SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 108

Name of Active Ingredient: AMG 108

Title of Study: A Long-term Assessment of Safety and Physical Function With AMG 108 Subcutaneous Monthly Treatment in Subjects With Rheumatoid Arthritis.

Investigators and Study Centers: This was a multicenter study at 116 sites [redacted].

Publications: No publications to date.

Study Period: 15 September 2006 (first subject enrolled) to 11 June 2008 (last subject visit)

Development Phase: 2

Introduction and Objectives: AMG 108 is a fully human, immunoglobulin subclass G2 monoclonal antibody that binds the third immunoglobulin domain of the interleukin-1 receptor type 1 (IL-1RI) and nonselectively inhibits the activity of both forms of IL-1 (IL-1α and IL-1β). Inhibiting the proinflammatory effects of these IL-1 isoforms may be useful in treating diseases such as rheumatoid arthritis (RA). Data from the initial phase 2 AMG 108 study (20050168) showed that AMG 108 administered at doses of 50, 125, and 250 mg subcutaneous (SC) every 4 weeks for 24 weeks (a total of 6 doses) to subjects with RA was generally well tolerated at all doses administered and AMG 108 at 250 mg was associated with significant improvements of RA symptoms. Per the protocol, eligible subjects who completed 24 weeks of Study 20050168 could enroll into this extension study (20060119). Study 20060119 was designed to monitor extended safety of monthly doses of AMG 108 (125 and 250 mg) for approximately 48 months (48 total doses). This study was prematurely terminated after all subjects were randomized because further development of AMG 108 was discontinued for reasons not related to subject safety. This report summarizes the safety, efficacy, and pharmacokinetic results of Study 20060119, with day 1 of Study 20060119 corresponding to week 24 of Study 20050168.

The primary objective of this study was to assess the long-term safety of AMG 108 (125 and 250 mg) administered subcutaneously once every 4 weeks for approximately 48 months (48 total doses) to subjects with RA who were previously enrolled in Study 20050168.

The secondary objectives were to: (1) assess impact of concomitant immunosuppressives on the long-term safety profile of AMG 108; (2) assess the impact of comorbidity on the adverse event profile of AMG 108; (3) determine whether long-term use of AMG 108 improves function in subjects with RA; (4) assess the change in mental and physical component summaries (MCS and PCS, respectively) and each of the 8 domain scores of short-form 36 (SF-36) from baseline to weeks 24, 48, 96, 144, and end-of-study; (5) determine effect of long-term use of AMG 108 on work productivity; (6) evaluate long-term pharmacokinetics (trough levels) of AMG 108; (7) assess the clinical effect of AMG 108 as determined by American College of Rheumatology 20% (ACR20) response at weeks 24, 48, 96, 144, and end-of-study; (8) determine whether immunogenicity of AMG 108 affects efficacy and safety as determined by frequency, subject incidence and time-to-onset of cardiovascular safety events and changes in biomarkers related to cardiovascular disease.

The exploratory objectives were to: [redacted]

[redacted]

Methodology: This was a long-term, blinded extension study to evaluate the safety of AMG 108 at a monthly dose of 125 and 250 mg SC in subjects with RA who completed 24 weeks of Study 20050168. Subjects were to be administered AMG 108 once every 4 weeks for approximately 48 months (48 total doses) or until an administrative decision was made to end the study. Subjects who received 125 or 250 mg AMG 108 in Study 20050168 continued to receive the same dose of AMG 108 in this extension study (20060119). Subjects who received 50 mg AMG 108 or placebo in Study 20050168 were randomized equally to receive either 125 or 250 mg AMG 108. Serum samples to determine AMG 108 concentrations were to be obtained at weeks 48, 96, 144, and at the end-of-study visit. Serum concentrations of AMG 108 were measured by a validated enzyme-linked immunosorbent assay. Serum samples were also to be collected to determine the presence of anti-AMG 108 antibodies. The safety profile was based on adverse events, clinically significant changes in vital signs, and clinical laboratory tests.

Number of Subjects Planned: Approximately 700 subjects

Number of Subjects Enrolled: A total of 690 subjects were enrolled and were randomized in this study (Table 1).

Table 1. Subject Demographics

	Placebo[a] / 125mg[b] (N = 89)	Placebo[a] / 250mg[b] (N = 89)	50mg[a] / 125mg[b] (N = 83)	50mg[a] / 250mg[b] (N = 84)	125mg[a] / 125mg[b] (N = 174)	250mg[a] / 250mg[b] (N = 171)
Sex n(%)						
Male	17 (19.1)	18 (20.2)	18 (21.7)	22 (26.2)	34 (19.5)	36 (21.1)
Female	72 (80.9)	71 (79.8)	65 (78.3)	62 (73.8)	140(80.5)	135(78.9)
Age (Years)[c]						
Mean (SD)	53.90 (10.52)	51.63 (11.30)	51.63 (12.24)	52.23 (12.56)	52.32 (11.07)	53.45 (9.92)
Ethnicity Group n(%)						
White	77 (86.5)	69 (77.5)	71 (85.5)	71 (84.5)	150(86.2)	152(88.9)
Black	0 (0.0)	4 (4.5)	1 (1.2)	1 (1.2)	1 (0.6)	4 (2.3)
Hispanic	10 (11.2)	15 (16.9)	11 (13.3)	10 (11.9)	17 (9.8)	14 (8.2)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	1 (0.6)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	1 (0.6)

% = n / N * 100; n = number of subjects; SD = standard deviation
[a] Treatment received in Study 20050168
[b] Treatment received in Study 20060119
[c] Baseline age = baseline (day 1) in Study 20050168

[redacted]

Diagnosis [redacted]

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects received 125 or 250 mg AMG 108 administered once every 4 weeks. AMG 108 was presented as a sterile, clear, colorless, preservative-free liquid in individual dose packs containing 2-blinded glass vials. Subjects randomized to receive 250 mg AMG 108 received 2 SC injections of 125 mg AMG 108. Subjects randomized to receive 125 mg AMG 108 received 1 SC injection of 125 mg AMG 108 and 1 SC injection of placebo. The manufacturing batch numbers were [redacted]

Duration of Treatment: 48 months (planned)

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No placebo was administered during Study 20060119.

Study Endpoints

Primary Endpoints: The primary endpoints included: adverse events; serious adverse events; serious infectious events; infectious events; injection site reactions; adverse events leading to withdrawal, life-threatening and fatal events; change (by Common Toxicity Criteria [CTC] grade) from baseline in laboratory values; infections in subjects with absolute neutrophil counts (ANC) < 1.5×10^9/L; opportunistic infections; malignant neoplasm and; anti-AMG 108 antibodies (by immunoassay and cell-based bioassay). This study was prematurely terminated due to the discontinuation of the AMG 108 program, therefore opportunistic infections and malignant neoplasms were not analyzed and antibody assays were not performed. Data regarding opportunistic infections and malignant neoplasms are on file and are available upon request.

Secondary Endpoints: The secondary endpoints included: change from baseline in MCS and PCS of SF-36, health assessment questionnaire-disability index (HAQ-DI) score, EuroQol-5 dimensions (EQ-5D), work productivity measured by work productivity and activity impairment (WPAI) questionnaire; ACR20 response; ACR20 response in subjects who are positive at least once or negative for anti-AMG 108 antibodies on both immunoassay and cell-based bioassay and; AMG 108 trough concentration (C_{min}). This study was prematurely terminated due to the discontinuation of the AMG 108 program, therefore antibody assays were not performed, and only data up to week 24 were reported for secondary endpoints due to insufficient data at week 48.

Exploratory Endpoints: [redacted]

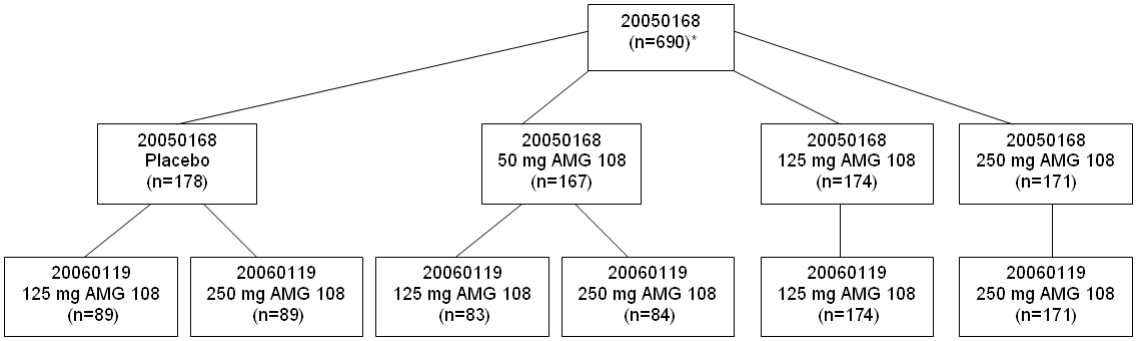
Statistical Methods: The data presented in this report was summarized by treatment assignments in both Studies 20050168 and 20060119 to take into account the varying exposure to AMG 108 in Study 20050168.

Summary statistics were provided for safety, efficacy, and patient-reported outcomes endpoints based on treatment assigned in both Studies 20050168 and 20060119. For categorical endpoints, the summary statistics included frequency and percentage. For continuous endpoints, the summary statistics included number of observations, mean, standard deviation, median, minimum, and maximum. Summary tables of crude subject incidence rates and subject listings were provided by treatment groups. All analyses were based on observed data.

Summary of Results:

Subject Disposition: All 690 subjects who were randomized received ≥ 1 dose of investigational product and were analyzed for safety and efficacy [redacted]. Overall subject disposition information is presented in Figure 1. In this extension study, the number of subjects in each AMG 108 dose group (125 and 250 mg) was generally balanced.

Figure 1. Subject Disposition



*A total of 690 of 813 subjects who completed 24 weeks of Study 20050168 were eligible to enroll into this extension study (20060119).

The naming convention in Study 20060119 for each treatment group was based on the treatment assignment in Studies 20050168 and 20060119 (Table 2).

Table 2. Treatment Assignment for Study 20060119

Treatment Group in Study 20050168 (parent study)	Treatment Group in Study 20060119	Treatment Group Naming Convention in Study 20060119
Placebo	125 mg AMG 108	Placebo/125 mg
Placebo	250 mg AMG 108	Placebo/250 mg
50 mg AMG 108	125 mg AMG 108	50 mg/125 mg
50 mg AMG 108	250 mg AMG 108	50 mg/250 mg
125 mg AMG 108	125 mg AMG 108	125 mg/125 mg
250 mg AMG 108	250 mg AMG 108	250 mg/250 mg

A total of 56.6% of the subjects (391 of 690) had at least 180.0 days of exposure to AMG 108 in this extension study and 18.3% of the subjects (126 of 690 subjects) had more than 1 year of exposure (data on file). The median duration of AMG 108 exposure was 197.0 days in this extension study (range: 197.0 to 225.0 days across all treatment groups) [redacted].

Due to the discontinuation of the AMG 108 program, no subjects completed study or investigational product [redacted]. Across all treatment groups, most subjects (range: 78.3% to 92.1%) were discontinued from study due to an administrative decision (Amgen decision to discontinue the AMG 108 program) [redacted]; similar results were reported for investigational product discontinuations (range: 79.5% to 92.4%) [redacted].

Subjects' mean baseline weight, height, and body mass index were similar across all treatment groups [redacted]. The mean duration of RA at baseline ranged from 7.19 to 8.32 years across all treatment groups [redacted]. Baseline RA medication use (ie, disease modifying

anti-rheumatic drugs, corticosteroids, nonsteroidal anti-inflammatory drugs, MTX) and baseline disease status (ie, duration of RA, morning stiffness) were similar across all treatment groups [redacted].

Efficacy Results: Although the objective of Study 20060119 did not include the statistical significance of AMG 108 on the effect of clinical signs and symptoms, AMG 108 provided clinically significant improvements in subjects with RA, as shown by ACR20 responses. At day 1 of this study, subjects in the 125 mg/125 mg and 250 mg/250 mg treatment groups had a higher ACR20 response rate compared with subjects in the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups (Table 3). By week 12, subjects in the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups had ACR20 responses that were similar to the ACR20 response at day 1 for the 125 mg/125 mg and 250 mg/250 mg treatment groups. By week 24, ACR20 responses were sustained in the 125 mg/125 mg and 250 mg/250 mg treatment groups and ACR20 response rates were similar across all 6 treatment groups (an exception includes the placebo/125 mg treatment group, which had a lower ACR20 response rate).

At day 1 of this study, the 250 mg/250 mg treatment group had a higher ACR20 response rate compared with the 125 mg/125 mg treatment group (Table 3). By week 24 of this study, the ACR20 response rates between these 2 treatment groups were similar.

Table 3. ACR20 Response Rate (%) in Study 20060119

Response Rate	Placebo[a]/ 125mg[b]	Placebo[a]/ 250mg[b]	50mg[a]/ 125mg[b]	50mg[a]/ 250mg[b]	125mg[a]/ 125mg[b]	250mg[a]/ 250mg[b]
Day 1 n/N1 (%)	28/88 (31.82)	28/86 (32.56)	30/81 (37.04)	34/83 (40.96)	74/172 (43.02)	87/170 (51.18)
Week 12 n/N1 (%)	31/76 (40.79)	41/84 (48.81)	26/76 (34.21)	30/73 (41.10)	86/158 (54.43)	84/154 (54.55)
Week 24 n/N1 (%)	31/71 (43.66)	36/75 (48.00)	34/68 (50.00)	33/69 (47.83)	67/132 (50.76)	76/141 (53.90)

n = number of subject who had an ACR20 response; N1 = number of subjects still on Study 20060119
Day 1 of Study 20060119 = Week 24 in Study 20050168
[a] Treatment in Study 20050168
[b] Treatment in Study 20060119
[redacted]

No notable improvements from day 1 were observed at week 24 in any treatment groups in SF-36 (PCS and MCS), HAQ-DI, EQ-5D, and WPAI [redacted].

Safety Results: All 690 subjects who were randomized in Study 20060119 received ≥ 1 dose of investigational product and were analyzed for safety [redacted].

AMG 108 was generally well tolerated at doses of 125 and 250 mg SC administered in this study. The incidence of adverse events did not appear to increase with increasing AMG 108 exposure; the rate of adverse events was highest in the placebo/125 mg treatment group (76.4%), lowest in the 50 mg/250 mg treatment group (59.5%), and ranged from 71.9% to 75.3% for all other treatment groups (Table 4). In general, the rate of adverse events among the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups (range: 59.5% to 76.4%) was similar compared with the 125 mg/125 mg and 250 mg/250 mg treatment groups (range: 71.9% to 73.0%) (Table 4). Adverse events were generally mild to moderate in severity [redacted]. The most common adverse event (occurring in ≥ 5% across all 6 treatment groups) was upper respiratory tract infection (12.4% [placebo/125 mg], 11.2% [placebo/250 mg], 10.8% [50 mg/125 mg], 7.1% [50 mg/250 mg], 9.8% [125 mg/125 mg], and 7.6% [250 mg/250 mg]) [redacted].

Across all treatment groups, the rate of adverse events leading to study discontinuation and investigational product withdrawal was < 10% (Table 4). No preferred term leading to investigational product withdrawal or investigational product discontinuation was reported by more than 2 subjects in any treatment groups [redacted]. Two subjects ([redacted] [125 mg/125 mg] and [redacted] [250 mg/250 mg]) were hospitalized during the study for medical procedures that were planned before enrollment (Table 4, [redacted]).

The incidence of infectious episodes did not appear to increase with increasing AMG 108 exposure; the rate of infectious episodes was highest in the placebo/125 mg treatment group (46.1%), lowest in the 125 mg/125 mg treatment group (37.9%), and ranged from 38.1% to 44.4% for all other treatment groups (Table 4). The rate of infectious episodes among the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups was similar compared with the 125 mg/125 mg and 250 mg/250 mg treatment groups (Table 4). Few infectious episodes led to study discontinuation (range: 0.0% to 1.2%) or investigational product withdrawal (range: 0.0% to 2.2%) (Table 4). Most infectious episodes were considered unrelated to investigational product [redacted]. The most common infectious episode (occurring in ≥ 5% across all treatment groups) was upper respiratory tract infection; the rate of upper respiratory tract infection was highest in the placebo/125 mg treatment group (12.4%), lowest in the 50 mg/250 mg treatment group (7.1%), and ranged from 7.6% to 11.2% for all other treatment groups [redacted]. With the exception of the 125 mg/125 mg treatment group (6.3%), the rates of infectious episodes considered by the investigator to be treatment-related were > 10.0% for all treatment groups [redacted]. In general, the rate of treatment-related infectious episodes among the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups (range: 10.1% to 14.3%) was similar compared with the 125 mg/125 mg and 250 mg/250 mg treatment groups (range: 6.3% to 14.0%) [redacted].

The incidence of serious adverse events did not appear to increase with increasing AMG 108 exposure; the rate of serious adverse events was highest in the 50 mg/125 mg treatment group (12.0%), lowest in the 50 mg/250 mg treatment group (3.6%), and ranged from 6.7% to 9.2% for all other treatment groups (Table 4). In general, the rate of serious adverse events among the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups (range: 3.6% to 12.0%) was similar compared with the 125 mg/125 mg and 250 mg/250 mg treatment groups (7.6% to 9.2%) (Table 4). With the exception of cellulitis (2 subjects [125 mg/125 mg]) and pyrexia (2 subjects [placebo/125 mg]), no preferred term was reported by more than 1 subject in any treatment group [redacted]. The rate of serious adverse events resulting in hospitalization was highest in the 50 mg/125 mg treatment group (10.8%), lowest in the 50 mg/250 mg treatment group (3.6%), and ranged from 5.6% to 7.9% for all other treatment groups (Table 4, [redacted]). Across all treatment groups, few serious adverse events that were considered by the investigator to be related to investigational product were reported (range: 0.0% to 2.3%) (Table 4). No treatment-related serious adverse event by preferred term was reported by more than 1 subject [redacted].

Few serious infectious episodes, which were a subset of serious adverse events, were reported across all treatment groups (range: 0.0% to 2.4%) (Table 4). The rate of serious infectious episodes among the placebo/125 to 250 mg and 50 mg/125 to 250 mg treatment groups (range: 0.0% to 2.4%) was similar compared with the 125 mg/125 mg and 250 mg/250 mg treatment groups (2.3% each) (Table 4). A total of 9 subjects (1 subject in the 50 mg/125 mg treatment group and 4 subjects each in the 125 mg/125 mg and 250 mg/250 mg treatment groups) had infectious episodes that resulted in hospitalization (Table 4, [redacted]). Five subjects reported at least 1 serious infectious episode that was considered by the investigator to be related to treatment; these events included cellulitis (125 mg/125 mg), fungal pneumonia (placebo/125 mg), localized infection (250 mg/250 mg), postoperative wound infection (250 mg/250 mg), and sepsis (125 mg/125 mg) [redacted]. Cellulitis was the only preferred term reported for more than 1 subject in any of the treatment groups (125 mg/125 mg) [redacted].

One death was reported during the study (Table 4). Subject [redacted] received placebo in Study 20050168 and 1 dose of 125 mg AMG 108 in this extension study (20060119). Two weeks after a repair of traumatic ankle fracture, she died of a pulmonary embolism that was not considered by the investigator to be related to treatment [redacted]. [redacted]

Rates of injection site reactions were similar across all treatment groups (0.6% to 2.9%) (Table 4). All injection site reactions were mild to moderate in severity and most (approximately 75%) lasted < 25 days [redacted].

Subjects who received 125 mg or 250 mg in both Studies 20050168 and 20060119 had the same amount of exposure to AMG 108. The incidence of adverse events, serious adverse events, serious infectious episodes (subset of serious adverse events), and deaths did not appear to increase with increasing AMG 108 dose; the rate of these safety endpoints was no higher among the 250 mg/250 mg treatment group compared with the 125 mg/125 mg treatment group (Table 4). The rate of injection site reaction was higher in the 250 mg/250 mg treatment group (2.9%) compared with the 125 mg/125 mg treatment group (0.6%) (Table 4). All injection site reactions were mild to moderate in severity and most (approximately 75%) lasted < 25 days [redacted]. The rate of non-serious infectious episodes was also higher in the 250 mg/250 mg treatment group (44.4%) compared with the 125 mg/125 mg treatment group (37.9%) (Table 4). However, the rate of serious infectious episodes was 2.3% for both the 125 mg/125 mg and 250 mg/250 mg treatment groups.

Table 4. Overall Summary of Subjects With Adverse Events by Treatment Group (Study 20060119)

	Placebo[a]/ 125mg[b] (N = 89) n (%)	Placebo[a]/ 250mg[b] (N = 89) n (%)	50mg[a]/ 125mg[b] (N = 83) n (%)	50mg[a]/ 250mg[b] (N = 84) n (%)	125mg[a]/ 125mg[b] (N = 174) n (%)	250mg[a]/ 250mg[b] (N = 171) n (%)	Total (N = 690) n (%)
Serious Adverse Events	8 (9.0)	6 (6.7)	10 (12.0)	3 (3.6)	16 (9.2)	13 (7.6)	56 (8.1)
Death	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Serious Infectious Episodes	1 (1.1)	0 (0.0)	2 (2.4)	0 (0.0)	4 (2.3)	4 (2.3)	11 (1.6)
Resulting in Hospitalization	7 (7.9)	5 (5.6)	9 (10.8)	3 (3.6)	13 (7.5)	12 (7.0)	49 (7.1)
Adverse Events	68 (76.4)	67 (75.3)	61 (73.5)	50 (59.5)	127 (73.0)	123 (71.9)	496 (71.9)
Leading to Study Discontinuation	5 (5.6)	0 (0.0)	6 (7.2)	0 (0.0)	5 (2.9)	5 (2.9)	21 (3.0)
Leading to Investigational Product Withdrawal	4 (4.5)	0 (0.0)	6 (7.2)	0 (0.0)	5 (2.9)	5 (2.9)	20 (2.9)
Resulting in Hospitalization[c]	7 (7.9)	5 (5.6)	9 (10.8)	3 (3.6)	14 (8.0)	13 (7.6)	51 (7.4)
Infectious Episodes	41 (46.1)	35 (39.3)	35 (42.2)	32 (38.1)	66 (37.9)	76 (44.4)	285 (41.3)
Leading to Study Discontinuation	1 (1.1)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.6)	2 (1.2)	5 (0.7)
Leading to Investigational Product Withdrawal	2 (2.2)	0 (0.0)	1 (1.2)	0 (0.0)	2 (1.1)	2 (1.2)	7 (1.0)
Resulting in Hospitalization[d]	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	4 (2.3)	4 (2.3)	9 (1.3)
Injection Site Reaction	1 (1.1)	1 (1.1)	1 (1.2)	2 (2.4)	1 (0.6)	5 (2.9)	11 (1.6)
All Treatment-related Adverse Events	19 (21.3)	17 (19.1)	20 (24.1)	18 (21.4)	23 (13.2)	37 (21.6)	134 (19.4)
All Treatment-related Serious Adverse Events	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	4 (2.3)	3 (1.8)	9 (1.3)

Note: Adverse events and serious adverse events are based on all adverse events including infectious episodes and injection site reactions
% = n / N * 100; N = number of subjects who were randomized and received at least 1 dose of investigational product; n = number of subjects reporting at least 1 occurrence of an adverse event

[a] Treatment in Study 20050168

[b] Treatment in Study 20060119

[c] Two of 51 subjects (1 subject each in the 125 mg/125 mg and 250 mg/250 mg groups) were hospitalized for medical procedures that were planned before enrollment.

[d] Infectious episodes resulting in hospitalization are a subset of serious adverse events.

[redacted]

Other Safety Findings: No notable changes were observed in laboratory values with the exception of expected decreases in ANC and platelet counts, which are discussed below. [redacted].

Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade 3 and 4 decreases in ANC were rare (0.6% and 0.3%, respectively) [redacted]. Of the 4 subjects who had grade 3 decreases (1 subject in the 50 mg/250 mg treatment group and 3 subjects the 250 mg/250 mg treatment group) and the 2 subjects who had grade 4 decreases (1 subject each in the 125 mg/125 mg and 250 mg/250 mg treatment group), the decreases in ANC were transient [redacted]. By each subject's last visit date, ANCs were similar compared with baseline (an exception includes 1 subject in the 125 mg/125 mg treatment group who had a grade 4 decrease but remained on study) [redacted].

A total of 17 subjects had ≥ 1 infectious episode and ≥ 1 low ANC (ANC < 1.5 x 10^9/L, ≥ grade 2 CTCAE) at any time point during the study [redacted]. Of these, 1 subject ([redacted]) had an infectious episode (nasopharyngitis) on day 137 and a preceding low ANC (1.24 x 10 /L, grade 2 CTCAE) that was collected 23 days before the onset of the infection (data on file). Additionally, of these 17 subjects, 5 subjects had a grade 3 or 4 ANC at any time point during the study (data on file).

Although there were limited time points of ANC collection in this study, there was no obvious association between a low preceding ANC and an infectious episode.

No clinically significant changes were observed in vital signs [redacted].

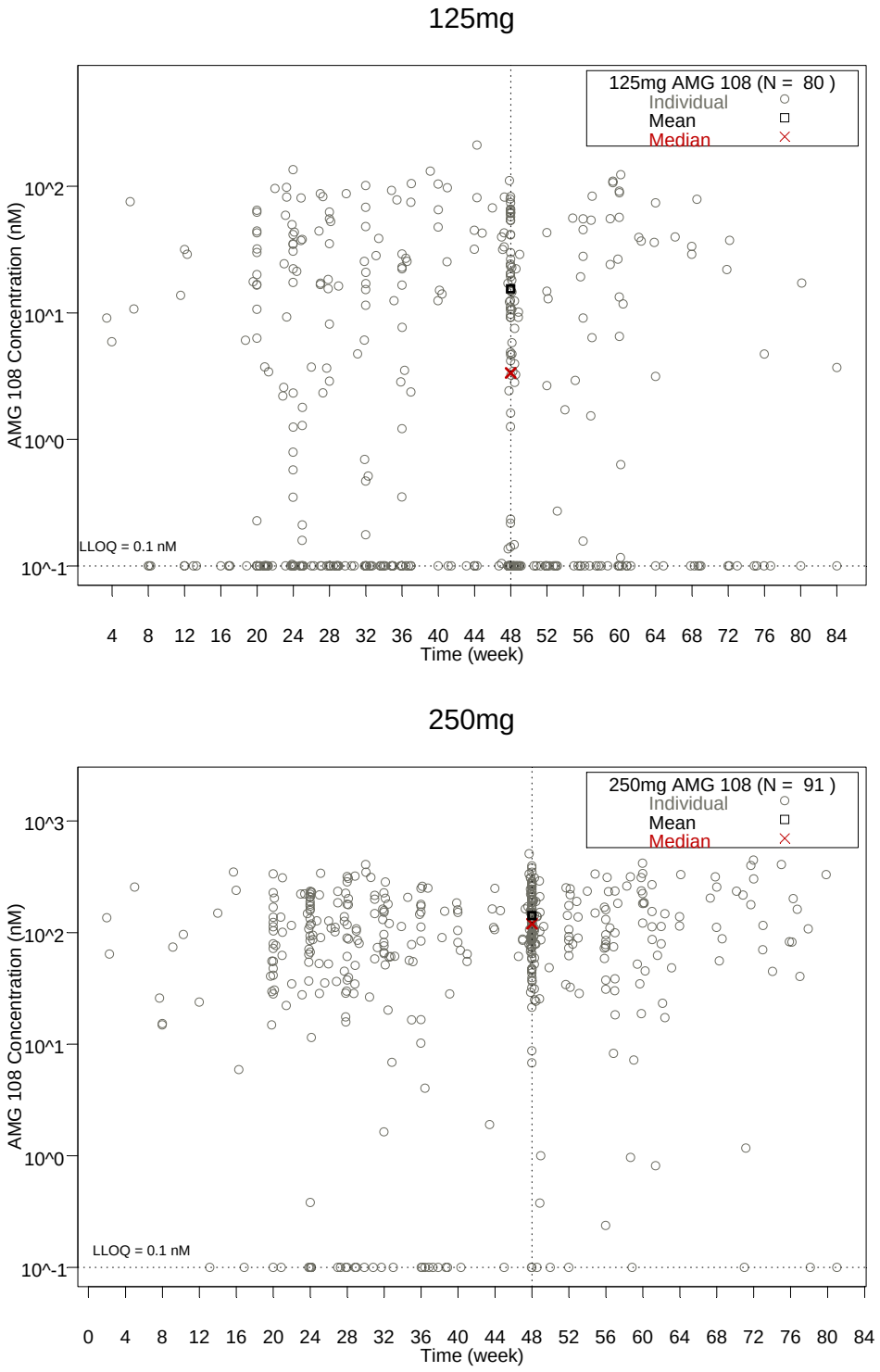
Pharmacokinetic Results: Trough mean and median values of AMG 108 concentrations at week 48 from this study were similar compared with the same dose group from Study 20050168 at week 24 indicating that the pharmacokinetics of AMG 108 had reached steady state by week 48 of Study 20060119. The trough concentration data at week 48 are summarized in Table 5. Individual concentration data from all pharmacokinetic samples along with mean and median values at week 48 for the 125 and 250 mg dose groups are depicted in Figure 2.

Table 5. Summary Trough Concentration of AMG 108 at Week 48 of Study 20060119

	125 mg AMG 108	250 mg AMG 108
N	80	91
Mean (nM)	15.4	141
SD (nM)	24.1	97.2
Min, Max (nM)	0.00, 111	0.377, 509
Median (nM)	3.35	120
CV%	156.6	68.8

Lower limit of quantification (LLOQ = 0.1 nM) reported as 0.000.
Samples for which the actual sampling time deviated from the nominal sampling time by >7 days were excluded from these summary statistics.
CV% = percent coefficient of variation; N = number of subjects who were randomized and received at least 1 dose of investigational product; SD = standard deviation
Source: PKS/20060119/Mean (v.3)/Tables MT_20060119-mean

Figure 2. Individual AMG 108 Concentrations (nM) With Mean and Median at Week 48



Source: [code] documentum\Docbases\usddms\R&D Candidates\Development\AMG 108 - 3060 - anti-IL-1R antibody\Study 20060119\PKDM\Final Analysis\Modified Data\119MedPlot.ssc
[graph] documentum\Docbases\usddms\R&D Candidates\Development\AMG 108 - 3060 - anti-IL-1R antibody\Study 20060119\PKDM\Final Analysis\Graphs\125mg plot.sgr and 250mg plot.sgr

Exploratory Endpoint Results: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Conclusions: AMG 108 was generally well tolerated at all doses administered during this extension study (125 and 250 mg). In general, the safety profile was similar regardless of dose. Improvements in signs and symptoms of RA as measured by ACR20 at week 24 were sustained among subjects who received 125 or 250 mg AMG 108 in both Studies 20050168 and 20060119; by week 24 of Study 20060119, ACR20 response in the other groups were similar to those in the 125 mg/125 mg and 250 mg/250 mg groups.

[redacted]