SYNOPSIS

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

Name of Finished Product: Brodalumab

Name of Active Ingredient: AMG 827

Title of Study: A Long-term Assessment of Safety and Efficacy of AMG 827 Treatment in Subjects With Crohn's Disease

Investigator(s) and Study Center(s): This study was conducted at 28 centers in Australia, Belgium, Canada, Spain, France, Netherlands, Poland, and the United States (US); centers and principal investigators are listed in Appendix 2.

Publication(s): None as of the date of this report.

Study Period: 02 February 2011 (first subject enrolled) to 18 October 2011 (last subject visit completed). The study was terminated early on 25 August 2011 due to an imbalance between the placebo and AMG 827-treated groups with regard to worsening of Crohn's disease and a lack of efficacy in the parent study (20090072).

Development Phase: Phase 2

Introduction and Objectives:

AMG 827 is a human, Chinese hamster ovary cell-derived IgG2 anti-interleukin-17A receptor (IL-17RA) monoclonal antibody that selectively targets human IL-17RA and antagonizes the IL-17A pathway. It binds with high affinity to human IL-17R 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).

In preclinical animal models of intestinal inflammation, the absence of IL-17A (Ito et al, 2008) or IL-17F (Yang et al, 2008) or IL-17R (Zhang et al, 2006) appeared to be protective in some murine models of chemically-induced colitis. Antibody blockade of IL-17A has also been demonstrated to abrogate inflammatory bowel disease (IBD) in the CD45RBhi T cell transfer model of intestinal inflammation (Yen et al, 2006; Leppkes et al, 2009). Collectively, these data suggest that blocking IL-17A and IL-17F may have therapeutic potential in IBD.

In other preclinical animal model studies, however, the data have been somewhat conflicting. For example, dextran sulphate sodium (DSS) studies by Yang et al (2008) report exacerbated disease in the absence of IL-17A, contrasting with the results from Ito et al, mentioned above. Exacerbation of disease has also been reported for IL-17A antibody blockade in DSS colitis by Ogawa et al (2004). Finally, the transfer of IL-17A-/- or IL-17R-/- T cells in the CD45RBhi T cell transfer model of colitis did not attenuate, and may even have accelerated, disease (Izcue et al, 2008; O'Connor et al, 2009).

The variable outcomes of these preclinical studies may have arisen as a result of (i) lack of neutralization of all 3 ligands for the IL-17R in the case of the antibody neutralization studies or (ii) dysregulation of the IL-17R ligands, IL-17A, IL-17F or IL-25, as a result of compensation for congenital cytokine/cytokine receptor deficiency in the gene knockout mouse studies. It remains to be determined whether antibody neutralization of IL-17R directly will be more effective across the breadth of preclinical animal models.

Some studies in humans have indicated a role for IL-17A in Crohn's disease. For example, Fujino et al (2003) demonstrated an increase in mucosal IL-17A-expressing cells in active Crohn's disease. Ileal biopsy samples from subjects with active or inactive Crohn's disease have shown elevated IL-17A expression (mRNA) compared with samples from control subjects (Holtta et al, 2008). Elevated IL-17A positive T-cells (CD8 positive and CD4 positive) have been seen in subjects with active Crohn's disease compared with controls (Holtta et al, 2008). More recently Rovedatti et al (2009) have shown an increase in spontaneous IL-17A production from cultured colonic biopsies from inflamed gut tissue compared with un-inflamed tissue. McGovern et al (2009) have also shown an association of the IL-17A and IL-17RA genes with Crohn's disease, and interactions with the IL-23R gene. Much less is known about the regulation of IL-17F and IL 25 in human IBD, including Crohn's disease.

Despite some conflicting preclinical IBD data, it is evident that IL-17A plays an important role in driving the biology of proinflammatory immune responses (Abraham and Cho, 2009; Andoh et al, 2008). There is also strong evidence that IL-17A is dysregulated in the gut tissues of patients with active intestinal inflammation. Therefore, a therapeutic agent with the ability to block the IL 17 pathway posed an attractive option for clinical research in Crohn's disease at the time this study was initiated.

The objectives of this study were:

Safety: To evaluate the safety of long-term exposure with AMG 827 in subjects with Crohn's disease.

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

- Harvey-Bradshaw Index (HBI) and the Crohn's Disease Activity Index (CDAI)
- To evaluate the maintenance of effect as measured by the HBI and CDAI

Efficacy analyses used Study 20090072 baseline for primary analyses, but also examined changes from the baseline values of Study 20100008.

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

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

This study was an open-label extension of Study 20090072 in subjects with Crohn's disease to evaluate the long-term efficacy and safety of AMG 827. Enrollment was planned to be approximately 195 subjects who had completed the week 12 visit of Study 20090072, signed the informed consent form, completed all screening assessments, if applicable, and met the safety-based eligibility criteria for Study 20100008. The screening visit was only required if the subject's baseline visit in this study was not on the same day as his or her week 12 visit in Study 20090072. Upon completing all screening / baseline assessments and meeting all eligibility criteria, subjects began receiving 350 mg AMG 827 IV at baseline (day 1) and every 4 weeks thereafter.

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

Early termination of the parent study (20090072) and this open-label extension study (20100008) was the result of the recommendation of the independent Data Review Team (DRT) and was based on the observation that there were a disproportionate number of cases of worsening of Crohn's disease in the active treatment groups. This report for Study 20100008 is presented in synopsis format because both the parent and the open-label extension studies (20090072 and 20100008) were terminated early and because AMG 827 will not be developed further in Crohn's disease.

Diagnosis and Main Criteria for Eligibility: Enrollment in this study was contingent on completion of the week 12 visit of parent Study 20090072 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 (Appendix 1), must have been free of infections at study entry and significant concurrent medical conditions as described in Section 4.2 of the protocol (Appendix 1), and must have met regional recommendations for immunizations, eg, US Centers for Disease Control and Prevention recommendations for subjects enrolled in the US. If applicable, women must have been willing to use highly effective birth control during treatment.

Depending upon the length of time between the week 12 visit of Study 20090072 and the first planned dose of AMG 827 in Study 20100008, subjects might have undergone additional tests, including serum pregnancy, if applicable, laboratory assessments for safety, and testing for latent tuberculosis.

For a full list of eligibility criteria, see Sections 4.1 and 4.2 of the protocol (Appendix 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Subjects received AMG 827, 350 mg IV, at baseline (day 1), week 4 and every 4 weeks thereafter. AMG 827 manufacturing batch numbers used were: [redacted], and [redacted].

Duration of Treatment: After completing participation in Study 20090072, subjects in this extension study were to receive AMG 827, 350 mg IV for approximately 132 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 was made to close the study for any reason, including, but not limited to, no proven or insufficient efficacy demonstrated in Study 20090072.

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

Study Endpoints:

Safety Endpoints:

- adverse events
- change in laboratory parameters (hematology, chemistry, and urinalysis profiles) and vital signs

Efficacy Endpoints:

- HBI response (reduction of ≥ 3 from baseline of Study 20090072) and remission (HBI ≤ 4) at all measured timepoints for all subjects, for subjects with response at baseline of
  Study 20100008, and for subjects in remission at baseline of Study 20100008
- CDAI response (reduction of ≥ 100 from baseline of Study 20090072) and remission (CDAI ≤ 150) at all measured timepoints for all subjects, for subjects with response at baseline of Study 20100008, and for subjects in remission at baseline of Study 20100008
- HBI and change in HBI at all measured timepoints
- CDAI and change in CDAI at all measured timepoints
- time to loss of HBI remission or CDAI remission among subjects with remission at baseline of Study 20100008

- time to loss of HBI response or CDAI response among subjects with remission at baseline of Study 20100008
- time to loss of HBI response or CDAI response among subjects with response at baseline of Study20100008

Other endpoints are summarized in Section 10.1.1 of the protocol (Appendix 1).

Statistical Methods: The goal of the primary statistical analysis was to evaluate the safety of long-term exposure with AMG 827 together with efficacy and maintenance of efficacy with AMG 827 in subjects with Crohn's disease. This study collected adverse events and safety laboratory assessments as well as efficacy and PRO assessments. Pharmacokinetic and anti-AMG 827 antibody samples were collected as well. It was recognized that these data might suffer from a selection bias associated with dropout from Study 20090072. Therefore, no formal statistical tests were performed. Missing date was not imputed.

All subjects who received at least 1 dose of AMG 827 in the extension study were included in the data summaries by the treatment groups allocated in Study 20090072, as well as an overall analysis of all subjects in the extension study.

To assess safety of long-term exposure with AMG 827, subject incidence and exposure-adjusted event rates of all treatment-emergent adverse events were tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, infections, serious infections, adverse events of interest, and adverse events leading to withdrawal from investigational product or from study were provided. Summaries of laboratory and vital sign values were tablulated over time for safety. Shift tables of the worst on-study laboratory toxicity relative to baseline were tabulated based on the Common Terminology Criteria for Adverse Events (CTCAE) grades.

Efficacy analyses were examined both as changes from the parent study (20090072) baseline as well as the baseline established at the start of the open-label extension study (20100008), with change from Study 20090072 as the primary analysis.

Proportions of subjects with response or remission with respect to the CDAI, along with CDAI scores, and changes from baseline values at all measured timepoints were described at all measured timepoints. Descriptive summaries of observed data were provided by treatment group and study visit.

The summary statistics for categorical endpoints contain the frequency and percentage. For continuous endpoints, the summary statistics contain number of observations, mean, standard deviation, median, minimum, and maximum. No formal statistical tests were performed.

Antibody data from the parent study (20090072) and this study (20100008) were integrated for subjects enrolled in Study 20100008.

The SAP was amended following the early termination of the study and the following analyses were removed from the protocol-specified analyses plan (Appendix 7):

- HBI-related analyses
- PRO-related analyses
- time to loss of response or remission analyses
- pharmacokinetics analyses
- all subgroup analyses

Summary of Results:

Number of Subjects Planned: Approximately 195 subjects

Number of Subjects Enrolled: 67

Subject Disposition: 67 subjects were enrolled in Study 20100008, and all 67 subjects received AMG 827, 350 mg IV at baseline, week 4 and every 4 weeks thereafter (Q4W).

Most subjects (41 [61.2%]) discontinued AMG 827 because of an administrative decision (study terminated) and 12 (17.9%) subjects discontinued AMG 827 because of disease progression. Other reasons for discontinuing AMG 827 are presented in Table 11-1.1.

Most subjects (41 [61.2%]) discontinued the study because of an administrative decision (study terminated) and 13 (19.4%) subjects discontinued the study because of disease progression. Other reasons for study discontinuation are presented in Table 11-1.1.

Overall,14 subjects discontinued AMG 827 or study because of disease progression; 11 subjects discontinued both AMG 827 and study due to disease progression, 1 subject only discontinued AMG 827 and 2 subjects only discontinued study.

The total number of subjects who had an important protocol deviation was 3 (4.5%). Two (3.0%) subjects had the most commonly cited important protocol deviation, which was “entered study even though entry criteria was not satisfied” ie, had an active CTCAE grade 2 or higher infection at the time of enrollment (Table 11-3.1 and Listing 5-1).

Subject Demographics:

Sex: 38 (56.7%) women; 29 (43.3%) men

Age: Mean (SD) 35.9 (12.0) years (range: 18 to 61)

Ethnicity (Race): white: 51 (76.1%); black: 1 (1.5%); other: 3 (4.5%); Hispanic/Latino: 1 (1.5%); Non-hispanic or Latino: 54 (80.6%); unknown: 12 (17.9%)

Baseline Disease Characteristics:

A summary of baseline disease characteristics for subjects in Study 20100008 at both Study 20090072 baseline and Study 20100008 baseline are provided in Table 11-2.3. The mean (SD) CDAI for the subjects in Study 20100008 at Study 20090072 baseline and at Study 20100008 baseline, was 320.94 (57.87) and 243.67 (102.89), respectively (Table 11-2.3).

Efficacy Results:

Efficacy endpoints analyzed were CDAI response (reduction of ≥ 100 from baseline), remission (CDAI ≤ 150), CDAI and change in CDAI from baseline at all measured timepoints. Data was available for a majority of the subjects through week 8 and the results are summarized below.

CDAI Response:

A summary of the CDAI response from Study 20090072 baseline by treatment group (Study 20090072) and Study 20100008 visit (observed) is presented in Table 11-4.3.1. The number of CDAI responders at week 8 (38 subjects) was 3/7 (42.9%), 6/15 (40.0%) and 5/6 (83.3%) across the 210-, 350- and 700-mg AMG 827 treatment groups, respectively, and 4/10 (40.0%) placebo group, or 18/38 (47.4%) overall.

A summary of CDAI response from Study 20100008 baseline by treatment group, gap between parent (Study 20090072) and open-label extension study (Study 20100008), and visit (observed) is presented in Table 11-4.3.2. There were no notable differences in the percent of CDAI responders between subjects with ≤ 4 weeks or > 4 weeks gap between Studies 20090072 and

20100008. At week 8 (38 subjects), there were 1/6 (16.7%), 0/13 (0.0%), and 1/6 (16.7%) responders across the 210-, 350- and 700-mg AMG 827 groups, gap ≤ 4 weeks; 0/1 (0.0%), 0/2 (0.0%), and 0/0 (-) responders across the 210-, 350- and 700-mg AMG 827 gap > 4 weeks; there were 0/10 (0.0%) responders in the placebo group.

CDAI Remission:

Summary of CDAI remission by treatment group (Study 20090072) and Study 20100008 visit (observed) is presented in Table 11-4.4. At week 8 (38 subjects), the proportion of subjects who exhibited CDAI remission was 0/7 (0.0%), 2/15 (13.3%), and 3/6 (50.0%) across the 210-, 350- and 700-mg AMG 827 treatment groups and 4/10 (40.0%) placebo group, or 9/38 (23.7%) overall.

CDAI and Change in CDAI at All Measured Timepoints:

A summary of mean (SD) CDAI score by treatment group (Study 20090072) and Study 20100008 visit (observed) is presented in Table 11-4.1. CDAI scores were similar across treatment groups and did not change appreciably by visit through week 8. At Study 20100008 baseline (63 subjects), mean (SD) CDAI scores by treatment group were 251.72 (85.23), 233.50 (110.74), and 226.76 (65.49) across the 210-, 350- and 700-mg AMG 827 treatment groups, respectively, and 257.70 (126.60) placebo group, or 243.67 (102.89) overall. At week 8 (38 subjects), mean (SD) CDAI scores by treatment group were 248.03 (70.86), 267.51 (173.20), and 159.39 (66.53) across the 210-, 350- and 700-mg AMG 827 treatment groups, respectively, and 250.95 (167.25) for placebo group, or 242.49 (144.80) overall.

A summary of mean (SD) change from Study 20090072 baseline in CDAI by treatment group (Study 20090072) and visit (observed) in Study 20100008 is presented in Table 11-4.2.1. At week 8 (38 subjects), the mean (SD) change from Study 20090072 baseline in CDAI by treatment group was -84.6 (79.8), -55.4 (157.2), and -150.4 (35.6) across the 210-, 350- and 700-mg AMG 827 treatment groups, respectively, and -48.7 (143.2) placebo group, or -74.0 (129.7) overall.

A summary of mean (SD) change from Study 20100008 baseline in CDAI by treatment group, gap between parent and open-label extension study, and visit (observed) is presented in Table 11-4.2.2. At week 8 (37 subjects), the mean change (SD) from Study 20100008 baseline was -5.8 (61.4), 37.5 (163.7) and -76.9 (59.0) across the 210-, 350- and 700-mg AMG 827 groups, gap ≤ 4 weeks; 11.3 (-), 8.6 (37.4), and - (-) across the 210-, 350- and 700 mg AMG 827 groups gap > 4 weeks. The mean change in the placebo group was 18.4 (88.9).

Other Results

Pharmacokinetics

In the amended SAP, pharmacokinetic analyses were removed from the analysis plan.

Antibody Assays

Blood was collected at baseline and weeks 4, 24, and every 6 months through week 132 for anti-AMG 827 antibody analysis. Samples were tested for binding antibodies to AMG 827 using an anti-AMG 827 immunoassay. Positive samples in the immunoassay were to be further analyzed for the presence of neutralizing antibodies using a bioassay.

Serum samples collected from 67 subjects were tested for the presence of anti-AMG 827 binding antibodies. Antibody data from Study 20090072 and 20100008 are integrated in Table 11-10.1 for subjects enrolled in Study 20100008. No subjects tested positive for anti-AMG 827 binding antibodies (Listing 5-9).

Patient-reported Outcomes

In the amended SAP, PRO-related analyses were removed from the analysis plan. PRO endpoints were derived in the analysis dataset in case post hoc exploratory analysis was required.

Safety Results:

An overall summary of adverse events is presented for all subjects in Study 20100008 and by Study 20090072 treatment group in Table 1.

Table 1. Overall Summary of Treatment Emergent Adverse Events
AMG827 Study 20100008
Safety Analysis Set

	Placebo / AMG827 350 mg Q4W (N = 20)	AMG827 210 mg Q4W / 350 mg Q4W (N = 16)	AMG827 350 mg Q4W / 350 mg Q4W (N = 20)	AMG827 700 mg Q4W / 350 mg Q4W (N = 11)	All (N = 67)
All treatment emergent adverse events - n (%)	14 (70.0)	12 (75.0)	18 (90.0)	8 (72.7)	52 (77.6)
Serious adverse events	4 (20.0)	4 (25.0)	5 (25.0)	2 (18.2)	15 (22.4)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	4 (20.0)	1 (6.3)	3 (15.0)	1 (9.1)	9 (13.4)
Leading to discontinuation from study	3 (15.0)	2 (12.5)	3 (15.0)	1 (9.1)	9 (13.4)
Treatment-related treatment emergent adverse events - n (%)	8 (40.0)	9 (56.3)	14 (70.0)	2 (18.2)	33 (49.3)
Serious adverse events	2 (10.0)	2 (12.5)	1 (5.0)	1 (9.1)	6 (9.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	2 (10.0)	1 (6.3)	1 (5.0)	0 (0.0)	4 (6.0)
Leading to discontinuation from study	1 (5.0)	1 (6.3)	1 (5.0)	0 (0.0)	3 (4.5)

Coded using MedDRA version 14.1
Treatment groups are coded as "randomized treatment group in 20090072 / treatment received in 20100008"
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 20100008

Program: /stat/amg827/ibd/20100008/analysis/final/prod/tables/t-ae-sum-inc-all-p.sas
Output: t11-06-001-ae-sum-inc-all-p.rtf (Date Generated: 30MAR2012:11:51) Source Data: adam.adsl, adam.adae

Extent of Exposure

All 67 subjects in Study 20100008 received at least 1 dose of AMG 827. The mean (SD) duration of exposure (includes exposure in Studies 20090072 and 20100008) to AMG 827 for all subjects was 114.2 (51.2) days with a range of 21 to 231 days. Duration of exposure by Study 20090072 treatment group is presented in Table 11-5.1.

A summary of dose changes is presented in Table 11-5.2.

Adverse Events

Deaths

No deaths occurred during the study (Table 11-6.7).

Withdrawals from AMG 827 or Study Due to Adverse Events

Not all subject discontinuations from AMG 827 or study due to disease progression were considered to be adverse events. Worsening of Crohn's disease, was reported as an adverse event only if it was considered by the investigator to be clinically significant worsening. Overall,14 subjects discontinued AMG 827 or study because of disease progression; 11 subjects discontinued both AMG 827 and study due to disease progression, 1 subject only discontinued AMG 827 and 2 subjects only discontinued study.

Eleven (16.4%) subjects discontinued from AMG 827 or from the study due to a treatment-emergent adverse event (Table 11-6.6, Listing 5-4, and Listing 5-5).

Nine subjects discontinued AMG 827 due to an adverse event (Listing 5-5). Of those, 3 subjects discontinued AMG 827 due to disease progression (Crohn's disease) that was also considered an adverse event.

- Crohn's disease, 5 subjects (1 grade 2, related; 4 grade 3)
- headache (grade 1, related) and cutaneous vasculitis (grade 2, related), both by 1 subject
- peritoneal abscess, 1 subject (grade 3)
- hyperaesthesia, 1 subject (grade 2, related)
- abdominal pain, 1 subject (grade 3, related)

Nine subjects discontinued the study due to an adverse event (Listing 5-4). Of those, 5 subjects discontinued the study due to disease progression (Crohn's disease) that was also considered an adverse event.

- Crohn's disease, 6 subjects (4 grade 3; 2 grade 2, 1 related)
- cutaneous vasculitis, 1 subject (grade 2, related)
- peritoneal abscess, 1 subject (grade 3)
- abdominal pain, 1 subject (grade 3, related)

Serious Adverse Events

Fifteen subjects reported 18 serious adverse events (Table 11-6.3, Table 11-6.5, and Listing 5-6) and of those, 6 subjects reported 7 serious adverse events considered by the investigator to be related to AMG 827 (Table 2).

Subject narratives for serious adverse events are provided in Appendix 4.

Table 2. Subject Incidence of Serious Adverse Events by Preferred Term
AMG 827 Study 20100008 (OLE Crohn's Disease)

Preferred Term	Placebo / AMG 827 350 mg Q4W (N = 20) n (%)	AMG 827 210 mg Q4W / 350 mg Q4W (N = 16) n (%)	AMG 827 350 mg Q4W / 350 mg Q4W (N = 20) n (%)	AMG 827 700 mg Q4W / 350 mg Q4W (N = 11) n (%)	Total (N = 67) n (%)
Number of Subjects Reporting Serious Adverse Events	4 (20.0)	4 (25.0)	5 (25.0)	2 (18.2)	15 (22.4)
Crohn's Disease	2 (10.0)	2 (12.5)	2 (10.0)	1 (9.1)	7 (10.4)
Pyrexia	0 (0.0)	1 (6.3)	1 (5.0)	1 (9.1)	3 (4.5)
Abdominal Pain	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)
Anal Stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (1.5)
Cutaneous Vasculitis	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.5)
Dehydration	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.5)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.5)
Intestinal Dilatation	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.5)
Peritoneal Abscess	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.5)
Related Serious Adverse Events					
Crohn's Disease	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)	2 (3.0)
Abdominal Pain	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Pyrexia	0 (0.0)	1 (6.3)	1 (5.0)	1 (9.1)	3 (4.5)
Cutaneous Vasculitis	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.5)

Treatment groups are shown as "randomized treatment group in 20090072 / treatment received in 20100008.
OLE = open-label extension; In Study 20100008, Q4W = day 1, week 4 and every 4 weeks thereafter.
Source: Study 20100008 Table 11-6.3 and Table 11-6.5.

Clinically Significant Adverse Events

Events of interest summarized for this study were neutropenia (identified risk), worsening of Crohn's disease (identified risk), infectious adverse events, and hypersensitivity. Infusion reactions for Study 20100008 were summarized post hoc. After Studies 20090072 and 20100008 were terminated, a decision was made to remove infusion reactions as a potential risk (even of interest) because IV administration of AMG 827 was no longer being studied. In addition, hypersensitivity was added as an event of interest in order to continue to capture AMG 827 administration-related events. For completeness, both are summarized in this report.

No adverse events of neutropenia were reported during the study (Table 11-6.11).

Twenty-six (38.8%) subjects experienced a treatment-emergent adverse event (Crohn's disease, abdominal pain, constipation, proctalgia, rectal hemorrhage, abdominal pain upper, anal fistula, anal stenosis, and anal abscess) that was associated with worsening of Crohn's disease (Table 11-6.10.4). Of these 26 subjects, 15 (22.4%) reported adverse events of Crohn's disease (Table 11-6.2) and 6 reported adverse events that were considered related to AMG 827 (Table 11-6.4). In addition, 7 (10.4%) subjects reported serious adverse events of Crohn's disease; of those, 2 serious adverse events of Crohn's disease were considered by the investigator to be related to AMG 827; both serious adverse events resolved (Table 11-6.3, Table 11-6.5, Listing 5-6, and Appendix 4). Of the 15 subjects who reported Crohn's disease, 5 subjects discontinued AMG 827 administration (Listing 5-5) and 6 subjects discontinued the study (Listing 5-4).

An infectious adverse event was reported in 22 (32.8%) subjects. The most commonly reported infectious events overall were oral candidiasis (3 [4.5%]), upper respiratory tract infection (3 [4.5%]), and urinary tract infection (3 [4.5%]). Incidence of infectious adverse events was higher in subjects with previous exposure to AMG 827 in the parent study (20090072) compared with placebo subjects (Table 11-6.8). Grade 3 infectious adverse events were noted in 3 subjects who experienced anal abscess, gastroenteritis (considered serious), and peritoneal abscess (considered serious). None of the grade 3 infectious adverse events was considered related to AMG 827 (Table 11-6.3, Table 11-6.5, Table 11-6.12, and Listing 5-6).

Ten (14.9%) subjects experienced a hypersensitivity reaction. The most frequently reported hypersensitivity reactions were erythema (2 [3.0%]) and cough (2 [3.0%]). Most hypersensitivity reactions were grade 1; hypersensitivity reactions of erythema nodosum, and dermatitis acneiform, both grade 2, were each reported by a single subject. One subject reported cutaneous vasculitis (grade 2) that was considered serious and related; the subject discontinued AMG 827 and was removed from the study (Table 11-6.11, Table 11-6.10.3, and Listing 5-6).

Eight (11.9%) subjects reported infusion reactions. The most frequently reported infusion reactions were fatigue (2 [3.0%]) and pyrexia (2 [3.0%]). All other infusion reactions were each reported by a single subject. All infusion reactions were grade 1 or grade 2 (Table 11-6.10.1 and Listing 5-6).

All Adverse Events

Subject incidence of all treatment-emergent adverse events was 77.6% (52 subjects) (Table 11-6.1). The system organ class of gastrointestinal disorders had the highest incidence of treatment-emergent adverse events (52.2%). The most common treatment-emergent adverse events (incidence rates) by preferred term were Crohn's disease (22.4%), pyrexia (14.9%), and abdominal pain (13.4%), (Table 11-6.2).

Subject incidence of all treatment-related, treatment-emergent adverse events was 49.3% overall. The system organ class of gastrointestinal disorders had the highest incidence of treatment-related adverse events (22.4%). The most common treatment-related adverse events (incidence rates) by preferred term were Crohn's disease (9.0%), pyrexia (7.5%), and headache (6.0%) (Table 11-6.4).

Overall, 18 (26.9%) subjects experienced 22 treatment-emergent grade 3 and above adverse events. Of those 18 subjects, 8 (11.9%) reported Crohn's disease, 5 (7.5%) reported abdominal pain, and 2 (3.0%) reported dehydration. All other grade 3 and above adverse events were reported by a single subject. One subject reported intestinal dilatation (grade 4). Five subjects reported grade 3 events that were considered related to AMG 827: 2 subjects, Crohn's disease; 2 subjects, abdominal pain;, and 1 subject, elevated ALT (Table 11-6.12 and Listing 5-6).

A summary of exposure-adjusted rates of adverse events experienced by subjects enrolled in Study 20100008 since the first dose date in Study 20090072 excluding the gap between Studies 20090072 and 20100008 is presented in Table 11-6.14. The overall number of treatment-emergent adverse events reported was 356 (1699.9 [exposure-adjusted event rate per 100 subject-years]).

Clinical Laboratory Evaluations

Shifts in CTCAE grade levels from Study 20100008 baseline are presented for each laboratory analyte in Table 11-7.3.1 through Table 11-7.3.22 and Listing 5-8. Shifts in CTCAE grade levels from Study 20090072 baseline are presented for each laboratory analyte in Table 11-7.2.1 through Table 11-7.2.22 and Listing 5-7. Summaries of blood levels for each laboratory analyte by Study 20090072 treatment group and visit in Study 20100008 are presented in Table 11-7.1.1 through Table 11-7.1.38.

Subjects with at least a 2-grade shift in CTCAE, version 4.0, laboratory values following the first dose in Study 20100008 compared with Study 20100008 baseline laboratory values and who reported an adverse event are summarized below. No other clinically significant abnormalities in clinical laboratory measures were observed, and no dose-related trends were noted in any laboratory abnormalities. No subjects experienced a shift in total bilirubin.

Adverse events, relevant concomitant medications, and medical history are presented in Listing 5-6, Listing 5-10, and Listing 5-11, respectively.

One subject ([redacted],) shifted up 2 grade levels (1 to 3) in ALT and (0 to 2) in AST from the 20100008 baseline, and adverse events of grade 3 ALT and grade 2 AST were reported on day 71, were considered related to investigational product, and were ongoing at the end of study (Listing 5-6 and Listing 5-8). Another subject ([redacted]) shifted up 3 grade levels (0 to 3) from the 20100008 baseline in ALT, which resolved by end of study and was not reported as an adverse event (Listing 5-8).

One subject ([redacted]) shifted up 3 grade levels (1 to 4) from the 20100008 baseline in glucose, and adverse events of grade 2 (not related) hyperglycemia and grade 2 (not related) diabetes mellitus were reported that were ongoing at the end of study (Listing 5-6 and Listing 5-8)

One subject ([redacted]) shifted up 3 grade levels (0 to 3) from the 20100008 baseline in triglycerides and an adverse event of grade 1 (not related) blood triglycerides increased was reported that was ongoing at end of study (Listing 5-6 and Listing 5-8).

Overall, shifts of ≥ 2 grade levels from Study 20090072 baseline were similar to shifts from the Study 20100008 baseline with the following exceptions (Listing 5-7 and Listing 5-8):

> Three subjects ([redacted], placebo; [redacted], placebo; [redacted], 350 mg) shifted down 2 grade levels (0 to 2) from the 20090072 baseline in albumin.
>
> One subject ([redacted], 350 mg) shifted up 2 grade levels (0 to 2) from the 20090072 baseline in lymphocytes.

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).

> Six subjects shifted up from Normal to High from Study 20100008 baseline (Table 11-7.3.21); 5 subjects shifted from Normal to High from Study 20090072 baseline (Table 11-7.2.21).

Overall, there were no clinically important trends noted in the laboratory findings for hematology, chemistry, and urinalysis. Two subjects experienced moderate ALT elevation (grade 3). For some subjects in Study 20100008 who experienced shifts in clinical laboratory values, medical history was contributory and for most subjects, no trends indicative of treatment-related effects were evident.

Vital Signs

Vital signs were assessed according to the schedule of assessments in Appendix A of the protocol (Appendix 1). Summaries of vital signs including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (beats/minute), respiration (breaths/minute), and temperature (ºC) by treatment group in Study 20090072 and by visit in Study 20100008 are presented in Table 11-8.1 through Table 11-8.5.

There were no clinically meaningful changes in blood pressure, pulse, respiration or temperature.

Conclusions:

The primary objective of this study was to evaluate the safety of long-term exposure to AMG 827 in subjects with Crohn's disease. Another objective was to evaluate efficacy as measured by CDAI.

Early termination of the parent study was the result of the recommendation of the independent DRT and was based on the observation that there were a disproportionate number of cases of worsening of Crohn's disease in the active treatment groups in the parent study 20090072. This report for Study 20100008 is presented in synopsis format because both the parent and open-label extension studies (20090072 and 20100008) were terminated early and because AMG 827 will not be developed further in Crohn's disease.

Overall adverse events were reported for 77.6% of subjects and 49.3% of subjects reported adverse events that were considered treatment related. Serious adverse events were reported for 22.4% of subjects. Six subjects reported 7 serious adverse events considered related to AMG 827 administration. Grade 3 or higher, treatment-emergent adverse events were reported for 26.9% of subjects.

Most subjects discontinued the study due to the administrative decision to terminate the study or disease progression (19.4%); 16.4% of subjects discontinued the study or AMG 827 due to adverse events.

No subject had an adverse event of neutropenia. Adverse events associated with worsening of Crohn's disease (Crohn's disease, abdominal pain, constipation, proctalgia, rectal hemorrhage, abdominal pain upper, anal fistula, anal stenosis, and anal abscess), were reported by 38.8% of subjects and of those, 7 subjects reported serious adverse events of Crohn's disease (2 related). Infectious adverse events were reported by 32.8% of subjects. Grade 3 infectious adverse events (anal abscess, gastroenteritis, and peritoneal abscess) were noted in 3 subjects, and gastroenteritis and peritoneal abscess were reported as serious adverse events (not considered related to AMG 827). Hypersensitivity reactions were reported by 14.9% of subjects; most hypersensitivity reactions were grade 1.

No subjects tested positive for anti-AMG 827 binding antibodies.

There was no evidence of clinically significant changes in laboratory parameters or vital signs following dosing with AMG 827 with the exceptions of 2 reports of moderate (grade 3) ALT elevation for 2 subjects.

Efficacy objectives included changes in CDAI. In Study 20100008, the percent of CDAI responders from Study 20090072 baseline was variable across Study 20090072 AMG 827 treatment groups and the number of subjects who responded did not change appreciably by visit in Study 20100008. The proportion of subjects who exhibited CDAI remission was variable across Study 20090072 AMG 827 treatment groups and did not change appreciably by visit in Study 20100008. Any efficacy data should be interpreted with caution because this was an open label extension study and there was the potential for a survival bias.

Overall, the benefit:risk assessment for this open-label extension study does not support further evaluation of AMG 827 in subjects with moderate to severe Crohn's disease.