 4.8±2.8 mcg/mL and 13.4±7.3 mcg/mL [mean (±SD)] for 140 and 210 mg, respectively, approximately 3 days post dose; the mean (±SD) area-under-the-concentration-time curve ($AUC_{0\text{-}day28}$) values were 27.8±20.5 mcg•day/mL and 111±64.4 mcg•day/mL for 140 and 210 mg, respectively; and the mean (±SD) apparent clearance (CL/F) was 14±23 L/day and 3.0±3.5 L/day for 140 and 210 mg, respectively.

  Following multiple subcutaneous doses of 140 mg or 210 mg every 2 weeks (Q2W), the mean (±SD) peak serum concentrations (C_{max}) at steady-state were 7.2±6.5 mcg/mL and 20.6±14.6 mcg/mL for 140 and 210 mg, respectively, observed 3 days post-dose. The mean (±SD) AUC_{tau} over the two-week dosing interval were 81.4±77.4 mcg•day/mL and 227±167 mcg•day/mL for 140 and 210 mg, respectively.
- *Intrinsic factors*: Age, sex, or race did not significantly influence the PK of brodalumab. On the other hand, brodalumab clearance and volume of distribution increase as body weight increases.

Drug interactions

- *CYP3A4 substrates*: In subjects with plaque psoriasis, one week following a single subcutaneous administration of 210 mg brodalumab, the exposure of midazolam (CYP3A4 substrate) was increased by 24% over baseline administration. One hypothesis to explain the increased midazolam exposure is that brodalumab treatment increased serum levels of cytokines which could inhibit the expression and/or activity of CYP enzymes. We note that the effect of peak brodalumab concentration occurring 3 days postdose has not been evaluated.
- *Substrates of other CYP450 isozyme:* Clinical studies have not been conducted.

Immunogenicity

- Following up to 52 weeks of treatment, 2.7% (120/4447) of subjects with psoriasis developed brodalumab treatment-emergent ADA across seven clinical trials; and 2.1% (86/4058) of subjects developed brodalumab treatment-emergent ADA in Phase 3 trials.
- Of the subjects who developed ADA, none (0%) were classified as positive for neutralizing antibodies. However, the incidence of neutralizing antibodies development could be underestimated because the assay to test for neutralizing antibodies has limitations in detecting neutralizing antibodies in the presence of brodalumab.
- At Week 52, a trend of numerically lower sPGA response rates was observed in ADA positive subjects when compared to ADA negative subjects in Phase 3 trials. However, brodalumab trough concentrations in ADA positive subjects appear to fall within the range of those observed in study 20120102. Note that the variability of brodalumab trough concentrations is large which may be attributable to the PK nonlinearity.

While a definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the large variability in brodalumab trough concentrations and a small number of subjects who developed ADA in psoriasis clinical trials, whether the numerically lower response rate in ADA positive subjects observed at Week 52 will continue to decrease after a longer term treatment remains to be evaluated.

Biopharmaceutics: PK comparability between the "to-be-marketed" and Phase 3 presentations

- The PK comparability between the to-be-marketed presentation [one injection with 1.5 mL PFS] and the Phase 3 presentations [2 injections with 1.0 mL PFS + 0.5 mL PFS] has been demonstrated in Study 20130307. The results showed that the point estimates [90% confidence interval] for geometric mean ratio of C_{max} and AUC_{last} were within the [0.8, 1.25] acceptance limit of the bioequivalence (BE) criteria.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The Applicant's proposed dosing regimen (210 mg at Weeks 0, 1, 2, followed by Q2W dosing) of brodalumab for the treatment of psoriasis is supported by efficacy data in three pivotal Phase 3 clinical trials: 20120102, 20120103, and 20120104.

The Phase 3 trials evaluated two brodalumab dosing regimens: 140 mg and 210 mg administered at Weeks 0, 1, and 2 followed by every 2 weeks (Q2W) dosing. Both brodalumab 210 mg Q2W and

140 mg Q2W achieved significantly higher response rates compared to placebo in each of the three Phase 3 trials. The brodalumab 210 mg Q2W also achieved significantly higher response rates than 140 mg Q2W both in the initial 12-week treatment period and in the maintenance treatment period up to 52 weeks.

2.2.2 Therapeutic individualization

No therapeutic individualization will be recommended. Although body weight was identified as a significant covariate that impacted brodalumab exposure and body weight also showed an effect on efficacy, alternative dosing regimens adjusting for body weight is not recommended based on the available data (*See section 3.3.3*)

2.3 Outstanding Issues

The safety data from all brodalumab clinical trials included a total of 6 completed suicides in (4 subjects with psoriasis, 1 subject with rheumatoid arthritis, and 1 subject with psoriatic arthritis). Long-term safety data related to suicidal ideation and behavior (SIB) in subjects with psoriasis are not available at this time because of the early termination of psoriasis trials by the IND Sponsor. All 4 psoriasis subjects who completed suicide were male with body weight ranging from 55 kg to 112 kg, and all received 210 mg Q2W dosing for various durations. The four suicide events occurred at a time ranging from approximately 13 to 120 weeks after the subjects began their brodalumab treatment at 210 mg dose and at 14-58 days after the subjects received their last 210 mg dose of brodalumab.

Because the serum brodalumab concentrations at the exact time when the suicide events occurred are unknown, it is not feasible to evaluate whether there is any potential relationship between the systemic brodalumab exposure and the completed suicide. Nonetheless, the brodalumab concentrations in these subjects at the time of event are likely to vary widely given the time after the last brodalumab dose spanned a large range (14-58 days). Additionally, the available PK data up to Week 52 of the Phase 3 trials showed that the brodalumab exposure in these 4 subjects were not remarkable, i.e., they were not among the highest in the study population (*See section 3.3.7*). Therefore, it is unlikely that the suicidal events could be attributable to high brodalumab exposure in these 4 subjects either throughout the study or at the time of event.

With respect to brodalumab PD effects in subjects with moderate to severe plaque psoriasis, serum levels of IL-17A were higher after receiving brodalumab treatment compared to the pre-treatment levels, which is consistent with the mechanism of action for brodalumab. When brodalumab engages the target IL-17RA, IL-17A binding to IL-17RA and presumably the subsequent receptor-mediated elimination of IL-17A could not occur; resulting in an increase in IL-17A levels. It is biologically plausible that brodalumab treatment may cause SIB due to cytokine regulations because immune dysregulation may have implications in psychiatric disorders. Upon close examination of data in Study 20120102, the serum IL-17A levels during the 52 weeks treatment period in three subjects who experienced SIB (including 1 completed suicide) were not among the highest of IL-17 levels (*See section 3.3.7*) and the changes in IL-17A level from baseline are not among the largest. The remaining three psoriasis subjects who completed suicide had no available data for the serum IL-17A concentrations. As such, the limited available clinical data did not suggest a direct correlation between brodalumab treatment-induced up-regulation of serum IL-17A levels and the SIB events.

Limited available data in the clinical development program do not provide insights into the relationship between brodalumab PK, PD, and suicide, especially given the variation in the time course of suicide events both in terms of the duration on brodalumab treatment and the time after the last brodalumab dose. Nonetheless, we cannot completely rule out that brodalumab has an effect on SIB through cytokine regulation. Therefore, we recommend the use of product labeling to communicate this potential risk.

2.4 Summary of Labeling Recommendations

If an approval action is taken, the Office of Clinical Pharmacology recommends inclusion of the following concepts in the respective section of the final product labeling for SILIQ:

- *Section 5:* In the clinical trials, 4 subjects with psoriasis and 2 subjects with other disease conditions completed suicide. A direct correlation between brodalumab treatment and suicidal ideation or suicide completion could not be established; however, immune dysregulation has been reported to have implications in psychiatric disorders.
- *Section 7 Drug Interactions*: Upon initiation or discontinuation of SILIQ 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.
- *Section 12.2 Pharmacodynamics:* Brodalumab treatment resulted in an increase of serum IL-17A levels in subjects with psoriasis.
- *Section 12.3 Pharmacokinetics:* Co-administration of brodalumab increased the exposure of midazolam (a CYP3A4 substrate) in subjects with psoriasis. Clinical studies evaluating drug interaction with substrates of other CYP450 isozyme have not been conducted.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Currently approved biologic products for the treatment of psoriasis

Currently, six biologic products have been approved for the treatment of adult patients with moderate to severe psoriasis, as summarized in the Table below.

Table 3.1. Approved biologic products for the treatment of adult patients with moderate to severe plaque psoriasis. IL, interleukin; RA, rheumatoid arthritis; TNF, tumor necrosis factor. (*Data source: Drugs@FDA*)

Product	Drug class or MOA	Approval date for the psoriasis indication (Initial US approval date, indication)
ENBREL (Etanercept)	TNFα-blocker	2004 (1998, RA)
REMICADE (Infliximab)	TNFα-blocker	2006 (1998, Crohn's disease)
HUMIRA (Adalimumab)	TNFα-blocker	2008 (2002, RA)
STELARA (Ustekinumab)	IL-12 and -23 antagonist	2009 (2009, psoriasis)
COSENTYX (Secukinumab)	IL-17A antagonist	2015 (2015, psoriasis)
TALTZ (Ixekizumab)	IL-17A antagonist	2016 (2016, psoriasis)

Current application

The Applicant submitted original BLA 761,032 for SILIQ (brodalumab, also known as AMG 827), an interleukin-17 receptor A (IL-17RA) antagonist, for the treatment of moderate to severe psoriasis.

- *Proposed indication:* For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
- *Proposed dosing regimens*: 210 mg administered by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks (Q2W).
- *Proposed brodalumab dosage forms/presentations:* Single-use prefilled syringe: 210 mg of brodalumab in 1.5 mL solution (140 mg/mL).

Clinical and clinical pharmacology program in the submission

The brodalumab psoriasis development program included 12 studies providing clinical and clinical pharmacology data as the primary support of the proposed indication:

- Seven Phase 1 PK/PD studies in healthy subjects and subjects with psoriasis:
  - Two PK studies in healthy subjects (20060279 and 20120337),
  - One intrinsic factor PK/PD study in healthy subjects and subjects with psoriasis (KHK4827-001)
  - One extrinsic factor PK study in subjects with psoriasis (20110184)
  - One PK device performance study (20110106)
  - Two PK comparability studies in healthy subjects (20090480 and 20130307)
- Two Phase 2 dose ranging studies in subjects with psoriasis
  - One dose ranging study in subjects with psoriasis (20090062)
  - One dose ranging study in Japanese subjects with psoriasis (KHK4827-002)
- Three Phase 3 efficacy/safety pivotal trials in subjects with psoriasis
  - One placebo-controlled study (20120102)
  - Two active comparator-controlled and placebo-controlled studies (20120103 and 20120104)

3.2 General Pharmacological and Pharmacokinetic Characteristics

Brodalumab is a human monoclonal IG2κ antibody that binds to interleukin-17 receptor A (IL-17RA). Brodalumab consists of two heavy chains (442 amino acids each) and two light chains (214 amino acids each) and has a molecular weight of 144 kDa.

Elevated levels of IL-17A are found in psoriatic plaques and IL-17A antagonists have been shown effective in the treatment of adult patients with moderate to severe psoriasis. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis. Blocking IL-17RA prevents its interaction with IL-17A. Because IL-17RA is a component of the heterodimer receptor for several cytokines, brodalumab inhibits the biological activities of IL-17A, IL-17F, IL-17A/F heterodimer, IL-25 (also known as IL-17E), and IL-17C.

General PK properties

- *Bioavailability:* Following subcutaneous administration, the estimated brodalumab bioavailability was approximately 55% based on population PK modeling.
- *PK non-linearity*: Following subcutaneous administrations, brodalumab exhibited non-linear PK with exposures that increased greater than dose-proportionally over a dose range from 140 mg to 350 mg in subjects with plaque psoriasis and from 70 mg to 420 mg in healthy subjects across clinical studies.

Single dose PK

Brodalumab PK parameters following a single subcutaneous dose of 140 mg or 210 mg in subjects with plaque psoriasis are summarized in Table 3.2.a. Brodalumab reached peak mean (±SD) serum concentration (C_{max}) of 4.8±2.8 mcg/mL and 13.4±7.3 mcg/mL for 140 and 210 mg, respectively, by approximately 3 days post dose. The mean (±SD) area-under-the-concentration-time curve ($AUC_{0\text{-day}28}$) was 27.8±20.5 day•mcg /mL and 111±64.4 day•mcg /mL for 140 and 210 mg, respectively.

**Table 3.2.a. Brodalumab PK parameters following a single SC administration of 140 mg and 210 mg in subjects with moderate to severe plaque psoriasis (Study 20110184). ***Tmax was reported as median value; $^{\#}AUC_{last}$ represents $AUC_{0\text{-day}28}$. (*Data source: Table 7, Summary of Clinical Pharmacology*)

Dose		C_{max} (mcg/mL)	T_{max} (day)	AUC_{last} (day•mcg /mL)	AUC_{inf} (day•mcg /mL)	CL/F (mL/hr)	Vz/F (L)
210 mg	n	19	19	19	18	18	18
	Mean±SD	13.4±7.3	3*	111±64.4$^{\#}$	119±66.6	123±144	8.9±9.4
140 mg	n	9	9	9	4	4	4
	Mean±SD	4.8±2.8	3*	27.8±20.5$^{\#}$	40.5±25.3	588±955	26.6±42.9

Multiple doses PK

Brodalumab PK parameters following multiple subcutaneous doses of 140 mg Q2W or 210 mg Q2W are summarized in Table 3.2.b for three Phase 3 trials in subjects with plaque psoriasis. In Study 20120103, for example, the mean (±SD) peak serum concentrations (C_{max}) at steady-state were 7.2±6.5 mcg/mL and 20.6±14.6 mcg for 140 and 210 mg, respectively; and the mean (±SD) AUC over the two-week dosing interval was 81.4±77.4 mcg•day/mL and 227±167 mcg•day/mL for 140 and 210 mg, respectively. PK data are consistent across all three studies.

Table 3.2.b. Brodalumab PK parameters following SC administrations of 140 mg Q2W and 210 mg Q2W dosing regimens in subjects with moderate to severe plaque psoriasis in Phase 3 Trials. Brodalumab was administered at Week 0, 1, 2 followed by Q2W dosing in each of the Phase 3 trials. Brodalumab serum concentrations were assessed in Phase 3 PK substudy at Week 10 (trough), Week 10+ 3 days, Week 10+ 7 days, Week 10 +10 days and Week 12 (trough) following a dose administration at Week 10. AUC_{tau} is the AUC during the dosing interval of 2 Weeks between Week 10 and Week 12. *****T_{max} was reported as median value. (*Data source: Table 14-16, Summary of Clinical Pharmacology*)

Dosing regimen	Studies		C_{max} (mcg/mL)	T_{max} (day)	AUC_{tau} (day•mcg /mL)
210 mg Q2W	20120102	n	32	32	22
		Mean±SD	18.8±18.7	3*	243±234
	20120103	n	91	91	63
		Mean±SD	20.6±14.6	4*	227±167

	20120104	n	71	71	51
		Mean±SD	22.1±19.1	4*	221±204
140 mg Q2W	20120102	n	33	33	22
		Mean±SD	7.64±5.36	3*	75.5±52.2
	20120103	n	90	87	45
		Mean±SD	7.22±6.54	3*	81.4±77.4
	20120104	n	72	70	40
		Mean±SD	8.03±5.55	3*	86.4±69.0

Intrinsic factors:

- *Body weight*: Brodalumab serum concentrations decrease as the body weight increases. Figure 3.2.a below shows that, in psoriasis Phase 3 trials, brodalumab trough concentrations at Week 12 decreases as body weight increases. See *section 3.3.3* for more information regarding the impact of body weight on PK and efficacy.
- *Age, sex or race*: Age, sex or race did not significantly influence brodalumab PK in subjects with plaque psoriasis. In psoriasis Phase 3 trials, age, sex or race did not show significant impact on Week 12 trough serum brodalumab concentrations (Figure 3.2.b-d).

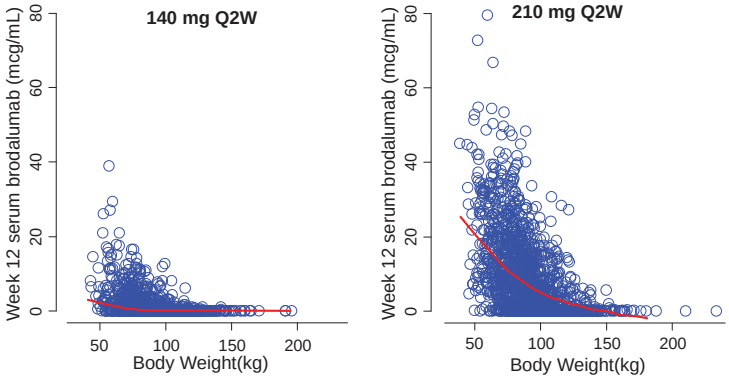


Figure 3.2.a. Effect of body weight on observed Week 12 brodalumab trough concentrations in subjects with plaque psoriasis for the 140 mg and 210 Q2W dosing regimens. (*Data source: Reviewer's plot using the meta-bromab-comb-16jan2015.xpt dataset*)

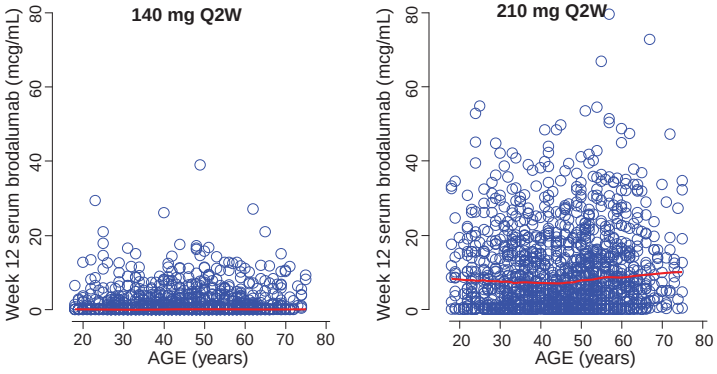


Figure 3.2.b. Effect of age on brodalumab Week 12 trough concentrations in subjects with plaque psoriasis treated with the 140 mg (left) and 210 Q2W (right) dosing regimens. (*Data source: Reviewer's plot using the meta-bromab-comb-16jan2015.xpt dataset*)

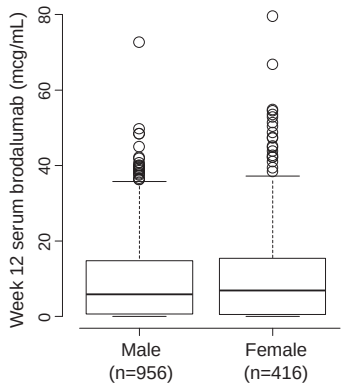


Figure 3.2.c. Effect of sex on brodalumab Week 12 trough concentrations in subjects with plaque psoriasis treated with the 210 Q2W dosing regimen. (*Data source: Reviewer's plot using the meta-bromab-comb-16jan2015.xpt dataset*)

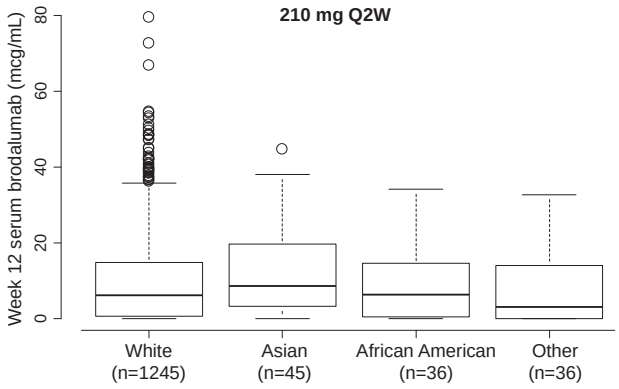


Figure 3.2.d. Effect of race on brodalumab Week 12 trough concentrations in subjects with plaque psoriasis treated with the210 Q2W dosing regimen. (*Data source: Reviewer's plot using the meta-bromab-comb-16jan2015.xpt dataset*)

Population PK analysis results

A 2-compartment model with a linear (first order) and a saturable (Michaelis-Menten) route of elimination was used to describe brodalumab PK (*See Appendix 4.2 for details*). The population PK analysis results showed the following PK properties of brodalumab in subjects with plaque psoriasis:

- In a typical individual, the linear clearance was 0.211 L/day and the steady-state volume of distribution (Vss = V1 + V2) was approximately 7.24 L. The estimates of inter-individual variability (coefficient of variation) for CL, V1, and V2 were 49.1% CV, 13.3% CV, and 135% CV, respectively.
- The saturable route of elimination, presumed to be mediated by the target IL-17RA, plays a major role in the overall clearance of brodalumab. At saturation, the target-mediated clearance is a zero-order process with an estimated value of 4.82 L/day, reflecting the kinetics described by Michaelis-Menten equation, Vmax*C/(Km+C), and when Km <<C. The inter-subject variability for Vmax or Km has not been assessed.
- Following SC administration the absolute bioavailability was estimated to be approximately 55%.
- The time to maximum serum concentration was approximately 3 days following a SC administration.
- Body weight was a significant covariate of clearance and volume parameters.
- Baseline PASI score was a significant covariate of the maximal saturable elimination rate.
- Age, sex or race was not a significant covariate on brodalumab PK.
- According to the population PK model-based simulations, serum brodalumab concentrations in 95% of subjects would drop below the assay quantification limit (BQL of 50 ng/mL) 32 days after discontinuation of brodalumab 140 mg Q2W treatment and 63 days after discontinuation of brodalumab 210 mg Q2W treatment.

Specific population

- *Renal impairment:* No formal studies were conducted in subjects with renal impairment. Brodalumab is a human monoclonal IgG2 with molecular size of approximately144 kDa; therefore, it is unlikely for intact brodalumab to be filtered by kidney or excreted in urine.
- *Hepatic impairment*: No formal studies were conducted in subjects with hepatic impairment. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of IgG antibodies such as brodalumab.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The overall Phase 3 efficacy results have clearly demonstrated that brodalumab is effective for the treatment of adult patients with moderate to severe psoriasis. The dose- and exposure-response relationships for efficacy (e.g., achieving sPGA [0,1] response at Week 12) have provided supportive evidence of effectiveness.

Phase 3 trial design

The efficacy of brodalumab is supported primarily by three Phase 3 trials (20120102, 20120103 and 20120104). Key design elements and dosage information of the Phase 3 trials are summarizes in the Table below (Table 3.3.1.a). *See Clinical Pharmacology filing review for a complete list of clinical studies in the BLA.*

Table 3.3.1.a. Summary of study design of Phase 3 trials. N, number of subjects randomized. (*Data source: Table 4 and Table 5, Summary of Clinical Efficacy*)

	Study 20120102	**Study 20120103**	**Study 20120104**
Design	Randomized, double-blind, placebo-controlled, 12-week induction followed by randomized withdrawal and retreatment.	Randomized, double-blind, double-dummy, placebo- and active (ustekinumab)-controlled 12-week induction followed by randomized maintenance.	Randomized, double-blind, double-dummy, placebo- and active (ustekinumab)-controlled 12-week induction followed by randomized maintenance.
N	661	1831	1881
Initial treatment period (12 weeks)	– 210 mg Q2W – 140 mg Q2W – Placebo	– 210 mg Q2W – 140 mg Q2W – Placebo – ustekinumab	– 210 mg Q2W – 140 mg Q2W – Placebo – ustekinumab
Withdrawal/ retreatment (up to 40 weeks)	Responder re-randomization at Week 12: – 210 mg Q2W or placebo – 140 mg Q2W or placebo Retreatment upon return of disease	n/a	n/a
Maintenance treatment period (up to 40 weeks)	n/a	– 210 mg Q2W – 140 mg Q2W – 140 mg Q4W – 140 mg Q8W – ustekinumab	– 210 mg Q2W – 140 mg Q2W – 140 mg Q4W – 140 mg Q8W – Ustekinumab

Efficacy endpoints

The Phase 3 trials used two endpoints for the primary efficacy evaluation: the Psoriasis Area and Severity Index (PASI) and the Static Physician's Global Assessment (sPGA). Specific endpoints for efficacy assessments are summarized in Table 3.3.1.b.

Table 3.3.1.b. Summary of efficacy endpoints used in brodalumab Phase 3 psoriasis clinical trials and the planned comparisons. (*Data source: Clinical Overview, Table 1*)

Week	Endpoints	Study 20120102	Study 20120103 & Study 20120104
12	*PASI 75 and sPGA (0,1)*	Primary endpoints for – 210 mg Q2W vs placebo – 140 mg Q2W vs placebo	Primary endpoints for – 210 mg Q2W vs placebo – 140 mg Q2W vs placebo
12	*PASI 100*	key secondary endpoint – 210 mg Q2W vs placebo – 140 mg Q2W vs placebo	Primary endpoint for – 210 mg Q2W vs ustekinumab – Weight-based (140 mg Q2W for subjects ≤100 kg and 210 mg Q2W for subjects >100 kg) vs ustekinumab
52	*sPGA (0/1)*	– 210 mg Q2W vs placebo – 140 mg Q2W vs placebo	Among brodalumab 210 mg Q2W, 140 mg Q2W, 140 mg Q4W, 140 mg Q8W, and ustekinumab

Primary efficacy results (initial 12-week treatment period)

The efficacy data in Phase 3 trials 20120102, 20120103 and 20120104 are tabulated in Table 3.3.1.c and summarized as follows:

- Both brodalumab 210 mg Q2W and 140 mg Q2W achieved significantly higher response rates for both co-primary efficacy endpoints compared to placebo ($p<0.001$).
- Brodalumab 210 mg Q2W achieved significantly higher response rates than 140 mg Q2W ($p<0.001$).
- Brodalumab 210 mg showed superior efficacy to ustekinumab ($p<0.001$).

Table 3.3.1.c. Summary of efficacy results for PASI 75, PASI 100 and sPGA (0,1) response rates at Week 12 by Phase 3 Trials. In the initial 12-week treatment period, subjects were randomized to a treatment group as summarized in Table 3.3.1.a. (*Data source: Figures 5, 6, 8, Clinical Overview*)

Phase 3 Trials	Efficacy Endpoints	Response rate (%) or N			
		Placebo	Ustekinumab	Brodalumab 140 mg	Brodalumab 210 mg
20120102	N	220	--	219	222
	PASI 75	2.7%	--	60.3%	83.3%
	PASI 100	0.5%	--	23.3%	41.9%
	sPGA (0/1)	1.4%	--	53.9%	75.7%
20120103	N	309	300	610	612
	PASI 75	8.1%	70.0%	66.6%	86.3%
	PASI 100	0.6%	21.7%	25.7%	44.4%
	sPGA (0/1)	3.9%	61.0%	58.0%	78.6%
20120104	N	315	313	629	624
	PASI 75	6.0%	69.3%	69.2%	85.1%
	PASI 100	0.3%	18.5%	27.0%	36.7%
	sPGA (0/1)	4.1%	57.2%	59.9%	79.6%

Exposure-response for sPGA (0,1) response at Week 12

The Week 12 efficacy data demonstrated an exposure-response (E-R) relationship, specifically between observed brodalumab concentrations at Week 12 and sPGA (0,1) response rates (Figure 3.3.1.a). See *section 4.3* for additional E-R analysis results. The E-R relationship shows the following:

- Approximately 44% of subjects who did not have measurable brodalumab concentrations at Week 12 were able to achieve sPGA (0,1) response.
- In subjects with measurable Week 12 trough serum brodalumab concentrations, subjects who had trough concentrations in the highest tertile had approximately 13% higher response rates than subjects who have trough concentrations in the lowest tertile (93% vs. 80%).
- The response rates in the top two tertiles ([2.5-9.9 mcg/mL] vs. [9.9-79.5 mcg/mL]) differ by <5% suggesting that a near-maximal effect has been achieved when brodalumab trough concentrations are above 2.5 mcg/mL.

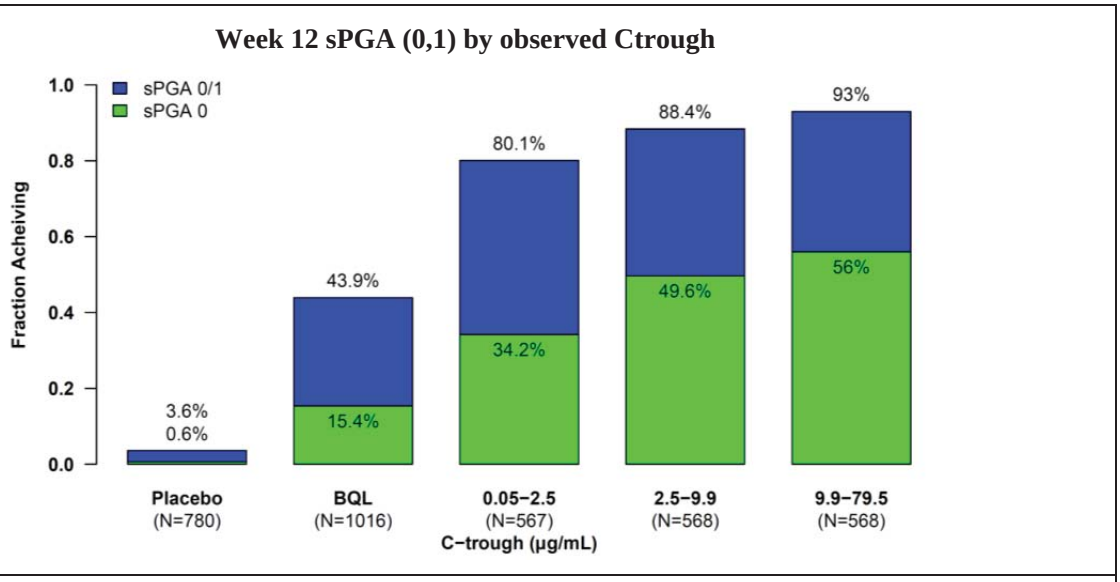


Figure 3.3.1.a. Exposure-response for achieving sPGA (0,1) and sPGA 0 at Week 12 by observed serum brodalumab trough concentrations (C_{trough}). (*Data source: Figure 30, Summary of Clinical Pharmacology; Similar E-R relationships were found for between sPGA (0,1) and predicted AUC values, Appendix 2, Response to FDA IR, 02 February 2016*)

Phase 2 dose-ranging results supporting Phase 3 dose selection

The Phase 2 dose ranging Study 20090062 evaluated doses of 70, 140 and 210 mg Q2W and 280 mg Q4W. All dose levels demonstrated statistically and clinically significant efficacy ($p < 0.0001$) based on the percent improvement from baseline in PASI score at Week 12, with 45.0%, 85.9%, 86.3%, and 76.0% improvement in 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively, compared to 16.0% in the placebo group (*See Appendix 4.3.1 and 4*.5.7).

Observed and model predicted dose-response showed that 140 and 210 mg Q2W resulted in near maximal %PASI improvement for lighter weight subjects and 210 mg Q2W achieved greater %PASI improvement than with 140 mg Q2W in heavier weight subjects (Figure 3.3.1.b). Based on these results, the Applicant selected 140 mg and 210 mg Q2W dosing regimens in Phase 3 trials.

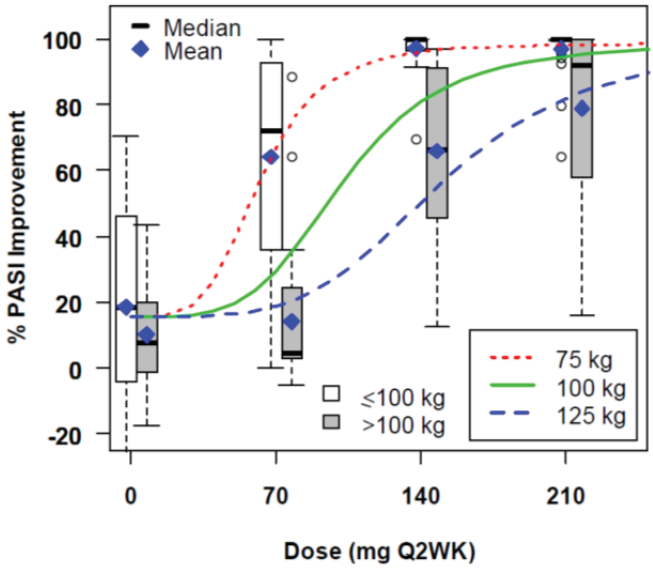


Figure 3.3.1.b. Observed and model predicted dose-response for percent PASI improvement at Week 12 in the Phase 2 dose ranging study 20090062. (*Data source: Figure 17, Summary of Clinical Pharmacology*)

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

Yes, the proposed dosing regimen, 210 mg administered by subcutaneous (SC) injection at Weeks 0, 1, and 2 followed by 210 mg Q2W, is appropriate. The supporting evidence includes primary efficacy results at Week 12, the efficacy results at Week 52, and the exposure-response for safety in three Phase 3 trials, which are summarized below.

Primary efficacy data at Week 12 (three Phase 3 trials)

As described in *section 3.3.1*, the brodalumab 210 mg Q2W achieved significantly higher response rates than 140 mg Q2W in the initial 12-week treatment period in all three Phase 3 trials.

Efficacy at Week 52

- **Trials 20120103 and 20120104**

Among subjects re-randomized to 1 of the 4 brodalumab treatment arms at Week 12 in Studies 20120103 and 20120104, the Week 52, efficacy results (summarized in Figure 3.3.2.a) showed that:

- Brodalumab 210 mg Q2W treatment group achieved the highest sPGA (0,1) response rates (62.6% in Study 20120103 and 60.8% in Study 20120104).
- Brodalumab 140 mg Q2W and ustekinumab treatment groups achieved similar sPGA (0,1) response rates at Week 52. Brodalumab 140 mg Q2W treatment group had a response rate of 42.7% in 20120103 and 44.9% in Study 20120104 and ustekinumab treatment group had a response rate of 44.6% in 20120103 and 45.8% in Study 20120104.
- Brodalumab 140 mg Q4W or Q8W dosing regimen achieved only 5-15% sPGA (0,1) response rates across the treatment arms and studies.

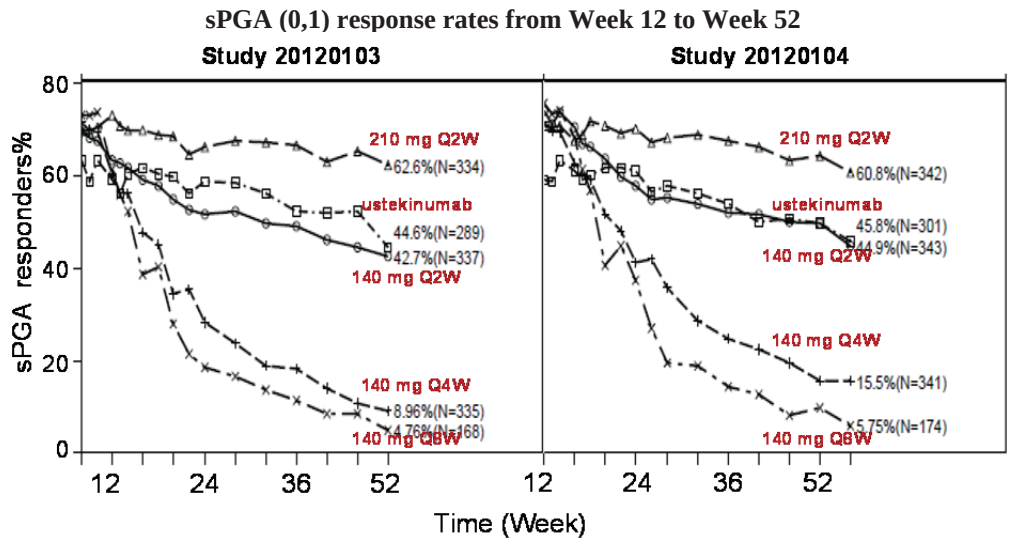


Figure 3.3.2.a. sPGA (0,1) responses rates by treatments arms in Phase 3 trials 20120103 and 20120104. In both studies, at the week 12 visit, subjects originally randomized to the brodalumab arms were re-randomized (2:2:2:1) into the maintenance phase to receive brodalumab 210 mg Q2W, 140 mg Q2W, 140 mg Q4W, or 140 mg Q8W. Subjects originally randomized to ustekinumab continued to receive ustekinumab and those originally randomized to receive placebo received brodalumab 210 mg Q2W. Subjects who did not attend their week 12 visit did not receive any further investigational product. (*Data source: Figure 9, Clinical Overview*)

- **Trial 20120102**

In Study 20120102, the 210 mg Q2W dosing regimen showed better maintenance of clinical response compared to the 140 mg Q2W dosing regimen. Among subjects who achieved the sPGA (0,1) response at Week 12 and continued the treatment with the same dosing regimen, 83.1% of subjects maintained sPGA success (0 or 1) at Week 52 for the 210 mg Q2W dosing regimen, comparing to the 70.2% for the 140 mg Q2W dosing regimen (Figure 3.3.2.b).

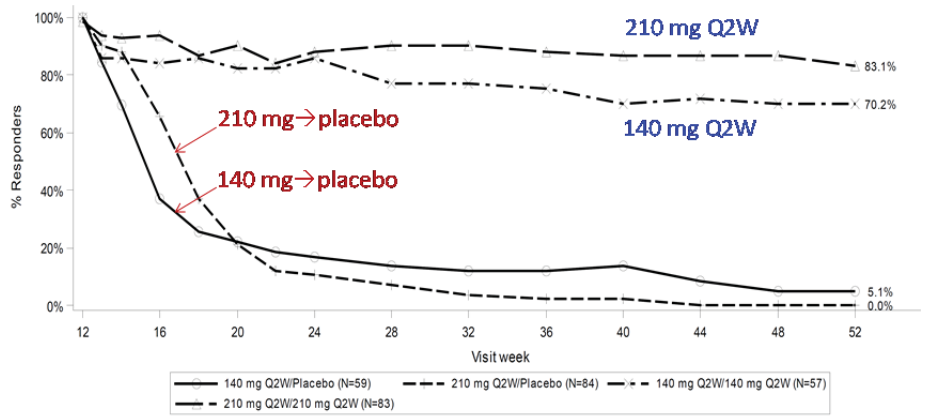


Figure 3.3.2.b. Percentage of subjects (responders at Week 12) who maintained sPGA (0,1) responses in withdrawal phase of Phase 3 Study 20120102. (*Data source: Figure 22, Summary of clinical efficacy***)**

Exposure-response for safety

The exploratory analysis results for E-R relationship on safety between brodalumab serum trough concentrations and treatment-emergent infections and infestations showed the following:

- In the initial 12-week treatment period there was no apparent trend of increased safety incidences (e.g., all infections and infestations) with increased brodalumab exposure (Table 3.3.2.a).
- In the treatment period through Week 52 there was no apparent trend of increased infections and infestations with increased brodalumab exposure in the completer population (subjects with week 52 visit). A trend of increased viral infection incidences were observed with increasing brodalumab exposure; however, only 1 subject (with brodalumab concentration <BQL) experienced Grade ≥3 viral infection (Table 3.3.2.b).
- Similar analysis was conducted with inclusion of subjects who did not have Week 52 visit and the response was quantified as exposure-adjusted event rates (Table 3.3.2.c). The analysis showed that there were numerically higher event rates for all infections and infestations and viral infections in the highest exposure subgroup as compared to any of the lower exposure subgroups; however, such relationship was not seen for serious infections, candida infections or Grade ≥ 3 viral infections category.

Table 3.3.2.a. Exposure-response for incidences of treatment-emergent infections and infestations adverse events in the initial 12-week treatment period by Week 12 trough concentration groups in subjects exposed to brodalumab 140 mg Q2W or 210 mg Q2W in Phase 3 psoriasis trials. N, subjects in Studies 20120102, 20120103, 20120104 with > 1 dose of brodalumab 140 mg Q2W or 210 mg Q2W during induction phase who have serum brodalumab concentration at Week 12; n, number of subjects reporting ≥ 1 occurrence of an adverse event through Week 12; % = n/N * 100. (*Data source: Table 20, Summary of Clinical Pharmacology*)

	Week 12 Brodalumab Trough Concentration Range (µg/ml)				
	Group 1 BQL(< 0.05) (N = 1016) n (%)	Group 2 ≥ 0.05 and < 2.48 (N = 568) n (%)	Group 3 ≥ 2.48 and < 9.88 (N = 568) n (%)	Group 4 ≥ 9.88 (N = 569) n (%)	All (N = 2721) n (%)
All Infections and infestations	252 (24.8)	159 (28.0)	136 (23.9)	146 (25.7)	693 (25.5)
Serious Infections	10 (1.0)	1 (0.2)	1 (0.2)	0 (0.0)	12 (0.4)
Candida Infections	2 (0.2)	8 (1.4)	4 (0.7)	6 (1.1)	20 (0.7)
Grade ≥ 3 Candida Infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral Infections	30 (3.0)	18 (3.2)	31 (5.5)	23 (4.0)	102 (3.7)
Grade ≥ 3 Viral Infections	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)

Table 3.3.2.b. Exposure-response for incidences of treatment-emergent infections and infestations adverse events through Week 52 by Week 12 trough concentration groups in subjects exposed to brodalumab 140 mg Q2W or 210 mg Q2W in Phase 3 psoriasis trials. N, subjects in Studies 20120102, 20120103, 20120104 exposed to constant brodalumab 140 mg Q2W or 210 mg Q2W and completed Week 52 visit who have serum brodalumab concentration at Week 12; n, number of subjects reporting ≥ 1 occurrence of an adverse event through Week 52; % = n/N * 100. (*Data source: Table 21, Summary of Clinical Pharmacology*)

	Week 12 Brodalumab Trough Concentration Range (µg/ml)				
	Group 1 BQL (< 0.05) (N=141) n(%)	Group 2 ≥0.05 and < 3.2 (N=155) n(%)	Group 3 ≥ 3.2 and < 10.3 (N=155) n(%)	Group 4 ≥10.3 (N=157) n(%)	All (N=608) n(%)
All Infections and infestations	85 (60.28)	88 (56.77)	94 (60.65)	96 (61.15)	363 (59.7)
Serious Infections	5 (3.55)	1 (0.65)	1 (0.65)	1 (0.64)	8 (1.32)
Candida Infections	1 (0.71)	5 (3.23)	8 (5.16)	4 (2.55)	18 (2.96)
Grade ≥3 Candida Infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral Infections	14 (9.93)	14 (9.03)	16 (10.32)	22 (14.01)	66 (10.86)
Grade ≥3 Viral Infections	1 (0.71)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.16)

Table 3.3.2.c. Exposure-response for exposure-adjusted event rates of treatment-emergent infections and infestations adverse events through Week 52 by Week 12 trough concentration groups in subjects exposed to constant brodalumab 140 mg Q2W or 210 mg Q2W in Phase 3 psoriasis trials. N, subjects in Studies 20120102, 20120103, 20120104 exposed to constant brodalumab 140 mg Q2W or 210 mg Q2W who have serum brodalumab concentration at Week 12; n, number of adverse events through Week 52; r = exposure-adjusted event rate per 100 subject-years (n/subj-yr*100); Subj-yr = Total subject years of exposure through Week 52. (*Data source: Table 5-3.1, Response to FDA IR, 02 February 2016*)

	Week 12 Brodalumab Trough Concentration Range (ug/ml)				
	Group 1 BQL (< 0.05) (Subj-yr=155.5) (N=175) n (r)	Group 2 >0.05 and <3.08 (Subj-yr=156.6) (N=162) n (r)	Group 3 >3.08 and < 10.3 (Subj-yr=159.6) (N=163) n (r)	Group 4 >10.3 (Subj-yr=159.1) (N=167) n (r)	All (Subj-yr=630.9) (N=667) n (r)
All Infections and infestations	172 (110.61)	170 (108.56)	178 (111.53)	218 (137.02)	738 (116.98)
Serious Infections	7 (4.5)	2 (1.28)	1 (0.63)	1 (0.63)	11 (1.74)
Candida Infections	1 (0.64)	7 (4.47)	9 (5.64)	4 (2.51)	21 (3.33)
Grade ≥3 Candida Infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral Infections	16 (10.29)	16 (10.22)	17 (10.65)	33 (20.74)	82 (13)
Grade ≥3 Viral Infections	1 (0.64)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.16)

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

Body weight was identified as a significant covariate affecting brodalumab exposure in subjects with psoriasis and body weight also showed an effect on efficacy. However, alternative dosing regimens adjusting for body weight is not recommended based on the following analysis results and considerations:

- The 210 mg dose consistently achieved greater PASI 75, PASI 90, PASI 100, sPGA (0,1) and sPGA (0) response rates at Week 12 than the 140 mg dose in subjects with body weight >70 kg (Table 3.3.3.a).
- For subjects with body weight ≤70 kg, the 210 mg dose achieved greater PASI 100 and sPGA (0) response rates at Week 12 than the 140 mg dose (Table 3.3.3.a). Therefore, using 70 kg as body weight cutoff for low body weight patients to receive the 140 mg dose will compromise clinical efficacy.
- The 210 mg dose achieved greater sPGA (0,1) response rates at Week 52 than the 140 mg dose in both body weight subgroups (>70 kg and ≤70 kg) (Table 3.3.3.b).
- The difference in the PASI75 response rates between 210 mg dose and 140 mg dose becomes larger when the body weight increases (Figure 3.3.3.a), which indicates that subgroup analyses using a body weight cutoff greater than 70 kg will also favor the 210 mg dose in each body weigh subgroup. The protocol predefined efficacy analyses using 100 kg as the cutoff indeed support that 210 mg dose is superior to 140 mg dose.
- To reduce the brodalumab dose to 140 mg in subjects with low body weight may not necessarily be associated with a lower risk for safety events like suicide or suicidal ideation and behavior because of the lack of direct correlation between brodalumab exposure and the safety events.

- As clinical response rate decreases with increasing body weight in subjects who received the 210 mg dose of brodalumab (Figure 3.3.3.a), we have also considered that a higher than 210 mg dose may allow subjects with high body weight (e.g., >130 kg) to achieve greater response rates; however, this approach is concerning because of the observation that the 4 subjects (weighing 55 to 112 kg) who completed suicide all received 210 mg for various durations although a direct correlation of the suicidal events to brodalumab exposure could not be established.

Table 3.3.3.a. Clinical response for different efficacy endpoints at Week 12 by body weight strata and treatment dose in pooled Studies 20120102, 20120103, and 20120104. NRI = non-responder imputation for binary missing data; % = n/N * 100 (*Data source: Table 32, summary of Clinical Efficacy*)

Efficacy endpoints	**Body weight ≤70 kg**		**Body weight >70 kg**	
	Brodalumab 140 mg Q2W (N=240)	**Brodalumab 210 mg Q2W (N=261)**	**Brodalumab 140 mg Q2W (N=1218)**	**Brodalumab 210 mg Q2W (N=1197)**
PASI 75 (NRI) – n (%)	217 (90.4%)	234 (89.7%)	756 (62.1%)	1010 (84.4%)
PASI 90 (NRI) – n(%)	196 (81.7%)	217 (83.1%)	525 (43.1%)	798 (66.7%)
PASI 100 (NRI) – n(%)	116 (48.3%)	144 (55.2%)	262 (21.5%)	450 (37.6%)
sPGA (0,1) – n(%)	206 (85.8%)	222 (85.1%)	643 (52.8%)	924 (77.2%)
sPGA (0) – n(%)	116 (48.3%)	145 (55.6%)	262 (21.5%)	451 (37.7%)

Table 3.3.3.b. Summary of efficacy results for sPGA (0,1) response rates at Week 52 by weight group and maintenance treatment dose in pooled Studies 20120103 and 20120104. Non-responder imputation (NRI) was done for binary missing data; % = n/N * 100 ; Subjects who achieved sPGA(0,1) response at Week 12 were re-randomized to different maintenance treatment groups. (*Data source: Reviewer's analysis*)

Body Weight Group	**% sPGA (0,1) Response rate (n/N)**	
	Brodalumab 140 mg Q2W (N=680)	**Brodalumab 210 mg Q2W (N=676)**
< 70 kg	**59.1%** (68/115)	**71.9%** (87/121)
≥ 70 kg	**40.7%** (230/565)	**59.5%** (330/555)

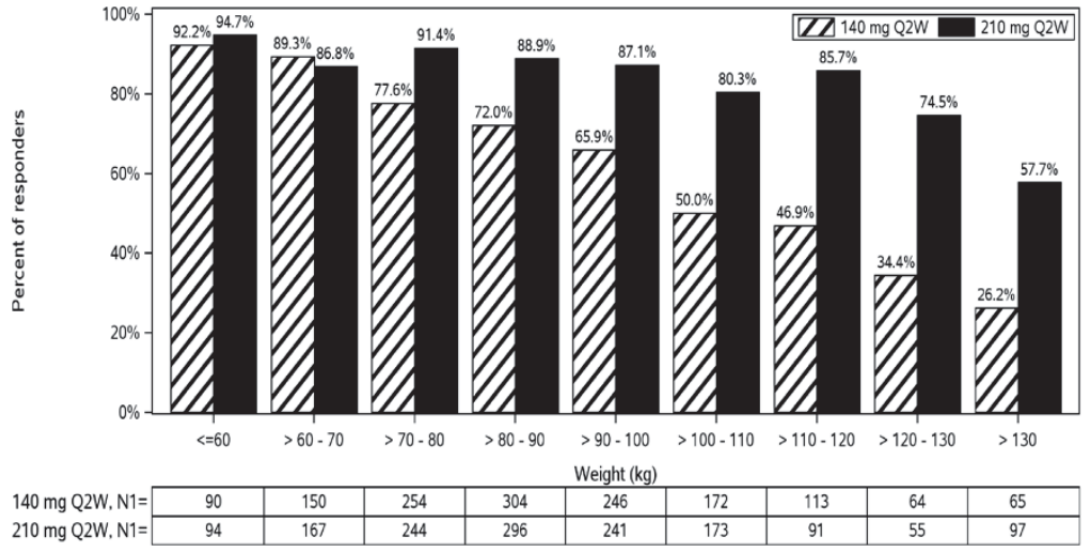


Figure 3.3.3.a. Summary of PASI 75 response at Week 12 by baseline body weight groups in pooled Phase 3 Trials 20120102, 20120103, and 20120104. (*Data source: Figure 33, summary of clinical efficacy.*)

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

Yes, the observed drug-drug interaction could be clinically relevant for CYP3A4 substrate drugs that have narrow therapeutic index. Specifically, the exposure (AUC_{inf}) of midazolam (CYP3A4 substrate) was increased by 24% in subjects with plaque psoriasis one week following a single subcutaneous administration of 210 mg brodalumab (Study 20110184). Note that the Tmax of brodalumab was 3 days after the SC administration. Given that only CYP3A4 isozyme was evaluated in the study, the effects of brodalumab treatment on other CYP isozymes are unknown.

As a general matter, inflammatory conditions often have elevated levels of proinflammatory cytokines which have been reported to suppress some CYP450 enzymes resulting in elevated CYP450 substrate exposures. Whereas effective treatments for inflammatory conditions are expected to reduce the level of proinflammatory cytokines, thereby indirectly modulate the CYP450 enzyme activity and decrease the exposure of CYP450 substrate (and potential loss of efficacy). As such, it would be prudent to consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate. The above general practice would be applicable to the use of brodalumab and its labeling. It is worth noting that the observed increase in midazolam exposure following brodalumab treatment was unexpected for an anti-inflammatory agent. The reason for the observed increase in midazolam AUC is unknown although the elevated IL-17A levels after brodalumab treatment may have implications.

Summary of the drug-drug interaction study data:

In Study 20110184 midazolam (2 mg, oral) was administered on Day 1 (prior to brodalumab dosing on Day 2) and on Day 9 (1 week after brodalumab dosing) to subjects with moderate to severe plaque psoriasis. Compared to Day 1 (prior to brodalumab administration), the midazolam PK results on Day 9 showed increases in the AUC_{last} by approximately 23%, in the AUC_{inf} by approximately 24%, and in the C_{max} by approximately 16%. The midazolam PK parameters pre- and post-administration of brodalumab are shown in Table 3.3.4.

Table 3.3.4. The midazolam PK parameters on Day 1 (prior to brodalumab administration) and Day 9 (1 week after brodalumab administration) in subjects with moderate-to-severe psoriasis in Study 20110184. Subjects with psoriasis received a 210 mg SC administration of brodalumab on Day 2 and received midazolam 2 mg (solution) oral administration on Day 1 and Day 9. Midazolam was administered after a 10-hour fast. Midazolam PK samples were collected on Day 1 and Day 9 at Predose and at the following time-points after each dose administration: 0.25 hours, 0.5 hours, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours, 10 hours, 12 hours, and 24 hours. (*Data source: Summary of Clinical Pharmacology Studies, Table 8*)

		C_{max} (ng/mL)	**t_{max} (hr)**	**$t_{1/2}$ (hr)**	**AUC_{last} (hr•ng/mL)**	**AUC_{inf} (hr•ng/mL)**
Day 1 (N=20)	Mean±SD	9.89±3.61	n/a	6.33±1.45	30.5±11.5	32.0±12.4
	Median	9.52	0.5	6.63	27.9	29.3
Day 9 (N=20)	Mean±SD	11.5±4.59	n/a	6.65±1.74	39.0±19.2	41.5±22.1
	Median	10.4	0.5	6.09	34.4	36.5
Day 9/Day 1 geometric mean ratio	Ratio (90% CI)	1.16 (1.00, 1.36)	--	--	1.23 (1.12, 1.37)	1.24 (1.12, 1.38)

3.3.5 What is the incidence of the formation of anti-drug antibodies (ADA)? What are the impacts of ADA on brodalumab PK and efficacy?

- Following up to 52 weeks of treatment, 2.7% (120/4447) of subjects with psoriasis developed brodalumab treatment-emergent ADA across seven clinical trials; and 2.1% (86/4058) of subjects developed brodalumab treatment-emergent ADA in Phase 3 trials. (Table 3.3.5.a).
- Of the subjects who developed ADA, none (0%) were classified as positive for neutralizing antibodies. However, the incidence of neutralizing antibodies development could be underestimated because the assay used to test for neutralizing antibodies has limitations in detecting neutralizing antibodies in the presence of brodalumab.
- At Week 52, a trend of numerically lower sPGA response rates was observed in ADA positive subjects when compared to ADA negative subjects in Phase 3 trials.
- However, brodalumab trough concentrations in ADA+ subjects appear to fall within the range of those observed in study 20120102. Note that the variability of brodalumab trough concentrations is large which may be attributable to the PK nonlinearity.

Although a definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the large variability in brodalumab trough concentrations and a small number of subjects who developed ADA in psoriasis clinical trials, the observed numerically lower response rate in ADA+ subjects at Week 52 may be a signal that the ADA has a negative impact. However, whether the response rate will continue to decrease after a longer term treatment remains to be evaluated.

ADA incidence by studies

The ADA and neutralizing ADA incidences in psoriasis clinical trials are summarized in Table 3.3.5.a below.

Table 3.3.5.a. Incidences of brodalumab treatment-emergent ADA in psoriasis clinical trials. Pre-existing ADA was defined as subjects with a positive ADA result at or before baseline. Treatment-emergent ADA was defined as ADA developed post-brodalumab treatment in subjects with negative baseline ADA prior to brodalumab treatment. (*Data source: Table 3, Brodalumab Integrated Immunogenicity Report, 11 May 2015*)

Trial Number	Study Phase	Pre-existing ADA	Treatment-emergent ADA	Neutralizing ADA
20060279	1	0% (0/20)	10% (2/20)	0% (0/2)
20110184	1	0% (0/28)	0% (0/30)	(0/0)
20090062	2	0% (0/195)	7.6% (12/158)	0% (0/12)
20090403	2	0% (0/175)	11.0% (20/181)	0% (0/20)
20120102	3	0.6% (4/645)	2.2% (14/645)	0% (0/14)
20120103	3	0.3% (6/1737)	2.0% (34/1729)	0% (0/34)
20120104	3	0.3% (5/1769)	2.3% (38/1684)	0% (0/38)
combined		**0.3% (15/4569)**	**2.7% (120/4447)**	**0% (0/120)**

Immunogenicity impact on PK

Examination of individual PK profiles in ADA+ subjects in psoriasis Phase 3 trials showed that the trough serum brodalumab concentrations in ADA+ subjects were within the range of those in ADA- subjects at the same dosing cohort (140 mg Q2W in Table 3.3.5.b and 210 mg Q2W in Table

3.3.5.c). The PK data also showed large inter-subject and intra-subject PK variability, which may be partly attributable to the nonlinear characteristics of brodalumab PK.

Table 3.3.5.b. Serum brodalumab concentrations in ADA+ subjects who received the 140 mg→140 mg dose through Week 52 in pooled Phase 3 Trials. *data measured at end-of-study visit (Week 44). Ref., referenced values calculated based on study 20120102. Values in ***red bold italic*** text represent time-points when immunogenicity samples were tested as positive for ADA. (*Data source: reviewer's analysis based on (a) Appendix 1, Response to FDA Information Request, 02 February 2016, (b) dataset pkadaeff.xpt, and (c) dataset mbc16jan.xpt)*

Subjects		Serum brodalumab concentrations (mcg/mL) by time (weeks)											
		1	2	4	6	10	12	16	18	20	24	48	52
10225002012		3.69	14.6	8.56	7.54	6.19	12.7	10.9	4.1	-	8.08	***7.44***	
10266004005		0.121	1.86	***0***	0	0	0.062	0	0	-	0	3.25	
10311007008		0.067	3.07	0	0	0	0	-	-	0	0	0	***3.84***
10312001004		0.182	-	0	0	0	***0***	-	-	0	-	-	-
10316006004		0	3.85	0	0	0	***0.477***	-	-	0.256	***0***	12.8	-
10342004007		0.74	3.79	0	0	0	0	-	-	0.073	0	0.951	***0***
10366038035		3.95	7.99	1.34	0.178	0	0	-	-	0	***2.17***	***9.05***	***7.36***
10366053009		9.46	9.47	2.53	-	0.067	0	-	-	0.102	***0***	0.964	-
10411004006		4.15	1.91	0	0	0	0	-	-	0	***0***	-	-
10416014007		2.41	2.87	0.82	0	0	0.079	-	-	0	***0***	7.62	-
10425002008		2.42	6.77	2.21	0.411	0	0			0	0	***3.85****	-
10433003001		-	0	0	0.077	0.866	0	-	-	0.193	***0***	***5.97***	-
10448014009		1.77	4.86	0.47	0	0	0	-	-	0	0	***0***	-
10466024006		0.915	1.31	0	0	0	0	-	-	0	***0***	0.483	-
Ref.	**Mean**		**6.0**	**3.5**			**1.3**				**2.2**	**2.5**	
	SD		**5.2**	**4.4**			**3.0**				**4.3**	**3.6**	
	Median		**5.0**	**1.6**			**0**				**0**	**0.46**	
	Range		**0-40**	**0-27**			**0-26**				**0-30**	**0-18**	

Table 3.3.5.c. Serum brodalumab concentrations in ADA+ subjects who received the 210 mg→210 mg dose through Week 52 in pooled Phase 3 trials. *data measured at end-of-study visit (Week 22). Values in ***red bold italic*** text represent time-points when immunogenicity samples were tested as positive for ADA. Ref., referenced values calculated based on study 20120102. (*Data source: reviewer's analysis based on (a) Appendix 1, Response to FDA Information Request, 02 February 2016; (b) dataset pkadaeff.xpt, and (c) dataset mbc16jan.xpt)*

Subjects		Serum brodalumab concentrations (mcg/mL) by time (weeks)											
		1	2	4	6	10	12	16	18	20	24	48	52
10266004004		15.2	28.2	***25.7***	19.9	24.1	23.0	18.1	20.7	-	15.1	18.5	-
10266005005		5.6	4.51	0	0	3.46	0.991	0.843	0	-	***0***	-	-
10266013018		0	1.16	0	0.05	0	***0***	0	0	-	0	0.423	-
10266042007		14.7	29.8	27.7	28.6	17.6	19.2		0		***3.92****		
10311002017		13.5	25	16.7	13.3	13.1	9.63	-	-	9.22	10.2	***0.052***	***0.055***
10366021006		12.9	22.1	11.2	-	0	1.77	-	-	1.79	***0.176***	***11.9***	***5.93***
10451351005		15.5	21.4	19	20	5.91	8.36	-	-	10.9	8.06	***9.46***	-
10466028007		5.16	7.28	2.61	1.23	2.43	1.01	-	-	3.72	***1.3***	***9.6***	-
10466030013		9.93	12.9	13.6	13	8.23	13.1	-	-	6.52	***4.78***	9.87	-
10466083023		3.04	1.78	0	0	0	0	-	-	0	***0***	***0***	
Ref.	**Mean**		**15.0**	**12.7**			**9.4**				**7.4**	**8.5**	
	SD		**10.3**	**10.4**			**11.1**				**9.8**	**9.4**	
	Median		**14.0**	**14.0**			**5.7**				**3.4**	**5.4**	
	Range		**0-57**	**0-54**			**0-51**				**0-49**	**0-43**	

Impact of immunogenicity on efficacy

Following 210 mg Q2W treatment, ADA+ subjects appeared to be associated with a numerically lower sPGA success rate at Week 12 and at Week 52 when compared with ADA- subjects in the psoriasis phase 3 trials. Following 140 mg Q2W treatment, ADA+ subjects also had a numerically lower sPGA success rate than ADA- subjects at Week 52, but not at Week 12.

During the 12-week initial treatment period in pooled psoriasis Phase 3 trials 20120102, 20120103, and 20120104, the sPGA success rates at Week 12 were 60% (3/5) in the brodalumab 210 mg Q2W group and 64.3% (9/14 subjects) in the brodalumab 140 mg Q2W group for ADA+ subjects, in comparison with the 79.1% (1131/1429) and 58.5% (827/1413) sPGA success rates in ADA- subjects, respectively (Table 3.3.5.d).

During the 52-week maintenance treatment period in pooled psoriasis Phase 3 trials 20120103 and 20120104, ADA+ subjects were associated with numerically lower sPGA success rates at Week 52 when compared with ADA- subjects. At Week 52 the sPGA success (0 or 1) rate was 50% (7/14) in the brodalumab 210 mg Q2W group and 23.8% (5/21) in the brodalumab 140 mg Q2W group for ADA+ subjects, comparing to the 62.3% (409/657) and 44.4% (292/657) sPGA success rates in ADA- subjects, respectively (Table 3.3.5.e).

Table 3.3.5.d. The effect of brodalumab treatment-emergent ADA on efficacy: sPGA clear or almost clear at Week 12 by immunogenicity status in psoriasis Phase 3 trials20120102, 20120102 and 20120104. (*Data source: Table 14-4.1.14.114, 5.3.5.3 Integrated Summary of Efficacy*)

	sPGA 0/1 response rates % (n/N) by treatment groups		
	Placebo	**brodalumab 140 mg**	**brodalumab 210 mg**
ADA-	3.4% (28/821)	58.5% (827/1413)	79.1% (1131/1429)
ADA+	0% (0/3)	64.3% (9/14)	60.0% (3/5)

Table 3.3.5.e. The effect of brodalumab treatment-emergent ADA on efficacy: sPGA clear or almost clear at Week 52 by immunogenicity status in psoriasis Phase 3 trials20120103 and 20120104. (*Data source: Table 14-4.1.151.314, 5.3.5.3 Integrated Summary of Efficacy*)

	sPGA 0/1 response rates % (n/N) by brodalumab treatment groups			
	210 mg Q2W	**140 mg Q2W**	**140 mg Q4W**	**140 mg Q8W**
ADA-	62.3% (409/657)	44.4% (292/657)	12.5% (83/664)	5.2% (17/329)
ADA+	50% (7/14)	23.8% (5/21)	0% (0/8)	8.3% (1/12)

3.3.6 What are the pharmacodynamic effects of brodalumab treatment on serum IL-17A levels in subjects with psoriasis?

- Serum levels of IL-17A are generally increased after receiving brodalumab treatment, compared to the pre-treatment levels, in subjects with moderate to severe plaque psoriasis. This is consistent with the mechanism of action of brodalumab, inhibiting the binding of IL-17A to IL-17RA and thereby preventing the internalization of the receptor-IL-17A complex which is presumably an elimination pathway for IL-17A.
- The median trough IL-17A levels generally approaches maximum after 12 weeks of treatment with brodalumab. The magnitude of increase in median trough serum IL-17A level appeared to be brodalumab dose-dependent; the post-treatment median trough serum levels of IL-17A were higher in 210 mg group than in 140 mg dose group.

- Within a dosing interval, the temporal profile of median IL-17A concentrations peaked at the same time as the temporal profile of median brodalumab concentrations. The IL-17A concentrations appeared to reach the plateau when the brodalumab concentrations achieved about 4 mcg/mL.

Serum IL-17A Data: Phase 3 Study 20120102

In Phase 3 Study 20120102, pre-dose serum IL-17A concentrations were measured at baseline, Week 12, Week 24, and Week 48 in a subgroup of subjects. Serum levels of IL-17A were higher after receiving 140 mg or 210 mg brodalumab treatment compared to the pre-treatment levels and the higher dose of brodalumab was associated with a greater increase in serum levels of IL-17A.

The observed median serum IL-17A concentrations were increased from 0.37 pg/mL at baseline to 0.76-0.92 pg/mL across 3 time-points following 140 mg Q2W brodalumab treatment, representing up to 2.5-fold increase in median IL-17A levels. The 210 mg dose had a greater increase of serum IL-17A levels: median serum IL-17A concentrations were increased from 0.48 pg/mL to 1.44-1.62 pg/mL for the 210 mg→210 mg treatment group and from 0.40 pg/mL to 1.45-1.70 pg/mL for the placebo→210 mg treatment group, representing up to 4.2-fold increase of median IL-17A levels (Figure 3.3.6.a). Note that in the placebo→210 mg treatment group subjects started the brodalumab treatment from Week 12.

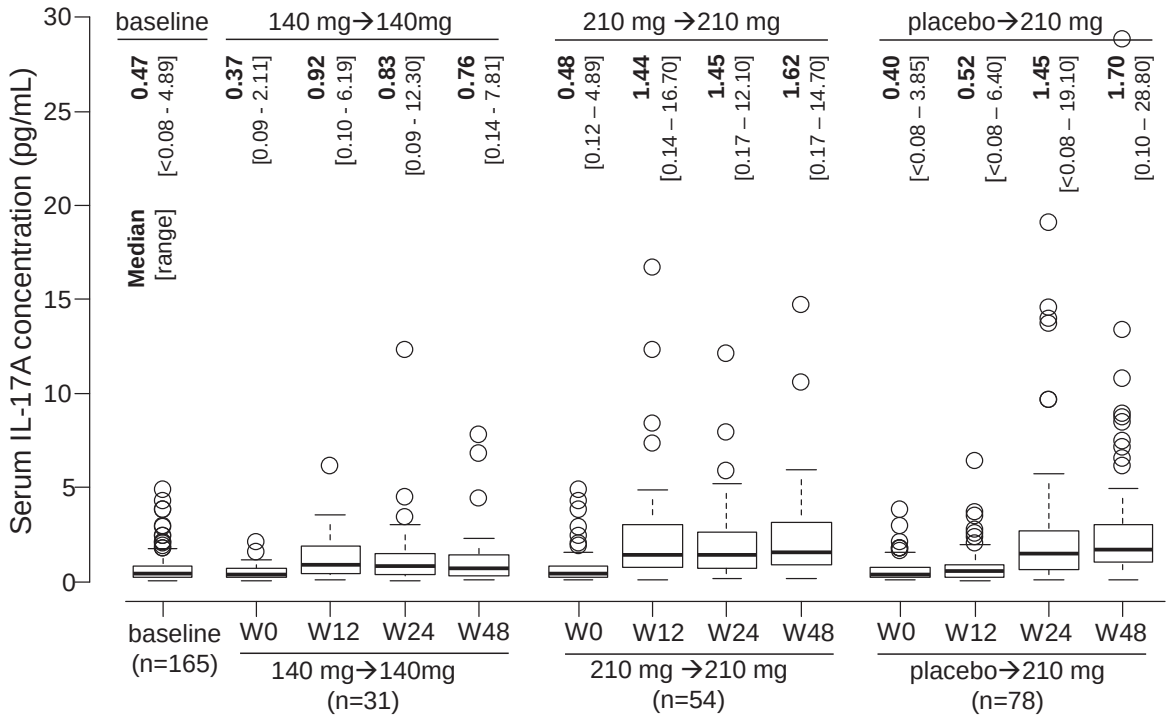


Figure 3.3.6.a. Brodalumab treatment increased serum IL-17A concentrations in Study 20120102. Placebo→210 mg treatment group received placebo at Week 0 and started brodalumab 210 mg treatment from Week 12. (*Data source: Reviewer's analysis and plot. The reviewer's analysis results were consistent with the Applicant's shown in Table 1, Study 20120102-Molecular Sciences serum analysis of IL-17A contributing scientist report, document name: MSCBCSR.20120102_IL-17A.*).

Serum IL-17A Data: Study 20110184

In Study 20110184, both serum brodalumab and serum IL-17A concentrations were measured at several time-points following a single brodalumab (210 mg or 140 mg) administration in subjects with psoriasis. The results showed that serum IL-17A levels were increased following brodalumab administration. The median baseline IL-17A levels were 0.756 pg/mL and 0.639 pg/mL in the 210 mg dose cohort and 140 mg dose cohort, respectively. The highest median IL-17A concentrations were 2.23 pg/mL and 2.35 pg/mL on Day 5 for cohort 1 and on Day 4 for cohort 2, respectively, which correspond to 3 days after brodalumab administration in each case (Table 3.3.6.a and Table 3.3.6.b) and the tmax for brodalumab.

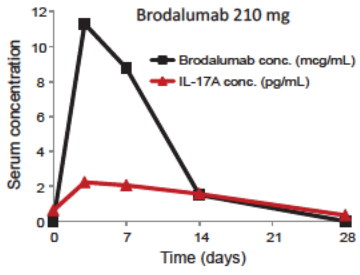
Over the dosing interval, higher serum brodalumab concentrations were associated with higher serum IL-17A concentrations; however, the increase of serum IL-17A levels appeared to be saturable at serum brodalumab concentrations greater than approximately 4 mcg/mL. IL-17A concentrations returned to the baseline range by Day 30 (Figure 3.3.6.b).

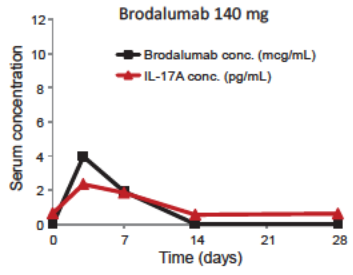
Table 3.3.6.a. Serum IL-17A concentrations following a single dose brodalumab 210 mg administration by SC injection on Day 2 in Study 20110184. EOS, end of study. (*Data source: Table 14-7.2.1, CSR 20110184*)

	Serum IL-17A concentrations (mcg/mL)					
	Baseline	**Predose**	**3 days postdose**	**7 days postdose**	**14 days postdose**	**28 days postdose**
n	19	19	20	20	20	20
Mean±SD	2.307±6.319	1.025±1.501	3.911±3.934	3.685±5.133	2.508±3.074	0.876±1.568
Median [range]	0.756 [0.13-27.90]	0.617 [0.11-6.85]	2.230 [0.85, 17.40]	2.055 [0.71-24.20]	1.565 [0.40, 13.20]	0.346 [0.07, 6.68]

Table 3.3.6.b. Serum IL-17A concentrations following a single dose brodalumab 140 mg administration by SC injection on Day 0 in Study 20110184. EOS, end of study. (*Data source: Table 14-7.2.1, CSR 20110184*)

	Serum IL-17A concentrations (mcg/mL)				
	Baseline	**3 days postdose**	**7 days postdose**	**14 days postdose**	**28 days postdose**
n	10	9	10	10	10
Mean±SD	0.678±0.538	2.210±1.066	1.970±0.897	0.842±0.831	0.618±0.445
Median [range]	0.639 [0.1-1.98]	2.350 [0.31, 3.95]	1.850 [0.87, 3.56]	0.560 [0.1, 2.83]	0.623 [0.09, 1.41]





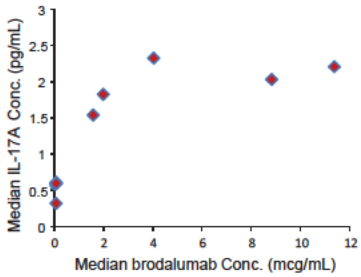


Figure 3.3.6.b. Serum brodalumab and IL-17A concentrations in subjects with psoriasis following a single 140 mg and 210 mg treatment. Each time-point represents the median value based on 19-20 subjects in the 210 mg treatment group (left) and 9-10 subjects in the 140 mg treatment group (middle). Note the different concentration scales (mcg/mL *versus* pg/mL) used for plotting brodalumab and IL-17A concentrations. (*Data source: reviewer's analysis*)

3.3.7 Is there correlation between the PK or pharmacodynamic effects of brodalumab and SIB in subjects with psoriasis?

The safety data from all brodalumab clinical trials included a total of 6 completed suicides in (4 subjects with psoriasis, 1 subject with rheumatoid arthritis, and 1 subject with psoriatic arthritis). All 4 psoriasis subjects who completed suicide were male with body weight ranging from 55 kg to 112 kg and all received 210 mg Q2W dosing for various durations (Table 3.3.7.a).

Limited available data in the clinical development program do not provide insights into the relationship between brodalumab PK, PD, and suicide, especially given the variation in the time course of suicide events both in terms of the duration on brodalumab treatment and the time after the last brodalumab dose. Nonetheless, we cannot completely rule out that brodalumab has an effect on SIB through cytokine regulation. ***See section 2.3 Outstanding Issues.***

Table 3.3.7.a. Patients profiles for the four completed suicides in psoriasis clinical trials. (*Data source: reviewer's summary based on the Applicant's Summary of Clinical Safety*)

Subjects	BW (kg)	Age (yr)	Sex	Race	Dose	SIB event from the first active dose (days)	SIB event from the last dose (days)
10216004001	73	56	Male	Asian	P→210 mg Q2W	97 (180*)	14
10248005019	55	58	Male	White	P→210 mg Q2W	329 (415*)	58
10366026003	112	54	Male	White	210 mg Q2W	846	19
10366026017	62	39	Male	White	P→210 mg Q2W	140 (224*)	27

Serum brodalumab concentrations in subjects with completed suicides

- The brodalumab exposure data during the 52 weeks study period in the 4 subjects with completed suicide were not remarkable, i.e., they were not among the highest in the study population of Phase 3 trials (Figure 3.3.7.a). A correlation between the systemic brodalumab exposure and the completed suicide could not be established; in other words, the completed suicidal events could not be attributed to high brodalumab exposure.

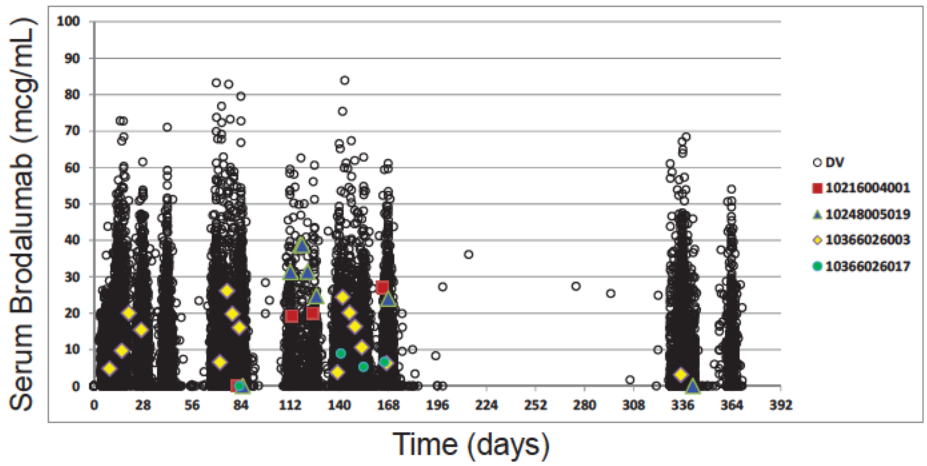


Figure 3.3.7.a. Serum brodalumab concentrations in the four completed suicide subjects in psoriasis clinical trials. The black circles represent serum brodalumab concentrations observed in psoriasis Phase 3 trials. The colored markers for square, triangle, diamond and solid circle represent serum brodalumab concentrations in the four subjects with completed suicide (*Data source: Reviewer's analysis and plot*).

Serum IL-17A levels and SIB events:

- Among the 165 subjects with available IL-17A serum concentration data in Study 20120102, three SIB events (including one completed suicide) occurred in three different subjects. The IL-17A data showed that these three subjects were not among those with the highest IL-17 levels (Figure 3.3.7.b). Additionally, by visual inspection the changes from baseline IL-17 levels in these subjects do not appear to be among the largest in the study population. The remaining three psoriasis subjects who completed suicide had no available data for the serum IL-17A concentrations. As such, the data do not provide evidence that IL-17A level may have contributed to SIB in three subjects.

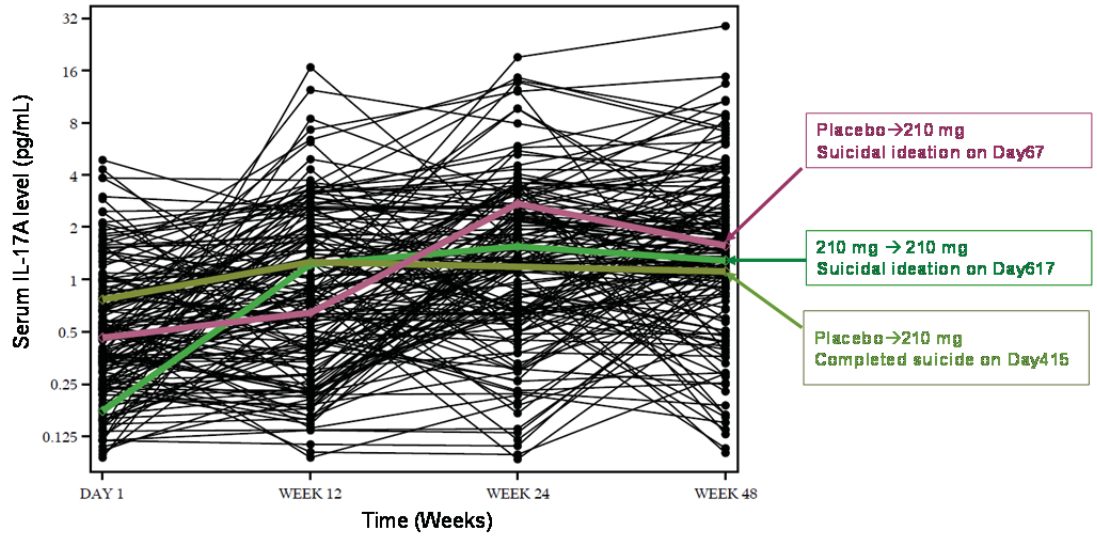


Figure 3.3.7.b. Serum IL-17A levels in the three SIB subjects in Study 20120102. Pre-dose serum IL-17A concentrations were assessed at baseline, Week 12, Week 24 and Week 48 in a subgroup of subjects in Phase 3 Study 20120102. (*Data source: Reviewer's analysis and plot*).

- *Literature reports on the potential role of cytokines in SIB:* Immune dysregulation has been reported to have implications in psychiatric disorders. A literature review was conducted to assess the biological plausibility of brodalumab causing SIB due to cytokine modulation. The literature findings are summarized below:
  - Th17 lymphocytes and IL-17 have been reported to promote blood-brain barrier disruption and central nervous system (CNS) inflammation[1,2]. It is postulated that IL-17 could induce the production of other cytokines including IL-6 in many different cell types (e.g., astrocytes). IL-17 and IL-6 are important in CNS disorders characterized by neuroinflammation[3].

[1] Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med*. 2007;13(10):1173-5.

[2] Huppert J, Closhen D, Croxford A, White R, Kulig P, Pietrowski E, et al. Cellular mechanisms of IL-17-induced blood-brain barrier disruption. *FASEB J*. 2010;24(4):1023-34.

[3] Ma X, Reynolds SL, Baker BJ, Li X, Benveniste EN, Qin H. IL-17 enhancement of the IL-6 signaling cascade in astrocytes. *J Immunol.* 2010;184(9):4898-906.

- In a small study of RA patients, serum IL-17 levels were higher in those with anxiety (n=4) than those without (n=14). The authors concluded that IL-17 played a role in anxiety and depression in patients with RA[4].
- In a meta-analysis of 22 studies concerning cytokines and suicidal ideation, suicide attempts, or suicide completion, elevated IL-6 levels were found to be associated with suicidal ideation, suicide attempts and completed suicide[5]. However, the authors acknowledged several limitations of the meta-analysis and indicated that larger, methodologically rigorous studies are needed to draw definitive conclusions regarding the association of inflammatory proteins and suicide.

Reviewer's comments: *Because the serum brodalumab concentrations at the exact time when the suicide events occurred are unknown, it is not feasible to evaluate whether there is any potential relationship between the systemic brodalumab exposure and the completed suicide. Nonetheless, the brodalumab concentrations in these subjects at the time of event are likely to vary widely given the time after the last brodalumab dose spanned a large range (14-58 days). Additionally, the available PK data up to Week 52 of the Phase 3 trials showed that the brodalumab exposure in these 4 subjects were not remarkable, i.e., they were not among the highest in the study population. Therefore, it is unlikely that the suicidal events could be attributable to high brodalumab exposure in these 4 subjects either throughout the study or at the time of event.*

With respect to brodalumab PD effects in subjects with moderate to severe plaque psoriasis, serum levels of IL-17A were higher after receiving brodalumab treatment compared to the pre-treatment levels, which is consistent with the mechanism of action for brodalumab. When brodalumab engages the target IL-17RA, IL-17A binding to IL-17RA and presumably the subsequent receptor-mediated elimination of IL-17A could not occur; resulting in an increase in IL-17A levels. It is biologically plausible that brodalumab treatment may cause SIB due to cytokine regulations because immune dysregulation may have implications in psychiatric disorders. Upon close examination of data in Study 20120102, the serum IL-17A levels during the 52 weeks treatment period in three subjects who experienced SIB (including 1 completed suicide) were not among the highest of IL-17 levels (See section 3.3.7) and the changes in IL-17A level from baseline are not among the largest. The remaining three psoriasis subjects who completed suicide had no available data for the serum IL-17A concentrations. As such, the limited available clinical data did not suggest a direct correlation between brodalumab treatment-induced up-regulation of serum IL-17A levels and the SIB events.

3.3.8 Is the proposed to-be-marketed drug product comparable to that used in the pivotal clinical trials with respect to PK?

Yes. The proposed brodalumab dosage form for registration is the single use prefilled syringe (PFS): 210 mg of brodalumab in 1.5 mL solution (140 mg/mL). Study 20130307 evaluated the PK comparability between the to-be-marketed presentation [one injection with 1.5 mL PFS] and the Phase 3 presentations [2 injections with 1.0 mL PFS + 0.5 mL PFS]. The PK comparability

[4] Liu Y, Ho RC, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *Int J Rheum Dis.* 2012;15(2):183-7.

[5] Gananca L, Oquendo MA, Tyrka AR, Cisneros-Trujillo S, Mann JJ, Sublette ME. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology*. 2016;63:296-310.

assessment relied on comparisons of C_{max} and AUC_{last} between two presentations at the SC dose of 210 mg brodalumab. The PK results showed that the point estimates [90% confidence interval] for geometric mean ratio of C_{max} and AUC_{last} were within the [0.8, 1.25] acceptance limit of the BE criteria (Table 3.3.8.a). PK data demonstrated the comparability between the to-be-marketed [1.5 mL PFS] and Phase 3 [1.0 mL PFS +0.5mL PFS] presentations.

Table 3.3.8.a. PK comparability results between to-be-marketed and Phase 3 presentations in Study 20130307. Study 20130307 is a 2-period cross-over study in 140 healthy subjects. See individual study summary for details. (*Data source: Summary of Clinical Pharmacology*)

	Test/Reference geometric mean	
	Ratio	**90% CI**
AUC_{last}	0.89	0.82 - 0.98
C_{max}	0.98	0.91 - 1.05

Drug product used in the development program

Several drug product (DP) manufacturing changes were introduced during the clinical development of brodalumab for the psoriasis indication. Six different brodalumab formulations/presentations including liquid-in-vial with 70 mg/mL formulation, PFS (0.5 mL, 1.0 mL, and 1.5 mL) and autoinjectors (0.75 mL and 1.0 mL) with 140 mg/mL formulation were used in psoriasis clinical trials(Table 3.3.8.b). In the pivotal psoriasis Phase 3 trials, the 140 mg dose was administered via a single injection with 1.0 mL PFS; and the 210 mg dose was administered via 2 injections: one with 1.0 mL PFS injection and the other one with 0.5 mL PFS injection. The Applicant proposes to register the 1.5 mL PFS in the BLA. As stated above, the Applicant has established the PK comparability between the to-be-marketed presentation [one injection of 1.5 mL PFS] and the Phase 3 presentations [2 injections of 1.0 mL PFS + 0.5 mL PFS] to support the proposed to-be- 1.5 mL PFS. The to-be-marketed product (1.5 mL PFS) contains the identical solution formulation as the PFS presentations used in Phase 3 trial, but the primary syringe was different.

Table 3.3.8.b. Brodalumab drug product formulations and presentations used in controlled psoriasis clinical trials. [a] Study 20130307 evaluated PK comparability between [1.5 mL PFS] and [1.0 mL PFS + 0.5 mL PFS] at the 210 mg dose. [b] Study 20090480 evaluated PK comparability between [0.75 mL AI + 0.75 mL AI] and [1.0 mL PFS + 0.5 mL PFS] at the 210 mg dose. PFS, prefilled syringe; AI, autoinjector

	brodalumab formulation (concentration) and devices/presentations by fill volume					
	70 mg/mL	**140 mg/mL**				
	Vial	**1 mL syringe**				**2.25 mL syringe**
		PFS		**AI**		**PFS**
	1 mL	**0.5 mL+1.0mL**	**1.0 mL**	**0.75 mL**	**1.0 mL**	**1.5 mL**
Phase1	20060279					
			20120337			
			KHK4827-001			
					20110106	
		20130307[a]				20130307
		20090480[b]		20090480		
		20110184				
Phase 2	20090062					
		KHK4827-002				
Phase 3		20120102	20120102			
		20120103	20120103			
		20120104	20120104			

Manufacturing processes of brodalumab drug substance

Several drug substance (DS) manufacturing changes were introduced during the clinical development of brodalumab for the psoriasis indication. Brodalumab drug substance (DS) was initially manufactured at Amgen [redacted] using a manufacturing process referred to as Process 1 [redacted]. DS from Process 1 [redacted] was used in early Phase 1 and Phase 2 clinical studies.

The Applicant optimized the Process 1 [redacted] to improve manufacturing robustness and the improved process is referred to as Process 2 [redacted]. The DS manufactured with Process 2 [redacted] was used in later phase of the development program including all pivotal Phase 3 clinical studies (Studies 20120102, 20120103, and 20120104) and PK comparability studies (Studies 20090480 and 20130307). The Applicant conducted analytical comparability assessment of DS by Process 1 [redacted] and Process 2 [redacted].

The commercial DS will be manufactured at [redacted] using Process 2 and is referred to as Process 2 [redacted] DS from Process 2 [redacted] was used after Week 52 in a subset of subjects in Study 20120103 to provide information on clinical exposure. The Applicant conducted analytical comparability assessment of DS by Process 2 [redacted] and Process 2 [redacted].

Reviewer's comments: *We defer to the OPQ review team for the determination of whether or not the analytical comparability data alone would support the manufacturing changes in the drug development program and support the commercialization of the DS by Process 2* [redacted].

4. APPENDICES

4.1 Bioanalytical Method Report

4.1.1. PK assay: ELISA for measurement of unbound brodalumab in human serum

Assay description and procedure

The Applicant developed an enzyme-linked immunosorbent assay (ELISA) to measure unbound brodalumab in human serum. The ELISA method uses two anti-idiotype anti-brodalumab antibodies for capture and detection of brodalumab not bound to IL-17RA.

Microplate wells are coated with mouse anti-brodalumab antibodies. Standards, quality control (QCs), and PK samples are loaded into the microplate wells after pre-treatment with dilution buffer. Brodalumab in study samples is captured by the immobilized mouse anti-brodalumab antibodies. Following washing, rat anti-brodalumab antibodies labeled with horseradish peroxidase (HRP) are added to the microplate wells. After washing, tetramethylbenzidine (TMB) substrate solution is added to the microplate wells. The TMB substrate solution reacts with peroxide and in the presence of HRP creates a colorimetric signal. The color development is then stopped and the intensity of the color is measured.

Assay validation

The validation parameters of the ELISA method for measurement of unbound brodalumab in human serum are summarized in Table 4.1.1.a. The assay accuracy and precision results for measurement of the PK samples in individual clinical trials are summarized in Table 4.1.1.b. This reviewer found the assay validation acceptable.

Table 4.1.1.a. Assay validation results of the ELISA method used for measurement of brodalumab (AMG827) in human serum. ELISA: enzyme linked immuno-sorbent assay; LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; QC, quality control. (*Data source: The information summarized in this table was primarily based on assay validation results provided in Report 109,693; when additional assay validation results are included, the related validation reports are also quoted.*)

Assay description and validation parameters	Assay validation results and data source
Supporting documents reviewed	– *Validation Report 109,693: Method validation for the determination of AMG 827 in human serum by ELISA* – *Validation Report 112,136: Partial method validation of an ELISA for the quantitative determination of AMG 827 in human serum; addendum report 1; addendum report 2* – *Validation Report 117,103: Quantification of AMG 827 in human serum by ELISA; addendum report 1* – *Summary of Clinical Pharmacology, Appendix 6.1* – *Summary of Biopharmaceutics and Associated Analytical Methods*
Method	Enzyme-linked immunosorbent assay (ELISA)
Platform	96-well microplate
Compound analyzed	Brodalumab (AMG 827)
Matrix	Human serum
LLOQ	50 ng/mL
ULOQ	2000 ng/mL

Standard Curve	Eight standard curve samples: 50, 100, 200, 350, 500, 1000, 1600, and 2000 ng/mL			
QC samples	50 ng/mL (LLOQ); 150, 400, and 1500 ng/mL (L, M, H); 2000 ng/mL (UPOQ)			
Dilution linearity and hoot effect	− 1:10, 1:50, 1:100, 1:500, 1:8,000, and 1:10,000 dilutions were demonstrated in the dilution linearity assay (*Report 112,136*) − No hook effect was observed. High-end hook effect was evaluated at the 0.01, 0.1, 1.0 mg/mL.			
Intra-assay precision (%CV)	− 1% to 6% (QC samples) − 1% to 36% (QC samples, *Report 112,136*; one 36% observation occurred at ULOQ level; 1% to 20% for dilution QC samples)			
Intra-assay accuracy (%Bias)	− -15% to 7% (QC samples) − -13% to 25% (QC samples, *Report 112,136*)			
Inter-assay precision (%CV)	− 3% to 8% (QC samples) − 0% to 3% (Standard curve) − 9% to 19% (QC sample, *Report 112,136*) − 1% to 9% (Standard curve, *Report 112,136*) − 1.9% to 3.7% (QC sample, Report *117,103*) − 0.25% to 1% (Standard curve, *Report 117,103*)			
Inter-assay accuracy (%Bias)	− -3% to -1% (QC samples) − -2 to 3% (Standard curve) − -1% to 2% (QC samples, *Report 112,136*) − -2% to 4% (standard curve, *Report 112,136*) − 2% to 7% (QC sample, *Report 117,103*) − -1.8% to 1.8% (Standard curve, *Report 117,103*)			
Stability	− Sample stability at room temperature: approximately 19 hours; overnight or approximately 22 hours (*Report 112,136*) − Long-term stability at -20°C: 297 days − Long-term stability at -70°C: 559 days − Freeze (-70°C)/thaw stability: 6 cycles			
Standard Curve Regression model	Logistic [4-Parameter] with 1/Y2 weighting			
Incurred sample reanalysis	− Twenty-four incurred study samples from healthy subjects in Study 20060279 were analyzed and 100% of the repeated samples were within the acceptance criteria (± 30.0% of original value). − Twenty-six incurred study samples from psoriasis subjects in Study 20060279 were re-analyzed and 100% of the repeated samples were within the acceptance criteria (± 30.0% of average value). − Sixty-eight incurred study samples from RA subjects in Study 20070264 were re-analyzed and 90% of the repeated samples were within the acceptance criteria (± 30.0% of average value).			
Specificity	No cross-reactivity was observed by testing the addition of a different IgG2 mAb (AMG 317) to the human serum with brodalumab levels at LQC or HQC.			
Selectivity (Matrix Effect)	All blank samples showed <LLOQ results. The matrix effect at brodalumab levels of 50 ng/mL and 1500 ng/mL in 18 individual serum lots showed acceptable results as below:			
			50 ng/mL	1500 ng/mL
	Six healthy subjects (3 M +3 F)	CV%	1% to 22%	0% to 3%
		%Bias	-14% to 0%	-9% to 6%
	Six subjects with psoriasis (3 M +3 F)	CV%	2% to 5%	1% to 7%
		%Bias	-8% to 17%	-7% to 20%
	Six subjects with RA (3 M +3 F)	CV%	2% to 7%	1% to 2%
		%Bias	-10% to 5%	-14% to 3%
Clinical Studies and	Validation report (Assay site)	Related clinical studies:		

Clinical Study Reports (CSR) related to each ELISA assay validation report	*Report 109,693*	20060279 and 20070264
	Report 112,136	20120337, 20090480, 20110106, 20130307, 20090062 and 20090403
	Report 117,103	20110184, 20120102, 20120103 and 20120104

Table 4.1.1.b. Assay accuracy and precision in the bioanalytical analysis for the measurement of brodalumab in human serum in individual clinical trials. (*Data source: Table 25, Summary of Clinical Pharmacology*)

Clinical Trial	Assay performance		
		Accuracy (%bias)	Precision (%CV)
20060279	Standards	-2 to 2	1 to 2
	QC	-9 to 5	8 to 10
20120337	Standards	-2 to 1	1 to 3
	QC	-1 to 1	3 to 4
20130307	Standards	-4 to 3	1 to 3
	QC	0 to 2	4 to 5
20110184	Standards	-1 to 2	0 to 1
	QC	-2 to 0	3 to 5
20090480	Standards	-1 to 1	1 to 3
	QC	-8 to -3	4 to 5
20110106	Standards	-4 to 3	1 to 5
	QC	-3 to 0	3 to 12
20090062	Standards	-2 to 3	1 to 3
	QC	-4 to -3	5 to 19
20090403	Standards	-1 to 3	1 to 5
	QC	-4 to 0	5 to 13
20120102	Standards	-2 to 2	0 to 3
	QC	-2 to 3	4 to 4
20120103	Standards	-1 to 2	0 to 2
	QC	-1 to 2	4 to 4
20120104	Standards	-1 to 2	0 to 2
	QC	-1 to 2	4 to 4

4.1.2. Immunogenicity assays

Refer to OBP reviews for the evaluation of the performance of the immunogenicity assays and assay validation results. This section provides a brief summary of the binding and neutralizing antibody assays procedures and focuses on the evaluation of the drug tolerance level of the assays.

Overall immunogenicity testing strategy

Samples were tested for anti-brodalumab binding antibodies using an electrochemiluminescence (ECL) bridging immunoassay. If positive, samples were then tested for neutralizing antibodies using a cell based assay.

ECL binding assay

This ECL-based immunoassay method utilized the Meso Scale Discovery (MSD) platform and followed a two-tiered assay approach consisting of a screening assay and specificity assay. The

screening assay was performed on samples to detect the presence of antibodies capable of binding to brodalumab. Samples with a signal-to-noise (S/N) value greater than the assay cutpoint were then tested to confirm specificity of the response. Samples tested in the specificity assay that demonstrated signal inhibition in the presence of excess soluble drug were reported as positive for the presence of anti-brodalumab antibodies.

Briefly, samples were treated with 300 mM acetic acid to enable antibody complex dissociation prior to analysis. Samples were then incubated with a mixture consisting of biotinylated-brodalumab, ruthenylated-brodalumab, 1 M Tris pH 9.5, and soluble drug (specificity assay only). The sample mixture was then added to a blocked MSD avidin microtiterplate. The biotinylated-brodalumab molecule bound to the avidin-coated surface of the well and immobilized the bridged complex. The plate was washed to remove any unbound complexes and tripropylamine read buffer was added to each well. The ECL signal was then measured and quantified as ECL units Using the MSD plate reader. The ECL binding assay has drug tolerance level up to 100 mcg/mL of brodalumab in human serum at 0.5 mcg/mL of anti-brodalumab antibody (Table 4.1.2.a).

Table 4.1.2.a. Performance of the ECL immunogenicity binding assay. (*Data source: Table 1, Brodalumab integrated immunogenicity report*)

Species	Lower limit of reliable detection (LLRD)	Drug tolerated at 500 ng/mL of anti-brodalumab antibody	Serum dilution
Rabbit	5 ng/mL	≥50 mcg/mL	5%
Cynomolgus monkey	4.4 ng/mL	≥50 mcg/mL	10%
Human	5 ng/mL	20 mcg/mL	5%
Human	15 ng/mL	100 mcg/mL	5%
Human	15 ng/mL	100 mcg/mL	5%

Neutralizing antibody assay

The neutralizing antibody bioassay uses IL-8 cytokine measurement as an assay endpoint. In the assay, IL-8 is secreted by human foreskin fibroblast cells (HFF) upon stimulation with IL-17 cytokine. In the presence of AMG 827, IL-8 secretion is inhibited by the antagonistic effects of AMG 827 binding to the IL-17 receptor. Conversely, the presence of neutralizing antibodies to AMG 827 will neutralize the AMG 827 biological activity and reverse its inhibition of the IL-8 secretion. DELFIA time-resolved fluorescence immunoassay is used to detect secreted IL-8 in cellular supernatants. The lower limit of reliable detection (LLRD) is 2.5 µg/mL of rabbit anti-AMG 827 antibody in neat human serum. At the LLRD, the assay is able to tolerate up to 1.25 µg/mL of excess AMG 827 in neat serum (Table 4.1.2.b).

Table 4.1.2.b. Performance of the neutralizing binding assay. (*Data source: Table 2, Brodalumab integrated immunogenicity report*)

Species	Lower limit of reliable detection (LLRD)	Drug tolerated at LLRD of anti-brodalumab antibody	Serum dilution
Cynomolgus monkey	5 mcg/mL	≥1.56 mcg/mL	1%
Human	2.5 mcg/mL	0.78-1.25 mcg/mL	5%
Human	2.5 mcg/mL	1.25 mcg/mL	5%

4.2 Population Pharmacokinetics (pop-PK)

Objective

The Applicant performed population pharmacokinetic (pop-PK) analyses in healthy volunteers and subjects with psoriasis to:

1. Quantitatively characterize brodalumab PK and between-subject variability (BSV) using data from Phase 1 to Phase 3 studies, and
2. Evaluate the effects of intrinsic and extrinsic factors on brodalumab PK

Data

The dataset included concentration-time data for brodalumab from 7 clinical studies in healthy subjects and subjects with psoriasis with or without psoriatic arthritis:

- 3 phase 1 studies (20060279, 20110106, and 20110184),
- 1 phase 2 study (20090062) and
- 3 phase 3 studies (20120102, 20120103, and 20120104)

The dataset used for pop-PK model building and covariate analysis included 14883 PK samples collected from 2348 subjects administered single or multiple IV or SC doses ranging from 7 mg to 700 mg of brodalumab in all the above mentioned studies except the Phase 3 study 20120103. The data from Phase 3 study 20120103 were used as external dataset to evaluate model performance and this consisted of 1473 subjects administered multiple SC doses of 140 mg or 210 mg of brodalumab. Finally the combined dataset consisting of data from all the above mentioned studies with 25407 PK samples of brodalumab from 3821 subjects was used for updating the final pop-PK model and conducting final covariate analysis. The details of doses tested and PK sampling scheme in these studies is listed in Table 4.2.a.

Methods

Various demographic factors (sex, age, race, body weight), renal function categories, disease status/characteristics (healthy/psoriasis/psoriatic arthritis and baseline PASI scores) and drug related characteristics (presence of anti-drug antibodies, drug product manufacturing) were considered for covariate analysis. Modeling was performed using NONMEM 7.2 software.

Table 4.2.a. Summary of Studies included in the Population PK Analysis. (*Data source: Table 11-1, Population PK Report*)

Study	Type	Doses (mg)	Sample Collection
Phase 1			Up to 12 weeks
20060279	HV	IV: 21, 210, 700 SC: 7, 21, 70, 210, 420	Predose, EOI, 4, 8, 24, 48 hours, days 4, 5, 8, 12, 15, 22, 29, 43, and 64 postdose
	PsO	IV: 700 SC: 140, 350	Predose, EOI, 2, 4, 8 hours, days 3, 8, 15, 29, 43, 64, and 85 postdose
20110106	HV	SC: 140 mg x 2	Predose, 4, 24 hours, days 3, 4, 5, 8, 12, 15, 18, 22, 25, 29, and 36 postdose
20110184	PsO	SC: 140 Q2W	Predose, 4, 24 hours, days 3, 4, 5, 8, 12, 15, 18, and 22 postdose
Phase 2			Up to 22 weeks
20090062	PsO	SC: 70, 140, 210, 280 Q2W + W1 for 12 weeks	Predose on day 1, weeks 2, 4, 8, 12, 16, and 22 PK substudy: W1, W1+3 days, W8+3 days, W8+7 days, and W10
Phase 3			Up to 52 weeks
20120102	PsO	SC: Placebo for 12 weeks then 210 Q2W + W1 140, 210 Q2W + W1 for 52 weeks	Predose, weeks 1, 2, 4, 6, 10, 12, 16, 18, 24, and 48 PK substudy: W2+3 days, W10+3 days, W10+7 days, W10+10 days, W16+3 days, W16+7 days, W16+10 days
20120103	PsO	SC: Placebo for 12 weeks then 210 Q2W + W1 140, 210 Q2W + W1 for 52 weeks	Predose, weeks 1, 2, 4, 6, 10, 12, 20, 22, 24, 48 and 52 PK substudy: W2+3 days, W10+3 days, W10+7 days, W10+10 days, W20+3 days, W20+7 days, and W20+10 days
20120104	PsO	SC: Placebo for 12 weeks then 210 Q2W + W1 140, 210 Q2W + W1 for 52 weeks	Predose, weeks 1, 2, 4, 6, 10, 12, 20, 22, 24, and 48 PK substudy: W2+3 days, W10+3 days, W10+7 days, W10+10 days, W20+3 days, W20+7 days, and W20+10 days

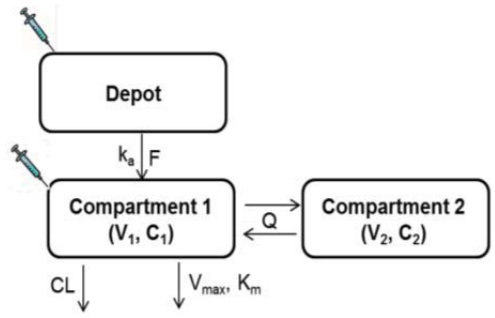
EOI: end of the 30 minute IV infusion period (for subjects receiving IV infusion only); PsO: Psoriasis

Results

The final pop-PK model consists of a 2-compartmental model with instantaneous (IV) or first-order (SC) input, and linear and saturable routes of elimination from central compartment.

Between-subject variability (BSV) was modeled on following parameters: rate of absorption (Ka), clearance (CL), volume of distribution for the central and peripheral compartments (V1 and V2) and maximal rate of saturable elimination (V_{max}). Residual variability was modeled using an additive plus proportional error model.

The structure of the pop-PK model is shown in Figure 4.2.a and the final parameter estimates for the pop-PK model are listed in Table 4.2.b.



CL = linear clearance;
V_{max} = maximal rate of saturable elimination;
Km = concentration at which the saturable elimination pathway is at half of maximal rate;
V_1 = volume of distribution for the central compartment;
V_2 = volume of distribution for the peripheral compartment;
Q = clearance between central and peripheral compartment;
ka = first-order absorption rate constant;
F = absolute bioavailability

Figure 4.2.a. Structural population PK model. (*Data source: Figure 24, Summary of Clinical Pharmacology*)

Table 4.2.b. Parameters estimates for the final population PK model. (*Data source: Table 17, Summary of Clinical Pharmacology*)

Parameter	Estimate	RSE(%)	Units
Ka	0.330	0.433	day^{-1}
CL	0.211	0.863	L/day
V_1	4.01	0.436	L
V_{max}, healthy subjects	4.60	2.02	mg/day
V_{max}, psoriasis	4.82	1.57	mg/day
Km	0.0223	fixed	mcg/mL
F[a]	0.547	fixed	--
Q	1.13	1.56	L/day
V_2	3.23	0.347	L
Power of weight (kg) on V_1 and V_2	0.784	0.316	--
Power of weight (kg) on V_{max}	0.573	0.195	--
Power of weight (kg) on CL and Q	0.903	0.162	--
Power of baseline PASI score on V_{max}	0.0866	0.0689	--
Inter-individual variability			
ω_{ka}	52.4	12.3	CV%
ω_{CL}	49.1	5.73	CV%
ω_{V1}	13.3	17.6	CV%
ω_{Vmax}	18.9	41.9	
ω_{V2}	135	10.4	CV%
Residual variability			
$\sigma_{proportional, phase 1 and 2}$	10.5	26.2	CV%
$\sigma_{additive, phase 1 and 2}$	0.726	34.7	SD
$\sigma_{proportional, phase 3}$	25.9	7.85	CV%
$\sigma_{additive, phase 3}$	1.37	6.77	SD

[a]Bioavailability F was modeled using a logit equation: F = exp(logitF)/(1+exp(logitF)), where the estimated logit F was 0.187.
RSE: Relative Standard Error;
Effect of body weight (BW) on CL: $CL = 0.211 \times (BW/80)^{0.903}$
Effect of body weight (BW) on Q: $Q = 1.13 \times (BW/80)^{0.903}$
Effect of body weight (BW) on Vmax, healthy: $Vmax = 4.60 \times (BW/80)^{0.573}$
Effect of body weight (BW) and PASI on Vmax, patients: $Vmax = 4.82 \times (BW/80)^{0.573} \times (PASI/17)^{0.0866}$
Effect of body weight (BW) on V1: $V1 = 4.01 \times (BW/80)^{0.784}$

Effect of body weight (BW) on V2: $V2 = 3.23 \times (BW/80)^{0.784}$
CV: Coefficient of variation.

The goodness-of-fit (observed vs individual predicted concentrations etc.) plots for the final model are provided in Figure 4.2.b.

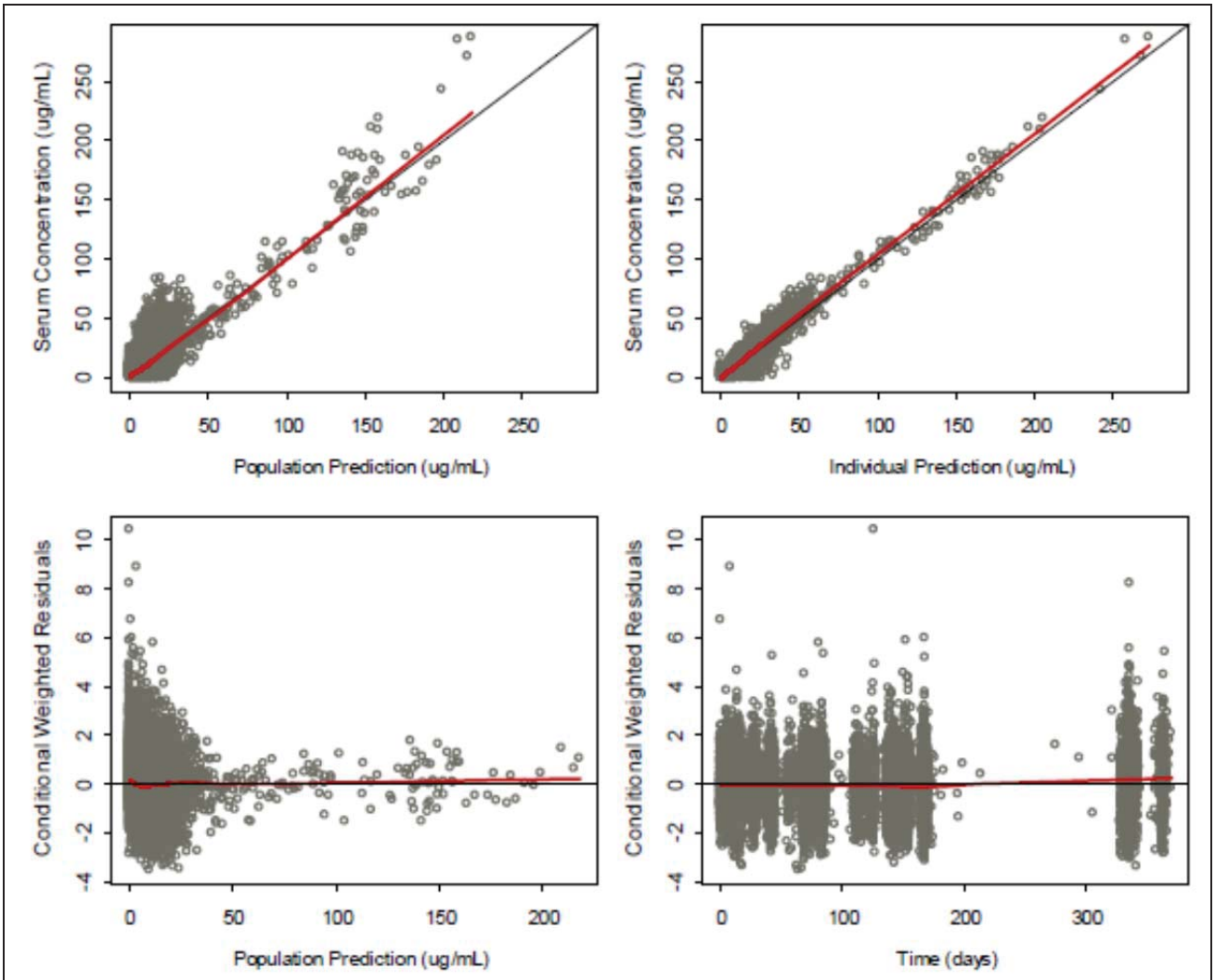


Figure 4.2.b. Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model. (*Data source: Figure 12-28, Population PK Report*)

Covariate effects: Body weight and baseline PASI score were the two key covariates identified to be important in the model:

- Body weight on clearance (CL, V_{max}) and distribution parameters (Q, V_1, V_2).
- Baseline PASI score on maximal saturable elimination rate (V_{max}).

The impact of these covariates on the exposure of brodalumab is as follows:

- Week 10-12 (steady state) exposures will be more than 1.5-fold higher for lighter subjects of 60 kg body weight and ~40% (0.4-fold) for heavier subjects with 130 kg body weight as compared to exposures in a typical individual with 84 kg body weight. See Figure 4.2.c.
- Within the range of baseline PASI scores simulated (add range here), week 10-12 (steady state) exposures are expected to be within 20% of such steady state exposures in a typical individual with baseline PASI of 17 and body weight of 84 kg. Thus, even though this was a statistically significant predictor of brodalumab exposure, this covariate had a small influence on brodalumab PK. See Figure 4.2.c.

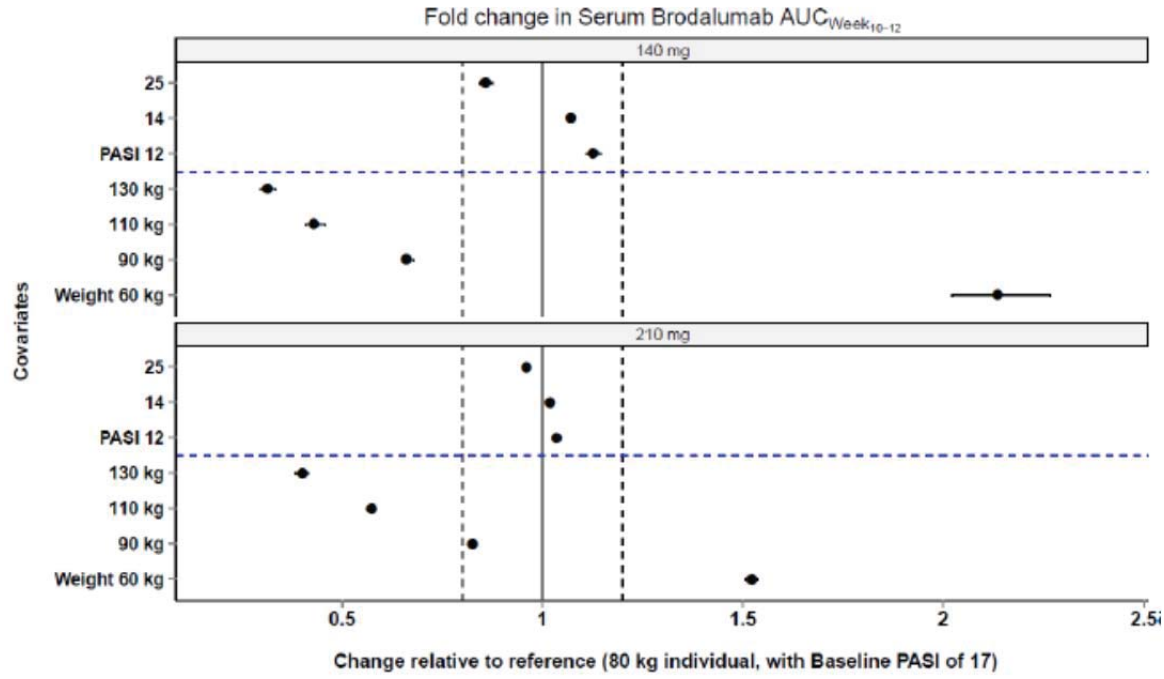
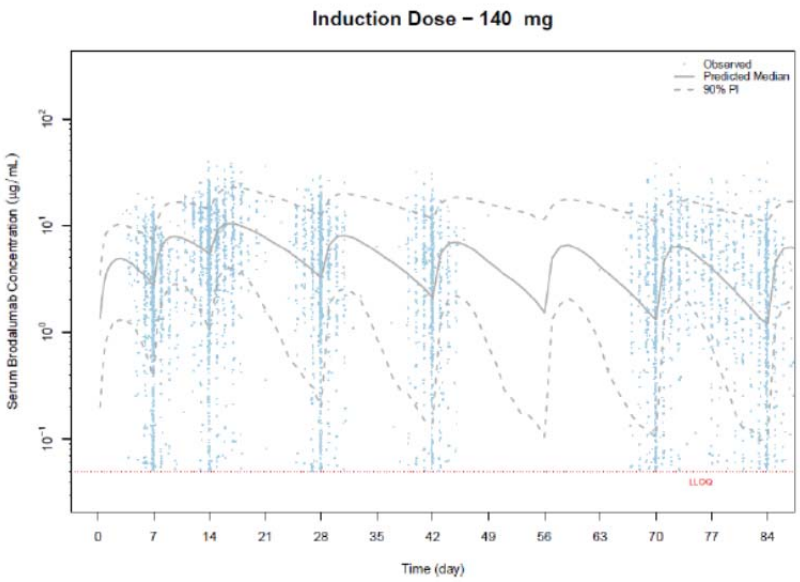


Figure 4.2.c. Effect of Body Weight and Baseline PASI Score on Brodalumab AUCweek10-12 (AUC between weeks 10 and 12 - steady state AUC). (*Data source: Figure 12-34, Population PK Report*)

This pop-PK model was utilized to perform simulations to define specific aspects of brodalumab PK, e.g., accumulation, with different dosing regimen. Results of the simulations at two different dose levels of 140 mg and 210 mg Q2W are shown in Figure 4.2.d. The corresponding model-predicted AUC_{tau} (Week 10- Week 12) across the observed quintiles of body weights for these two dosing regimen (140 mg and 210 mg Q2W) are shown in Figure 4.2.e. Model-based simulations predicted that after the last steady state dose the time for brodalumab concentrations in 95% of subjects to drop BQL are 32 days and 63 days for the 140 and 210 mg doses, respectively.



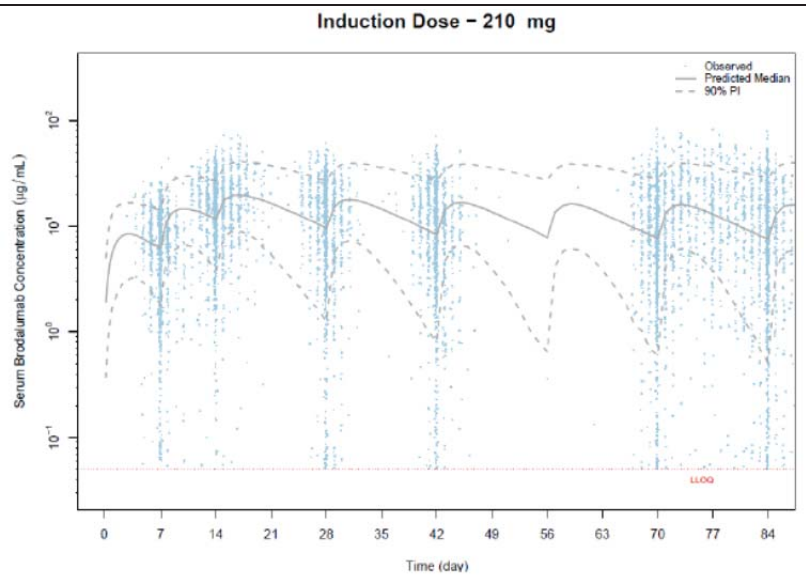


Figure 4.2.d. Pop-PK Model-Predicted Time Courses (Median and 90% Prediction Interval) and Observed Concentrations of brodalumab from Phase 3 Studies. (*Data source: Figure 12-33, Population PK Report*)

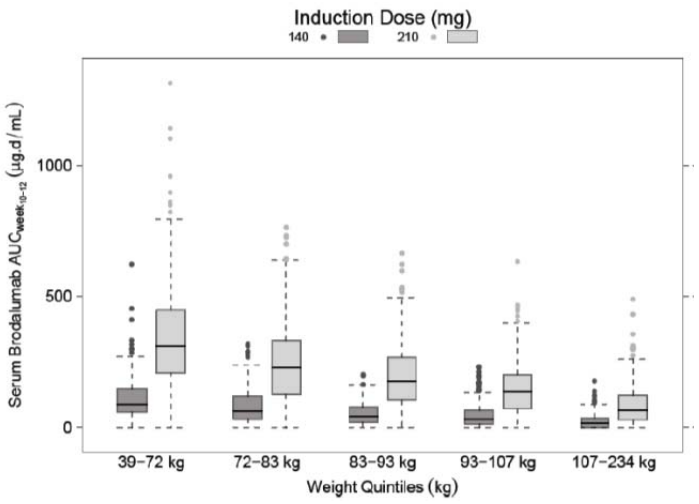


Figure 4.2.e. Population PK model-predicted brodalumab exposure AUC_{tau} (Week 10- Week 12) across the observed quintiles of body weights with 140 mg and 210 Q2W dosing regimens in subjects with plaque psoriasis. (*Data source: Figure 27, Summary of Clinical Pharmacology*)

The individual parameter/exposure estimates generated from the final pop-PK model were used as the driving function for subsequent pharmacokinetic-pharmacodynamic (PK/PD) and exposure-response (E-R) analyses.

***Reviewer's comments**: The Applicant's Pop-PK model provides reasonable description of brodalumab serum concentrations for individual predictions (observed vs. individual predicted concentrations in Figure 4.2.b) over a range of concentrations from the included studies.*

4.3 Exposure-Response

The Applicant performed graphical and tabular analysis by exposure subgroups to explore the exposure-response relationship for efficacy and safety. Observed trough concentrations (C_{trough}) at Week 12 were used as the exposure metric.

Efficacy response measure was sPGA (0,1) and sPGA 0 response status at Week 12.

Safety analysis was conducted with incidence of following adverse events (AEs) up to Week 12 for all subjects randomized to an induction dose of 140 mg Q2W or 210 mg Q2W; and with incidence of events up to Week 52 for subjects randomized to an a constant dose of 140 mg Q2W or 210 mg Q2W with a completed Week 52 visit:

- all infections and infestations, serious infections, candida infections, grade ≥3 candida infections, viral infections and grade ≥3 viral infections

Further, as per the reviewers' request, the Applicant also conducted exposure-efficacy analyses at Week 12 with model predicted C_{trough} and AUC_{τ} at week 12 and exposure-safety analysis with inclusion of subjects who did not complete week 52 visit, by calculating the exposure-adjusted incidence rates for the above mentioned AEs.

Data

The dataset included concentration-time data (PK), efficacy measures and adverse events for brodalumab treatment from 3 Phase 3 clinical studies (20120102, 20120103, and 20120104) in subjects with psoriasis. With respect to PK, trough and sparse sampling had been employed in all these 3 studies.

Methods

All the subjects were grouped by exposure (C_{trough}) values as described below:

- Subjects with placebo as induction dosing until week 12 were considered to have zero exposure to brodalumab.
- Subjects with induction dosing of either 140 mg or 210 mg Q2W and with BLQ concentrations at Week 12, were considered as BLQ group.
- All the other subjects with induction dosing of either 140 mg or 210 mg Q2W and with concentration above BLQ at Week 12 were divided into tertiles of exposure.

Results

Exposure-Efficacy Relationship

There was an exposure-response relationship between sPGA (0,1) and sPGA 0 response rates and observed brodalumab concentrations at Week 12 as shown in Figure 3.3.1.a above. Similar relationship was also observed with model predicted brodalumab C_{trough} and AUC_{τ} at week 12 as shown in Figure 4.3.a below. The response rates appears to be approaching the plateau at the top two tertiles and slightly more so for sPGA 0/1 response than for sPGA 0 response.

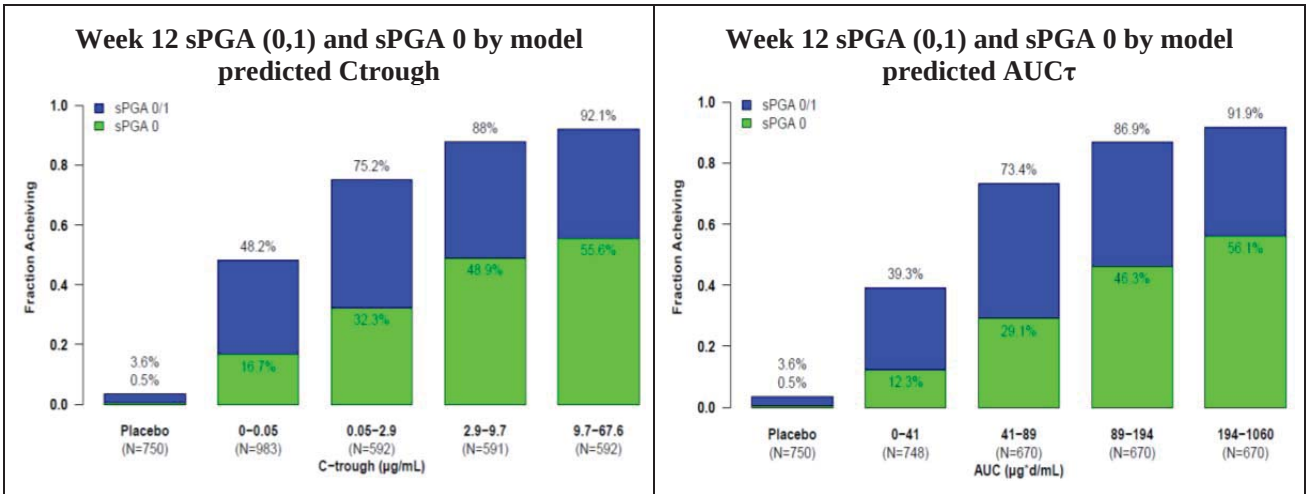


Figure 4.3.a. Exposure-response for achieving sPGA (0,1) and sPGA 0 at Week 12 by model predicted trough concentrations (C_{trough}) and AUCτ of serum brodalumab. (*Data source: Appendix 2, Response to FDA IR, 02 February 2016*)

Exposure-Safety Relationship

Based on the completer dataset, Exploration of exposure-response relationship for safety (infection related) did not identify any trend between incidences of safety events and brodalumab exposure (Table 3.3.2.a and Table 3.3.2.b). Table 3.3.2.b above shows the relationship for completer population (subjects with week 52 visit). However, when subjects who did not have week 52 visit,

i.e., non-completers, were included in the analysis, the highest exposure subgroup showed a numerically higher exposure-adjusted event rates for all infections and infestations and viral infections compared to any of the lower exposure subgroups, although such relationship was not seen for serious infections, candida infections or Grade ≥ 3 viral infections category (Table 3.3.2.c). The difference between two analyses suggests that the infection related safety events may have contributed to the non-completer status; therefore, the possibility exists that safety event may be related to the brodalumab exposure.

Table 4.3.a. Analysis Datasets and Codes

Study# / Analysis	**Name**	**EDR:** \\cdsesub1\evsprod\BLA761032\ **Review Files:** \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Brodalumab_BLA761032_DDM\
Pop-PK Analysis		
Input file	mbc16jan xpt	0008\m5\datasets\119155a\analysis\legacy\datasets
Code	36750422c13-ctl.txt	0000\m5\datasets\119155a\analysis\legacy\programs
Output files	36750422c13par-tab.txt	0008\m5\datasets\119155a\analysis\adam\datasets
	36750422c13-tab.txt	
Exposure-Efficacy Analyses		
Input files	Pkpd102.xpt	
	Pkpd103.xpt	0008\m5\datasets\119155a\analysis\adam\datasets
	Pkpd104.xpt	
	pksim1-tab.txt	0008\m5\datasets\119155b\analysis\adam\programs
Code	er-pk-spga-r.txt	0008\m5\datasets\119155b\analysis\adam\programs
Exposure-Safety Analyses		
Input files	Adsl.xpt	0000\m5\datasets\iss-for-psoriasis\analysis\adam\datasets
	Adae.xpt	0000\m5\datasets\iss-for-psoriasis\analysis\adam\datasets
	Adpc xpt	0000\m5\datasets\d5190c00493-20120102\analysis\adam\datasets
	Adpc xpt	0000\m5\datasets\d5190c00494-20120103\analysis\adam\datasets
	Adpc xpt	0000\m5\datasets\d5190c00495-20120104\analysis\adam\datasets
Codes	t-ae-sub-exp-wk12.sas	
	t-ae-sub-exp-wk52.sas	0008\m5\datasets\119155b\analysis\adam\programs
	t-ae-sub-exp-wk52-v2.sas	
IL-17-SIB relationship analysis		
Input file	adpds.xpt	0008\m5\datasets\d5190c00493-20120102\analysis\adam\datasets
Code	IL17_analysis.sas	ER_Analyses\codes

4.3.1 Dose selection for Phase 3

The selection of doses and dosing regimen for Phase 3 was based on safety and efficacy observed in the Phase 2 study 20090062 (multiple dose study) and PK/PD modeling results of the combined Phase 1 study 20060279 (single dose study) and Phase 2 study 20090062.

Observed Data

The Phase 2 dose ranging study 20090062 in adult subjects with moderate to severe plaque psoriasis evaluated doses of 70, 140 and 210 mg subcutaneous (SC) injections of brodalumab every two weeks (Q2W) and 280 mg SC Q4W. All dose levels demonstrated statistically and clinically significant efficacy (with $p < 0.0001$) by percent improvement from baseline in PASI score at week 12, with 45.0%, 85.9%, 86.3%, and 76.0% improvement in 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively, compared to 16.0% in the placebo group. PASI 75 and PASI 100 responses were higher in the 210 mg Q2W group (82.5% and 62.5%) compared to 140 mg Q2W group (76.9% and 38.5%), while 0% subjects achieved PASI 75 or PASI 100 response in placebo group (Table 4.3.1.a).

Analysis by weight subgroup suggested that heavier subjects had highest efficacy with 210 mg Q2W dosing and heavier subjects seemed to require higher doses to achieve similar efficacy as that with lower doses in lighter subjects (Table 4.3.1.b).

Table 4.3.1.a. Primary and Secondary Efficacy Results at Week 12 across Treatment Groups in Phase 2 study 20090062. (*Data source: Table 14, Summary of Clinical Efficacy*)

	Placebo (N=38)	Brodalumab			
		70 mg Q2W (N = 39)	140 mg Q2W (N = 39)	210 mg Q2W (N = 40)	280 mg Q4W (N = 42)
Percent improvement from baseline in PASI score; Mean (SD)*	16.0 (27.0)	45.0 (41.7)	85.9 (22.5)	86.3 (27.6)	76.0 (32.7)
PASI 75** n/N (%)	6/38 (15.8)	20/39 (51.3)	35/39 (89.7)	36/40 (90.0)	34/42 (81.0)
PASI 100** n/N (%)	0/38 (0.0)	4/39 (10.3)	15/39 (38.5)	25/40 (62.5)	12/42 (28.6)
sPGA 0/1** n/N (%)	1/38 (2.6)	10/39 (25.6)	33/39 (84.6)	32/40 (80.0)	29/42 (69.0)

* Primary endpoint at Week 12
** Secondary endpoints at Week 12

Table 4.3.1.b. PASI Responses at Week 12 by Baseline Weight Groups and Treatment in Phase 2 study 20090062. (*Data source: Table 1, Summary of Weight-based Dosing Analysis*)

PASI Response Baseline weight group	Placebo (N = 38)	Brodalumab 70 mg Q2W (N = 39)	Brodalumab 140 mg Q2W (N = 39)	Brodalumab 210 mg Q2W (N = 40)	Brodalumab 280 mg Q4W (N = 42)
PASI 75 - n/N1 (%)					
≤ 75 kg	0/11 (0.0)	10/13 (76.9)	8/8 (100.0)	11/11 (100.0)	8/9 (88.9)
> 75 to 90 kg	0/13 (0.0)	1/8 (12.5)	7/8 (87.5)	8/11 (72.7)	11/14 (78.6)
> 90 to 100 kg	0/7 (0.0)	1/5 (20.0)	9/9 (100.0)	5/5 (100.0)	6/8 (75.0)
> 100 kg	0/7 (0.0)	1/13 (7.7)	6/14 (42.9)	9/13 (69.2)	3/11 (27.3)
PASI 100 - n/N1 (%)					
≤ 75 kg	0/11 (0.0)	4/13 (30.8)	7/8 (87.5)	9/11 (81.8)	4/9 (44.4)
> 75 to 90 kg	0/13 (0.0)	0/8 (0.0)	4/8 (50.0)	6/11 (54.5)	5/14 (35.7)
> 90 to 100 kg	0/7 (0.0)	0/5 (0.0)	4/9 (44.4)	4/5 (80.0)	3/8 (37.5)
> 100 kg	0/7 (0.0)	0/13 (0.0)	0/14 (0.0)	6/13 (46.2)	0/11 (0.0)

N = number of subjects randomized to the specified dose; N1 = number of subjects in each baseline weight class; Q2W = every 2 weeks; Q4W = every 4 weeks; PASI 75 = ≥ 75% improvement from baseline psoriasis area and severity index score; PASI 100 = 100% improvement from baseline PASI score

Results from Dose-Response Modeling

The Applicant performed an analysis to characterize the dose-response relationship for brodalumab treatment of subjects with psoriasis in Phase 2 study 20090062. An E_{max} dose-response model was used to characterize percent improvement in PASI at Week 12. The final model accounted for weight effect on ED_{50}.

The dose-response model equation is as follows:

$$E = E_0 + \frac{(E_{max} - E_0)D^{\gamma}}{ED_{50}^{\gamma} + D^{\gamma}}$$

where E_0 is the response for subjects administered placebo (D = 0), E_{max} is the theoretical maximum response, ED_{50} is the dose (mg Q2W) to achieve half-maximal response, γ is the Hill slope coefficient, and E is the predicted response for any dose D administered SC Q2W. Data from subjects administered 280 mg Q4W in the Phase 2 study were excluded from this analysis.

To evaluate the effect of total body weight on percent PASI improvement, ED_{50} was modeled as a function of weight:

$$ED_{50} = \overline{ED}_{50}\left(WT/90\right)^{\theta}$$

where WT is the subject total body weight, θ is the weight effect exponent, and ED_{50} is the dose to achieve half-maximal response for a 90 kg subject.

The final parameter estimates for the dose-response model are listed in Table 4.3.1.c.

Table 4.3.1.c. Parameters estimates for the Dose-Response model for percent improvement in PASI. (*Data source: Background material submitted to EDR on 01/31/2011 for EOP2 briefing on 03/09/2011 for IND 104671*)

Parameter	Estimate	SE (%)	Units

E_{max}	98.7	2	%
ED_{50} (WT=90 Kg)	85.7	6	mg Q2W
ED_{50} (WT=75 Kg)	62.5	9	mg Q2W
ED_{50} (WT=100 Kg)	103	8	mg Q2W
ED_{50} (WT=125 Kg)	152	19	mg Q2W
θ	1.7	18	-
E_0	15.6	28	%
γ	4.21	26	-

Large Hill slope coefficient (4.21) was needed to capture the sigmoid-shaped response curve, which was likely due to the highly nonlinear PK. The residual standard deviation was 23.5% (SE: 16%). As per the Applicant, dose and weight provided a superior predictor of efficacy than dose and BMI, while the performance was similar with steady state Css exposure (data not shown).

Figure 3.3.1.b shows the observed percent improvement in PASI for subjects with >100 kg and ≤100 kg body weight and dose-response model predicted percent PASI improvement for typical subjects weighing 75, 100, and 125 kg. Observed and model predicted dose response by body weight for Week 12 percent PASI improvement showed that doses of 140 and 210 mg Q2W resulted in near maximal PASI response for lighter weight subjects. Further, analysis by body weight confirmed that dosing with 210 mg achieved higher response than with 140 mg Q2W in heavier weight subjects (Figure 3.3.1.b). Based on these findings, 140 mg and 210 mg Q2W were carried forward in Phase 3 trials.

4.4 Clinical PD assessments: changes in mRNA expression

4.4.1 Background

Brodalumab is a human monoclonal IgG2 antibody that binds to human interleukin 17 Receptor A (IL-17RA). IL-17RA, a member of the IL-17 receptor family, is a protein that is ubiquitously expressed on the surface of a wide range of tissues and cell types. IL-17RA, when stimulated by the IL-17 family of cytokines that have variable binding affinities, forms a heterodimeric receptor complex with other IL-17 receptor family members (e.g., IL-17RB, IL-17RC, and IL-17RE). This leads to the initiation of the downstream signaling pathways that induce the production of pro-inflammatory molecules [PMID: 24011563, 18684971]. Significant alterations in IL-17 family cytokine concentrations have been reported in the psoriatic skin [PMID: 19016708]. Additionally, keratin subfamily, including keratin16 (KRT16), which is involved in keratinocyte differentiation and hyperproliferation are dysregulated in the psoriatic skin [PMID: 7577575].

According to the Applicant, IL-17RA antagonism blocks the biological activities of the pro-inflammatory cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer, and IL-25, leading to inhibition of inflammation in the skin, and consequently improving clinical symptoms associated with psoriasis. The purpose of this review is to evaluate the pharmacodynamics (PD) effect of brodalumab on the expression of IL-17, IL-6, IL-12, IL-23, and KRT16 mRNAs, and whether labeling changes or additional pharmacogenetic studies are indicated based on these results. For evaluation of changes in serum IL-17A protein levels, refer to Section 3.3.6.

4.4.2 Submission contents related to mRNA expression

The Applicant collected mRNA data in the following four Phase 1-3 studies (Table 4.4.2.a).

Table 4.4.2.a: Studies evaluating the pharmacodynamic effect of brodalumab on mRNA expression

Study name	Design	Dose/ Regimen	Objective	mRNA evaluated	PD sampling rate (%)
20120102	Phase 3, multi-center, double-blind, randomized, placebo controlled study in patients with stable moderate to severe plaque psoriasis	Induction: placebo or brodalumab 140 or 210 mg SC Q2W + week 1 (day 1 to week 10) Withdrawal: assigned to brodalumab 210 mg SC Q2W (weeks 12 to 266) or rerandomized to placebo or brodalumab 140 mg or 210 mg SC Q2W + week 13 (weeks 12 to 266 or inadequate response)	Efficacy and Safety	IL-17A, IL-17C, IL-17F, IL-12B, IL-23A	37/661 (5.6%)
20060279	Phase 1, 2 part, multi-center, randomized, double-blind, placebo controlled study Part A: healthy adults Part B: subjects with moderate to severe	Part A: Placebo or brodalumab: 7, 21, 70, 210, or 420 mg SC (single dose), Or placebo or brodalumab: 21, 210, or 700 mg IV (single dose) Part B: Placebo or brodalumab: 140 or 350 mg SC (single	Safety, Tolerability, PK, PD	IL-6, KRT16	IL6 Part A: 57/58 (98.3%) and Part B: 11/26 (42.3%)

	psoriasis	dose), or placebo or brodalumab: 700 mg IV (single dose)			KRT16 Part B: 25/26 (96.1%)
KHK4827 -001	Phase 1, 2 part, multi-center, ascending single-dose study Part A: single-blind, placebo controlled study in healthy male adults Part B: open-label, non-controlled study in patients with active but clinically stable plaque psoriasis	Part A: Placebo or brodalumab: 70, 140, 210, or 420 mg SC (single dose), Or placebo or brodalumab 210 mg IV (single dose) Part B: Brodalumab 140 or 350 mg SC (single dose)	Safety, Tolerability, PK	IL-6	Part A: 30/40 (75%) Part B: 13/13 (100%)
20090062	Phase 2, multi-center, randomized, double-blind, placebo controlled, multiple-dose study in patients with psoriasis	Brodalumab: 70, 140, or 210 mg SC Q2W + week 1 (day 1 to week 10), Or brodalumab: 280 mg SC Q4W (day 1 and weeks 4 and 8) + placebo (weeks 1, 2, 6, and 10), Or Placebo: Q2W + week 1 (day 1 to week 10)	Efficacy, Safety	KRT16	24/198 (12.1%)

Note: PD = Pharmacodynamics, PK = Pharmacokinetics, IL = Interleukin, KRT16 = Keratin 16.

Reviewer's comments:

- *The PD mRNA biomarker analysis is an exploratory analysis based on data from four different studies. The mRNA biomarker assessment was inconsistent across studies with low sample acquisition, specifically in Phase 2 and Phase 3 studies (Table 4.4.2.a).*
- *Table 4.4.2.a does not include PD data for IL-6 mRNA collected in Study 20070264 that was performed in patients with rheumatoid arthritis.*
- *Additionally, in Study 20120102 data for KRT16 mRNA were not included in the current submission.*

4.4.3 Changes in mRNA expression

4.4.3.1 Changes in the expression of interleukin mRNAs

The PD effect of brodalumab on the expression of IL-17A, IL-17C, IL-17F, IL-12B, and IL-23A cytokine mRNAs was evaluated in Study 20120102.

Study 20120102 evaluated the efficacy, safety, and effect of withdrawal and retreatment with brodalumab in patients with moderate to severe plaque psoriasis (Table 4.4.2.a). In this study, 661 patients were treated at a 1:1:1 ratio with either brodalumab (210 mg Q2W or 140 mg Q2W) or placebo during the induction phase (12 weeks). At Week 12, based on the static physician's global assessment, patients were re-randomized in a 1:1 ratio to either placebo or to continue brodalumab at their induction dose. This study included an exploratory skin biopsy biomarker sub-study in which biopsies could be collected from consenting subjects at baseline, weeks 12, 16, 24, and 52.

RNA and cDNA were generated using an undescribed method and cytokine mRNA transcripts (IL-17A, IL-17C, IL-17F, IL-12B, and IL-23A) were measured using droplet-digital PCR. Differences in mRNA expression between each brodalumab treatment group (N=10 in the 140 mg and N=12 in the 210 mg) and the placebo group (N=15) at week 12 were analyzed. Cytokine mRNA gene expression was normalized by taking the log ratio of cytokine gene expression level over the reference RNA binding motif containing (RBM) gene expression level. The p-value was calculated from an ANCOVA model adjusting for total body weight at baseline (≤100 kg/>100 kg), prior biologic use (yes/no), geographic region, and normalized baseline cytokine value.

Per the Applicant's analysis, IL-17A, IL-17C, and IL-17F mRNAs were significantly decreased (p-value ≤0.001) in lesional skin in patients treated with 140 mg or 210 mg brodalumab at week 12 when compared to patients on placebo (Table 4.4.3.a). Additionally, IL-12B and IL-23A mRNAs were significantly decreased in lesional skin in patients treated with 140 mg (p-value =0.002) or 210 mg brodalumab (p-value ≤0.001) compared to lesional skin from patients on placebo. However, these p-value are reported to be nominal after multiplicity correction. No significant decrease in cytokine mRNA was reported for biopsies from non-lesional skin biopsies. No statistical analysis for significance was performed for the withdrawal period (weeks 16, 24, and 52).

Table 4.4.3.a: Summary of normalized IL-17A, IL-17C, IL-17F, IL-12B, and IL-23A mRNA in lesional skin biopsies by treatment group during the induction phase

	IL-17A		IL-17C		IL-17F		IL-12B		IL-23A	
Treatment Difference [α]	140 mg Q2W [β]	210 mg Q2W [γ]	140 mg Q2W [β]	210 mg Q2W [γ]	140 mg Q2W [β]	210 mg Q2W [γ]	140 mg Q2W [β]	210 mg Q2W [γ]	140 mg Q2W [β]	210 mg Q2W [γ]
LS Mean	-5.1	-6.9	-4.7	-5.5	-4.1	-5.2	-3.5	-5.0	-1.7	-2.7
SE	1.1	1.1	0.9	0.9	1.0	1.0	1.0	1.0	0.5	0.5
(95% CI)	(-7.4, -2.9)	(-9.2, -4.6)	(-6.7, -2.8)	(-7.3, -3.6)	(-6.2, -2.0)	(-7.3, -3.1)	(-5.5, -1.4)	(-6.9, -3.0)	(-2.8, -0.7)	(-3.6, -1.7)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	0.002	<0.001

Source: Applicant's Tables 14-4.99.11.11-15 of Clinical Study Report: 20120102; [α] Treatment difference between baseline and week 12 of brodalumab treatment compared to placebo (N=15 at week 12); [β] N=10; [γ] N=12; CI=confidence interval; LS Mean=least squares mean; SE=standard error.

Reviewer's comments: *Exploratory biomarker data are available from a subset of patients included in the study. Because of the small sample size (5.6% of the subjects enrolled and 1.8% of the patients treated at the proposed dose of 210 mg SC), large variance, and lack of multiplicity adjustment, the data should be interpreted with caution.*

4.4.3.2 Changes in the expression of IL-6 mRNA

As IL-17A-dependent IL-6 mRNA induction was expected to be competitively inhibited by brodalumab, in two studies 20060279 and KHK4827-001, the Applicant explored brodalumab-dependent shift in the half-maximal effective concentration (EC_{50}) of the IL-17A induced increase in IL-6 mRNA. This was performed using the whole blood stimulation (WBS) assay, a functional *ex vivo* assay in which peripheral blood samples that were collected from subjects were stimulated with various concentrations of IL-17A in the presence of TNFα. IL-6 mRNA expression was then measured in whole blood lysate using QuantiGene Plex Branched-DNA (bDNA) Assay (Panomics). Changes from baseline in EC_{50} of IL-17A were determined from the dose-response curve of the

IL-17A-dependent IL-6 mRNA production and were expressed in terms of summary statistics by treatment group and blood sampling time point.

Study 20060279 was the first-in-human study that evaluated the safety, tolerability, pharmacokinetics (PK), and PD of brodalumab in healthy subjects and subjects with moderate to severe psoriasis (Table 1). In Part A, 58 healthy subjects received single dose of placebo or brodalumab (SC: 7, 21, 70, 210, or 420 mg or IV: 21, 210, or 700 mg) and in Part B, 26 patients with moderate to severe psoriasis received single injections of placebo or brodalumab (SC: 140 or 350 mg, or IV: 700 mg). The exploratory PD endpoints included changes in psoriasis skin and blood biomarkers (changes in the expression of pre-specified IL-17-induced gene, IL-6, in whole blood pre- and post-dose, as well as quantitative measurements of RNA levels of psoriasis (keratin 16, (KRT16); Part B only; see Section 4.4.3.3). WBS data were collected from 68 subjects (57 subjects from Part A (N=43 brodalumab and N=14 placebo) and 11 patients from Part B (N=8 brodalumab and N=3 placebo)). The Applicant reported that a dose-dependent increase in the amounts of IL-17A was needed to reach the EC_{50} in subjects who received brodalumab (Table 4.4.3.b).

Table 4.4.3.b. Functional blockade of IL-17 signaling brodalumab in an ex-vivo assay as measured by EC_{50} shift

		Log_{10} (EC_{50}) Shift from Baseline						
Cohort	Dose	Day 1 (30 min)	Day 5	Day 8	Day 15	Day 29	Day 43	Day 64
1	7 mg SC	--	-0.04	-0.27	--	--	-0.24	--
2	21 mg SC	--	0.22	0.22	--	--	0.35	--
3	21 mg IV	2.08	--	0.4	--	--	0.19	--
4	70 mg SC	--	1.32	0.91	--	--	-0.04	--
5	210 mg SC	--	2.35	--	1.22	--	--	-0.13
6	210 mg IV	2.49	--	--	2.09	--	--	-0.24
7	420 mg SC	--	2.1	--	2.12	--	--	0.15
8	700 mg IV	1.72	--	--	1.74	--	--	-0.99
9	700 mg IV	--	--	--	--	1.95	1.46	--
10	140 mg SC	--	--	--	--	0.45	0.27	--
11	350 mg SC	--	--	--	--	2.02	0.45	--
	Placebo	0.03	-0.08	0.19	0	0.04	0.27	0.05

Source: Applicant's Tables 10-4 of Clinical Study Report: 20060279; -- = no data available; EC_{50} = half maximal effective concentration of IL-17 (ng/mL); IV = intravenous; SC = subcutaneous.

Study KHK 4827-001 was a group-sequential dose-escalation study conducted in Japan (Table 4.4.2.a). Subjects received placebo or brodalumab (SC: 70, 140, 210, 350, or 420 mg, or IV: 210 mg). The exploratory endpoints included PD changes in IL-17A (EC_{50}) by WBS assay. Of the 53 subjects enrolled, 43 (N=30 healthy adults and N=13 patients) were included in the PD analysis. An increase in the EC_{50} value of IL-17A after treatment (Day 3 and/or Day 8) with single-dose brodalumab when compared to baseline was reported in both healthy subjects and patients with psoriasis.

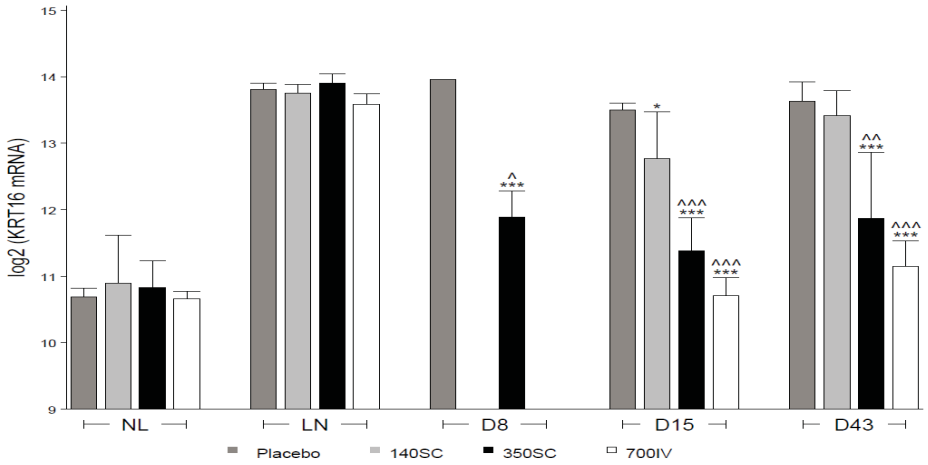
Reviewer's comments: *Applicant's exploratory data from studies 20060279 and KHK4827-001 suggest a brodalumab-dependent shift in the half-maximal effective concentration (EC_{50}) of the IL-17A induced increase in IL-6 mRNA.*

4.4.3.3 Changes in the expression of KRT16 mRNA

PD changes in KRT16 mRNA were measured in Studies 20120102 (data not included in the current submission), 20060279, and 20090062. In both studies 20060279 and 20090062, RNA was isolated from samples frozen in liquid nitrogen. Messenger RNA was analyzed by microarray using Nugen Ovation RNA labeling kits and Affymetrix U133p2 microarrays (representing approximately 39,000 genes). For statistical analysis, KRT16 expression values were converted to log values.

In Study 20060279 Part B, microarray analysis was performed in 25 subjects (N=20 brodalumab and N=5 placebo) with approximately 4 skin biopsies each (N=99 samples). Based on 20 patients, dose-dependent PD effect of brodalumab, as well as, significant difference in baseline KRT16 mRNA between lesional and non-lesional tissue (p-value <0.001), and treatment with brodalumab on days 15 and 43 when compared to baseline (p-value <0.05) was reported (Figure 4.4.3.a).

Figure 4.4.3.a. Mean and standard error of log2 KRT16 mRNA for non-lesional, lesional measurements by the different time points and treatment group



Source: Applicant's Figure 10-11 from Clinical Study Report: 20060279. D=day; IV=intravenous; LN=lesional; NL=non-lesional; SC=subcutaneous; Day 8 data was available only from 5 subjects. Test a=Test for the significance that if post assessment is less than baseline lesional assessment for each treatment group *: P<0.05, **: P<0.01, and ***: P<0.001; Test b=Test for the significance if assessment for brodalumab treated group is less than placebo group at each time point ^: P<0.05, ^^: P<0.01, and ^^^: P<0.001.

Study 20090062 evaluated the safety and efficacy of brodalumab in patients with psoriasis (Table 4.4.2.a). This study enrolled 198 patients randomized to 1:1:1:1:1 receive brodalumab 70, 140, or 210 mg on day 1 and weeks 1, 2, 4, 6, 8, and 10, or 280 mg at day 1 and weeks 4 and 8, or placebo. KRT16 mRNA expression was measured as a part of the exploratory objective. In the optional biomarker sub-study, 24 patients had up to 4 skin biopsies (lesional and non-lesional sites) at baseline, week 2, and week 12 (total 88 samples, 20 subjects provided samples at all 3 time points). Data for KRT16 mRNA expression was reported in 4 patients in each of the 5 different treatment groups. KRT16 mRNA expression was significantly higher (p-value <0.001) in the lesional biopsy when compared to non-lesional biopsy at the baseline. The Applicant reported that treatment with brodalumab significantly decreased (p-value <0.05) the expression of KRT16 mRNA in the lesional skin biopsy at weeks 2 and 12, with a trend for dose-dependent decrease in mRNA expression. No significant difference was reported in patients treated with placebo.

Reviewer's comments: *In both studies, biomarker data are from an optional sub-study, and therefore data are limited because of the requirement of additional consent, as well as, some instances of sample losses and RNA integrity issues. Though mRNA expression was analyzed using a microarray, data for only KRT16 mRNA expression are included in the study results. Results are considered premature given that data are only available from a small subset of patients treated with brodalumab (Table 4.4.2.a). Additionally, limited biomarker data are available from patients treated at the proposed dose (210mg SC); none of the patients in Study 20060279 Part B and only 2% (N=4/198) in Study 20090062 were treated with brodalumab at the proposed dose (210 mg SC).*

4.4.4 Summary and Conclusions

Brodalumab is a human monoclonal IgG2 antibody that binds to human IL17RA. In this submission, the Applicant explored the PD effect of brodalumab on the expression of select mRNA biomarkers, namely, IL-17A, IL-17F, IL-17C, IL-12B, IL-23A, IL-6, and KRT16. Based on the exploratory analysis from a small subset of patients, treatment with brodalumab reportedly reduces the levels of pro-inflammatory cytokines and other psoriasis skin biomarker, which can potentially lead to inhibition of the inflammation and improvement of clinical symptoms associated with psoriasis. (b) (4) Please see integrated labeling recommendations in Section 2.4.

4.5 Individual Study Summary

4.5.1 Study 20110184 (Phase 1 extrinsic factor: disease-DDI)

Title

- An Open-label Study to Evaluate the Effect of Brodalumab on the Pharmacokinetics of Midazolam and Assess Single-dose Brodalumab Pharmacokinetics in Subjects with Moderate to Severe Plaque Psoriasis

Study period

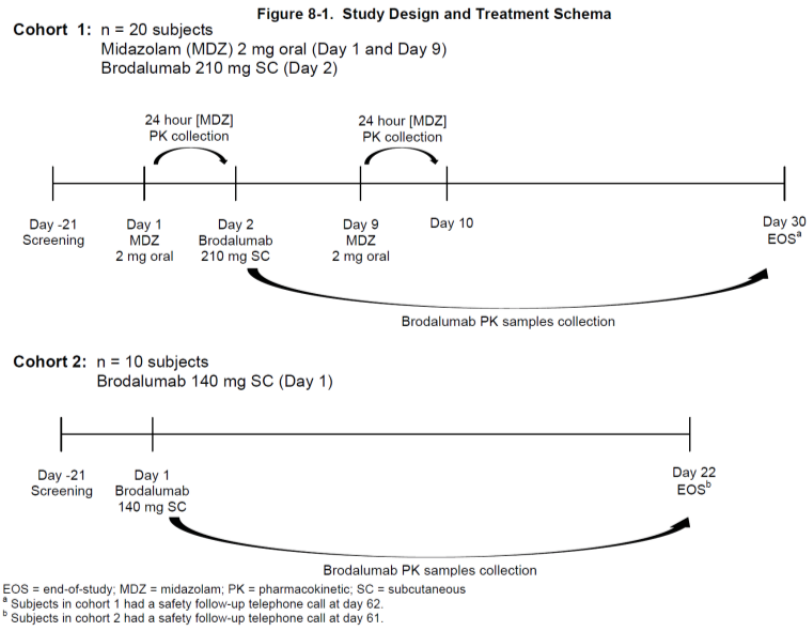
- 17 September 2013 (the first subject enrolled) to 26 July 2014 (the last subject completed follow-up)

Objectives

- **Primary Objective**: To characterize the effect of brodalumab on the PK of midazolam in subjects with moderate to severe plaque psoriasis based on area under the concentration-time curve (AUC) and maximum observed drug concentration (Cmax).
- **Secondary Objectives:**
  - To assess brodalumab PK after single 140 mg and 210 mg dose subcutaneous (SC) administration in subjects with moderate to severe plaque psoriasis
  - To assess additional PK parameters of midazolam
  - To evaluate the safety, tolerability, and immunogenicity profile of brodalumab
- **Exploratory Objective**: To evaluate the effect of brodalumab on biomarkers, such as C-reactive protein (CRP) and IL-17.

Study design

Study design is shown in the figure below:



20110184-Figure-8-1. Study design for study 20110184. (*Data source: CSR 20110184, Figure 8-1*)

Study population:

Eligible subjects were men and women ≥18 to ≤75 years of age at the time of screening, with stable moderate to severe plaque psoriasis diagnosed at least 6 months before the first dose of investigational product, with involved body surface area (BSA) ≥10%, psoriasis area and severity index (PASI) ≥12, and static physician global assessment (sPGA) ≥3 at screening and at baseline.

Of the 31 subjects enrolled in the study, 24 were men and 7 were women. The majority (24 subjects) were white.

Investigational products

The investigational product used in this study was brodalumab (140 mg/mL, 0.5 and 1.0 mL PFS). Cohort 1 subjects received a 210 mg SC dose of brodalumab on day 2, administered as one 1 mL and one 0.5 mL PFS. Cohort 2 subjects received a 140 mg SC dose of brodalumab on day 1, administered as one 1.0 mL PFS.

Non-investigational products

The non-investigational product used in this study was midazolam 2 mg (solution) administered orally. Subjects in cohort 1 received a 2 mg oral dose of midazolam on Day 1 and Day 9. Midazolam was administered after a 10-hour fast. Midazolam was not administered to subjects in cohort 2.

Midazolam PK sample collection:

Midazolam PK samples were collected at Day 1 and Day 9 at Predose and at the following time-points following each dose administration: 0.25 hours, 0.5 hours, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours, 10 hours, and 12 hours, 24 hours.

Brodalumab PK blood sample collection

Brodalumab PK samples were collected at Baseline (Day 2), and Days 3, 4, 5, 6, 9, 13, 16, 19, 23, 26 and 30 (EOS).

Immunogenicity blood sample collection

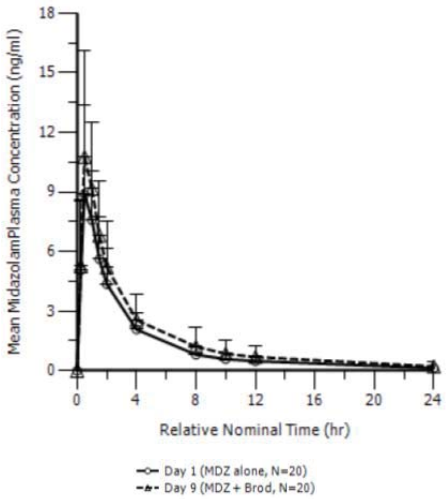
Immunogenicity samples were collected at Baseline (Day 2) and Day 30 (EOS).

Study results

Midazolam pharmacokinetics

Mean (+SD) plasma concentration-time profiles of midazolam are presented in Figure 20110184-11-1. Summary descriptive statistics of PK parameter estimates for midazolam are presented in Table 20110184-11-1 and Table 2011-0184-11-2.

One week after brodalumab administration, there were increases in the AUC_{last} of midazolam by approximately 23%, in the AUC_{inf} of midazolam by approximately 24%, and in the C_{max} of midazolam by approximately 16%. The 90% CIs for the ratios of geometric means for Day 9 (with brodalumab) versus Day 1 (without brodalumab) were [1.12, 1.37] for AUC_{last}, [1.12, 1.38] for AUCinf, and [1.00, 1.36] for C_{max}. It's worth noting that brodalumab concentrations peak 3 days after SC dose administration as such the observed effect of brodalumab on midazolam PK at 7 days after brodalumab SC dosing may not be the maximum effect.



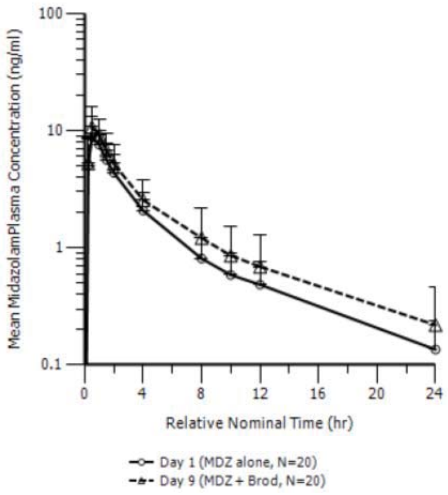


Table 11-1. Midazolam Pharmacokinetic Parameter Estimates After Single Oral Administration of Midazolam 2 mg on Day 1 and Day 9 and SC Single Administration of Brodalumab 210 mg on Day 2 in Subjects with Moderate to Severe Plaque Psoriasis

	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC_{last} (hr•ng/mL)	AUC_{inf} (hr•ng/mL)	AUC_{extrap} (%)	CL/F (mL/min/kg)
	Midazolam Only (Day 1)						
N[a]	20	20	20	20	20	20	20
Mean	9.89	NR	6.33	30.5	32.0	4.09	13.5
SD	3.61	NR	1.45	11.5	12.4	2.06	5.18
Min	3.76	0.25	2.94	16.5	17.5	1.37	7.01
Median	9.52	0.50	6.63	27.9	29.3	3.87	12.2
Max	16.0	2.0	9.39	49.8	54.9	9.22	24.4
CV%	36.5	NR	22.9	37.6	38.7	50.5	38.4
	Midazolam + Brodalumab (Day 9)						
N[a]	20	20	20	20	20	20	20
Mean	11.5	NR	6.65	39.0	41.5	4.68	11.1
SD	4.59	NR	1.74	19.2	22.1	3.58	4.67
Min	5.05	0.50	4.57	18.2	18.8	1.31	3.96
Median	10.4	0.50	6.09	34.4	36.5	3.20	11.1
Max	23.4	1.5	11.0	82.5	97.1	15.1	19.7
CV%	39.8	NR	26.2	49.3	53.4	76.6	41.9

AUC_{extrap} = AUC_{inf} percent extrapolation; AUC_{inf} = AUC from time zero extrapolated to infinity; AUC_{last} = AUC from time zero to time of last quantifiable concentration; CL/F = apparent drug clearance after extravascular administration, adjusted for individual body weight; C_{max} = maximum observed concentration; CV = coefficient of variation; max = maximum; min = minimum; NR = Not reported; SC = subcutaneous; SD = standard deviation; $t_{1/2}$ = half-life; t_{max} = time of C_{max}

[a] All subjects were orally administered midazolam 2 mg on day 1 and day 9; brodalumab 210 mg was administered SC to all subjects on day 2.

Table 11-2. Comparison of Midazolam PK Parameters for Day 1 and Day 9 – Cohort 1, PK Parameter Analysis Set

	Day 1 (N = 20)		Day 9 (N = 20)		Geometric Mean Ratio of Day 9/Day 1[b]	
Parameter (unit)	n	Mean[a]	n	Mean[a]	Estimate	90% CI
AUC_{last} (ng*hr/mL)	20	28.56	20	35.24	1.23	(1.12, 1.37)
AUC_{inf} (ng*hr/mL)	20	29.79	20	37.00	1.24	(1.12, 1.38)
C_{max} (ng/mL)	20	9.24	20	10.75	1.16	(1.00, 1.36)

Figure 20110184-11-1, Table 20110184-11-1 and Table 20110184-11-2. Midazolam PK profiles and PK parameters after single oral administration of 2 mg on Day 1 and Day 9 with single SC administration of brodalumab 210 mg on Day 2 in subjects with moderate-to-severe psoriasis. *(Data source: CSR 20110184)*

Brodalumab pharmacokinetics

Mean (±SD) serum brodalumab concentration-time profiles for cohorts 1 and 2 are presented in Figure 20110184-11-2, and summary descriptive statistics of PK parameter estimates for brodalumab after a single 140 mg or 210 mg SC dose are presented in Table 20110184-11-3.

After a single SC 140 mg dose of brodalumab, the mean AUC_{inf}, AUC_{last}, C_{max}, and median t_{max} were 40.5 mcg•day/mL, 27.8 mcg•day/mL, 4.79 mcg/mL, and 3 days, respectively. After a single SC 210 mg dose of brodalumab, the mean AUC_{inf}, AUC_{last}, C_{max}, and median tmax were 119 mcg•day/mL, 111 mcg•day/mL, 13.4 mcg/mL, and 3 days, respectively.

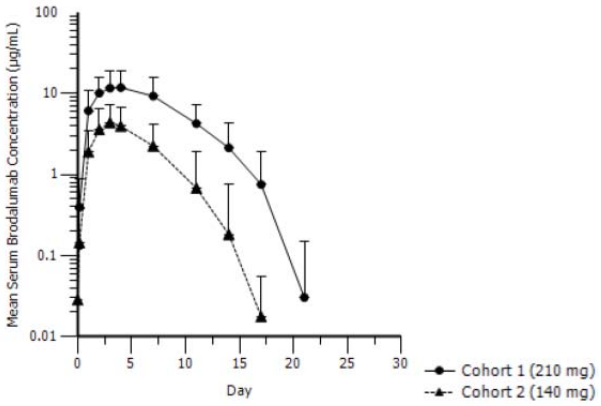


Table 11-3. Brodalumab Pharmacokinetic Parameter Estimates Following a Single SC Administration of Brodalumab 140 mg and 210 mg in Subjects with Moderate to Severe Plaque Psoriasis

		C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (day•µg/mL)	AUC_{inf} (day•µg/mL)
Cohort 1 210 mg	N	19	19	19	18
	Mean	13.4	NR	111	119
	SD	7.29	NR	64.4	66.6
	Min	1.69	2.0	13.0	13.2
	Median	12.6	3.0	104	119
	Max	27.9	4.0	239	253
	CV%	54.3	NR	57.9	55.8
Cohort 2 140 mg	N	9	9	9	4
	Mean	4.79	NR	27.8	40.5
	SD	2.84	NR	20.5	25.3
	Min	1.08	1.0	2.40	2.89
	Median	5.60	3.0	24.4	51.1
	Max	8.68	4.0	56.5	56.7
	CV%	59.2	NR	73.7	62.5

Figure 20110184-11-2 and Table 20110184-11-3. Brodalumab concentration-time profiles and summary descriptive statistics of PK parameter estimates after a single 140 mg or 210 mg SC dose in subjects with psoriasis. (Data source: CSR 20110184)

Pharmacodynamics of serum IL-17A

Summaries of serum IL-17A levels overtime are presented in Tables 20110184-14-7.2.1 and 20110184-14-7.2.2 for cohorts 1 and 2, respectively.

The median baseline IL-17A levels were 0.756 pg/mL and 0.639 pg/mL in cohort 1 and cohort 2, respectively. Increases in serum IL-17A levels were observed in both cohorts. The highest

median IL-17A concentrations were 2.23 pg/mL and 2.35 pg/mL on Day 5 for cohort 1 and Day 4 for cohort 2, respectively, which correspond to 3 days after brodalumab administration in each case. Concentrations returned to the baseline range by the end of the study.

Table 14-7.2.1. Summary of IL-17A (pg/mL) over Time-Cohort 1
Safety Analysis Set

IL-17A (pg/mL)	Baseline	Day 2 Pre-dose	Day 5	Day 9 Pre-dose	Day 16	EOS
Cohort 1 (N = 21)						
n	19	19	20	20	20	20
Mean	2.307	1.025	3.911	3.685	2.508	0.876
SD	6.319	1.501	3.934	5.133	3.074	1.568
SE	1.450	0.344	0.880	1.148	0.687	0.351
Median	0.756	0.617	2.230	2.055	1.565	0.346
Min	0.13	0.11	0.85	0.71	0.40	0.07
Max	27.90	6.85	17.40	24.20	13.20	6.68
Change from Baseline (N = 21)						
n		19	19	19	19	19
Mean		-1.282	1.680	1.476	0.252	-1.397
SD		6.241	6.435	7.063	5.697	5.566
SE		1.432	1.476	1.620	1.307	1.277
Median		0.036	1.695	1.350	0.509	-0.035
Min		-27.02	-21.94	-22.27	-21.61	-24.30
Max		1.16	11.71	18.51	7.51	0.99

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N = Number of subjects in the analysis set, n = number of subjects with non-missing data at the timepoint of interest;SD=standard deviation
Cohort1=2 mg oral dose of midazolam on day 1 and day 9, 210 mg subcutaneous dose of brodalumab on day 2.

Table 14-7.2.2. Summary of IL-17A (mg/L) over Time-Cohort 2
Safety Analysis Set

IL-17A (pg/mL)	Baseline	Day 4	Day 8	Day 15	EOS
Cohort 2 (N = 10)					
n	10	9	10	10	10
Mean	0.678	2.210	1.970	0.842	0.618
SD	0.538	1.066	0.897	0.831	0.445
SE	0.170	0.355	0.284	0.263	0.141
Median	0.639	2.350	1.850	0.560	0.623
Min	0.10	0.31	0.87	0.10	0.09
Max	1.98	3.95	3.56	2.83	1.41
Change from Baseline (N = 10)					
n		9	10	10	10
Mean		1.536	1.291	0.164	-0.060
SD		0.837	0.658	0.692	0.413
SE		0.279	0.208	0.219	0.131
Median		1.410	1.317	0.000	-0.020
Min		0.21	0.32	-0.43	-1.01
Max		3.18	2.79	2.06	0.51

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N = Number of subjects in the analysis set, n = number of subjects with non-missing data at the timepoint of interest; SD=standard deviation
Cohort 2=140 mg subcutaneous dose of brodalumab on day 1.

Table 20110184-14-7.2.1 and Table 20110184-14-7.2.2. Summaries of serum IL-17A levels overtime.

Immunogenicity

No subject was tested positive for the presence of anti-brodalumab antibodies at baseline or anytime during the study.

4.5.2 Study 20130307 (Phase 1: PK comparability)

Title

- A Bioequivalence Study Comparing a Single Subcutaneous Injection With a 1.5 mL Prefilled Syringe Versus 2 Subcutaneous Injections of 1 mL and 0.5 mL Prefilled Syringes of Brodalumab 140 mg/mL to Healthy Subjects

Study period

- 10 September 2014 (the first subject enrolled) to 16 November 2014 (the last subject completed follow-up)

Objectives

- **Primary Objective**: To demonstrate pharmacokinetic bioequivalence (the area under the serum concentration-time curve from time 0 to the time of the last quantifiable concentration [AUC_{last}] and maximum observed serum concentration [C_{max}]) of brodalumab administered in the abdomen of healthy subjects using single injection of a 1.5 mL prefilled syringe ([PFS]; test) relative to the 2 injections of 1 mL and 0.5 mL (PFS; reference)
- **Secondary Objectives:**
  - To characterize other brodalumab pharmacokinetic parameters (including area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}) and time at which Cmax was observed [t_{max}]) after a single 210 mg subcutaneous (SC) dose of brodalumab administered to the abdomen of healthy subjects using single injection PFS test versus 2 injections PFS reference.
  - To evaluate the safety, tolerability, and immunogenicity of a 210 mg SC dose of brodalumab administered to the abdomen of healthy subjects.

Study design

This was a multicenter, open-label, randomized, 2-period crossover study (Figure 20130307-8-1).

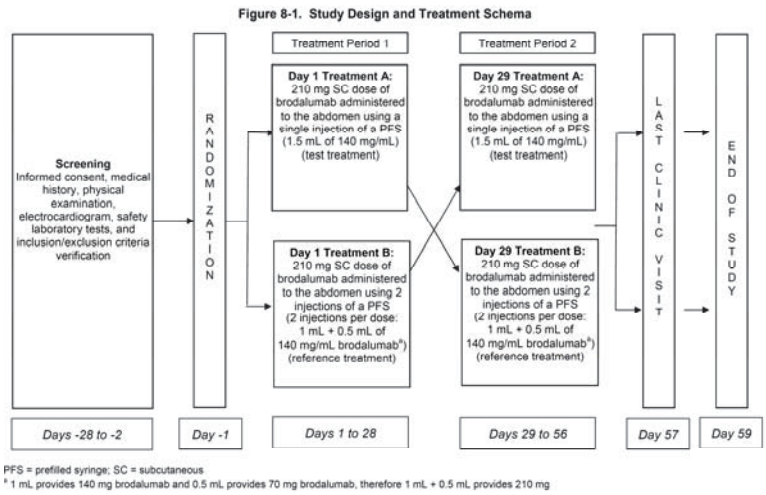


Figure 20130307-8-1. Study design. (*Data source: CSR 20130307, Figure 8-1*)

Test and reference treatment and dose administration

The *test treatment* was 210 mg SC dose of brodalumab administered by a single injection of a PFS (1.5 mL of 140 mg/mL brodalumab (treatment A). The *reference treatment* was 210 mg SC dose of brodalumab administered by 2 injections (2 PFS injections per dose: PFS injection of 1 mL of 140 mg/mL and PFS injection of 0.5 mL of 140 mg/mL brodalumab (Treatment B). Subjects were randomized to receive investigational treatment in 1 of 2 sequences: A/B or B/A (1:1 randomization). Doses were separated by a washout period of approximately 28 days.

Study population: disposition and demographics

- *Study subjects disposition:*
  - Number of subjects randomized: 145 subjects (73 sequence 1 [A/B], 72 sequence 2 [B/A]).
  - Number of subjects who completed: 127 subjects (59 sequence 1, 68 sequence 2).
  - Number of subjects who discontinued: 18 subjects (14 sequence 1, 4 sequence 2).
- *Study subjects (randomized) baseline demographics:*
  - Sex: 91 men (62.8%) and 54 women (37.2%)
  - Age: 40.8±10.7 years (mean±SD); range of 18 to 55 years
  - Race: 116 (80.0%) white, 23 (15.9%) black or African American and 6 (4.1%) others

Study results

Pharmacokinetic Results:

The mean±SD serum brodalumab concentration-time profiles and box plots of PK parameters (AUC_{last}, C_{max}, and AUC_{inf}) after a dose of 210 mg SC administered as a single injection of a 1.5 mL PFS or as 2 injections of 1.0 and 0.5 mL PFS were shown in Figure 20130307-11-1. A summary of PK parameters is provided in Table 20130307-11-1. Statistical evaluation of PK parameters between treatment A and B is provided in Table 20130307-11-2.

The PK results overall demonstrated PK comparability between the two treatments (single 1.5 mL PFS injection and 2 PFS injections [1 mL + 0.5 mL] of brodalumab), as the 90% CIs for the ratio of the geometric least squares means for all 3 PK parameters (AUC_{last}, C_{max}, and AUC_{inf}) were within the [0.8, 1.25] bioequivalence boundaries.

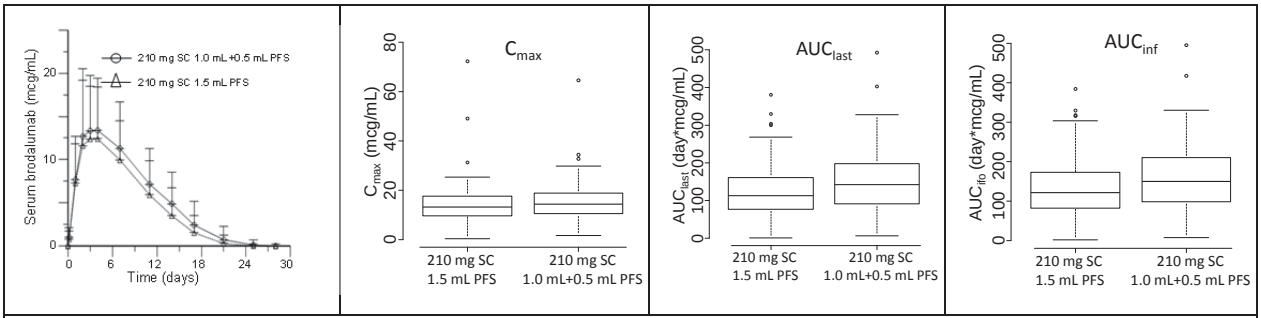


Figure 20130307-11-1. Comparison of the Mean±SD serum brodalumab concentration-time profiles and PK parameters (C_{max}, AUC_{last}, and AUC_{inf}) after 210 mg brodalumab SC administered as a single injection of a 1.5 mL PFS (test) or as 2 injections of 1.0 and 0.5 mL PFS (reference). (*Data source: CSR 20130307, Figure 11-1; reviewer's box plot based on dataset adpp.xpt*)

Table 20130307-11-1. Summary of brodalumab 210 mg SC PK parameters (C_{max}, AUC_{last}, and AUC_{inf}) after 210 mg brodalumab SC administered as a single injection of a 1.5 mL PFS (test) or as 2 injections of 1.0 and 0.5 mL PFS (reference). (*Data source: CSR 20130307, Table 11-1; the results were consistent with reviewer's analysis based on dataset adpp.xpt*)

	1.5 mL PFS (test)			1.0mL+0.5 mL PFS (reference)		
	C_{max} (mcg/mL)	AUC_{last} (day*mcg/mL)	AUC_{inf} (day*mcg/mL)	C_{max} (mcg/mL)	AUC_{last} (day*mcg/mL)	AUC_{inf} (day*mcg/mL)
N	138	138	129	131	131	119
Mean±SD	13.8±7.85	125±69.0	133±71.2	14.8±7.7	149±81.5	158±82.9
Median [range]	13.3 [0.54, 72.3]	113 [2.14, 381]	121 [15.2, 384]	14.4 [1.58, 64.6]	143 [6.53, 493]	150 [6.92, 496]

Table 20130307-11-2. Statistical evaluation of PK parameters (C_{max}, AUC_{last}, and AUC_{inf}) after 210 mg brodalumab SC administered as a single injection of a 1.5 mL PFS (test) or as 2 injections of 1.0 and 0.5 mL PFS (reference). (*Data source: CSR 20130307, Table 11-2*)

		Geometric mean		Geometric mean ratio (test/reference) and 90% confidence interval	
		1.5 mL PFS (test)	1.0 mL+0.5 mL PFS (reference)		
C_{max} (mcg/mL)	N=124	12.52	12.81	0.98	[0.91, 1.05]
AUC_{last} (day*mcg/mL)	N=124	110.89	124.01	0.89	[0.82, 0.98]
AUC_{inf} (day*mcg/mL)	N=112	119.70	132.34	0.90	[0.83, 0.98]

Immunogenicity and its impact on PK

Samples from 7 out of 145 (4.8%) subjects tested positive for anti-brodalumab binding antibodies (ADA) after receiving the first administration of brodalumab on Day 29 prior to the second dose administration. Neutralizing anti-brodalumab antibodies were not detected in any subjects. Individual and mean±SD PK parameters for the ADA positive subjects are provided in Table 20130307-1. The PK results did not suggest that formation of ADA would influence the PK of brodalumab.

Table 20130307-1. PK parameters in subjects tested positive for ADA in Study 20130307. *Subject 30766004012 had early termination from the study and did not have PK data in Period 2 of the study. The mean±SD calculation did not include PK data from subject 30766004012. (*Data source: Reviewer's analysis based on individual PK parameters submitted in CSR 20130307, 16.1.13.2 Supportive Pharmacokinetic Information and dataset adpp.xpt.*)

	Period 1			Period 2		
	C_{max}	AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}
30766003016	17.9	153	154	13.8	127	129
30766003019	4.08	42.5	42.8	18.9	184	187
30766004001	14.6	151	158	18.8	210	214
30766004005	7.84	111	115	8.7	113	119
30766004007	14.1	141	141	11.2	111	111
30766004010	8.93	81.5	81.6	16.0	182	183
30766004012*	17.8	220	223	n/a	n/a	n/a
Mean±SD (n=6)	11.2±5.1	113.3±44.3	115.4±45.5	14.6±4.1	154.5±42.6	157.2±42.8

4.5.3 Study 20090480 (Phase 1: PK comparability)

Title

- An Open-label, Randomized, 2-period Crossover Study to Compare the Pharmacokinetic Bioequivalence of a Single 210 mg Dose of Brodalumab Administered to Healthy Subjects by Subcutaneous Injection Using a Prefilled Syringe and an Autoinjector

Primary Objective

- To demonstrate bioequivalence in pharmacokinetic parameters (the area under the serum concentration-time curve from time 0 to the time of the last quantifiable concentration [AUC_{last}] and maximum observed serum concentration [C_{max}]) of a 210 mg subcutaneous (SC) dose of brodalumab administered in the abdomen of healthy subjects using an autoinjector/pen ([AI]; test) relative to the prefilled syringe ([PFS]; reference) as used in the Phase 3 psoriasis studies.

Study design

In Study 20090480, subjects received single brodalumab 210 mg SC administrations on Days 1 and 29 through either an AI (treatment A, 2 × 0.75 mL injections of 140 mg/mL brodalumab) or a PFS (treatment B, 1.0 mL PFS + 0.5 mL PFS of 140 mg/mL brodalumab). There were 2 treatment periods. Subjects were randomized (1:1) to receive investigational treatment in 1 of 2 sequences: AB or BA in a 2-period crossover design.

Subjects were healthy men and women ≥ 18 to ≤ 55 years of age. A total of 141 subjects were enrolled, of whom 129 subjects completed the study and 12 subjects discontinued. Subjects were mostly men (74.5%) with a mean (SD) age of 38.5 (10.8) years, 120 subjects (85.1%) were white, with a mean (SD) body mass index of 25.87 (2.61) kg/m^2, and a mean (SD) weight of 77.78 (10.82) kg.

Study results

Pharmacokinetics

The PK parameters (two treatment periods combined) of brodalumab after a single 210 mg SC dose delivered using AI or PFS were shown in Table 20090480.1. Statistical evaluation of brodalumab PK comparability between AI and PFS are shown in Table 20090480.2.

Table 20090480.1. Brodalumab PK parameters after a single 210 mg dose administered SC using an AI versus a PFS in healthy subjects. (*Data source*: Table 9, Summary of Clinical Pharmacology; Table 11-1, CSR Study 20090480)

	Brodalumab 210 mg SC AI (Test)				Brodalumab 210 mg SC PFS (Reference)			
	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (day*µg /mL)	AUC_{inf} (day*µg /mL)	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (day*µg /mL)	AUC_{inf} (day*µg /mL)
	Both Periods Combined							
N	138	138	138	125	134	134	134	123
Mean	10.8	NR	109	119	10.6	NR	102	112
SD	4.84	NR	58.2	58.1	5.62	NR	60.1	58.2
Min	0.121	1.0	0.516	28.0	0.824	0.92	4.06	16.9
Median	9.99	3.0	101	109	9.81	3.0	96.1	106
Max	33.1	7.1	362	396	32.7	7.0	334	340
CV%	44.8	NR	53.6	48.8	53.2	NR	58.7	51.9

Table 20090480.2. Statistical evaluation of brodalumab PK parameters after a single 210 mg dose administered SC between AI and PFS. (*Data source*: Table 11-2, CSR Study 20090480)

Parameter (unit)	Treatment B (PFS) (N = 131)		Treatment A (AI) (N = 131)		Geometric Mean Ratio Treatment AB	
	n	Mean[a]	n	Mean[a]	Mean[b]	90% CI
$AUC_{0\text{-}inf}$ (day•µg/mL)	114	99.44	114	110.13	1.11	1.03, 1.19
$AUC_{0\text{-}last}$ (day•µg/mL)	131	82.03	131	92.89	1.13	1.03, 1.24
C_{max} (µg/mL)	131	9.00	131	9.64	1.07	0.99, 1.16

The PK results showed that parameters including AUC_{last}, C_{max}, and AUC_{inf} (not a primary endpoint) of a 210 mg SC dose of brodalumab administered by 2 different methods (2 × 0.75 mL AI and 1.0 mL + 0.5 mL PFS of 140 mg/mL brodalumab) were considered comparable, as the 90% CIs for the ratio (AI/PFS) of the geometric least squares means for all 3 PK parameters were within the [0.80, 1.25] bioequivalence acceptance criteria. The point estimates [90% CI] for AUC_{last}, AUC_{inf}, and C_{max} were 1.13 [1.03, 1.24], 1.11 [1.03, 1.19], and 1.07 [0.99, 1.16], respectively. Note that the Applicant did not propose to register the AI presentations in the BLA.

Immunogenicity and its impact on PK

Samples from 2 subjects were tested positive for anti-drug antibodies (ADA) on Day 29. Neutralizing ADA was not detected in any of these two subjects. Individual PK parameters for the two ADA positive subjects are provided in Table 20090480.3. The PK results suggest that formation of ADA did not appear to influence the PK of brodalumab because (1) the PK parameters were similar before and after ADA formation in ADA+ subjects; and (2) the PK parameters were within the range of these in ADA negative subjects.

Table 20090480.3. PK parameters in subjects tested positive for ADA in Study 20090480. (*Data source: CSR 20090480, Appendix Table 5-3.*)

	Period 1			Period 2		
	C_{max}	**AUC_{last}**	**AUC_{inf}**	**C_{max}**	**AUC_{last}**	**AUC_{inf}**
48066004015	9.52	88.8	89.2	16.6	152	159
48066004021	12.6	143	143	10.1	99.2	102

4.5.4 Study 20110106 (Phase 1: PK and device performance)

Title

- A Randomized, Open-Label Study in Healthy Subjects Evaluating the Tolerability, Safety, Acceptability and Performance of Two Auto-Injector (AI) Devices Used to Subcutaneously Administer AMG 827

Objectives and study design

The overall primary objectives of Study 20110106 were to evaluate the tolerability, safety and performance of two AI devices (b) (4). One of the secondary objectives was to characterize the PK of brodalumab in a substudy. Sixteen subjects participated

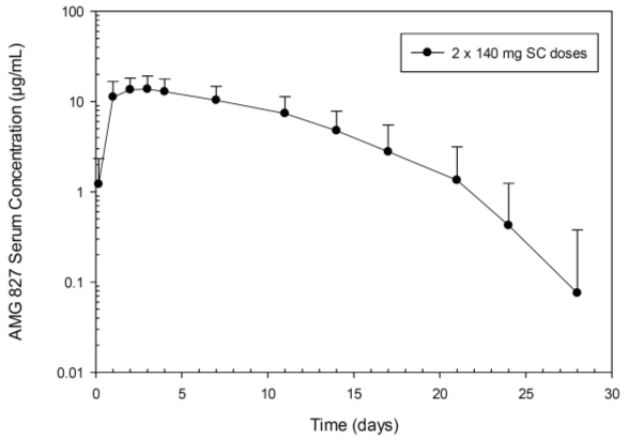
in the pharmacokinetic substudy in which subjects received 2 consecutive injections of brodalumab 140 mg using [redacted] (b) (4) AI.

Study results

Pharmacokinetics

The mean±SD concentration-time profile for serum brodalumab is presented in Figure 20060106.1. The PK parameters are summarized in Table 20060106.1. Following SC administration of brodalumab 280 mg (2 × 140 mg AI administrations), the mean (SD) C_{max} was 14.3 (5.42) mcg/mL, AUC_{last} was 159 (82.4) mcg*day /mL, and AUC_{inf} was 165 (84.4) mcg*day/mL.

Table 20060106.1. Summary of PK parameters of brodalumab after SC administration of 280 mg (2 times 140 mg) in healthy subjects in Study 20110106. (*Data source: Table 10, Summary of Clinical Pharmacology*).



	t_{max} (day)	C_{max} (µg/mL)	AUC_{last} (µg•day /mL)	AUC_{inf} (µg•day /mL)
n	16	16	16	16
Mean	NR	14.3	159	165
SD	NR	5.42	82.4	84.4
CV%	NR	38.0	51.8	51.1
Median	2.2	13.5	140	151
Min-Max	1.1 - 4.2	7.26 - 23.6	55.3 - 309	60.8 - 323

4.5.5 Study 20060279 (Phase 1: PK)

Title

- A Randomized, Double-blind, Placebo-controlled, Ascending Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 827 in Healthy Subjects and Subjects with Moderate to Severe Psoriasis

Study period

- 07 December 2007 (the first subject enrolled) to 02 September 2009 (the last subject visit)

Primary objective

- To assess the safety and tolerability of brodalumab following single dose subcutaneous (SC) or intravenous (IV) administration in healthy subjects and subjects with moderate to severe psoriasis.

Study design

The overall study design and treatment schema is shown in Figure 20060279.1. Study 20060279 consisted of 2 parts: Part A and Part B. In Part A, healthy subjects were randomized to receive a single dose of placebo or brodalumab administered by SC (7, 21, 70, 210, 420 mg) or IV (21, 210, 700 mg) injection. In Part B, subjects with moderate to severe psoriasis were randomized to receive a single dose of placebo or brodalumab at 700 mg IV, 140 mg SC or 350 mg SC.

All subjects (58 enrolled and 57 received planned treatment) in Part A were men with a mean (standard deviation [SD]) age of 24.5 (5.7) years, 52 subjects (91%) were white, had a median BMI of 23.33 kg/m^2, and a median weight of 73.05 kg.

In Part B, 26 subjects with moderate to severe psoriasis enrolled in the study (21 brodalumab, 5 placebo). Subjects were mostly men (76%; 24% women), 23 subjects (92%) were white, with a mean (SD) age of 41.0 (11.4) years, a median BMI of 31.16 kg/m2, and a median weight of 94.60 kg.

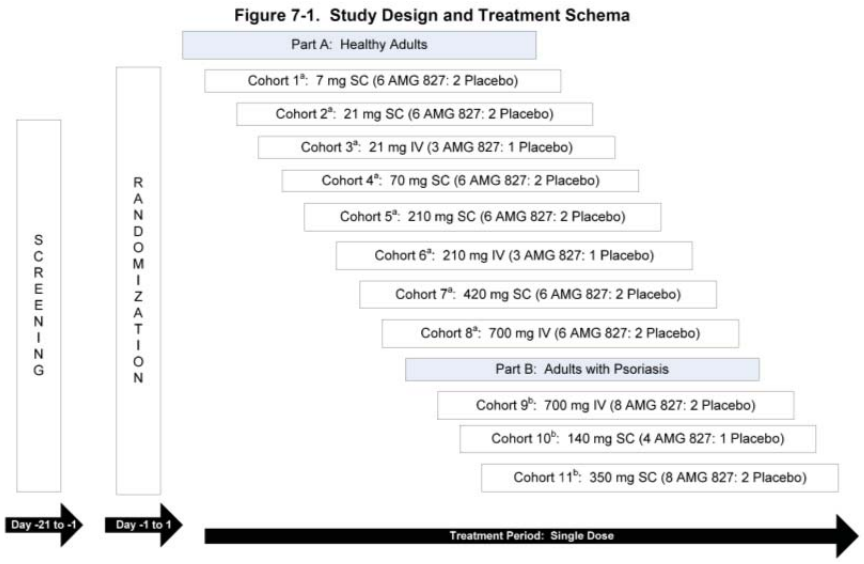


Figure 20060279.1. Study design. *(Data source: Figure 7-1, CSR 20060279)*

Study results

Part A: PK in healthy subjects

Serum brodalumab concentration-time profiles in healthy subjects after IV administration of 21, 210, or 700 mg or after SC administration of 21, 70, 210, or 420 mg are shown in Figure 20060279.2 and Figure 20060279.3. The PK parameters are summarized in Table 20060279.1. Brodalumab exhibited nonlinear pharmacokinetics in healthy subjects after single dose SC or IV administration. Serum brodalumab exposure increased greater than dose-proportionally across the dose range of 21 to 700 mg IV and 70 to 420 mg SC.

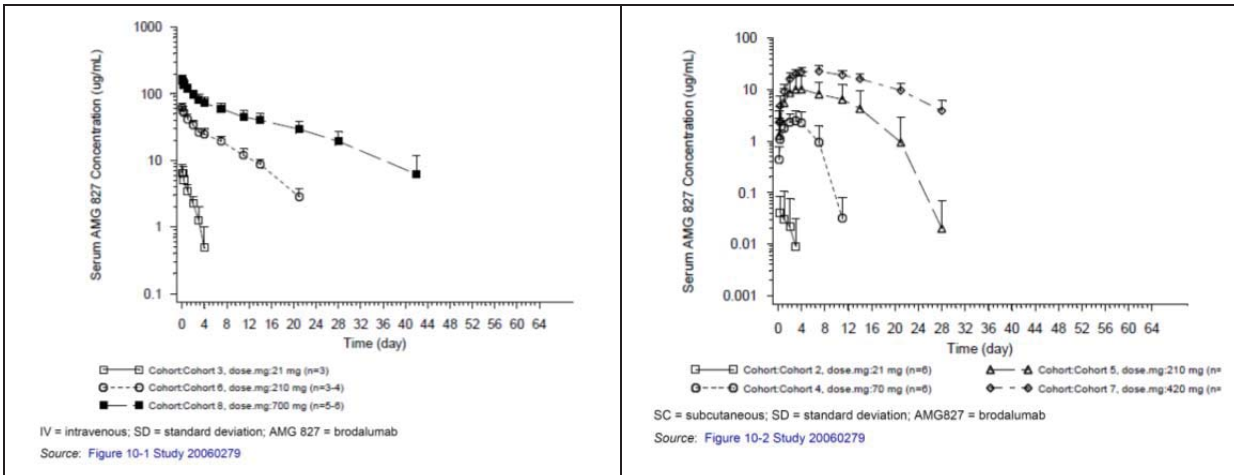


Figure 20060279.2 and Figure 20060279.3. Serum brodalumab concentration-time profiles in healthy subjects after IV administration of 21, 210, or 700 mg (left) or after SC administration of 21, 70, 210 or 420 mg (right). (*Data source: Figure 1 and Figure 2, Summary of Clinical Pharmacology*)

Table 20060279.1. Mean (SD) pharmacokinetic parameters of brodalumab after single dose IV or SC administration in healthy subjects in Study 20060279. (*Data source: Table 2, Summary of Clinical Pharmacology*)

Part	Route	Cohort	Dose (mg)	N	t_{max} (day)[a]	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)
A	IV	3	21	3	0.63 hr (0.63 – 4.0 hr)	6.67 (2.11)	9.92 (3.29)
		6	210	4	0.65 hr (0.63 – 0.65 hr)	63.9 (12.6)	345 (60.1)
		8	700	6	0.67 hr (0.67 – 0.75 hr)	159 (29.5)	1500 (369)
	SC	4	70	6	2.0 (2.0 – 4.0)	2.54 (1.37)	13.0 (8.87)
		5	210	6	4.0 (3.0 – 4.0)	10.6 (8.93)	116 (114)
		7	420	6	7.0 (4.0 – 7.0)	23.6 (5.37)	390 (106)

Part B: PK in subjects with psoriasis

Serum brodalumab concentration-time profiles in subjects with psoriasis after IV administration of 700 mg or after SC administration of 140 or 350 mg are shown in Figure 20060279.4. The PK parameters are summarized in Table 20060279.1. Brodalumab exhibited nonlinear pharmacokinetics in subjects with psoriasis. A greater than dose-proportional increase (5.8-fold) in AUC_{last} was observed over a 2.5-fold increase in brodalumab from 140 to 350 mg SC.

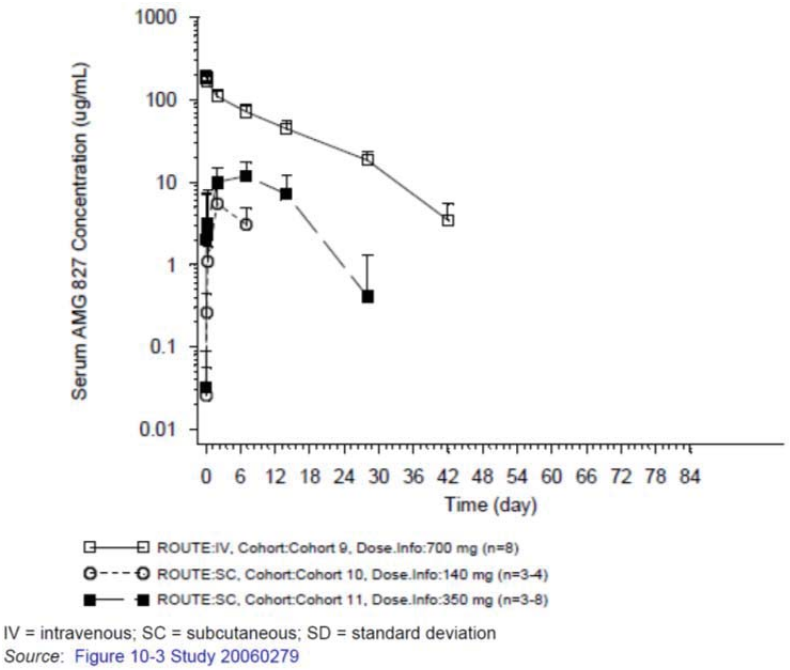


Figure 20060279.4. Serum brodalumab concentration-time profiles in subjects with psoriasis after IV administration of 700 mg or after SC administration of 140 or 350 mg. (*Data source: Figure 7, Summary of Clinical Pharmacology*)

Table 20060279.2. Mean (SD) pharmacokinetic parameters of brodalumab after single dose IV or SC administration in subjects with psoriasis in Study 20060279. (*Data source: Table 6, Summary of Clinical Pharmacology*)

Part	Route	Cohort	Dose (mg)	N	t_{max} (day)[a]	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)
B	IV	9	700	8	2.0 hr (0.68 – 4.9 hr)	198 (39.6)	1660 (352)
	SC	10	140	4	2.0 (1.8 – 2.2)	5.47 (3.00)	26.3 (14.5)
		11	350	8	7.0 (1.9 – 7.0)	12.3 (5.75)	151 (104)

4.5.6 Study 20130337 (Phase 1: PK)

Title

- A Study to Evaluate the Intra-subject Variability of Brodalumab Pharmacokinetic Parameters in Healthy Subjects

Study period

- 14 December 2013 (the first subject enrolled) to 10 May 2013 (the last subject end of study visit)

Primary objective

- To evaluate the intra-subject variability in the pharmacokinetics of brodalumab after SC administration of 140 mg doses in healthy subjects.

Study design

Subjects received 140 mg doses of brodalumab administered as SC injections on Days 1 and 22. A total of 26 subjects received brodalumab on Day 1. Of the 26 subjects, 25 subjects received brodalumab on Day 22. Of the 26 subjects, the mean (SD) age was 37.5 (10.1) years and the mean (SD) weight was 75.39 (9.70) kg.

Study results

PK results

The brodalumab PK parameters after 140 mg dose administration on Day 1 and Day 22 are provided in Table 20120337.1. The C_{max} and AUC_{last} were similar between the doses administered on Day 1 and Day 22. The intra-subject variability (%CV) was 46.6% for C_{max} and 56.3% for AUC_{last}.

Descriptive Statistics	t_{max} (day)	C_{max} (µg/mL)	AUC_{last} (day•µg/mL)	AUC_{inf} (day•µg/mL)
Period 1				
N	26	26	26	20
Mean	NR	7.80	57.9	69.5
SD	NR	4.51	38.3	38.1
Min	1.0	0.181	0.902	4.03
Median	3.0	7.51	52.0	66.9
Max	4.0	18.9	169	170
CV%	NR	57.8	66.1	54.7
Period 2				
N	24	24	23	19
Mean	NR	7.45	56.8	67.4
SD	NR	4.32	36.1	35.4
Min	2.0	0.601	2.07	2.49
Median	3.0	6.55	52.2	65.0
Max	4.0	17.4	145	150
CV%	NR	58.1	63.5	52.6

Table 20120337.1. PK parameters of brodalumab after a single 140 mg dose on Day 1 (Period 1) and Day 22 (Period 2) in healthy subjects in Study 20120337. (*Data source: Table 11-1, CSR 20120337*)

Immunogenicity

No subjects were tested positive for anti-drug antibodies (ADA).

4.5.7 Study 20090062 (Phase 2: Dose-ranging)

Title

- A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of AMG 827 in subjects with psoriasis

Study period

- 09 December 2009 (the first subject enrolled) to 27 September 2010 (last subject follow-up)

Objectives

The primary objectives of the study were to establish a dose-response efficacy profile of brodalumab compared with placebo as measured by the percent improvement from baseline in PASI score at Week 12 and to identify an appropriate dose regimen for future studies.

Study design

Subjects were randomized in a 1:1:1:1:1 ratio to receive brodalumab 70, 140, or 210 mg at Day 1 and Weeks 1, 2, 4, 6, 8, and 10 or 280 mg at Day 1 and Weeks 4 and 8. A total of 198 subjects were enrolled: 160 to AMG 827 and 38 to placebo. The study design is illustrated in Figure 20090062-7.1.

Figure 7.1. Study Design and Treatment Schema

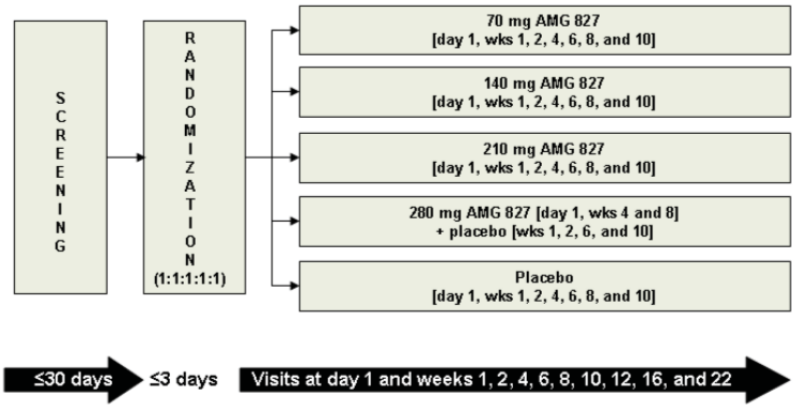


Figure 20090062-7.1. Study design. (*Data source: Figure 7.1, CSR 20090062*)

Efficacy endpoints

The primary efficacy endpoint is percent improvement from baseline in PASI at Week 12.

Secondary and exploratory efficacy endpoints include PASI 75, 90, and 100, sPGA (0,1), and sPGA(0) response rates at Week 12 and other time-points.

Pharmacokinetics

For all subjects, the PK of brodalumab was assessed by evaluating the trough concentrations at weeks 1, 2, 4, and 8, and at weeks 12, 16, and 22 after the last dose administration. For subjects in the PK sub-study, additional 5 blood samples were collected for PK assessment (Table 20090062-Appendix A1).

			Treatment Period											
Study Visit	Screening	Baseline	Wk 1		Wk 2	Wk 4	Wk 6	Wk 8			Wk 10	Wk 12	Wk 16 /ET	Wk 22
Study Day	≤ 30 days	Day 1	Day 8	Day 10 to Day 12 (44 to 100 hours after week 1 dose)	Day 15	Day 29	Day 43	Day 57	Day 59 to Day 61 (44 to 100 hours after week 8 dose)	Day 64 (160 to 176 hours after week 8 dose)				
Dosing of IP		▼	▼		▼	▼	▼	▼			▼			
PK Sub-study Blood Collection			X[a]	X					X	X	X[a]			

[a]Pharmacokinetic samples should be taken prior to IP administration.

Table 20090062-Appendix A1. Blood sampling scheme in the PK sub-study. (*Data source: Appendix A1, CSR 20090062*)

Immunogenicity

Blood samples were collected at baseline, Weeks 4, 16 and 22 for immunogenicity assessment.

Study results

Primary efficacy: percent improvement from baseline in PASI score

The mean percent improvement from baseline in PASI score at Week 12 were 16.0%, 45.0%, 85.9%, 86.3%, and 76.0% improvement in the placebo, 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively (all p-values < 0.0001, compared with placebo) (Table 20090062-9-4).

		AMG827			
	Placebo (N = 38)	70 mg Q2WK (N = 39)	140 mg Q2WK (N = 39)	210 mg Q2WK (N = 40)	280 mg Q4WK (N = 42)
Week 12					
N1	38	39	39	40	42
Mean	16.0	45.0	85.9	86.3	76.0
SD	27.0	41.7	22.5	27.6	32.7
Median	11.8	53.7	96.3	100.0	92.4
Min, Max	-43.8, 70.4	-65.3, 100.0	12.4, 100.0	0.0, 100.0	-4.3, 100.0
P-value		<.0001	<.0001	<.0001	<.0001

Table 20090062-9-4. Primary efficacy results for percent PASI improvement by treatment group at Week 12. (*Data source: CSR 20090062, Table 9-4*)

PASI 75, PASI 90 and PASI 100

The efficacy results for PASI 75, PASI 90 and PASI 100 response rates at both Week 12 and Week 16 are summarized in Table 20090062-9-5. The Week 12 results showed that:

- The proportions of subjects who achieved PASI 75 response were 0%, 33.3%, 76.9%, 82.5%, and 66.7% in the placebo, 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively.
- The proportions of subjects who achieved PASI 90 response were 0%, 17.9%, 71.8%, 75.0%, and 57.1% in the placebo, 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively.
- The proportions of subjects who achieved PASI 100 response were 0%, 10.3%, 38.5%, 62.5%, and 28.6% in the placebo, 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively.

	Placebo (N = 38) n/N1(%)	AMG827 70 mg Q2WK (N = 39) n/N1(%)	AMG827 140 mg Q2WK (N = 39) n/N1(%)	AMG827 210 mg Q2WK (N = 40) n/N1(%)	AMG827 280 mg Q4WK (N = 42) n/N1(%)
PASI 75 Response					
Week 12	0/38 (0.0)	13/39 (33.3)	30/39 (76.9)	33/40 (82.5)	28/42 (66.7)
p-value		<.0001	<.0001	<.0001	<.0001
Week 16	2/38 (5.3)	8/39 (20.5)	25/39 (64.1)	27/40 (67.5)	19/42 (45.2)
p-value		0.0469	<.0001	<.0001	<.0001
PASI 90 Response					
Week 12	0/38 (0.0)	7/39 (17.9)	28/39 (71.8)	30/40 (75.0)	24/42 (57.1)
p-value		0.0057	<.0001	<.0001	<.0001
Week 16	0/38 (0.0)	3/39 (7.7)	17/39 (43.6)	21/40 (52.5)	8/42 (19.0)
p-value		0.0861	<.0001	<.0001	0.0039
PASI 100 Response					
Week 12	0/38 (0.0)	4/39 (10.3)	15/39 (38.5)	25/40 (62.5)	12/42 (28.6)
p-value		0.0452	<.0001	<.0001	0.0003
Week 16	0/38 (0.0)	3/39 (7.7)	7/39 (17.9)	14/40 (35.0)	3/42 (7.1)
p-value		0.0861	0.0049	<.0001	0.0900

Table 20090062-9-5. Summary of PASI 75, 90, 100 responses (NRI) by treatment group at Weeks 12 and 16.*)* P-value is for comparison between each brodalumab dose group and placebo. Non-Responder Imputation (NRI) is used to impute missing data. *(Data source: Table 9-5, CSR 20090062)*

sPGA (0,1) and sPGA (0)

The efficacy results for sPGA (0,1) and sPGA (0) response rates at both Week 12 and Week 16 are summarized in Table 20090062-9-6. The Week 12 results showed that:

- The proportions of subjects who achieved sPGA (0,1) response were 2.6%, 25.6%, 84.6%, 80.0%, and 69.0% in the placebo, 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively.
- The proportions of subjects who achieved sPGA (0) response were 0%, 10.3%, 41.0%, 62.5%, and 28.6% in the placebo, 70, 140, and 210 mg Q2W, and 280 mg Q4W treatment groups, respectively.

	Placebo (N = 38) n/N1(%)	AMG827 70 mg Q2WK (N = 39) n/N1(%)	AMG827 140 mg Q2WK (N = 39) n/N1(%)	AMG827 210 mg Q2WK (N = 40) n/N1(%)	AMG827 280 mg Q4WK (N = 42) n/N1(%)

sPGA (0 or 1)						
	Week 12	1/38 (2.6)	10/39 (25.6)	33/39 (84.6)	32/40 (80.0)	29/42 (69.0)
	p-value		0.0036	<.0001	<.0001	<.0001
	Week 16	2/38 (5.3)	9/39 (23.1)	26/39 (66.7)	25/40 (62.5)	14/42 (33.3)
	p-value		0.0243	<.0001	<.0001	0.0013
sPGA (0)						
	Week 12	0/38 (0.0)	4/39 (10.3)	16/39 (41.0)	25/40 (62.5)	12/42 (28.6)
	p-value		0.0435	<.0001	<.0001	0.0003
	Week 16	0/38 (0.0)	3/39 (7.7)	7/39 (17.9)	14/40 (35.0)	3/42 (7.1)
	p-value		0.0831	0.0052	<.0001	0.0881

Table 20090062-9-6. Summary of sPGA (0,1) and sPGA (0) responses (NRI) by treatment group at Weeks 12 and 16. P-value is for comparison between each brodalumab dose group and placebo. Non-Responder Imputation (NRI) is used to impute missing data. *(Data source: Table 9-6, CSR 20090062)*

Pharmacokinetics

Brodalumab exhibited nonlinear PK: serum brodalumab exposure increased greater than dose proportionally across the dose range of 70 to 210 mg after multiple SC doses of brodalumab (Table 20090062-10-4).

- For a 3-fold increase in brodalumab dose from 70 mg Q2W to 210 mg Q2W, serum brodalumab C_{max} and AUC_{0-t} increased approximately 18- and 25-fold, respectively.
- For a 1.5-fold increase in brodalumab dose from 140 mg Q2W to 210 mg Q2W, serum brodalumab C_{max} and AUC_{0-t} increased approximately 2.4- and 2.7-fold, respectively. !

Cohort	Treatment.	N	t_{max} (day)[a]	C_{max} (μg/mL)	AUC_{tau} (day•μg/mL)
1	70 mg Q2W	9	1.95 (0.00-6.88)	1.33 (1.41)	9.45 (11.1)
2	140 mg Q2W	11	2.81 (1.94-11.80)	9.55 (7.47)	87.7 (86.0)
3	210 mg Q2W	9	1.99 (0.00-7.90)	23.3 (13.6)	237 (186)
4	280 mg Q4W	7	2.89 (1.94-6.80)	11.4 (9.02)	119 (102)

Table 20090062-10-4. Mean (SD) pharmacokinetic parameter of brodalumab in subjects with psoriasis following SC administrations of 70, 140, or 210 mg Q2W or 280 mg Q4W. t_{max} is reported as median and range. (*Data source: Table 10-4, CSR 20090062*)

Dose-/exposure-response analysis

The Applicant used an E_{max} model to evaluate the relationship between brodalumab dose and Week 12 efficacy. Figure 20090062-10-6 shows the dose-response for observed and model predicted mean percent PASI improvement. Figure 20090062-10-8 shows the dose-response for the observed and model predicted PASI 75, PASI 90 and sPGA (0,1) response rates. The analysis exercise in general shows that the 140 mg Q2W dosing regimen achieved near the maximum response.!

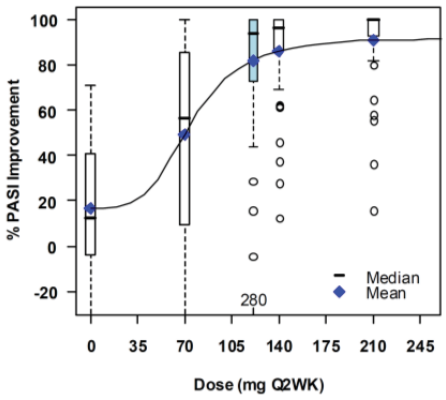


Figure 20090062-10-6. Observed and model predicted dose response for Week 12 percent PASI improvement. The observed percent improvement is represented as box-and-whisker plots where the box represents the 25th to 75th percentile. The curve represents model-predicted dose-response for a typical subject. (*Data source: Figure 10-6, CSR 20090062*)

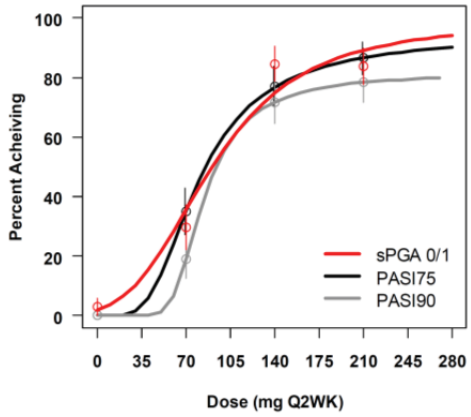


Figure 20090062-10-8. Observed and model predicted percent of subjects achieving PASI 75 and PASI 90 response at Week 12. Lines represent modeled results. Points represent observed results. Error bars depict the data standard deviation computed assuming the data were binomially distributed. (*Data source: Figure 10-8, CSR 20090062*)

Immunogenicity

Through Week 22, the incidence for ADA formation was 7.6% (12/158) and no subjects were tested positive for neutralizing antibodies (*Data source: Table 14-10.1, CSR 20090062*).

4.5.8 Study 20110102 (Phase 3)

Title

- A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1

Study period

- 29 August 2012 (the first subject enrolled) to 12 March 2014 (data cutoff for primary analysis)

Objectives

- **Primary Objectives (compared with placebo):**
  - To evaluate the efficacy of brodalumab (210 mg every 2 weeks [Q2W]; and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the

proportion of subjects achieving 75% improvement in Psoriasis Area and Severity Index (PASI; PASI 75) at week 12.

- To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving success (clear [0] or almost clear [1]) on the static physician's global assessment (sPGA) at week 12.

- **Key Secondary Objectives (compared with placebo):**
  - To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in clearing psoriasis, as measured by the proportion of subjects achieving PASI 100 at week 12.
  - To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in clearing psoriasis, as measured by the proportion of subjects achieving sPGA of 0 at week 12.
  - To evaluate maintenance of effect with continued brodalumab treatment (210 mg Q2W and 140 mg Q2W), as measured by the proportion of subjects achieving sPGA success at week 52.
  - To evaluate the effect of brodalumab (210 mg Q2W and 140 mg Q2W) on patient-reported symptoms of psoriasis, as measured by the proportion of subjects who meet the responder definition for the Psoriasis Symptom Inventory (PSI) (total score ≤ 8, with no item scores > 1) at week 12.

Study design

The overall study design is illustrated by a study schema in Figure 20120102-8-1.

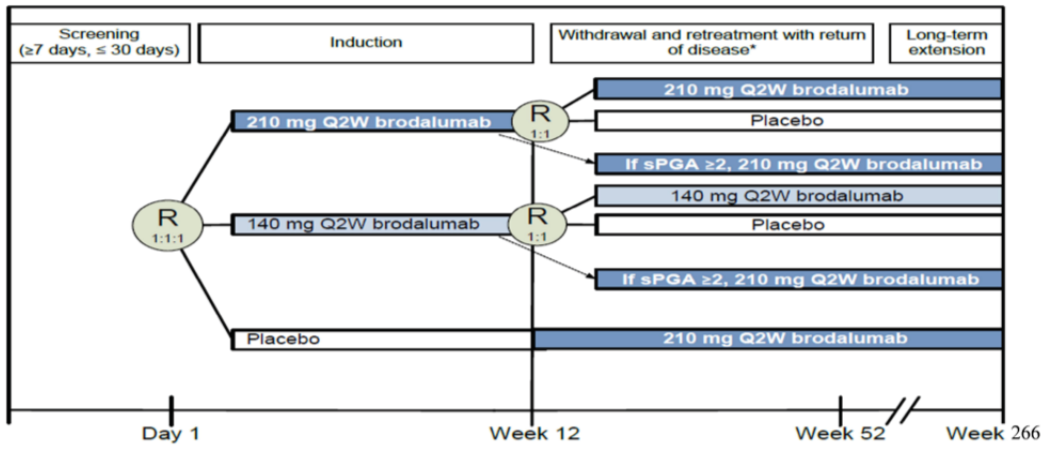


Figure 20120102-8-1. Study design.

Induction phase:

After the screening period, this study began with a 12-week, double-blind, placebo-controlled induction phase. In this phase, subjects were randomized in a 1:1:1 ratio to receive 210 mg Q2W brodalumab, 140 mg Q2W brodalumab, or placebo. During the induction phase, subjects randomized to 210 mg Q2W received 2 injections of brodalumab (1 injection of 1.0 mL and 1 injection of 0.5 mL), subjects randomized to 140 mg Q2W received 2 injections (1 injection of 1.0 mL of brodalumab and 1 injection of 0.5 mL of placebo), and subjects randomized to

placebo received 2 injections of placebo (1 injection of 1.0 mL and 1 injection of 0.5 mL). These doses were administered at Weeks 0, 1, 2, 4, 6, 8, and 10.

Randomized withdrawal phase:

At the week 12 visit,

- Subjects originally randomized to brodalumab who have success on sPGA (clear [0] or almost clear [1]) at week 12 were rerandomized 1:1 to receive placebo or continued brodalumab at their induction dose.
- All subjects originally randomized to placebo and any subject not qualifying for rerandomization received 210 mg Q2W brodalumab.
- Subjects who did not attend their week 12 visit did not receive any further treatment.

During the randomized withdrawal phase, all subjects received 2 injections (1 injection of 1.0 mL and 1 injection of 0.5 mL) of investigational product (either brodalumab or placebo) at Weeks 12, 13, 14, and every other week thereafter. Subjects continued after their week 12 visit the randomized treatment unless they had "return of disease" (sPGA $\geq$ 3) at or after week 16. If a subject had return of disease through week 52, he or she began retreatment with his or her induction dosage in the initial 12-week double-blind phase of the study.

Original and rerandomized treatment assignments remained blinded until all subjects reached week 52 or terminate the study, whichever came first.

Co-Primary

- PASI 75 at week 12
- sPGA success at week 12

Investigational Product

Brodalumab was presented as 140 mg/mL solution supplied in single-use PFS:

- brodalumab 1.0 mL PFS
- brodalumab 0.5 mL PFS

Subjects

A total of 661 subjects were randomized into the study: 222 received 210 mg Q2W, 219 received 140 mg Q2W, and 220 subjects received placebo during the induction phase.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Weeks 0 (baseline), 4, 12, 24, and 48.

Pharmacokinetics

In all subjects, blood samples for brodalumab PK assessment were collected at Weeks 0 (baseline), 1, 2, 4, 6, 10, 12, 16, 18, 24 and 48. In a subset of subjects (target enrollment of about 110 subjects), intensive PK samples (Predose, Day 3, Day 7, Day 10, Day 14 [predose]) were collected between a dose interval following dose administration at Week 10 and Week 16.

Study results

Primary efficacy

Results of the primary analysis and key secondary analyses are presented in Table 20120102-10-1. For the co-primary endpoints, the response rates in both the 210 mg Q2W and 140 mg Q2W groups were statistically significantly different from that of the placebo group based on the adjusted p-values ($p < 0.001$). The percentage of PASI 75 responders at week 12 was 83.3% in the 210 mg Q2W group, 60.3% in the 140 mg Q2W group, and 2.7% in the placebo group. The percentage of subjects who achieved sPGA success at week 12 was 75.7% in the 210 mg Q2W group, 53.9% in the 140 mg Q2W group, and 1.4% in the placebo group.

Table 10-1. Summary of Adjusted p-values for Primary and Key Secondary Endpoints (NRI) by Sequential Testing Procedure (Full Analysis Set)

Comparison	Brodalumab		Placebo			
(brodalumab vs placebo)	n/N (%)	95% CI of %	n/N (%)	95% CI of %	Nominal p-value	Adjusted p-value
PASI 75[a]: 210 mg Q2W	185/222 (83.3)	(77.8, 88.0)	6/220 (2.7)	(1.0, 5.8)	<.001	<.001
sPGA success[a]: 210 mg Q2W	168/222 (75.7)	(69.5, 81.2)	3/220 (1.4)	(0.3, 3.9)	<.001	<.001
PASI 75[a]: 140 mg Q2W	132/219 (60.3)	(53.5, 66.8)	6/220 (2.7)	(1.0, 5.8)	<.001	<.001
sPGA success[a]: 140 mg Q2W	118/219 (53.9)	(47.0, 60.6)	3/220 (1.4)	(0.3, 3.9)	<.001	<.001
PASI 100[a]: 210 mg Q2W	93/222 (41.9)	(35.3, 48.7)	1/220 (0.5)	(0.0, 2.5)	<.001	<.001
sPGA of 0[a]: 210 mg Q2W	93/222 (41.9)	(35.3, 48.7)	1/220 (0.5)	(0.0, 2.5)	<.001	<.001

Comparison	Brodalumab		Placebo			
(brodalumab vs placebo)	n/N (%)	95% CI of %	n/N (%)	95% CI of %	Nominal p-value	Adjusted p-value
sPGA success[b]: 210 mg Q2W	69/83 (83.1)	(73.3, 90.5)	0/84 (0.0)	(0.0, 4.3)	<.001	<.001
PASI 100[a]: 140 mg Q2W	51/219 (23.3)	(17.9, 29.5)	1/220 (0.5)	(0.0, 2.5)	<.001	<.001
sPGA of 0[a]: 140 mg Q2W	51/219 (23.3)	(17.9, 29.5)	1/220 (0.5)	(0.0, 2.5)	<.001	<.001
sPGA success[b]: 140 mg Q2W	40/57 (70.2)	(56.6, 81.6)	3/59 (5.1)	(1.1, 14.1)	<.001	<.001
PSI responder[a]: 210 mg Q2W	135/222 (60.8)	(54.1, 67.3)	9/220 (4.1)	(1.9, 7.6)	<.001	<.001
PSI responder[a]: 140 mg Q2W	116/219 (53.0)	(46.1, 59.7)	9/220 (4.1)	(1.9, 7.6)	<.001	<.001

Table 20120102-10-1. Efficacy results for primary and key secondary efficacy endpoints at Week 12. (*Data source: CSR 20120102, Table 10-1*)

Pharmacokinetics

Mean (±SD) brodalumab serum concentration-time profiles at Week 10 and Week 16 are presented in Figure 11-1 and Figure 11-2, respectively. Descriptive statistics of PK parameter estimates at Week 10 and Week 16 are presented in Table 11-1 and Table 11-2, respectively. After multiple subcutaneous injections of brodalumab, C_{max} and AUC_{tau} increased greater than dose proportionally from the 140 mg Q2W to 210 mg Q2W dose. C_{max} increased approximately 2.5-fold and AUC_{tau} increased approximately 3.2-fold for a 1.5-fold increase in dose. The median t_{max} value remained around 3 days across all the different treatment groups at week 10 and week 16.

Figure 11-1. Mean (±SD) Serum Brodalumab Concentration-Time Profiles on Intensive Week 10 Sampling After Multiple Q2W Subcutaneous Administrations o Brodalumab to Subjects With Moderate to Severe Plaque Psoriasis

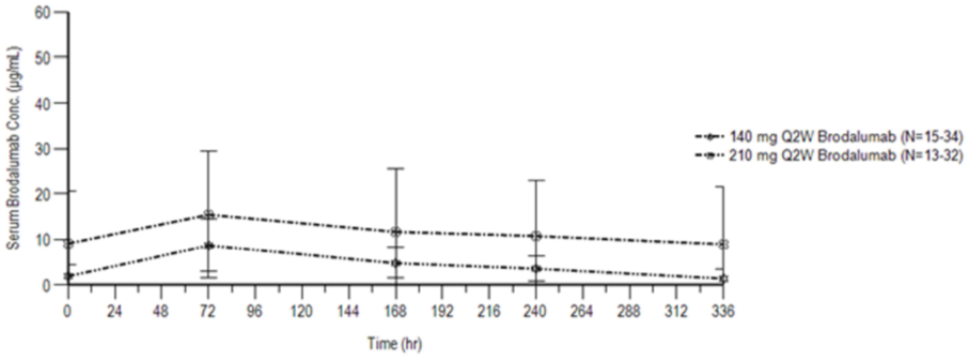


Figure 11-2. Mean (±SD) Serum Brodalumab Concentration-Time Profiles on Intensive Week 16 Sampling After Multiple Q2W Subcutaneous Administrations of Brodalumab to Subjects With Moderate to Severe Plaque Psoriasis

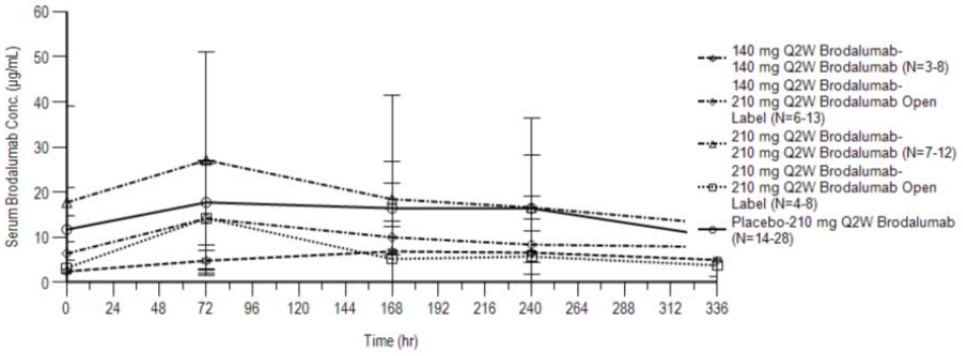


Table 11-1. Descriptive Statistics of Brodalumab Pharmacokinetic Parameter Estimates on Week 10 After Multiple Subcutaneous Administrations of Brodalumab

Descriptive Statistics	C_{max} (µg/mL)	t_{max} (day)	AUC_{tau} (day•µg/mL)
140 mg Q2W Brodalumab			
N	33	33	22
Median	7.33	3.0	77.0
Mean	7.64	NR	75.5
SD[a]	5.36	0.0-9.9	52.2
CV%	70.2	NR	69.2
210 mg Q2W Brodalumab			
N	32	32	22
Median	12.1	3.0	173
Mean	18.8	NR	243
SD[a]	18.7	1.9-14	234
CV%	99.4	NR	96.2

[a]The range is provided for t_{max}.
AUC_{tau} = Area under the serum concentration-time curve during the dosing interval tau, with tau equal to 336 hours; C_{max} = Maximum observed drug concentration; CV = coefficient variation; NR = Not reported;

Table 11-2. Descriptive Statistics of Brodalumab Pharmacokinetic Parameter Estimates on Week 16 After Multiple Subcutaneous Administrations of Brodalumab

Descriptive Statistics	C_{max} (µg/mL)	t_{max} (day)	AUC_{tau} (day•µg/mL)
140 mg Q2W/140 mg Q2W			
N	8	8	5
Median	9.17	4.1	76.6
Mean	10.5	NR	94.3
SD[a]	7.33	1.9-14	64.0
CV%	69.7	NR	67.9
140 mg Q2W/210 mg Q2W Open-label			
N	13	13	7
Median	12.1	3.0	163
Mean	16.0	NR	211
SD[a]	13.9	1.9-14	176
CV%	86.9	NR	83.5
210 mg Q2W/210 mg Q2W			
N	12	12	9
Median	14.7	2.9	131
Mean	24.4	NR	284
SD[a]	21.8	0.0-6.9	266
CV%	89.7	NR	93.5

Descriptive Statistics	C_{max} (µg/mL)	t_{max} (day)	AUC_{tau} (day•µg/mL)
210 mg Q2W/210 mg Q2W Open-label			
N	8	7	3
Median	4.80	3.0	247
Mean	9.67	NR	194
SD[a]	11.6	1.9-7.9	147
CV%	120.5	NR	75.5
Placebo/210 mg Q2W			
N	28	28	16
Median	18.2	3.1	214
Mean	21.2	NR	267
SD[a]	12.8	1.7-11	149
CV%	60.1	NR	55.7

Figure 20120102-11-1 and Figure 20120102-11-2. Mean (±SD) brodalumab serum concentration-time profiles after one dose subcutaneous brodalumab administration at Week 10 and Week 16, respective. Table 20120102-11-1 and Table 20120102-11-2. Descriptive statistics of PK parameter estimates at Week 10 and Week 16, respectively. (*Data source: CSR 20120102, Figure 11-1, Figure 11-2, Table 11-1, and Table 11-2*)

Pharmacodynamics: C-reactive protein

At baseline, mean C-reactive protein levels were similar across the treatment groups: 5.64 mg/L in the 210 mg Q2W group, 6.88 mg/L in the 140 mg Q2W group, and 5.24 mg/L in the placebo group. There was only a slight decrease of CRP level in the brodalumab treatment groups at Week 12 with median decreases from baseline in C-reactive protein in the 210 mg Q2W group of (-0.10 mg/L) and in the 140 mg Q2W group of (-0.13 mg/L) (Table 20120102-14-7.2.2.1).

Table 14-7.2.2.1. Summary of Change From Study Baseline in C-Reactive Protein (CRP) at Selected Time Points During the Induction Phase
Brodalumab Study 20120102
Safety Analysis Set

Panel Laboratory Parameter Visit	Placebo (N = 220)	Brodalumab 140 mg Q2W (N = 219)	Brodalumab 210 mg Q2W (N = 222)	Brodalumab All (N = 441)
Chemistry				
C-Reactive Protein (Nhs) (Mg/L)				
Baseline				
n	213	215	216	431
Mean	5.24	6.88	5.64	6.26
SD	8.25	18.40	7.50	14.03
SE	0.57	1.25	0.51	0.68
Median	2.36	2.53	2.96	2.68
Q1, Q3	1.10, 5.04	1.19, 5.91	1.14, 6.46	1.17, 6.37
Min, Max	0.20, 53.50	0.20, 192.00	0.20, 46.50	0.20, 192.00

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N = Number of subjects randomized and received at least one dose of investigational product
SD = standard deviation; SE = standard error; Q1, Q3 = first and third quartiles; Min, Max = minimum, maximum
Treatment groups are defined as planned treatment for the induction phase

Table 14-7.2.2.1. Summary of Change From Study Baseline in C-Reactive Protein (CRP) at Selected Time Points During the Induction Phase
Brodalumab Study 20120102
Safety Analysis Set

Panel Laboratory Parameter Visit	Placebo (N = 220)	Brodalumab 140 mg Q2W (N = 219)	Brodalumab 210 mg Q2W (N = 222)	Brodalumab All (N = 441)
Change from baseline at Week 12				
n	199	203	206	409
Mean	0.56	-1.94	-0.28	-1.10
SD	8.87	12.19	9.00	10.72
SE	0.63	0.86	0.63	0.53
Median	0.00	-0.13	-0.10	-0.12
Q1, Q3	-0.74, 0.86	-1.58, 0.80	-1.92, 0.71	-1.76, 0.79
Min, Max	-48.4, 54.5	-141.6, 19.4	-27.7, 64.7	-141.6, 64.7

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N = Number of subjects randomized and received at least one dose of investigational product
SD = standard deviation; SE = standard error; Q1, Q3 = first and third quartiles; Min, Max = minimum, maximum
Treatment groups are defined as planned treatment for the induction phase

Table 20120102-14-7.2.2.1. Effect of brodalumab treatment on CRP at Week 12. (*Data source: CSR, 20120102, Table 14-7.2.2.1*)

Immunogenicity

Of the 645 subjects exposed to brodalumab, 4 (0.6%) subjects tested positive for pre-existing binding antibodies, 14 (2.2%) subjects developed binding anti-brodalumab antibodies after brodalumab administration through the data cutoff (12 March 2014). Neutralizing anti-brodalumab antibodies were not detected in any subjects in this study.

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/s/

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Concur with all recommendations as written.