2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA

Name of Finished Product: Brodalumab

Name of Active Ingredient: Brodalumab

Title of Study: 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

Investigators and Study Centers: This study was conducted at 4 centers in the United States (Section 16.1.4).

Publications: None

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

Development Phase: 1

Previous Reports for This Study: None

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 C_{max} 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.

Methodology:

This was a multicenter, open-label, randomized, 2-period crossover study. The treatment periods are presented below.

One administration was a single PFS injection (treatment A) and the other administration was 2 PFS injections (treatment B). Doses were separated by a washout period of approximately 28 days. Subjects were randomized to receive investigational treatment in 1 of 2 sequences, ie, A/B or B/A (1:1 randomization).

Number of Subjects Planned: 140

Diagnosis and Main Criteria for Eligibility: Eligible subjects were healthy men and women ≥ 18 to ≤ 55 years of age with no history or evidence of clinically relevant

medical disorders as determined by the investigator in consultation with the Amgen physician, and no evidence of clinically important systemic disease

A complete list of eligibility criteria is provided in Protocol Section 4 (Section 16.1.1 of this report).

Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number: The test therapy was 210 mg SC dose of brodalumab administered by a single injection of a PFS (1.5 mL of 140 mg/mL brodalumab [210 mg brodalumab] [brodalumab drug substance: process 2 Amgen Thousand Oaks]).

The reference therapy 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 [140 mg brodalumab] and PFS injection of 0.5 mL of 140 mg/mL brodalumab [70 mg brodalumab] [brodalumab drug substance: process 2 Amgen Thousand Oaks]). Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: Subjects received 2 single doses of 210 mg separated by 28 days. See Protocol Study Design and Treatment Schema.

Study Endpoints:

The primary endpoints were AUC_{last} and C_{max}. Secondary endpoints were other pharmacokinetic parameters (including AUC_{inf} and t_{max}), subject incidence of adverse events, vital signs, clinical laboratory tests, electrocardiograms, and presence of binding or neutralizing anti-brodalumab antibodies.

Statistical Methods: Descriptive statistics, including mean, standard deviation (SD), median, minimum, and maximum were provided by treatment for brodalumab serum concentrations for each time point and for all pharmacokinetic parameters. Graphs of serum concentration-time profiles for individual subjects by treatment are provided. For pharmacokinetic parameters AUC_{last} and C_{max}, a mixed-effect analysis of variance was performed.

For a detailed description of statistical methods, see Statistical Analysis Plan, Section 10 (Section 16.1.9 of this report).

Summary of Results:

Subject 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).

Baseline Demographics:

Sex: 91 men (62.8%) and 54 women (37.2%)

Age (mean [SD]; range): 40.8 (10.7) years; 18 to 55 years

Race: 116 white (80.0%), 23 black or African American (15.9%), 3 American Indian or Alaska Native (2.1%), 2 Asian (1.4%), 1 multiple (0.7%)

Ethnicity: 76 not Hispanic/Latino (52.4%) and 69 Hispanic/Latino (47.6%)

Pharmacokinetic Results:

The mean serum brodalumab concentration-time profiles 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 similar, suggesting that the absorption characteristics and systemic pharmacokinetics were similar for both treatments. A summary of pharmacokinetic parameters is provided below.

	Brodalumab 210 mg SC Single PFS Injection (Test)				Brodalumab 210 mg SC 2 PFS Injections (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)
N	138	138	138	129	131	131	131	119
Mean	13.8	NR	125	133	14.8	NR	149	158
SD	7.85	NR	69.0	71.2	7.70	NR	81.5	82.9
Min	0.538	1.0	2.14	15.2	1.58	1.0	6.53	6.92
Median	13.3	3.0	113	121	14.4	3.9	143	150
Max	72.3	11	381	384	64.6	11	493	496
CV%	56.9	NR	55.3	53.5	52.2	NR	54.8	52.6

AUC_{inf} = AUC from time 0 to infinity; AUC_{last} = AUC from time zero to time of last quantifiable concentration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; Max = maximum; Min = minimum; NR = not reported; PFS = prefilled syringe; SC = subcutaneous; SD = standard deviation; t_{max} = time to reach C_{max}

A summary of the statistical bioequivalence evaluation of pharmacokinetic parameters of brodalumab between treatment A and B is provided below.

	Treatment A (Single PFS Injection) (N = 124)		Treatment B (2 PFS Injections) (N = 124)		Geometric Mean Ratio Treatment A/B	
Parameter (unit)	n	Mean[a]	n	Mean[a]	Mean[b]	90% CI
$AUC_{0\text{-}inf}$ (day•μg/mL)	112	119.70	112	132.34	0.90	0.83, 0.98
$AUC_{0\text{-}last}$ (day•μg/mL)	124	110.89	124	124.01	0.89	0.82, 0.98
C_{max} (μg/mL)	124	12.52	124	12.81	0.98	0.91, 1.05

Injections were Treatment A = Brodalumab 210 mg SC (single PFS injection); Treatment B = Brodalumab 210 mg SC (2 PFS injections).
AUC_{inf} = AUC from time 0 to infinity; AUC_{last} = AUC from time zero to time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed drug concentration; PFS = prefilled syringe
[a] Mean = Geometric Least Squares Mean from the SAS PROC MIXED procedure
[b] The geometric mean ratio and CI are based on natural log scale data converted back to the original scale
Brodalumab administered as 2 PFS injections is the reference treatment.
Mixed-effects analysis of variance model was used with ln(AUC) [or $ln(C_{max})$] as the dependent variable, treatment, period, and sequence as fixed effect and subject within sequence as random effect

Pharmacokinetic parameters (AUC_{last}, C_{max}, and AUC_{inf}) of a 210 mg SC dose of brodalumab administered by 2 treatments (single 1.5 mL PFS injection and 2 PFS injections [1 mL + 0.5 mL] of brodalumab) were considered bioequivalent, as the 90% CIs for the ratio (single PFS injection/2 PFS injections) of the geometric least squares means for all 3 parameters were between 0.80 and 1.25.

Safety Results: Treatment-emergent adverse events were reported for 39 subjects (27.7%) who received a single PFS injection and 41 subjects (31.3%) who received 2 PFS injections.

In the single PFS injection treatment period, preferred terms reported by > 2.0% of subjects were: headache (7 subjects [5.0%]), arthralgia (5 subjects [3.5%]), and muscle strain and neutropenia (3 subjects [2.1%] each).

In the 2 PFS injections treatment period, preferred terms reported by > 2.0% of subjects were headache (10 subjects [7.6%]), followed by upper respiratory tract infection (5 subjects [3.8%]), neutropenia (4 subjects [3.1%]), and nausea and ecchymosis (3 subjects [2.3%] each).

All adverse events were Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 2, with the exception of 1 subject with a grade 3 event in each treatment group (upper respiratory tract infection in the single PFS injection treatment period, and neutropenia in the 2 PFS injections treatment period).

Three subjects had events that led to withdrawal of brodalumab; all were in the single PFS injection treatment period. One subject withdrew from brodalumab treatment due to tooth abscess, 1 due to lower limb fracture, and 1 due to blood bilirubin increased. None of the withdrawals were considered by the investigator to be related to treatment.

Most event of interest terms retrieved with the prespecified search strategy were not specific to the event of interest. There were only 2 events of interest which were grade 3 or above: 1 subject with grade 3 upper respiratory tract infection on treatment A and 1 subject with grade 3 neutropenia on treatment B.

Samples from 7 out of 145 (4.8%) subjects tested positive for anti-brodalumab binding antibodies after receiving 1 administration of brodalumab (all on day 29 predose), and all but a sample from 1 subject tested negative for anti-brodalumab binding antibodies at the end of study. Neutralizing anti-brodalumab antibodies were not detected in any subjects. The presence of anti-brodalumab binding antibodies in these subjects had no effect on serum brodalumab concentrations.

Conclusions:

Comparison of the parameter estimates of $AUC_{0\text{-}last}$, AUC_{inf}, and C_{max} of a 210 mg SC dose of brodalumab, administered as a single PFS injection (1.5 mL) and as 2 PFS injections (1 mL + 0.5 mL), demonstrated bioequivalence between the 2 treatments. Adverse events for both treatments were consistent with the known safety profile of brodalumab.