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 299)

Investigators and Study Centers: This study was conducted at 33 centers in Australia, Canada, New Zealand, Russia, Spain, Singapore, and the United States. Centers and principal investigators are listed in Section 16.1.4.

Publications: None

Study Period: 03 May 2012 (date first subject enrolled) to 14 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 patients 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 in 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 (CGI-I) scales
- to evaluate the effect of AMG 747 on cognitive function as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)
- 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 18-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18) and 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 was a phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with schizophrenia with prominent negative symptoms and who were 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), AMG 747 5 mg QD, AMG 747 15 mg QD, or AMG 747 40 mg QD, respectively. After signing informed consent, eligible subjects entered a 4- to

6-week screening phase, which comprised 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 to placebo treatment) 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 20110165, with a similar study design, was being conducted concurrently with Study 20101299. Both studies were terminated early on 21 May 2013 because of a serious adverse event of Stevens-Johnson syndrome/toxic epidermal necrolysis that was reported in 1 subject receiving AMG 747 40 mg QD in Study 20101299.

Number of Subjects Planned: Approximately 270 subjects (60 each in the AMG 747 5-, 15-, and 40-mg groups and 90 in the placebo group) were planned to be enrolled. However, only 121 subjects (29 in the AMG 747 5-mg group, 26 each in the AMG 747 15- and 40-mg groups, 40 in the placebo group) were enrolled since the study was 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), were to be receiving stable antipsychotic therapy, and have a total score of ≥ 20 on the PANSS Marder Negative Symptom Factor Scale (NSFS), a total score of ≤ 30 on the PANSS Marder Positive Symptom Factor Scale (PSFS), and a score of ≤ 4 on PANSS item P2. Before randomization, subjects were to have a < 20% change (ie, increase or decrease) from the initial screening phase visit on the PANSS PSFS and on the NSFS. Subjects with current schizoaffective disorder, bipolar disorder, panic disorder, or obsessive compulsive disorder; with evidence of mental retardation by history or clinical examination or known premorbid intelligence quotient (IQ) ≤ 70; or subjects with clinically significant 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, 10, 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, 15, 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 MCCB
- change from baseline to week 12 on the PSP 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 Calgary Depression Scale for Schizophrenia (CDSS), Columbia-Suicide Severity Rating Scale (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS).

[redacted]

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, 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.

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 compared with the placebo group using appropriate contrasts separately. For continuous secondary efficacy endpoints, the mixed effect repeated measure 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.

Details of the statistical analysis methods are presented in the SAP Section 10 (Section 16.1.9).

Summary of Results:

Subject Disposition: A total of 227 subjects were screened and 121 were randomized to study treatment (29 in the AMG 747 5-mg group, 26 each in the AMG 747 15- and 40-mg groups, and 40 in the placebo group). All subjects received at least 1 dose of investigational product and 76 subjects (62.8%) completed their treatment with the investigational product. A total of 45 subjects (37.2%) discontinued the investigational product and the same number of subjects also discontinued the study (including those who discontinued because of early termination of the study). For subjects who were on the study when the study was terminated, the end of study reason was reported as

administrative decision. A total of 27 subjects (22.3%) discontinued the study because of the administrative decision by the sponsor (termination of this study was due to a serious adverse event of Stevens-Johnson syndrome/toxic epidermal necrolysis reported in 1 subject receiving AMG 747 40 mg QD).

Baseline Demographics:

Sex: 91 men (75.2%), 30 women (24.8%)

Age: mean (SD) = 43 (10.9) years; range: 19 to 60 years

Ethnicity/Race: 57 white (47.1%), 48 black (39.7%), 11 Asian (9.1%), 1 multiple (0.8%), 4 other (3.3%)

Efficacy Results:

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 = 29)	AMG 747 15 mg (N = 26)	AMG 747 40 mg (N = 26)	
NSA-16 total score	0.5 (-3.8, 4.9), 0.85	0.8 (-3.7, 5.2), 0.78	0.1 (-4.2, 4.5), 0.96	Table 14-4.6.1
PANSS total score	1.1 (-5.4, 7.5), 0.78	-5.8 (-12.4, 0.7), 0.14	-1.4 (-7.9, 5.1), 0.72	Table 14-4.6.8
PANSS – PSFS	0.8 (-1.5, 3.1), 0.57	-1.0 (-3.3, 1.4), 0.49	-0.6 (-2.9, 1.7), 0.68	Table 14-4.6.9
PANSS – NSFS	-0.3 (-2.5, 2.0), 0.85	-1.2 (-3.5, 1.0), 0.37	0.3 (-1.9, 2.6), 0.80	Table 14-4.6.10
MCCB composite T score	1.9 (-1.3, 5.0), 0.34	0.2 (-3.0, 3.4), 0.93	-1.0 (-4.2, 2.2), 0.60	Table 14-4.6.14
PSP overall rating score	-1.0 (-6.1, 4.2), 0.76	3.4 (-1.8, 8.6), 0.28	-2.7 (-7.9, 2.6), 0.40	Table 14-4.6.31
Q-LES-Q-18 General quality of life Index	0.0 (-0.3, 0.4), 0.88	0.2 (-0.1, 0.6), 0.25	0.1 (-0.3, 0.4), 0.73	Table 14-4.6.32
SDS – work/school	-2.6 (-5.2, -0.1), 0.093	-2.0 (-4.5, 0.6), 0.20	-1.0 (-3.3, 1.3), 0.48	Table 14-4.6.38
SDS – social life	0.7 (-0.6, 2.0), 0.37	-0.3 (-1.6, 1.1), 0.73	0.0 (-1.3, 1.4), 0.98	Table 14-4.6.39
SDS – family life/home responsibilities	0.4 (-1.0, 1.7), 0.65	-0.3 (-1.7, 1.0), 0.71	0.3 (-1.1, 1.6), 0.73	Table 14-4.6.40
Results at Week 12:	**Odds Ratio [vs placebo][b] (90% CI), p-value**			
Improvement in NSA-16 total score ≥ 20%	1.0 (0.3, 2.7), 0.94	0.7 (0.2, 1.9), 0.54	0.9 (0.3, 2.5), 0.89	Table 14-4.13.1
CGI-I Value at Week 12:	**%[c], Overall p-value vs placebo[d]**			
Very much improved or much improved [CGI-I value for placebo = 21.7%]	35.3, 0.67	35.3, 0.51	17.6, 0.23	Table 14-4.15.1

N = Number of subjects in the analysis set, CI = Confidence interval, NSA-16 = Negative Symptom Assessment 16 items, PANSS = The Positive and Negative Syndrome Scale, PSFS = Marder Positive Symptom Factor Scale, NSFS = Marder Negative Symptom Factor Scale, MCCB = MATRICS Consensus Cognitive Battery, PSP = Personal and Social Performance Scale, Q-LES-Q-18 = Quality of Life Enjoyment and Satisfaction Questionnaire 18 items, SDS = Sheehan Disability Scale, CGI-I = Clinical Global Impressions – Improvement

[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.

Safety Results: A total of 121 subjects (81 in the 3 AMG 747 groups combined, 40 in the placebo group) received ≥ 1 dose of investigational product and were included in the safety analysis set (Table 14-1.2). The mean (SD) number of days of overall exposure to the investigational product in the AMG 747 5-, 15-, and 40-mg groups were 66.7 (25.1), 67.2 (26.5), and 71.6 (22.9) days, respectively, and 70 (22.6) 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 = 40)	AMG 747 5 mg (N = 29)	AMG 747 15 mg (N = 26)	AMG 747 40 mg (N = 26)
All treatment-emergent adverse events - n (%)	21 (52.5)	14 (48.3)	13 (50.0)	15 (57.7)
Grade ≥ 3	1 (2.5)	1 (3.4)	2 (7.7)	3 (11.5)
Serious	1 (2.5)	0 (0.0)	0 (0.0)	2 (7.7)
Leading to withdrawal of investigational product	1 (2.5)	0 (0.0)	0 (0.0)	2 (7.7)
Leading to discontinuation from study	1 (2.5)	0 (0.0)	0 (0.0)	2 (7.7)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 14-6.1

Of the 121 subjects in the safety analysis set, 63 subjects had treatment-emergent adverse events (42 subjects [51.9%] in the AMG 747 groups combined, 21 subjects [52.5%] in the placebo group). Adverse events occurring in ≥ 5% of subjects in any treatment group were: headache, vomiting, tooth extraction, insomnia, dyspepsia, anxiety, nasopharyngitis, toothache, dizziness, upper respiratory tract infection, and urinary tract infection (Table 14-6.4.1).

Most adverse events were of mild (grade 1) or moderate (grade 2) severity. Adverse events with a Common Toxicity Criteria for Adverse Events (CTCAE) grade of ≥ 3 occurred in 7 subjects: 1 subject in the AMG 747 5-mg group (diarrhea, pyrexia, and headache), 2 subjects in the AMG 747 15-mg group (conjunctivitis, neutrophil count decreased), 3 subjects in the AMG 747 40-mg group (dyspepsia, muscle spasms, maculo-papular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, and deep vein thrombosis), and 1 subject in the placebo group (dengue fever) (Table 14-6.2.6).

No fatal adverse events were reported in this study (Table 14-6.2.5). Treatment-emergent adverse events that led to withdrawal of investigational product were reported in 3 subjects (2 [7.7%] in the AMG 747 40-mg group, 1 [2.5%] in the placebo group) and included bacteremia, muscle spasms, acute renal failure, macula-papular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, and deep vein thrombosis; each event had a single occurrence and all events occurred in the AMG 747 40-mg group; and dengue fever in the placebo group (Table 14-6.2.3). Serious adverse events were reported in 3 subjects (2 [7.7%] in the AMG 747 40-mg group, 1 [2.5%] in the placebo group) and were maculo-papular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis (all in 1 subject); and deep vein thrombosis (1 subject) in the AMG 747 40-mg group; and dengue fever (1 subject) in the placebo group (Table 14-6.2.2). Of these, 3 events (maculo-papular rash which appeared

approximately 1 month after treatment, followed by Stevens-Johnson syndrome/toxic epidermal necrolysis overlap) all occurring in 1 subject in the AMG 747 40-mg group were considered by the investigator to have a reasonable possibility of being related to the investigational product (Section 14.6.2). The serious adverse event of Stevens-Johnson syndrome/toxic epidermal necrolysis that occurred in 1 subject in the AMG 747 40-mg group led to early termination of the study.

A total of 3 subjects showed ≥ grade 3 increases/decreases from baseline in laboratory parameters: 1 subject in the AMG 747 40-mg group had a grade 3 increase in creatine kinase, 1 subject in the placebo group had a grade 3 increase in triglycerides, and 1 subject from the AMG 747 15-mg group had a grade 3 decrease in total neutrophils (Table 14-7.2). The change from baseline to week 12 in mean hemoglobin (g/dL) value was -0.24, -0.03, and -0.61 in the AMG 747 5-, 15-, and 40-mg groups, respectively, and -0.27 in the placebo group (Table 14-7.1.2). The change from baseline to week 12 in mean hematocrit (%) value was -0.7, 0.0, and -1.8 in the AMG 747 5-, 15-, and 40-mg groups, respectively, and -0.7 in the placebo group (Table 14-7.1.3).

There were no notable changes in vital signs or ECGs. No clinically meaningful changes from baseline in the AIMS total score (item 1 to 9), BARS total score (item 1 to 3), CDSS total score (item 1 to 9), or SAS average score (item 1 to 10) were noted in any of the subjects at various study visits. A total of 5 subjects had a post-baseline suicidal ideation based on the C-SSRS (2 in the AMG 747 40-mg group, 1 each in the AMG 747 5-mg, 15-mg, and placebo groups).

Conclusions:

The study was terminated early due to a sponsor administrative decision after the occurrence of a serious adverse event of Stevens-Johnson syndrome/toxic epidermal necrolysis in a subject receiving AMG 747 40 mg QD. A total of 270 subjects were planned for enrollment; however, only 121 were enrolled and 27 subjects (22.3%) were withdrawn for administrative reasons when the study was terminated early.

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

With the exception of the event of Stevens-Johnson syndrome/toxic epidermal necrolysis, the adverse event profile of AMG 747 did not appear to differ across doses and was comparable with placebo. There seemed to be a 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.