2. SYNOPSIS

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

Name of Finished Product: AMG 139

Name of Active Ingredient: AMG 139

Title of Study: A Randomized, Double-blind, Placebo-controlled, Ascending Multiple-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 139 in Healthy Subjects and Subjects With Mild to Severe Crohn's Disease

Investigators and Study Centers: This study was conducted at 3 centers in Australia and 2 centers in the United States (US) (see Section 16.1.4).

Publication: Pan W-J, Rees W, Towne J, et al. Clinical pharmacology, safety, and effects of anti-IL-23 antibody AMG 139. *United European Gastoenterol J.* 2013:1(Suppl 1):A378. Abstract.

Study Period: 28 February 2011 (first subject enrolled) to 18 February 2015 (last subject completed follow-up)

Development Phase: 1b

Previous Report for This Study: None

Objectives:

Study 20090519 was a phase 1b study with the primary objective of assessing the safety and tolerability of AMG 139 following multiple intravenous (IV) or subcutaneous (SC) dose administrations in healthy subjects and subjects with mild to severe Crohn's disease. The secondary objective was to characterize the pharmacokinetics (PK) of AMG 139 following multiple IV or SC dose administration in healthy subjects and subjects with mild to severe Crohn's disease. [redacted]

Methodology:

This was a phase 1b, 2-part study enrolling healthy subjects in Part A and subjects with mild to severe Crohn's disease in Part B; Part A followed a randomized, double-blind, placebo-controlled, sequential ascending-multiple-dose design, and Part B followed a randomized, double-blind, placebo-controlled, multiple-dose design.

The duration of the screening period was up to 21 days (Part A) or 28 days (Part B) for each subject. The planned cohort sizes, randomization ratios, routes of administration, investigational product dosages (dose levels and schedules), and dose-escalation sequences for each Part were as shown in the following table:

Planned Cohort Sizes, Randomization Ratios, Routes of Administration, Investigational Product Dosages, and Dose-escalation Sequences

Cohort	Dosage (Dose Level and Schedule[a])	Route of Administration	No. of Subjects (AMG 139:Placebo)[b]
Part A (healthy subjects)[c]			
A1	70 mg	IV	8 (6:2)
A2	210 mg	IV	8 (6:2)
A3	420 mg	IV	8 (6:2)
A4	210 mg	SC	8 (6:2)
A5	700 mg	IV	8 (6:2)
Part B (subjects with mild to severe Crohn's disease)[d]			
B1	210 mg	IV	4 (3:1)
B2	700 mg	IV	4 (3:1)

IV = intravenous(ly); SC = subcutaneous(ly); US = United States

[a] Indicated doses of investigational product were administered on days 1, 29, and 57.

[b] Subjects within each cohort were randomized in a 3:1 allocation ratio to AMG 139 or placebo.

[c] Conducted at 3 study centers in Australia

[d] Conducted at 4 study centers in the US

In Part A, cohorts A1 through A5 were dosed sequentially, and dose escalation occurred at approximately 49-day intervals and only after the Dose Level Review Meeting (DLRM) members had reviewed at least up to and including the day 43 visit (± 2-day window) blinded safety data (ie, adverse event[s], electrocardiograms [ECGs], laboratory safety data, and vital signs) from the current cohort and all available safety data from all subjects in the previous cohort(s) and had determined that the reviewed dosages were well tolerated (voting members of the DLRM included the Amgen Medical Monitor, the Amgen Global Safety Officer (or designated safety scientist), and all participating investigators who had enrolled subjects. Cohort A4 could be enrolled in parallel with cohort A3. Dosing in cohort A5 was not initiated until after the DLRM members had reviewed blinded safety data from cohorts A3 (420 mg IV) and A4 (210 mg SC) in healthy subjects at least up to and including the day 43 visit (± 2-day window), as well as all available safety data from all subjects in the previous cohorts, and had determined that AMG 139 was well tolerated.

In Part B, the enrollment of the first cohort of subjects with Crohn's disease (B1 - 210 mg IV) initiated only after the DLRM members had reviewed blinded safety data from cohort A1 (70 mg IV) in healthy subjects at least up to and including the day 43 visit (± 2-day window) and had determined that AMG 139 was well tolerated. The enrollment of the second cohort of subjects with Crohn's disease (B2 - 700 mg IV) initiated only after the DLRM members had reviewed blinded safety data from cohort A3 (420 mg IV) in healthy subjects at least up to and including the day 43 visit (± 2 day window), as well as all available safety data from all subjects in the previous cohorts including 4 subjects in cohort B1, and had determined that AMG 139 was well tolerated. The study protocol also had provisions whereby additional subjects could be enrolled into a dose cohort, dose cohorts could be repeated, intermediate dose cohorts could be initiated, and dosing within a cohort could be stopped.

Subjects in Part A were admitted to the study center on day -1, resided until all day 1 assessments were completed (4 hours post dose), and returned to the study center on an outpatient basis for additional assessments on days 4, 8, 15, 29, 36, 43, 57, 60, 64, 71, 85, 99, 113, 141, 169, 197, 225 and 253 (end of study [EOS] for cohorts A1 through A5). In Part B, overnight admission to the study center was not required; subjects could check into the study center on day 1, remained at the study center until all day 1 assessments were completed

(4 hours post dose), and returned to the study center on an outpatient basis for additional assessments on days 4, 8, 15, 29, 36, 43, 57, 60, 64, 71, 85, 99, 113, 141, 169, 197, 225, and 253 (EOS for cohorts B1 and B2).

[redacted]

Number of Subjects Planned: 48 (40 in Part A; 8 in Part B)

Criteria for eligibility included healthy male or female subjects between 18 and 45 (inclusive) years of age (Part A), and male or female subjects with Crohn's disease between 18 and 55 (inclusive) years of age (Part B) at the time of screening. In addition, criteria for eligibility in Part B (subjects with Crohn's disease) included:

- diagnosis of ileal or ileo-colonic Crohn's disease for a minimum of 6 months prior to randomization
- mildly to severely active Crohn's disease, as defined by a CDAI score ≥ 180 and ≤ 450 at screening

and criteria that excluded subjects from Part B included:

- short bowel syndrome (defined as requiring oral or parenteral supplemental or total nutrition in order to maintain stable body weight, or more than 100 cm of small bowel resected)
- stricture with obstructive symptoms within 3 months prior to randomization
- active/on-going fistulizing disease
- bowel surgery within 12 weeks prior to randomization

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

The investigational product in this study was AMG 139 and AMG 139 placebo (matching vehicle control). Active AMG 139 investigational product was packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL. AMG 139 was formulated with [redacted]. Placebo was packaged and formulated to match the active AMG 139 but without AMG 139 protein. Planned doses (70 to 700 mg) and modes of administration (SC or IV) are indicated by cohort in the "Methodology" section above in this Synopsis.

Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: See "Methodology" section above in this Synopsis.

Study Endpoints:

The primary endpoints were:

- Treatment-emergent adverse events
- Clinically significant changes in safety laboratory tests, physical examination findings, vital signs, or ECGs
- Worsening of Crohn's disease defined by an increase of CDAI score > 70 from baseline (Crohn's disease-subject cohorts only)
- Absolute and percentage changes in T cells, B cells, and natural killer (NK) cells (healthy-subject and Crohn's disease-subject cohorts)
- Anti-AMG 139 antibodies

The secondary endpoint was: PK parameters (area under the serum concentration-time curve [AUC] from during the dosing interval tau [AUC_{tau}], maximum observed concentration [C_{max}], time to C_{max} [t_{max}]) for AMG 139 after multiple IV and SC dose administrations in healthy subjects and subjects with mild to severe Crohn's disease (Other PK parameters could be derived based on the PK data obtained.)

[redacted]

[redacted]

Statistical Methods:

Analyses were performed separately for Part A and Part B. Descriptive statistics are provided for selected demographics, safety, PK, pharmacodynamics (PD), and efficacy data for each dose. Data for subjects receiving placebo were combined across all cohorts, separately for Part A and Part B. Data for subjects receiving placebo were combined across all cohorts regardless of route of administration (ie, IV or SC) within Part A, and the same approach was taken for Part B data summaries. Descriptive statistics on continuous measurements include means, medians, standard deviations, and ranges; categorical data are summarized using frequency counts and percentages.

The safety analysis set included all subjects who received at least 1 dose of investigational product. Subject incidences are summarized by system organ class (SOC) and by preferred term in descending order of frequency for all treatment-emergent adverse events and for adverse events that were serious, were reported as treatment related, were serious and reported as treatment related, led to withdrawal of investigational product, or were fatal. Summaries of laboratory data, vital signs, and ECGs over time, and tables of maximum shifts from baseline for selected laboratory values, are provided. With respect to ECG data, subjects were categorized into the following groups per their maximum change from baseline in QTcF and QTcB: ≤ 30 msec; > 30 to 60 msec; > 60 msec. Categorizations of subjects in each treatment group are summarized. Subjects were also categorized into the following groups per their maximum postbaseline QTcF and QTcB: ≤ 450 msec; > 450 msec to 480 msec; > 480 msec to 500 msec; > 500 msec, and these categorizations of subjects in each treatment group are also summarized. A summary of anti-AMG 139 antibody test results over time are provided.

The PK analysis set included all subjects for whom at least 1 PK parameter or endpoint could be adequately estimated. Individual-subject serum AMG 139 concentration-time data were tabulated and are presented graphically. PK parameters were estimated using noncompartmental methods. PK parameters (AUC_{tau}, C_{max}, t_{max}) are summarized for each treatment using descriptive statistics.

[redacted]

Summary of Results:

Subject Disposition:

Part A: A total of 40 subjects were randomized and received investigational product in Part A (30 AMG 139, 10 placebo). Of these 40 subjects, 8 subjects (6 AMG 139, 2 placebo) received investigational product by the SC route of administration, and 32 subjects (24 AMG 139, 8 placebo) received investigational product by the IV route. All 40 of the subjects (100%) who received investigational product in Part A completed investigational product, ie, received all 3 planned dose administrations. Thirty-five of the 40 subjects (87.5%) who received investigational product in Part A completed the study. The most frequent reason for early discontinuation of study was “full consent withdrawn” (n = 3).

Part B: A total of 8 subjects were randomized and received investigational product in Part B (6 AMG 139, 2 placebo). All 8 of the subjects received investigational product by the IV route of administration, completed investigational product (ie, received all 3 planned dose administrations), and completed study.

Baseline Demographics:

Part A (n = 30 for AMG 139 groups and n = 10 for [pooled] placebo group)

Sex: AMG 139 – 30 (100%) men; placebo – [redacted]

Age (mean [SD])*:* AMG 139 -- 25.8 (6.4) years; placebo – 23.0 (3.4) years

Race: AMG 139 – 25 (83%) White, 3 (10%) Asian, 2 (6.7%) Other; placebo – [redacted]

Ethnicity: AMG 139 – 29 (97%) Not Hispanic/Latino, 1 (3.3%) Hispanic/Latino; placebo – 10 (100%) Not Hispanic/Latino

Part B (n = 6 for AMG 139 groups and n = 2 for [pooled] placebo group)

[redacted]

Age (mean [SD])*:* AMG 139 – 43.5 (11.1) years; placebo – 36.5 (0.7) years

Race: AMG 139 – [redacted] White, [redacted] Asian; placebo [redacted]

Ethnicity: AMG 139 – 6 (100%) Not Hispanic/Latino; placebo – 2 (100%) Not Hispanic/Latino

Efficacy Results (Part B Only): Because of the small number of subjects in the treatment groups and because of data variability, it is not possible to arrive at conclusions about possible effects of AMG 139 on disease activity ([redacted]) in subjects with Crohn's disease.

[redacted]

Pharmacokinetics Results:

AMG 139 appeared to exhibit linear PK after 3 once-every-4 week (Q4W) IV administrations in the dose range of 70 to 700 mg AMG 139. After the third IV administration on day 57, AMG 139 exposure increased dose-proportionally, with C_{max} and AUC_{tau} values increasing 10.2- and 10.3-fold for the 10-fold increase in dose from 70 mg to 700 mg. Mean accumulation ratios ranged from 1.49 to 1.82 for the IV cohorts.

Following SC administration, the median t_{max} value was observed at approximately 7 days postdose after a single 210 mg AMG 139 SC dose on day 1, and at 14 days postdose after the third SC dose on day 57. Modest accumulation (approximately 2-fold) was observed following 3 SC doses of 210 mg AMG 139 administered Q4W. The SC:IV area AUC from time 0 to infinity (AUC_{inf}) ratio for the 210 mg dose on day 57 (last dose) was 0.91.

Based on C_{max} and AUC_{tau} values after the first and third dose, AMG 139 exposure in subjects with Crohn's disease was comparable to that in healthy subjects; however, it should be noted that this conclusion is based on results from a limited number of subjects with Crohn's disease (n = 3 for the 210 mg IV and 700 mg IV dose groups).

Safety Results:

Part A

All subjects in Part A had ≥ 1 adverse event, except for 1 of the 30 subjects who received AMG 139 and 1 of the 10 subjects who received placebo. Adverse events with the highest subject incidences were upper respiratory tract infection (AMG 139, 13/30 = 43%; placebo, 7/10 = 70%), headache (AMG 139, 10/30 = 33%; placebo, 5/10 = 50%), dizziness (AMG 139, 2/30 = 7%; placebo, 4/10 = 40%), and back pain (AMG 139, 5/30 = 17%; placebo, 0/10 = 0%). No adverse events appeared to increase in subject incidence as a function of increased dosage of AMG 139.

Among the 40 subjects in Part A (30 AMG 139, 10 placebo), a total of 212 adverse events were reported (AMG 139, 152; placebo, 60). All adverse events were reported as CTCAE grade 1 or grade 2 in severity except for an event of laceration (verbatim term = laceration to scalp post assault) for a subject in the AMG 139 210 mg IV dose group that was reported as grade 3 in severity.

Overall subject incidences of adverse events reported as treatment related were 20% (6/30) in the all AMG 139 group and 60% (6/10) in the all placebo group. Adverse events reported as treatment related with the highest subject incidences were dizziness (AMG 139, 1/30 = 3.3%; placebo, 2/10 = 20%) and headache (AMG 139, 2/30 = 7%; placebo, 1/10 = 10%). All other adverse events reported as treatment related occurred in only a single subject.

In Part A, no subjects discontinued early due to adverse events, no adverse events were reported as serious, and no deaths occurred.

There were no trends indicative of clinically important treatment-related laboratory abnormalities in Part A. Transient grade increases in creatine kinase (CK) values were observed in some subjects in all treatment groups, including the pooled placebo group; transient increases such as these are typically associated with physical activity. There was no apparent relationship between the times of AMG 139 dosing and times of occurrence of the increases.

From review of vital sign data (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, and body temperature) for Part A, it was apparent that there were no notable changes in vital signs and no notable differences in vital signs between treatment groups. From review of the electrocardiogram data, and as expected for a large molecule, there was no evidence of a treatment-related change in QT interval.

Concomitant medications administered for treatment of adverse events were reported during Part A for 30 subjects (23 AMG 139 [23/30 = 77%], 7 placebo [7/10 = 70%]). Most of the concomitant medications reported were over-the-counter medications commonly used for conditions such as headaches, mild infections including upper respiratory tract infections, and minor aches and pains – conditions typically observed in an otherwise healthy outpatient population.

Part B

All subjects in Part B had ≥ 1 adverse event, except for 1 of the 6 subjects who received AMG 139. The only adverse events that were reported for > 1 subject were headache (AMG 139, 2/6 = 33%; placebo, 1/2 = 50%) and diarrhoea (AMG 139, 0/6 = 0%; placebo, 2/2 = 100%).

Among the 8 subjects in Part B (6 AMG 139, 2 placebo), a total of 43 adverse events were reported (AMG 139, 17; placebo, 26). All adverse events were reported as Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or grade 2 in severity.

Overall subject incidences of adverse events reported as treatment related were 83% (5/6) in the all AMG 139 group and 100% (2/2) in the all placebo group. No adverse event reported as treatment related occurred in >1 subject.

In Part B, no subjects discontinued early due to adverse events, no adverse events were reported as serious, and no deaths occurred.

There were no trends indicative of clinically important treatment-related laboratory abnormalities in Part B. Small, transient grade increases in CK values were observed in 2 of the 6 subjects who received AMG 139, and in neither of the 2 subjects who received placebo.

From review of vital sign data (diastolic blood pressure, pulse rate, respiratory rate, systolic blood pressure, and body temperature) for Part B, it was apparent that there were no notable changes in vital signs and no notable differences in vital signs between treatment groups. From review of the electrocardiogram data, and as expected for a large molecule, there was no evidence of a treatment-related change in QT interval.

Concomitant medications administered for treatment of adverse events were reported during Part B for 7 subjects (6 AMG 139 [6/6 = 100%], 1 placebo [1/2 = 50%]). Use of over-the-counter concomitant medications was similar to that reported for Part A. In addition, as would be expected given the population of subjects in Part B, many of the concomitant medications were associated with the condition of Crohn's disease.

Anti-AMG 139 antibodies: No anti-AMG 139 antibodies were detected in any subjects in this study.

Conclusions:

- Overall, AMG 139 appeared to be well tolerated at the IV and SC doses administered in this study. Within Part A (healthy subjects)and within Part B (subjects with Crohn's disease), there were no trends indicative of clinically important adverse events attributable to AMG 139. In addition, no trends indicative of clinically important adverse effects of AMG 139 on laboratory or other safety-related clinical parameters were apparent. No anti-AMG 139 antibodies were detected in any subject who received AMG 139 or placebo.
- AMG 139 exhibited linear PK over the dose range of 70 to 700 mg. Modest accumulation (up to 2-fold) was observed after IV or SC administration, and the SC:IV AUC_{inf} ratio was 0.91 for the 210 mg dose. AMG 139 exposure in a limited number of subjects with Crohn's disease was comparable with that in healthy subjects.

[redacted]