2. SYNOPSIS

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

Name of Finished Product: AMG 827

Name of Active Ingredient: AMG 827

Title of Study: A Long-term Assessment of the Safety and Efficacy of AMG 827 Subcutaneous Treatment in Subjects with Rheumatoid Arthritis

Investigator(s) and Study Center(s): This study was conducted at 45 centers in the United States (US), Bulgaria, Canada, Czech Republic, Latvia, Mexico, Poland, and the United Kingdom. Investigators and the centers where the subjects were treated during the study are listed in Attachment 2.

Publication(s): None

Study Period: 03 June 2010 (first subject enrolled) to 18 May 2011 (last subject visit completed). The study was terminated early due to lack of efficacy in the parent study (Study 20090061).

Development Phase: 2

Introduction and Objectives:

AMG 827 is a human, Chinese hamster ovary cell-derived IgG2 monoclonal antibody that selectively targets human interleukin 17 receptor A (IL-17RA) and antagonizes the IL-17 pathway. It binds with high affinity to human IL-17RA and blocks the biological activity of IL-17A and IL-17F. Recent studies have revealed that AMG 827 also blocks IL-25 (or IL-17E) in a dose-dependent manner (R20080129).

A potential role for IL-17A signaling in rheumatoid arthritis (RA) has been supported by data from several studies. Interleukin-17A can directly stimulate synoviocyte production of inflammatory mediators including IL-6, granulocyte macrophage colony stimulating factor, and prostaglandin E2 (Fossiez et al, 1996). Increased levels of IL-17A have been detected in the synovial fluid of patients with RA (Kotake et al, 1999; Ziolkowska et al, 2002; Raza et al, 2005) and, furthermore, blockade of IL-17A signaling can inhibit osteoclast formation induced by culture media of RA synovial tissues. In an ex vivo model using explanted synovial tissue from human RA patients, blockade of IL-17A can reduce the spontaneous production of IL-6 and collagen breakdown products (C-telopeptide of type I collagen) (Chabaud and Miossec, 2001). Finally, in a prospective study synovial membrane mRNA levels of IL-17A were predictive of damage progression, and the effects of IL-17A were shown to be synergistic with TNF (Kirkham et al, 2006).

The objectives of this study were:

Safety: To evaluate the safety of long-term exposure with AMG 827 in subjects with RA.

Efficacy: To evaluate the efficacy of AMG 827 as measured by the following:

- The proportion of subjects achieving an American College of Rheumatology (ACR) 20, 50, and 70 response
- Change in Disease Activity Score 28 joint (DAS28) score
- The proportion of subjects with DAS28 < 2.6

- DAS28 score
- ACR individual components

Other:

Other objectives are listed in Section 1.3 of the protocol in Attachment 1.

Methodology: The protocol and complete text of the amendment are provided in Attachment 1.

This study was an open-label extension of Study 20090061 in subjects with RA who had an inadequate response to methotrexate. This study evaluated the long-term efficacy and safety of AMG 827. Enrollment was planned to be approximately 216 subjects who had completed the week 16 visit of Study 20090061, signed the informed consent form, completed all screening assessments, if applicable, and met the safety-based eligibility criteria for Study 20090402.

After the screening period, the first 12 weeks of this extension study included visits at baseline and weeks 1, 2, 4, 6, 8, 10, and 12 as subjects were restarting AMG 827 after at least a 6-week hiatus (last dose of investigational product in Study 20090061 was at week 10 and subjects continued the study through at least week 16), and some were starting treatment with AMG 827 for the first time (subjects from the placebo arm in Study 20090061).

All subjects in Study 20090402 received 210 mg AMG 827 and continued to receive their weekly methotrexate. At week 12, subjects were evaluated for response; subjects lacking satisfactory response at this visit or later visits were eligible for additional therapy within the restrictions specified in Sections 6.3 and 6.4 of the protocol (Attachment 1).

Clinical assessments were performed and patient-reported outcomes (PRO) were collected at predefined times. Safety assessments and blood collection timepoints for laboratory safety tests are described in the schedule of assessments in Appendix A of the protocol (Attachment 1).

This study report for Study 20090402 is presented in synopsis form because AMG 827 was not shown to be efficacious in the parent study (Study 20090061) when compared to placebo at any dose as measured by ACR 20, 50, or 70 responses. In addition, there was no observed difference compared to placebo in responses as measured by the individual components of the ACR response criteria. Based on these findings, Amgen made the decision to terminate Study 20090402. The last date of AMG 827 administration was 06 April 2011. All study subjects were required to attend an early termination visit 28 days after their last dose of AMG 827 and subjects were transitioned to other appropriate therapies for their RA.

Number of Subjects Planned: Approximately 216 subjects

Number of Subjects Enrolled: 211

Sex: 167 (79.1%) women; 44 (20.9%) men

Age: Mean (SD) 52.2 (10.5) years (range: 20 to 71)

Ethnicity (Race): white: 166 (78.7%); black: 3 (1.4%); Hispanic/Latino: 40 (19.0%); Asian: 2 (0.9%)

Diagnosis and Main Criteria for Eligibility: Enrollment in this study was contingent upon completion of the week 16 visit of Study 20090061 and safety-based exclusion criteria (ie, subjects had not experienced any serious adverse events that were reported to be related to study drug). Subjects must have completed appropriate washout periods for drugs specified in Section 4.2 of the protocol (Attachment 1), must have been free of infections (at study entry), and significant concurrent medical conditions as described in Section 4.2 of the protocol (Attachment 1) If applicable, subjects must have been willing to use 2 methods of highly effective birth control during the study and for a specified period after the study ended. Depending upon the length of

Depending upon the length of time between the week 16 visit of the parent study and the first planned dose of AMG 827 in Study 20090402, subjects could require additional tests, including serum pregnancy if applicable, laboratory assessments for safety, and testing for latent tuberculosis.

For a complete list of eligibility criteria, refer to Sections 4.1 and 4.2 of the protocol (Attachment 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: AMG 827 was administered subcutaneously at a dose of 210 mg at day 1, week 1, week 2, and every other week thereafter. The manufacturing batch numbers of AMG 827 administered in this study were: [redacted] (Listing 5-2).

Duration of Treatment: After completing participation in the parent study (20090061), subjects in this extension study were to receive 210 mg AMG 827 for approximately 264 weeks or until the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the subject's decision to discontinue for any reason, or an administrative decision to close the study (except in the UK). In the UK, subjects were to be treated for up to 104 weeks in response to an MHRA request, as described in the Statistical Analysis Plan (Attachment 7). Study 20090402 was terminated on 18 May 2011.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: No reference therapy was administered during this study.

Study Endpoints

Safety endpoints included:

- Adverse events
- Change in laboratory parameters (hematology, chemistry, and urinalysis profiles) and vital signs

Efficacy endpoints included:

- ACR 20, 50, and 70 at all measured timepoints
- DAS28 improvement from baseline at all measured timepoints
- DAS28 < 2.6 at all measured timepoints
- DAS28 score at all measured timepoints
- ACR individual components at all measured timepoints

Other Endpoints are described in Section 10.1.1 of the protocol (Attachment 1).

Statistical Methods: The goal of the primary statistical analysis was to evaluate the safety of long-term exposure with AMG 827 in subjects with RA to provide some insight into the restart of study drug, and the longer-term durability of response based on the endpoints utilized in the parent study (20090061). This study collected adverse events and safety laboratory assessments as well as efficacy assessments, PROs, and anti-AMG 827 antibody samples. An additional goal of the study was to evaluate the transition from the first-in-human (FIH) formulation to the phase 3 formulation of the investigational product, however due to the administrative decision to terminate Study 20090402 the phase 3 formulation was not dosed.

Maintenance of efficacy was assessed by ACR 20, 50, and 70 responses, individual components of ACR and DAS28. Descriptive summaries of observed data are provided by treatment group in the parent study and by study visit in Study 20090402 for efficacy endpoints (ACR 20, 50, and 70,

DAS28, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]). No formal statistical testing was planned for efficacy endpoints.

Endpoints were examined both as changes from the parent study (20090061) baseline as well as the baseline established at the start of the open-label extension study (20090402), with change from Study 20090061 baseline as the primary analysis.

Per the SAP (Attachment 7), no summary tables were planned for PRO endpoints. Disability Index of the Health Assessment Questionnaire (HAQ-DI) score, subject global assessment of disease activity (SGA), and patient global assessment of joint pain contributed in determining ACR 20, 50, and 70 responses.

Summary statistics of continuous variables included: n, mean, median, standard deviation, minimum, maximum, and 95% confidence interval (except for safety laboratory assessments). All summaries presenting frequencies and incidences included n, %, and N, where N is the total number of subjects with recorded values in the corresponding arm.

Subject incidence and exposure-adjusted event rates of all treatment-emergent adverse events were tabulated by system organ class and preferred term. Laboratory assessments were evaluated by study visit for safety. Shift tables of the worst on-study laboratory toxicity relative to baseline for Study 20090061 and Study 20090402 were tabulated based on Common Terminology Criteria for Adverse Events (CTCAE) grades. Missing safety data were not imputed.

Summary of Results:

Subject Disposition: 211 subjects were enrolled in Study 20090402, and all 211 subjects received AMG 827 210 mg every other week with an additional dose at week 1.

Most subjects discontinued the study (183 [86.7%]) because of an administrative decision (study terminated). Nine (4.3%) subjects discontinued the study because of disease progression; 8 (3.8%) subjects because of full consent withdrawn, and 5 (2.4%) subjects because of adverse event; 2 (0.9%) subjects were lost to follow-up, 1 (0.5%) subject died, and 3 (1.4%) subjects discontinued because of other reasons (lack of efficacy) (Table 11-1.1).

Most subjects (182 [86.3%]) discontinued AMG 827 because of an administrative decision (study terminated). Nine (4.3%) subjects discontinued AMG 827 because of disease progression; 8 (3.8%) because of full consent withdrawn, 6 (2.8%) because of adverse event, 2 (0.9%) subjects were lost to follow-up and 4 (1.9%) subjects discontinued because of other reasons (eg, lack of efficacy) (Table 11-1.2).

One subject (20090061 placebo group) discontinued the study and investigational product due to an adverse event that started prior to the first dose in Study 20090402 (Table 11-1.1 and Table 11-1.2), and therefore was not included in the treatment-emergent adverse event summaries.

The total number of subjects who had an important protocol deviation was 37 (17.5%). Thirty-two (15.2%) subjects had the most commonly cited important protocol deviation, which was “missing data (other than treatment administration or treatment compliance)” (Table 11-3.1). Six (2.8%) subjects received the wrong treatment or the incorrect dose, ie, “received investigational product dose outside stability range” (Listing 5-1).

Efficacy Results:

Efficacy endpoints were examined as changes from the parent-study (20090061) baseline. The changes from the extension study (20090402) baseline were summarized as a supportive analysis for subjects on placebo in Study 20090061 and subjects on AMG 827 if the gap was

ACR 20, 50, and 70 at All Measured Timepoints

Summaries of ACR 20, 50, and 70 responses based on Study 20090061 baseline by treatment group in Study 20090061 and by visit in Study 20090402 are presented in Table 11-4.3, Table 11-4.1, and Table 11-4.5, respectively. The percent ACR 20, 50, and 70 responders based on Study 20090061 baseline were similar across all Study 20090061 treatment groups, including placebo, and did not increase appreciably over time by visit in Study 20090402.

Summaries of ACR 20, 50, and 70 responders based on Study 20090402 baseline by treatment group in Study 20090061, gap between Study 20090061 and Study 20090402 and by visit in Study 20090402 are presented in Table 11-4.4, Table 11-4.2, and Table 11-4.6, respectively. The number of ACR responders was small and there were no notable differences in the percent of ACR 20, 50, and 70 responders between subjects with ≤ 4 weeks or > 4 weeks gap between Study 20090061 and Study 20090402.

DAS28 Improvement from Baseline at All Measured Timepoints

A summary of change in DAS28 from Study 20090061 baseline by treatment group in Study 20090061, and by visit in Study 20090402 is presented in Table 11-4.15. The changes in DAS28 values (mean [SD]) were similar across Study 20090061 treatment groups, including placebo and did not vary appreciably over time by visit in Study 20090402.

A summary of change in DAS28 (mean [SD]) from Study 20090402 baseline by treatment group in Study 20090061, gap between Study 20090061 and Study 20090402, and by visit in Study 20090402 is presented in Table 11-4.16. The number of subjects with > 4 weeks gap between Study 20090061 and Study 20090402 was small. There were no consistent differences in DAS28 mean values across 20090061 treatment groups or over time by visit in Study 20090402 between subjects with ≤ 4 weeks or > 4 weeks gap between Study 20090061 and Study 20090402.

DAS28 < 2.6 at All Measured Timepoints

A summary of subjects with DAS28 values < 2.6 by treatment group in Study 20090061 and by visit in Study 20090402 is presented in Table 11-4.17. The number of subjects with DAS28 < 2.6 across Study 20090061 treatment groups was variable and sample sizes were small.

DAS 28 at All Measured Timepoints

A summary of DAS28 values by treatment group in Study 20090061 and by visit in Study 20090402 is presented in Table 11-4.14. DAS28 values (mean [SD]) for all subjects in Study 20090402 and across all Study 20090061 treatment groups were decreased from Study 20090061 baseline values and similar to Study 20090402 baseline values. In Study 20090402, DAS28 values (mean [SD]) were similar across Study 20090061 treatment groups, including placebo and did not decrease appreciably over time by visit in Study 20090402.

ACR Individual Components at All Measured Timepoints

HAQ-DI score, SGA and patient global assessment of joint pain contributed in determining ACR 20, 50, and 70 responses. The changes for ACR 20, 50 and 70 responses for Study 20090402 based on Study 20060061 baseline as summarized previously were similar across all Study 20090061 treatment groups, including placebo and did not improve appreciably over time by visit in Study 20090402.

A summary of CRP (mg/L), and percentage change in CRP from 20090061 baseline by treatment group in Study 20090061 and by visit in Study 20090402 are presented in Table 11-4-7, and Table 11-4.8, respectively. CRP values (mean [SD]) for all subjects in Study 20090402 and

across all Study 20090061 treatment groups were not appreciably different from Study 20090061 and study 200900402 baseline values (Table 11-4.7). The percent change in CRP based on Study 20090061 baseline was variable across Study 20090061 treatment groups, including placebo, and did not show consistent changes over time by visit in Study 20090402 (Table 11-4.8).

A summary of percentage change in CRP (mg/L) from Study 20090402 baseline by treatment group in Study 20090061, gap between Study 20090061 and Study 20090402, and by visit in Study 20090402 are presented in Table 11-4.9. The numbers of subjects with a gap > 4 weeks was small and there were no notable differences in the percent change in CRP between subjects with ≤ 4 weeks or > 4 weeks gap between Study 20090061 and Study 20090402.

A summary of ESR (mm/hr), and a summary of percentage change in ESR from Study 20090061 baseline by treatment group in Study 20090061 and by visit in Study 20090402 are presented in Table 11-4.10, and Table 11-4.11, respectively. ESR values (mean [SD]) for all subjects in Study 20090402 and across all Study 20090061 treatment groups were decreased from Study 20090061 baseline values and similar to Study 20090402 baseline values (Table 11-4.10). The percentage change in ESR was similar across Study 20090061 treatment groups, including placebo and did not vary meaningfully over time by visit in Study 20090402 (Table 11-4.11).

A summary of percentage change in ESR from Study 20090402 baseline by treatment group in Study 20090061, gap between Study 20090061 and Study 20090402, and by visit in Study 20090402 is presented in Table 11-4.12. The numbers of subjects with a gap > 4 weeks was small and there were no notable differences in the percent change in ESR between subjects with ≤ 4 weeks or > 4 weeks gap between Study 20090061 and Study 20090402.

Other Results

No summary tables were planned for PRO endpoints.

Safety Results:

The summary of adverse events is presented for all subjects in Study 20090402 and by Study 20090061 treatment group in Table 1. Subject incidence of all adverse events in Study 20090402 was 58.3% overall. Subject incidence of all treatment-related adverse events was 20.4% overall.

Subject incidences of treatment-emergent grade 3 and above adverse events was 7.6% overall (Table 1).

The most common treatment-emergent adverse events (incidence rates) overall, were upper respiratory tract infection (9.0%), RA (5.7%), arthralgia (5.7%), nasopharyngitis (5.2%), and injection site pain (5.2%) (Table 11-6.2).

Eight subjects reported serious adverse events; none were reported as related to AMG 827 (Table 11-6.4, Table 11-6.5, and Listing 5-4). One subject died from a completed suicide (Table 11-6.4, Table 11-6.7, and Listing 5-4).

Five subjects had adverse events leading to withdrawal from investigational product administration (Table 11-1.2, Table 11-6.6, and Listing 5-6). One adverse event of sinusitis leading to discontinuation of investigational product was considered by the investigator to be related to AMG 827 (Listing 5-6).

Table 1. Overall Summary of Subject Incidence of Adverse Events
AMG827 Study 20090402
Safety Analysis Set

	Placebo / 210 mg Q2WK (N = 49) n (%)	70 mg Q2WK / 210 mg Q2WK (N = 55) n (%)	140 mg Q2WK / 210 mg Q2WK (N = 53) n (%)	210 mg Q2WK / 210 mg Q2WK (N = 54) n (%)	Total (N = 211) n (%)
Adverse events regardless of relationship					
All	28 (57.1)	32 (58.2)	31 (58.5)	32 (59.3)	123 (58.3)
Serious	2 (4.1)	5 (9.1)	1 (1.9)	0 (0)	8 (3.8)
Fatal	0 (0)	1 (1.8)	0 (0)	0 (0)	1 (0.5)
Leading to study discontinuation	0 (0)	4 (7.3)	0 (0)	1 (1.9)	5 (2.4)
Leading to investigational product discontinuation	0 (0)	4 (7.3)	0 (0)	1 (1.9)	5 (2.4)
CTCAE Grade 3, 4,or 5	3 (6.1)	7 (12.7)	4 (7.5)	2 (3.7)	16 (7.6)
Adverse events related to investigational product					
All	11 (22.4)	10 (18.2)	11 (20.8)	11 (20.4)	43 (20.4)
Serious	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leading to study discontinuation	0 (0)	1 (1.8)	0 (0)	0 (0)	1 (0.5)
Leading to investigational product discontinuation	0 (0)	1 (1.8)	0 (0)	0 (0)	1 (0.5)
CTCAE Grade 3, 4,or 5	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (0.5)

CTCAE = common terminology criteria for adverse events; Q2WK = day 1 + weeks 1 and 2 + every other week.
Coded using MedDRA version 14 and CTCAE version 4.0
Treatment groups are coded as "randomized treatment group in 20090061 / treatment received in 20090402"
N = Number of subjects who were enrolled and received at least one dose of investigational product
n = Number of subjects reporting at least one occurrence of an adverse event
% = n/N * 100
Includes only treatment-emergent adverse events after initiation of investigational product in 20090402

Program: /stat/amg827/ra/20090402/analysis/final/prod/tables/t-aesum.sas
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Extent of Exposure

All 211 subjects in Study 20090402 received at least 1 dose of AMG 827. The mean (SD) duration of exposure (includes exposure in Study 20090061 and Study 20090402) to AMG 827 for all subjects was 219.9 (79.7) days with a range of 23 to 366 days. Duration of exposure by Study 20090061 treatment group is presented in Table 11-5.1.

Although a dose change was not allowed per study design, 64 (30.3%) subjects had missed doses with the following reasons provided: 35 (16.6%) subjects because of an adverse event, 19 (9.0%) subjects because of "other" reasons (missed visit was the most frequent reason provided), 17 (8.1%) subjects because of noncompliance, and 1 (0.5%) subject each due to dose administration error, per protocol, and investigator decision (Table 11-5.2).

All 211 subjects discontinued AMG 827: most subjects (182 [86.3%]) discontinued because of an administrative decision (eg, study termination), 9 (4.3%) because of disease progression; 8 (3.8%) because of full consent withdrawn, 6 (2.8%) (1 subject discontinued investigational product due to an adverse event that started prior to the first dose in Study 20090402, thus it is not included in the treatment-emergent adverse event summaries), 2 (0.9%) were lost to follow-up, and 4 (1.9%) discontinued because of other reasons (eg, lack of efficacy) (Table 11-1.2).

The average weekly methotrexate dose (mean ± SD) for all AMG 827 subjects was 16.6 mg (3.6), range 7.5 to 25 mg. Most subjects received methotrexate via oral route (191 [90.5%]). Fourteen (6.6%) subjects received methotrexate via subcutaneous (SC) injection, and 6 (2.8%) subjects received methotrexate via intramuscular injection (Table 11-5.3).

Adverse Events

Deaths

One subject [redacted] (20090061 AMG 827, 70 mg group) died on study day 119 of a completed suicide (Table 11-6.7 and Listing 5-7). The subject was a [redacted] who did not have a history of depression, suicidal ideation, or psychotropic or antidepressant drug intake. During the parent study, the subject experienced grade 1 chest pain on day 46 in sternum area after the injection of the investigational product, and a grade 2 upper respiratory tract infection occurred on day 80 of the study. Both adverse events were considered not related to AMG 827 administration. The following concomitant medications were reported for the subject at the time of Study 20090402: folic acid, Loestrin, Percocet, multivitamin, zyrtec, Lasix for pedal edema treatment, tramadol and methotrexate (Listing 5-14). During the study the subject experienced grade 2 malaise on day 3 of the study which resolved within 2 days, increased RA pain (grade 2) on day 5, and influenza (grade 1) on day 109. On day 119 of the study, 1 week after the last dose of AMG 827, the subject took [redacted] own life because of emotional distress and financial issues. [redacted] death was assessed as not related to the administration of AMG 827. The full narrative for this subject death is provided in Attachment 4.

Withdrawals from Study Due to Adverse Events

Four subjects discontinued the study (Listing 5-7) and investigational product (Table 11-6.6 and Listing 5-6) due to a treatment-emergent adverse event: 3 subjects from Study 20090061 AMG 827, 70 mg group (drug intolerance [grade 3]; nephrotic syndrome [grade 3and sinusitis [grade 2]) and 1 subject from Study 20090061 AMG 827, 210 mg group (RA [worsening of RA] [grade 2]). A fifth subject discontinued the study due to completed suicide (grade 5). The events of nephrotic syndrome and completed suicide were also considered serious adverse events. The event of sinusitis was reported as related to AMG 827 (Listing 5-7). One additional subject (Study 20090061 placebo group) discontinued the study and investigational product due to an adverse event that started prior to the first dose in Study 20090402, thus it is not included in the treatment-emergent adverse event summaries.

Serious Adverse Events

Eight subjects reported serious adverse events (Table 11-6.4 and Listing 5-4).

Five subjects from Study 20090061 AMG 827, 70 mg group experienced serious adverse events:

- 1 subject [redacted] reported traumatic brain injury (grade 4)
- 1 subject [redacted] reported cholelithiasis (grade 4)
- 1 subject [redacted] reported dysphagia, gastritis, and esophageal achalasia (all grade 3)
- 1 subject [redacted] reported nephrotic syndrome (grade 3)
- 1 subject [redacted] died as a result of a completed suicide (grade 5).

One subject [redacted] from Study 20090061 AMG 827, 140 mg group reported osteoarthritis (grade 3).

Of the 2 subjects from the placebo group in Study 20090061 who reported serious adverse events in Study 20090402, 1 subject [redacted] reported hypersensitivity (grade 3), and another subject [redacted] reported chest pain (grade 2) and pneumonia (grade 3). None of the serious adverse events were reported as related to AMG 827 (Table 11-6.4, Table 11-6.5 and Listing 5-4). Subject narratives for these serious adverse events are provided in Attachment 4.

Clinically Significant Adverse Events

Events of interest for this study were neutropenia, infectious episodes, injection site reactions, and immunogenicity.

Neutropenia is classified as an identified risk in the Investigator's Brochure (Edition 6, 19 October 2011) and therefore is considered an event of interest. Two subjects [redacted] from Study 20090061, AMG 827, 70 mg group reported adverse events of neutrophil count decreased (both grade 1) (Table 11-6.2, Table 11-6.12, and Listing 5-4). Both events were considered related to AMG 827 and both resolved without intervention (they occurred at day 57 and 111 and normalized by day 76 and 127, respectively), and with continued AMG 827 therapy.

A third subject [redacted] from Study 20090061, AMG 827, 70-mg group shifted down 3 grade levels (0 to 3) in absolute neutrophil count and in total neutrophil count and shifted down 2 grade levels (0 to 2) in white blood cells from Study 20090402 baseline at day 106 (last day on study) (Table 11-7.1, Table 11-7.6, Table 11-7.11, and Listing 5-10) and shifted up 3 grade levels in glucose from 20090061 baseline at day 56 (Listing 5-9). Follow-up indicated that secondary leucopenia and neutropenia were considered to be due to methotrexate toxicity and methotrexate was suspended. Adverse events of moderate leucopenia and neutropenia (added to the eCRF after the administrative study termination date) resolved and were considered not related to AMG 827.

An infectious adverse event was reported in 29.4% of subjects in Study 20090402. The most commonly reported infectious events overall were upper respiratory tract infection (19 [9.0%]), and nasopharyngitis (11 [5.2%]) (Table 11-6.10). Grade 3 infectious adverse events were noted in 3 subjects: tonsillitis (20090061, 70 mg), pneumonia (20090061, placebo) also reported as a serious adverse event, and otitis media (20090061, 210 mg) (Table 11-6.8, Table 11-6.9, and Listing 5-4). None of the grade 3 infectious adverse events was considered related to AMG 827.

Twelve (5.7%) subjects in Study 20090402 experienced an injection site reaction (injection site pain or rash). All injection site reactions were grade 1 (Table 11-6.11 and Listing 5-4).

Antibody Data and Their Relationship to Safety Data

Antibody data from Study 20090061 and Study 20090402 were integrated in the summary for subjects enrolled in Study 20090402. Five (2.4%) subjects [redacted] tested positive for anti-AMG 827 binding antibodies. Four subjects were from Study 20090061, AMG 827, 70 mg group and 1 subject [redacted] was from Study 20090061, AMG 827, 140 mg group. Two subjects [redacted] tested positive for the presence of neutralizing anti-AMG 827 antibodies (Table 11-10.1, and Listing 5-13). The full antibody report for this study is found in Attachment 6.

Adverse events in subjects who developed anti-AMG 827 binding antibodies are provided in Listing 5-8. Three [redacted] of the 5 subjects who tested positive for anti-AMG 827 binding antibodies experienced adverse events during Study 20090402. Adverse event profiles for these subjects were nonspecific and did not allow for a meaningful analysis of any potential association between the presence of antibody and safety data. Two subjects, who tested positive for anti-AMG 827 binding antibodies, experienced the following treatment-emergent adverse events during Study 20090402: decreased neutrophil count (grade 1) was reported for Subject [redacted] that was considered related, non-serious, and asymptomatic and resolved within 2 weeks; Subject [redacted] reported rhinopharyngitis (grade 2) and conjunctivitis (grade 2). In addition subject [redacted] reported an adverse event of gastroenteritis on study day 1, 42 days after the last dose of 70 mg AMG 827 in Study 20090061. One subject [redacted] who tested positive for anti-AMG 827 binding antibodies and neutralizing antibodies experienced treatment-emergent adverse events of grade 1 malaise and grade 2 dry eyes. The other subject who tested positive for both binding and neutralizing anti-AMG 827 antibodies did not experience any adverse events during the study. There did not appear to be any trend toward a safety signal for any of the subjects who tested positive for AMG 827 binding antibodies.

Adverse Events by Age, Sex, Race and Region

Subject Incidence of adverse events by system organ class and preferred term and age (< 65, ≥ 65), sex, race, and region are presented in Table 11-6.17, Table 11-6.18, Table 11-6.19 and Table 11-6.20, respectively.

Majority of the adverse events occurred in subjects < 65 year old. Infections and infestations was the most common system organ class with reported events for subjects in both age groups (< 65 and ≥ 65 years).

The frequency of the adverse events was higher for females (48.8%) than males (9.5%). This can be explained by the demographic disproportion at baseline (79.1% females and 20.9% males) due to higher prevalence of the female population diagnosed with RA.

All Adverse Events

Adverse events occurring in ≥ 1% of subjects overall and by Study 20090061 treatment group are presented by system organ class in Table 11-6.13. Subject incidence of all adverse events was 58.3% overall. The system organ class of Infections and Infestations had the highest incidence of adverse events (29.4%) overall. The most common treatment-emergent adverse events (incidence rates) were upper respiratory tract infection (9.0%), RA (worsening) (5.7%), arthralgia (5.7%) nasopharyngitis (5.2%), and injection pain (5.2%) (Table 11-6.13).

Subject incidence of all treatment-related adverse events was 20.4% overall. The system organ class of Infections and Infestations had the highest incidence of treatment-related adverse events (9.0%) overall. The most common treatment-related adverse events (incidence rates) overall were injection site pain (5.2%), upper respiratory tract infection (3.8%), RA (2.4%), and nausea (1.9%) (Table 11-6.15).

Overall 16 (7.6%) subjects experienced treatment-emergent grade 3 and above adverse events. Of those 16 subjects, 1 subject [redacted] died from a completed suicide (grade 5); 1 subject [redacted] reported traumatic brain injury (grade 4), and another subject [redacted] reported cholelithiasis (grade 4) (Table 11 6.8). One subject [redacted] reported RA (grade 3) considered related to AMG 827 (Table 11-6.9 and Listing 5-5).

Subject incidences of treatment-emergent grade 2 and above adverse events in Study 20090402 were 44.1% overall (Table 11-6.8). Incidences of grade 2 or above, treatment-related events were 10.4% overall (Table 11-6.9).

A summary of adverse events experienced by subjects enrolled in Study 20090402 during Study 20090061 is presented in Table 11-6.21. Subject incidence of adverse events was 54.0% overall.

A summary of adverse events experienced by subjects enrolled in Study 20090402 since the first dose day in the Study 20090061 excluding the gap between Study 20090061 and Study 20090402 is presented in Table 11-6.22. Subject incidence of adverse events was 75.8% overall.

A summary of exposure adjusted rate of adverse events experienced by subjects enrolled in Study 20090402 since the first dose date in Study 20090061 excluding the gap between Study 20090061 and Study 20090402 is presented in Table 11-6.23. The number of treatment-emergent adverse events reported (exposure-adjusted event rate per 100 subject-years) was 663 (522.0) overall.

Clinical Laboratory Evaluations

Shifts in CTCAE grade levels from Study 20090402 baseline are presented for each laboratory analyte in Table 11-7.1 through Table 11-7.12 and Listing 5-10. Shifts in CTCAE grade levels from Study 20090061 baseline are presented for each laboratory analyte in Table 11-7.13 through Table 11-7.24 and Listing 5-9. Summaries of blood levels for each laboratory analyte by treatment group and visit are presented in Table 11-7.25 through Table 11-7.44.

Subjects with at least a 2-grade shift in CTCAE, version 4.0, laboratory values following the first AMG 827 210 mg dose in Study 20090402 compared to Study 20090402 baseline laboratory values are summarized below. Adverse events, relevant concomitant medications, and medical history are presented in Listing 5-4, Listing 5-14, and Listing 5-15.

Four subjects [redacted] shifted down 2 grade levels (0 to 2) in albumin (Listing 5-10).

Three subjects [redacted] shifted down 2 grade levels (0 to 2) in calcium. Subject [redacted] also shifted down 2 grade levels (0 to 2) from Study 20090402 baseline in calcium corrected (Listing 5-10).

Five subjects [redacted] shifted up 2 grade levels (0 to 2) in glucose. One subject [redacted] shifted down 2 grade levels (0 to 2) in glucose (Listing 5-10).

Three subjects [redacted] shifted down 2 grade levels (0 to 2) from Study 20090402 baseline in potassium. One subject [redacted] shifted down 3 grade levels (0 to 3) on day 59, and 2 grade levels (0 to 2) on day 85 and day 116 from Study 20090402 baseline. Two subjects [redacted] shifted up 2 grade levels (0 to 2) from Study 20090402 baseline in potassium (Listing 5-10).

Twelve subjects [redacted] shifted down 2 grade levels (0 to 2) from the 20090402 baseline in lymphocytes. Two subjects, [redacted] shifted up 2 grade levels (0 to 2) from the 20090402 baseline in lymphocytes (Table 11-7.5, and Listing 5-10).

Six subjects [redacted] shifted up 2 grade levels (0 to 2) from the 20090402 baseline in sodium. One subject [redacted] shifted up 3 grade levels (0 to 3, day 29) from the 20090402 baseline in sodium (resolved by day 113) (Listing 5-10).

One subject [redacted] shifted down 2 grade levels (0 to 2) from the 20090402 baseline in absolute neutrophil count and in total neutrophil count that was reported as an adverse event. One subject [redacted] shifted down 3 grade levels (0 to 3) from the 20090402 baseline in absolute neutrophil count and in total neutrophil count (Table 11-7.6, Listing 5-10, and Listing 5-4). Adverse events of moderate leucopenia and neutropenia were added to the eCRF after the administrative study termination date for this subject.

Two subjects [redacted] shifted down 2 grade levels (0 to 2) and 2 subjects [redacted] shifted down 3 grade levels (0 to 3) from the 20090402 baseline in phosphorus (Listing 5-10).

Two subjects [redacted] shifted up 2 grade levels (0 to 2) from the 20090402 baseline in aspartate aminotransferase (AST) (Table 11-7.8 and Listing 5-10). Subject [redacted] experienced ALT and AST elevation as grade 1 on study day 85 and ALT elevation as grade 3 on study day 113. AST and ALT remained elevated to grade 1 for AST and grade 2 for ALT at days 122 and 155. Adverse events of grade 2 ALT and AST were reported on day 113 of the study. Methotrexate was reduced on day 158. Subject [redacted] experienced grade 1 AST and ALT elevation on days 29, and 113, and grade 2 elevation on day 183 of the study.

Four subjects [redacted] shifted up 2 grade levels (0 to 2) from the 20090402 baseline in ALT (Table 11-7.9 and Listing 5-10). Subjects [redacted] are summarized above for AST and ALT.

Two subjects [redacted] shifted down 2 grade levels (0 to 2) from the 20090402 baseline in white blood cells (Table 11-7.11 and Listing 5-10). An adverse event of neutrophil count decrease (grade 1) was reported for Subject [redacted] (day 111) (Listing 5-4). Subject [redacted] experienced a grade 3 ANC decrease, a grade 2 WBC decrease and a grade 3 decrease in creatinine on day 106 of the study. Adverse events of moderate leucopenia and neutropenia which were added to the eCRF after the administrative study termination date and both events were resolved approximately 3 weeks later.

One subject [redacted] shifted up 2 grade levels (0 to 2) from the 20090402 baseline in creatinine (Listing 5-10).

Shifts in grade levels from Study 20090061 baseline were similar to shifts in grade levels from Study 20090402 baseline with the following exceptions:

- Three additional subjects [redacted] shifted up 2 grade levels (0 to 2) and 1 additional subject [redacted] shifted up 3 grade levels (0 to 3) from Study 20090061 baseline in glucose. One additional subject [redacted] shifted down 2 grade levels (0 to 2) from Study 20090061 baseline in glucose (Listing 5-9)
- Three additional subjects [redacted] shifted down 2 grade levels (0 to 2) from the Study 20090061 baseline in lymphocytes, and

1 additional subject [redacted] shifted up 2 grade levels (0 to 2) from the 20090061 baseline in lymphocytes (Table 11-7.17, and Listing 5-9).

- One additional subject [redacted] shifted up 2 grade levels (0 to 2) from the Study 20090061 baseline in sodium (Listing 5-9).
- One additional subject [redacted] shifted down 3 grade levels (0 to 3) from the Study 20090061 baseline in phosphorous (Listing 5-9).
- One additional subject [redacted] shifted up 2 grade levels (0 to 2) from the Study 20090061 baseline in ALT (Table 11-7.21 and Listing 5-9).

Shifts of 0 to 2 from Study 20090402 baseline (Listing 5-10) were reported for 0 subjects with no corresponding shifts from the Study 20090061 baseline (Listing 5-9). Nine subjects shifted down 2 grade levels (2 in albumin, 1 in potassium, 6 in lymphocytes), and 1 subject shifted up 2 grade levels in glucose) from Study 20090402 baseline.

Uric acid shifts are summarized based on absolute values. For standard normal range-based shift tables, data are presented using Low (below normal range), Normal (within normal range) and High (above normal range). Eight subjects shifted up from Normal to High from Study 20090402 baseline (Table 11-7.12 and Listing 5-12) and 11 subjects shifted from Normal to High from the Study 20090061 baseline (Table 11-7.24 and Listing 5-11).

Overall, there were no clinically important trends noted in the laboratory findings for Hematology, chemistry and urinalysis. For some subjects in study 20090402 who experienced shifts in clinical laboratory values, medical history were contributory and for most subjects, no trends indicative of treatment-related effects were evident, and no out-of-range laboratory result was reported as an adverse event with exceptions noted.

Although a few isolated elevations of ALT and AST were noted, when Hy's law was applied no cases met the criteria for drug-induced liver toxicity

Amgen continues to monitor laboratory values for subjects in the AMG 827 program.

Fasting Lipids

Fasting lipids were scheduled to be assessed at week 48 of Study 20090402. However, at the time of study termination, no subjects had reached week 48, so the assessment of fasting lipids was not done. Summaries of total cholesterol, HDL, LDL, and triglycerides baseline values in Study 20090061 and Study 20090402 are presented in Table 11-7.29, Table 11-7.32, Table 11-7.34, and Table 11-7.43, respectively.

Vital Signs

Vital signs were assessed according to the schedule of assessments in Appendix A of the protocol (Attachment 1). Summaries of vital signs including body weight (kg), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (beats/minute), respiration (breaths/minute), and temperature (ºC) by treatment group in Study 20090061 and by visit in Study 20090402 are presented in Table 11-8.1, through Table 11-8.6, and Listing 5-16.

There were no clinically meaningful changes in body weight, systolic blood pressure, diastolic blood pressure, pulse, respiration and temperature.

Conclusions:

The primary objective of this study was to evaluate the safety of long-term exposure to AMG 827 in subjects with RA. Efficacy objectives included ACR 20, 50, and 70 responses, DAS28 scores and changes in DAS28 scores, the proportion of subjects with DAS28 < 2.6, and ACR individual components. Other objectives were to evaluate effect of AMG 827 on PROs, the proportion of subjects who develop anti-AMG 827 antibodies and to explore lipid profiles in subjects receiving AMG 827.

In the parent study (Study 20090061), AMG 827 was not shown to be more efficacious than placebo at any dose as measured by ACR 20, 50, or 70 responses or by the individual components of the ACR response criteria. Based on these efficacy findings in Study 20090061, an administrative decision was made to terminate Study 20090402.

The percent ACR 20, 50, and 70 responders was similar across all Study 20090061 treatment groups, including placebo and did not increase appreciably over time by visit in Study 20090402.

Overall adverse events were reported for 58.3% of subjects and 20.4% of subjects reported adverse events that were considered treatment-related. Serious adverse events were reported for a few subjects (3.8%) and none of them were considered related to AMG 827 administration. There were few, grade 3 or higher, adverse events. One subject (20090061, AMG 827, 70 mg) died of completed suicide on day 119, and the event was reported as not related to AMG 827.

Most subjects discontinued the study due to the administrative decision to terminate the study. A few subjects (2.4%) discontinued the study or AMG 827 due to adverse events. Infectious adverse events were grade 1 or 2, and none of the grade 3 infectious adverse events (pneumonia, tonsillitis, or otitis media) were reported as serious adverse events or considered related to AMG 827 by the investigator. The incidence of injection site reactions was low and all were grade 1.

Two subjects reported adverse events of neutrophil count decreased during the study (both grade 1); both events were asymptomatic, considered related to AMG 827 and both resolved without intervention with continued AMG 827 therapy. A third subject shifted down 3 grade levels in absolute neutrophil count, total neutrophil count and shifted down 2 grade levels in white blood cells on day 106 (last study visit). The start dates and resolution dates of adverse events of moderate leucopenia and neutropenia (considered not related to AMG 827) were added after the administrative study termination date.

There was no evidence of clinically significant changes in laboratory parameters or vital signs following dosing with AMG 827.

The cumulative rate for subjects testing positive to anti-AMG 827 antibodies (binding antibodies) was 2.4%; 2 subjects tested positive for neutralizing antibodies to AMG 827. There did not appear to be any trend toward a safety signal for any of the subjects who tested positive for AMG 827 binding or neutralizing antibodies.

In conclusion, the observed adverse events following treatment with AMG 827 during this open-label extension study would not have precluded continued development of AMG 827 if benefit had been observed in this patient population as noted in the parent protocol, Study 20090061.