2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: To be determined

Name of Active Ingredient: AMG 747

Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of Add-on AMG 747 on Schizophrenia Negative Symptoms (Study 165)

Investigators and Study Centers: This study was conducted at 25 centers in Malaysia, Poland, the Czech Republic, the United Kingdom, and the United States. Names and affiliations of principal or coordinating investigators are presented in Section 16.1.4.

Publications: None

Study Period: 30 May 2012 (date first subject enrolled) to 19 June 2013 (last subject completed follow-up)

Development Phase: 2

Objectives:

The primary objective was to evaluate the treatment effect of AMG 747 compared to placebo on negative symptoms as measured by the Negative Symptom Assessment Scale (NSA-16) in subjects with schizophrenia stabilized with ongoing antipsychotic therapy.

The secondary objectives were as follows:

- to evaluate the effect of AMG 747 on the proportion of subjects achieving clinically meaningful improvement from baseline, as defined by a ≥ 20% decrease from baseline on negative symptoms as measured by the NSA-16
- to evaluate the effect of AMG 747 on symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score and Marder factor scores
- to evaluate the effect of AMG 747 on global change as measured by the Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement Scale (CGI-I)
- to evaluate the effect of AMG 747 on cognitive function as measured by the CogState Schizophrenia Battery (CogState)
- to evaluate the effect of AMG 747 on everyday functioning as measured by the Personal and Social Performance (PSP) Scale
- to evaluate the effect of AMG 747 on patient-reported outcomes (PROs) as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18) and the Sheehan Disability Scale (SDS)
- to evaluate safety and tolerability of AMG 747

The exploratory objectives are presented in Protocol Section 1.3 (Section 16.1.1).

Methodology: This study was a phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with schizophrenia with prominent negative symptoms and stabilized on current antipsychotic therapy. Subjects were to be randomized in a 3:2:2:2 ratio, stratified by sex, to 1 of 4 treatment groups: placebo once daily (QD), or AMG 747 5 mg QD, AMG 747 15 mg QD, or AMG 747 40 mg QD, respectively, with approximately 90 subjects in the placebo group and approximately

60 subjects in each AMG 747 group. After signing informed consent, eligible subjects entered a 4- to 6-week screening phase, which included a 2- to 4-week initial screening phase followed by a 2-week single-blind placebo run-in phase. During the run-in phase, placebo was administered to all subjects in a single-blind fashion (ie, only subjects were blinded and received placebo) to evaluate subjects' positive and negative symptoms stability and compliance with protocol procedures. Eligibility criteria were assessed throughout the screening phase, up to the baseline/day 1 visit. At the baseline/day 1 visit and after the completion of all run-in procedures, eligible subjects were randomized into the 12-week double-blind treatment phase, followed by the 2-week follow-up phase.

Study 20101299, with a similar design, was being conducted concurrently along with Study 20110165. Both studies were terminated early on 21 May 2013 due to a sponsor administrative decision after the occurrence of a serious adverse event of Stevens-Johnson syndrome / toxic epidermal necrolysis reported in 1 subject receiving AMG 747 40 mg QD in Study 20101299.

Number of Subjects Planned: Approximately 270 subjects (90 in the placebo group, and 60 each in the AMG 747 5-mg, 15-mg, and 40-mg groups) were planned to be enrolled. However only 111 subjects were enrolled (36 in the placebo group, and 25 each in the AMG 747 5-, 15-, and 40-mg groups) as the study terminated early.

Diagnosis and Main Criteria for Eligibility: Men and women considered for inclusion were to be 18 to 60 years of age, have a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), be receiving stable antipsychotic therapy, and have a total score ≥ 20 on the PANSS Marder Negative Symptom Factor Scale (NSFS), a total score ≤ 30 on the PANSS Marder Positive Symptom Factor Scale (PSFS), and a score ≤4 on PANSS item P2. Before randomization, subjects were to have a change (ie, increase or decrease) of < 20% from the initial screening phase visit on the PANSS PSFS and the NSFS scores. Subjects with current schizoaffective disorder, bipolar disorder, panic disorder, or obsessive compulsive disorder, or subjects with suicidal ideation were to be excluded from the study. A complete list of inclusion and exclusion criteria is provided in the Protocol Sections 4.1 and 4.2, respectively (Section 16.1.1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 747 dimethanesulfonate was presented as white to light brown round, immediate-release tablets for oral use at strengths of 5 mg, 10 mg, and 30 mg of AMG 747 as the [redacted] equivalent, and packaged in blistercards; no film coating, imprinting, or debossing was used. Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo tablets, provided as a reference therapy, were identical in appearance to those of active drug and were packaged similarly. Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: The planned duration of study participation was up to 20 weeks, which included 2 to 4 weeks for the initial screening phase, 2 weeks for the single-blind placebo run-in phase, 12 weeks for the treatment phase in which subjects received QD doses of AMG 747 5 mg, 15 mg, or 40 mg, or placebo, and 2 weeks for the follow-up phase.

Study Endpoints:

The primary endpoint was change from baseline to week 12 in negative symptoms, as measured by the NSA-16 total score.

The secondary efficacy endpoints were as follows:

- response defined as a ≥ 20% decrease in the NSA-16 total score at week 12
- change from baseline to week 12 on the PANSS total score and Marder factor scores
- change from baseline to week 12 on the CGI-S score
- CGI-I scores at week 12
- change from baseline to week 12 on the CogState score
- change from baseline to week 12 on the PSP scale score
- change from baseline to week 12 on the Q-LES-Q-18 and SDS scores

The safety endpoints were adverse events, clinical laboratory values and vital signs, 12-lead electrocardiograms (ECGs), and scores on the Calgary Depression Scale for Schizophrenia (CDSS), the Columbia-Suicide Severity Rating Scale (C-SSRS), the Abnormal Involuntary Movement Scale (AIMS),the Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS).

[redacted] a detailed list is provided in the Statistical Analysis Plan (SAP) Section 4.4 (Section 16.1.9).

Statistical Methods:

Descriptive statistics were presented for all endpoints. Summary statistics for continuous variables included number of subjects, mean, median, standard deviation (SD), standard error (SE), lower and upper quartiles, minimum, and maximum. For categorical variables, frequency and percentage were provided. Any hypothesis testing was 2-sided with a significance level of 0.1. No multiplicity adjustment was applied. Subject disposition, demographics, and baseline characteristics were summarized. Subjects were analyzed according to their original randomized treatment regardless of the actual treatment received during the study, except for safety analyses (SAP Section 10.1, Section 16.1.9).

The change from baseline throughout the study in the NSA-16 total score was analyzed using the mixed effects repeated measures model. The primary endpoint was tested for each AMG 747 treatment group by comparing with the placebo group using appropriate contrasts separately. For continuous secondary efficacy endpoints, the mixed effects repeated measures model was used. For categorical endpoints, multinomial logistic regression utilizing generalized estimating equations (GEE) was used. Nominal p-values were provided for the comparisons between each AMG 747 treatment group and the placebo group (SAP Section 10.5, Section 16.1.9).

Details of the statistical analysis methods are presented in Protocol Section 10 and in the SAP Section 10.

Summary of Results:

Subject Disposition: A total of 200 subjects were screened; 111 were randomized, enrolled, and received at least 1 dose of investigational product; 36 received placebo, 25 each received AMG 747 5 mg, 15 mg, and 40 mg; 79 subjects completed the study; and 19 subjects discontinued from the study due to an administrative decision by the sponsor after a serious adverse event of Stevens-Johnson syndrome / toxic epidermal necrolysis was reported in 1 subject receiving AMG 747 40 mg QD in Study 20101299.

Baseline Demographics:

Sex: Overall 46 women (41.4%), 65 men (58.6%)

Age: Mean (SD) age 44.8 (9.9) years; range 22 to 60 years

Ethnicity/Race: 65 subjects (58.6%) were white, 32 subjects (28.8%) were Black or African American, 13 subjects (11.7%) were Asian, 1 subject (0.9%) was American-Indian or Alaska Native; 2 subjects (1.8%) were Hispanic or Latino.

Efficacy Results: All 111 subjects who received at least 1 dose of investigational product were included in the efficacy analysis set. Results of analyses of the primary and secondary efficacy endpoints for the 3 AMG 747 groups compared with the placebo group are summarized in the table below.

Change from Baseline at week 12	Treatment Difference [vs Placebo][a] (90% CI), p-Value			Reference Source Table
	AMG 747 5 mg (N = 25)	AMG 747 15 mg (N = 25)	AMG 747 40 mg (N = 25)	
NSA-16 total score	-0.4 (-4.5, 3.6), 0.86	-2.0 (-5.9, 2.0), 0.41	6.0 (2.0, 10.1), 0.015	14-4.6.1
PANSS total score	-2.9 (-7.4, 1.7), 0.30	-1.4 (-5.8, 3.1), 0.62	4.7 (0.1, 9.3), 0.095	14-4.6.8
PANSS – PSFS	0.5 (-0.9, 1.9), 0.55	0.6 (-0.7, 2.0), 0.44	2.2 (0.8, 3.6), 0.010	14-4.6.9
PANSS – NSFS	-1.6 (-3.5, 0.3), 0.16	-2.2 (-4.0, -0.3), 0.058	1.0 (-1.0, 2.9), 0.41	14-4.6.10
CogState	0.016 (-0.312, 0.344), 0.94	-0.062 (-0.375, 0.251), 0.74	-0.190 (-0.516, 0.135), 0.33	14-4.6.23
PSP overall rating score	0.2 (-4.2, 4.7), 0.93	-2.4 (-6.7, 1.8), 0.35	-4.8 (-9.2, -0.4), 0.073	14-4.6.31
Q-LES-Q-18 General quality of life Index	0.2 (0.0, 0.5), 0.17	0.2 (0.0, 0.5), 0.12	-0.2 (-0.4, 0.1), 0.23	14-4.6.32
SDS – work/school	-0.6 (-1.6, 0.5), 0.35	-2.3 (-3.3, -1.2), <0.001	-2.3 (-3.4, -1.1), 0.001	14-4.6.38
SDS – social life	-0.8 (-1.8, 0.2), 0.16	-1.0 (-2.0, -0.1), 0.069	-0.8 (-1.8, 0.1), 0.15	14-4.6.39
SDS – family life/home responsibilities	-0.8 (-1.9, 0.2), 0.18	-0.7 (-1.7, 0.3), 0.25	-1.1 (-2.1, -0.1), 0.073	14-4.6.40
Results at week 12 Improvement in NSA-16 total score ≥ 20%	Odds Ratio [vs Placebo][b] (90% CI), p-Value			
	1.0 (0.4, 2.7), 1.00	0.6 (0.2, 1.5), 0.31	0.3 (0.1, 1.0), 0.098	14-4.13.1
CGI-I value at week 12 Very much improved and much improved CGI-I value for placebo: 16.0%	%[c], Overall p-Value (vs Placebo)[d]			
	31.3, 0.44	31.6, 0.27	12.5, 0.11	14-4.15.1

CGI-I = Clinical Global Impressions – Improvement; CI = confidence interval; CogState = CogState Schizophrenia battery; N = Number of subjects in the analysis set; NSA-16 = 16-item Negative Symptom Assessment Scale; PANSS = Positive and Negative Syndrome Scale; PSFS = Marder Positive Symptom Factor Scale; NSFS = Marder Negative Symptom Factor Scale; PSP = Personal and Social Performance; Q-LES-Q-18 = 18-item Quality of Life Enjoyment and Satisfaction Questionnaire; SDS = Sheehan Disability Scale; vs = versus.

[a] MMRM = Mixed Effect Repeated Measures Model. The MMRM model includes the factors of treatment group, visit, treatment by visit, stratification factor (female vs male), and baseline value as covariates and assuming an unstructured variance-covariance matrix structure.

[b] The odds ratio and p-values are obtained from a logistic regression model with logit link, utilizing generalized estimating equation, including the factors of treatment group, visit, treatment by visit, stratification factor (male and female). An odds ratio > 1.0 indicates a higher response (improvement ≥ 20%) for AMG 747 treatment group relative to placebo.

[c] % = percentage of subjects achieving CGI-I grade of very much improved and much improved.

[d] The p-values are obtained from a multinomial logistic regression with logit link, utilizing generalized estimating equation, including the factors of treatment group, visit, treatment by visit, stratification factor (male vs female). The CGI-I categories of "No Change", "Minimally Worse", "Much Worse" and "Very Much Worse" were grouped to "No Improvement." The p-value is based on all 4 CGI-I categories: Very Much Improved, Much Improved, Minimally Improved, and No Improvement.

Sources: Mentioned in the table.

Safety Results: All 111 subjects (25 in each of the AMG 747 group and 36 in the placebo group) who were enrolled and randomized received at least 1 dose of investigational product and were included in the safety analysis set. The mean (SD) number of days of overall exposure to the investigational product in the AMG 747 5-, 15-, and 40-mg groups were 67.6 (24.1), 73.4 (22.3), and 67.9 (25.6) days, respectively, and 73.0 (20.3) days in the placebo group (Table 14-4.1).

An overall summary of subject incidence of treatment-emergent adverse events is provided in the table below.

	Placebo (N = 36)	AMG 747 5 mg (N = 25)	AMG 747 15 mg (N = 25)	AMG 747 40 mg (N = 25)
All treatment-emergent adverse events, n (%)	12 (33.3)	9 (36.0)	7 (28.0)	15 (60.0)
Grade ≥ 3	2 (5.6)	1 (4.0)	1 (4.0)	3 (12.0)
Serious	2 (5.6)	1 (4.0)	0 (0.0)	0 (0.0)
Leading to withdrawal of investigational product	3 (8.3)	1 (4.0)	0 (0.0)	2 (8.0)
Leading to discontinuation from study	3 (8.3)	1 (4.0)	0 (0.0)	1 (4.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 14-6.1

Treatment-emergent adverse events were reported for 43 subjects: 9 subjects (36.0%), 7 subjects (28.0%), and 15 subjects (60.0%) in the AMG 747 5-, 15-, and 40-mg groups, respectively, and 12 subjects (33.3%) in the placebo group.

Most adverse events were mild (grade 1) or moderate (grade 2) in severity. Adverse events with a Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 were reported for 7 subjects overall: 1 subject (4.0%) in the AMG 747 5-mg group (suicidal ideation), 1 subject (4.0%) in the 15-mg group (dizziness), 3 subjects (12.0%) in the 40-mg group (periodontitis, back pain, worsening of schizophrenia), and 2 subjects (5.6%) in the placebo group (worsening of schizophrenia) (Table 14-6.2.6).

Withdrawals from investigational product due to adverse events were reported for 6 subjects overall: 1 subject (4.0%) in the AMG 747 5-mg group, 2 subjects (8.0%) in the 40-mg group, and 3 subjects (8.3%) in the placebo group (Table 14-6.2.3). Reasons for withdrawal were suicidal ideation (n = 1) in the AMG 747 5-mg group; hyperglycemia and schizophrenia (n = 1 each) in the 40-mg group; and nausea, alcohol abuse, and drug abuse (n = 1 each) and worsening of schizophrenia (n = 2) in the placebo group.

Serious adverse events were reported for 3 subjects: suicidal ideation was reported for 1 subject (4.0%) in the AMG 747 5-mg group and worsening of schizophrenia was reported for 2 subjects (5.6%) in the placebo group (Table 14-6.4.2). Of these, 1 event of worsening of schizophrenia was considered by the investigator to have a reasonable possibility of being related to investigational product.

There were no fatal adverse events in this study (Table 14-6.2.5).

No subject had CTCAE grade 4 or 5 laboratory events during the study (Table 14-7.3). Grade 3 events reported at week 12 were decreased phosphorus (n = 1 in the AMG 747 5-mg group) and increased triglycerides (n = 2 in the placebo group, n = 1 in the AMG 747 5-mg group).

The change from baseline to week 12 in mean hemoglobin (g/dL) values was -0.36, -0.24, and -1.07 in the AMG 747 5-, 15-, and 40-mg groups, respectively, and 0.07 in the placebo group (Table 14-7.1.2). The change from baseline to week 12 in mean hematocrit (%) values was -1.2, -0.2, and -2.4 in the AMG 747 5-, 15-, and 40-mg groups, respectively, and 0.3 in the placebo group (Table 14-7.1.3).

There were no other notable changes in laboratory parameters and laboratory evaluation did not reveal any clinical meaningful changes from baseline (Tables 14-7.1.1 to 14-7.1.9).

There were no notable changes in vital signs (blood pressure, pulse, temperature, and body weight; Tables 14-8.1.1 to 14-8.1.5 and Table 14-8.2) and electrocardiogram (ECG) (Tables 14-8.4 and 14-8.5).

The mean (SD) change from baseline over time to week 12 for AIMS items 1 to 7, BARS total score for items 1 to 3, shifts from baseline in AIMS items 8 to 10, and shifts from baseline in BARS score for item 4 were not clinically meaningful (Tables 14-8.6.1 to 14-8.7.4). A SAS average score > 0.6 was not reported for any subject at any time points during the study (Table 14-8.8.2).

At week 12, only 1 subject in the AMG 747 5-mg group had a CDSS total score > 9 (Table 14-8.8.1). Suicide category was analyzed using the C-SSRS. Any suicidal ideation during all postbaseline visits was reported for 3 subjects: 1 subject each in the placebo group and the AMG 747 5-mg and 40-mg groups (Table 14-8.9.1). No suicidal behavior was reported for any subjects in any group.

Conclusions: Study 20101299 with a similar design was being conducted concurrently along with Study 20110165. Both studies were terminated early on 21 May 2013 due to a sponsor administrative decision after the occurrence of a serious adverse event of Stevens Johnson syndrome / toxic epidermal necrolysis serious adverse event reported in 1 subject receiving AMG 747 40 mg QD in Study 20101299.

A total of 270 subjects were planned for enrollment in the current study; however, 111 subjects were enrolled, and 19 subjects (17.1%) were withdrawn due to administrative sponsor decision when the study was terminated.

There was no clear evidence of a treatment effect in the primary efficacy endpoint, the NSA-16. The ability to detect treatment effects may have been limited due to early study termination.

The adverse event profile of AMG 747 did not appear to differ across doses and was comparable with placebo. There was an apparent dose-response relationship with mean hemoglobin and hematocrit concentration. None of these changes were reported as adverse events. No signs or symptoms of anemia were reported.