2. SYNOPSIS

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

Name of Finished Product: Brodalumab

Name of Active Ingredient: Brodalumab

Title of Study: 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

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

Publications: None

Study Period: 20 May 2014 (first subject enrolled) to 07 September 2014 (last subject completed follow-up)

Development Phase: 1

Previous Reports for This Study: None

Objectives:

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.

Secondary Objectives:

- To characterize other brodalumab pharmacokinetic parameters (including AUC from time 0 to infinity [AUC_{inf}] and time at which C_{max} was observed [t_{max}]) after a single 210 mg SC dose of brodalumab administered to the abdomen of healthy subjects using an AI versus that administered by PFS.
- 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, crossover study designed to assess the bioequivalence of the pharmacokinetic parameters of brodalumab 210 mg SC administered in the abdomen by AI versus brodalumab 210 mg SC administered by PFS.

One administration was by AI (treatment A) and the other administration was by PFS (treatment B). There were 2 treatment periods and doses were separated by a washout period of approximately 28 days. Healthy adult men and women were enrolled in the study and randomized to receive investigational treatment in 1 of 2 sequences, ie, AB or BA (1:1 randomization) in a 2-period crossover design.

Number of Subjects Planned: 140

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men and women ≥ 18 to ≤ 55 years of age at the time of screening, with no history or evidence of clinically relevant medical disorders as determined by the investigator in consultation with the Amgen physician. 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 AI (2 AI injections per dose: 0.75 mL of 140 mg/mL brodalumab per AI injection each provided 105 mg of brodalumab, therefore 210 mg in total [brodalumab drug substance: process 2 Amgen Thousand Oaks]).

The reference therapy was 210 mg SC dose of brodalumab administered by PFS (2 PFS injections per dose: 1 mL PFS injection of 140 mg/mL brodalumab provided 140 mg and 0.5 mL PFS injection of 140 mg/mL brodalumab provided 70 mg, therefore 210 mg in total [brodalumab drug substance: process 2 Amgen Thousand Oaks]). Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: The total duration of treatment for each subject was approximately 59 days, which included 2 separate dose administrations, each followed 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 were 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: A total of 141 subjects were enrolled (71 sequence 1 [AB], 70 sequence 2 [BA]). A total of 129 subjects completed the study (63 sequence 1, 66 sequence 2), and 12 subjects discontinued (8 sequence 1, 4 sequence 2).

Baseline Demographics:

Sex: 105 men (74.5%) and 36 women (25.5%)

Age, mean (SD) and range: Mean 38.5 (10.8) years with a range of 18 to 55 years

Race: 120 white (85.1%), [redacted]

Ethnicity: 105 not Hispanic/Latino (74.5%) and 36 Hispanic/Latino (25.5%)

Pharmacokinetic Results:

The mean serum brodalumab concentration-time profiles after a single 210 mg SC dose of brodalumab delivered using an AI or PFS were similar, suggesting that the absorption characteristics were similar for both treatments. A summary of pharmacokinetic parameters is provided below.

	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)
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

AI = autoinjector/pen; 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; Miugh minimum; NR = not reported; PFS = prefilled syringe; SD = standard deviation; SC = subcutaneous; t_{max} = time to reach C_{max}

The geometric least squares mean point estimates for the ratio (90% confidence intervals [CIs]) of AI/PFS for C_{max}, AUC_{last}, and AUC_{inf} were 1.07 (0.99 to 1.16), 1.13 (1.03 to 1.24), and 1.11 (1.03 to 1.19), respectively. Pharmacokinetic parameters (AUC_{last}, C_{max}, and AUC_{inf}) of a 210 mg SC dose of brodalumab administered by 2 different treatments (2 x 0.75 mL AI and 1 mL + 0.5 mL PFS of 140 mg/mL brodalumab) were considered bioequivalent, as the 90% CIs for the ratio (AI/PFS) 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 30 subjects (21.7%) for treatment group A (AI) and 35 subjects (26.1%) for treatment group B (PFS).

In the AI treatment period, the most common preferred term was headache (5 subjects [3.6%]), followed by musculoskeletal pain and nausea (3 subjects [2.2%] each), and pain in extremity, contusion, vomiting, and ecchymosis (2 subjects [1.4%] each). There were no other preferred terms reported for more than 1 subject. In the PFS treatment period, the most common preferred term was arthralgia (4 subjects [3.0%]), followed by excoriation, headache, and ecchymosis (3 subjects [2.2%] each), and laceration, neutropenia, and blood creatine phosphokinase increased (2 subjects [1.5%] each). There were no other preferred terms reported for more than 1 subject. Adverse events were Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 2, with the exception of 1 subject with 1 or more grade 3 events in each treatment group (leukopenia in the AI treatment period, and chance fracture, thoracic vertebral fracture, and sternal fracture, secondary to motor vehicle accident, in the PFS treatment period).

Three subjects had events that led to withdrawal of brodalumab (2 in the AI treatment period [leukopenia and upper respiratory tract infection] and 1 in the PFS treatment period [chance fracture and thoracic vertebral fracture]). One of these events was

serious (preferred term of chance fracture). None of these events were considered by the investigator to be related to treatment.

Thirteen subjects (9.4%) in the AI treatment period and 10 subjects (7.5%) in the PFS treatment period had adverse events associated with an event of interest search.

More subjects reported adverse events associated with the event of interest category of injection site reaction in the AI treatment period (5 subjects) compared with the PFS treatment period (1 subject) but all were mild (grade 1). Overall, there were no trends suggesting clinically meaningful changes but 1 subject in the AI treatment group discontinued due to leukopenia. There were no notable changes from baseline were observed for vital signs or physical examination and electrocardiogram findings.

Samples from 2 subjects tested positive for anti-brodalumab binding antibodies on days 29 and tested negative for anti-brodalumab binding antibodies at the end-of-study visit (day 59). The presence of anti-brodalumab binding antibodies in these subjects had no effect on serum brodalumab concentrations. Samples from both of these subjects tested negative for anti-brodalumab neutralizing antibodies on day 29 predose.

Conclusions:

Comparison of the AUC and C_{max} of single 210 mg SC dose of brodalumab, administered with AI (2 x 0.75 mL) and with the PFS (1 mL + 0.5 mL), demonstrated bioequivalence between the 2 treatments. Brodalumab had an acceptable safety profile which was consistent with the currently known profile.