2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 151

Name of Active Ingredient: AMG 151

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Explore Dose Effect and Frequency of Administration of AMG 151 in Subjects with Type 2 Diabetes Mellitus

Investigators and Study Centers: This study was conducted at 59 centers in the Czech Republic, Estonia, Poland, and the United States. The coordinating investigator for this study was [redacted]. Centers and principal investigators are listed in Section 16.1.4.

Publications: None

Study Period: 06 October 2011 (first subject enrolled) to 25 October 2012 (last subject's final follow-up visit)

Development Phase: 2a

Objectives:

The primary objective was to evaluate the dose-effect relationship of AMG 151 compared with placebo, on fasting plasma glucose in subjects with type 2 diabetes treated with metformin.

The secondary objective was to assess the effect of AMG 151 on postprandial glucose levels in response to a meal tolerance test. The safety objective was to evaluate the safety and tolerability of AMG 151.

Exploratory objectives are listed in Protocol Section 1.4 (Section 16.1.1 of this report).

This clinical study report is in the synopsis format since development of AMG 151 has been discontinued [redacted]

Methodology: This phase 2a, multicenter, parallel-group, fixed-dose study evaluated AMG 151 in subjects with type 2 diabetes treated with metformin for at least 3 months before randomization. Changes in metformin dose or frequency were not allowed during the study. Eligible subjects were randomly assigned in a 1:1:1:1:1:1:1 ratio to receive AMG 151 at 50, 100, or 200 mg twice daily (BID), AMG 151 at 100, 200, or 400 mg once daily (QD), or matching placebo for 28 days. Randomization was stratified by screening glycated hemoglobin (HbA1c) ≤ 8.5% or > 8.5% and by metformin dose < 1,500 or ≥ 1,500 mg per day.

The study consisted of a screening period of up to 14 days, a 14-day run-in period, a 28-day treatment period, and a 14-day follow-up period with weekly study visits during the run-in and treatment period.

Number of Subjects Planned: 224

Diagnosis and Main Criteria for Eligibility: Men and women between 18 to 75 years of age who had type 2 diabetes, with a body mass index ≥ 25 to ≤ 45 kg/m^2 and HbA1c levels ≥ 7.5% to ≤ 11.0% at screening were eligible for the study. Subjects who did not meet the eligibility criteria within 0.2% of the lower and upper range, at the discretion of

the investigator, could have been re-screened and randomized if the second screening HbA1c value was within the biological variability of ± 0.2% (7.3% to 11.2%) (Protocol Section 7.1.2 [Section 16.1.1]). Subjects were required to be treated with metformin for at least 3 months before randomization and the metformin dose was ≥ 850 mg daily for at least the 2 months immediately before randomization. Subjects were excluded if they had a history of type 1 diabetes; if they used any oral or injectable anti-hyperglycemic medication (other than metformin) within 3 months before randomization, or if they were on chronic and/or continuous insulin administration for > 15 days to achieve and maintain glycemic control before randomization. Subjects who had ≥ 2 emergency room visits or hospitalizations due to poor glucose control, or subjects who had > 1 episode of severe hypoglycemia in the previous 6 months were also excluded from the study. Additional eligibility criteria are provided in Protocol Section 4 (Section 16.1.1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 151 was provided as [redacted] Subjects received AMG 151 as oral tablets at the following doses: 50, 100, or 200 mg BID; 100, 200, or 400 mg QD.

AMG 151 manufacturing lot numbers were: [redacted], and [redacted] (Section 16.1.6).

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo tablets were provided with the matching color, size, and shape of the active tablets and contained the same ingredients, with the exception of active AMG 151.

Placebo manufacturing lot number was [redacted] (Section 16.1.6).

Duration of Treatment: The estimated study duration was approximately 70 days and subjects received the study drug for 28 days. Subjects were followed-up for 14 days after the end of treatment.

Study Endpoints:

Efficacy Endpoints:

Primary Endpoint:

- change in fasting plasma glucose levels from baseline to day 28

Secondary Endpoints:

- change in area under the curve 0-4 hours (AUC_{0-4hr}) glucose after a meal tolerance test from baseline to day 28
- change in incremental AUC_{0-4hr} glucose after a meal tolerance test from baseline to day 28

Safety Endpoints:

- incidence of hypoglycemic episodes as defined by the American Diabetes Association Working Group on Hypoglycemia (ie, severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia), by treatment group during run-in, during 28 days of treatment, and during the 14-day follow-up period

- change in fasting triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol levels from baseline to 28 days of treatment, and during the 14-day follow-up period
- adverse events
- 12-lead electrocardiogram (ECG) at baseline, and at the day 7, 14, and 28 study visits
- physical examination including body weight and vital signs (blood pressure, heart rate)
- laboratory assessments

Details for exploratory endpoints are provided in Protocol Section 10.1.4 (Section 16.1.1).

Statistical Methods:

Unless specified otherwise, all hypothesis testing was 2-sided with a significance level of 0.05; no correction for multiple comparisons were made. Subjects were analyzed based on their randomized treatment group assignment.

The primary endpoint was tested for a linear trend of treatment effect separately within QD (placebo, 100, 200, and 400 mg) and BID (placebo, 50, 100, and 200 mg) regimens using a linear contrast with contrast coefficient of (-3, -1, 1, 3). A mixed-effects repeated-measures model for each regimen was used to estimate the change in means from baseline to day 28 for each dose. The model included treatment, stratification variables (HbA1c ≤ 8.5% or > 8.5%, metformin dose < 1,500 or ≥ 1,500 mg per day), baseline fasting plasma glucose as covariates, and a random subject effect.

Hypoglycemic/hyperglycemic events were summarized separately from all adverse events by run-in, treatment period, follow-up period, and overall study period for each of the treatment groups (Section 16.1.9).

Summary of Results:

Subject Disposition: A total of 683 subjects were screened and 236 were randomized to study treatment (202 in AMG 151 group, 34 in placebo). Of these, 235 subjects (99.6%) received at least 1 dose of investigational product and 208 subjects (88.1%) completed their treatment with the investigational product. A total of 219 subjects (92.8%) completed the study (Table 14-1.1). Subjects were randomized to 1 of 7 treatment groups as follows:

Treatment Group	Number of Subjects Randomized N	Number of Subjects who Completed Study n (%)
Placebo	34	33 (97.1)
50-mg BID	33	31 (93.9)
100-mg BID	34	31 (91.2)
200-mg BID	34	29 (85.3)
100-mg QD	32	30 (93.8)
200-mg QD	34	32 (94.1)
400-mg QD	35	33 (94.3)

% = n/N*100, BID = twice daily, QD = once daily
Source: Tables 14-1.1 and Table 14-1.2

Baseline Demographics:

Sex: 129 men (54.9%), 106 women (45.1%)

Age: Mean (standard deviation): 53.7 (9.6) years; range: 23 to 75 years

Ethnicity/Race: 176 white (74.9%), 46 black (19.6%), 5 Asian (2.1%), 3 American Indian or Alaska Native (1.3%), 3 Native Hawaiian or Other Pacific Islander (1.3%), 2 other (0.9%)

Overall baseline demographics are summarized in Table 14-2.1.1 and Table 14-2.1.2, and demographics based on subgroup analyses are summarized in Table 14-2.2.1 to Table 14-2.2.16. Overall baseline disease characteristics are summarized in Table 14-2.5.1.1 and Table 14-2.5.1.2, and disease characteristics based on subgroup analyses are summarized in Table 14-2.6.1 to Table 14-2.6.16.

Efficacy Results

Primary Endpoint:

A statistically significant linear trend of treatment effect for dose levels was observed in the BID regimen (p = 0.004) for change in fasting plasma glucose from baseline to day 28. A statistically significant decrease in mean fasting plasma glucose compared with placebo was noted only for the AMG 151 200-mg BID dose group (-1.38 mmol/L, 95% confidence interval [CI]: [-2.52, -0.25], p = 0.017) (Table 14-4.19). No statistically significant trend was observed with the QD regimen (p = 0.19), and no AMG 151 QD dose group had a statistically significant decrease in mean fasting plasma glucose compared with placebo (Table 14-4.20). There was no statistically significant interaction between the covariates (disease duration, baseline fasting glucose level, baseline HbA1c, baseline metformin dose, BMI, and smoking status) and the primary endpoint for the QD and BID dosing regimens (Table 14-4.47 and Table 14-4.48).

Secondary Endpoints:

Both the QD and BID dosing regimens showed a statistically significant linear trend of treatment for dose level in $AUC_{0\text{-}4hrs}$ of plasma glucose after a meal tolerance test from baseline to day 28 (BID: p = 0.001, QD: p = 0.006). A statistically significant decrease was noted in mean $AUC_{0\text{-}4hrs}$ of plasma glucose compared with placebo for all QD doses (100 mg: p = 0.041, 200 mg: p = 0.003, 400 mg: p = 0.009) and the 200-mg BID dosing regimen (p = 0.002) (Table 14-4.61 and Table 14-4.62). Both the QD and BID dosing regimens showed a statistically significant trend in incremental $AUC_{0\text{-}4hrs}$ of plasma glucose after a meal tolerance test from baseline to day 28 (BID: p = 0.047, QD: p = 0.025). A statistically significant decrease was noted in incremental $AUC_{0\text{-}4hrs}$ plasma glucose compared with placebo for all QD doses (100 mg: p = 0.015, 200 mg: p = 0.004, 400 mg: p = 0.029) and the 200-mg BID dosing regimen (p = 0.016) (Table 14-4.77 and Table 14-4.78). Results of sensitivity analyses conducted on secondary efficacy endpoints are summarized in Table 14-4.63 to Table 14-4.76 for $AUC_{0\text{-}4hrs}$ and Table 14-4.79 to Table 14-4.96 for incremental $AUC_{0\text{-}4hrs}$.

Safety Results

Treatment-emergent Adverse Events:

A total of 235 subjects (201 AMG 151, 34 placebo) received ≥ 1 dose of investigational product and were included in the safety analysis set (Table 14-2.7.1). The mean number of days that subjects received AMG 151 was 26.6 days and the mean number of total tablets taken was 209.8 tablets (Table 14-3.3).

There were no fatal adverse events (Table 14-6.1) in this study. No serious adverse events occurred during the treatment period (Table 14-6.9); 1 subject (0.5%) in the 50-mg dose group had 2 serious adverse events (dyspnea and chest pain) during the follow-up period and the events were not related to investigational product (Table 14-6.10, Listing 14-6.3). Three subjects discontinued investigational product due to treatment-emergent adverse events (2 AMG 151 [nausea, dizziness, hepatic steatosis, alanine aminotransferase increased, and aspartate aminotransferase increased]; 1 placebo [urticaria]) (Table 14-6.12). No subject discontinued the study due to treatment-emergent adverse events (Table 14-6.1).

Most adverse events were of mild (grade 1) or moderate (grade 2) severity. A total of 6 subjects who received AMG 151 (3 each from the 100-mg QD and 50-mg BID groups) had adverse events with grade 3 severity (depression, viral upper respiratory tract infection, edema peripheral, anxiety, alanine aminotransferase increased, aspartate aminotransferase increased, toothache, syncope, cough, nephrolithiasis, and flank pain) and 1 subject (50-mg BID group) had events with grade 4 severity (dyspnea and chest pain; Listing 14-6.5). No subject who received placebo had adverse events with severity $\geq$ grade 3.

Of the 235 subjects (201 AMG 151, 34 placebo) in the safety analysis set, 79 subjects had treatment-emergent adverse events (68 AMG 151 [33.8%], 11 placebo [32.4%]). The common adverse events occurring in > 2% of subjects receiving AMG 151 were: headache (10 subjects [5%]), upper respiratory tract infection (6 subjects [3%]), diarrhea (5 subjects [2.5%]), and nausea (5 subjects [2.5%]). None of these adverse events occurred in the placebo group except diarrhea (1 subject [2.9%]) (Table 14-6.6). Of these, headache (7 subjects AMG 151 [3.5%]), diarrhea (3 subjects AMG 151 [1.5%]), and nausea (2 subjects AMG 151 [1%]) were considered to be related to the investigational product (Table 14-6.7).

Treatment-emergent Hypoglycemic and Hyperglycemic Events:

There were no serious or fatal events associated with hypoglycemia or hyperglycemia in this study (Table 14-6.2, Table 14-6.3). Hypoglycemia was observed in 80 subjects (72 AMG 151 [35.8%], 8 placebo [23.5%]). The highest incidence was observed in the 200-mg QD (18 subjects [52.9%], 400-mg QD (14 subjects [40%]), and 200-mg BID (15 subjects [44.1%]) groups. Eight subjects (4%) receiving AMG 151 (4 from 400-mg QD group, and 2 each from the 200-mg QD and 200-mg BID groups) discontinued investigational product, and 2 subjects receiving AMG 151discontinued the study (1 each from the 200-mg QD and 200-mg BID groups) due to hypoglycemic events. No subject from the placebo group discontinued investigational product or study due to hypoglycemic events (Table 14-6.2). A total of 24 subjects (18 AMG 151 [9%], 6 placebo [17.6%]) had hyperglycemic events. None of the hyperglycemic events led to discontinuation of investigational product or the study (Table 14-6.3).

In subjects receiving AMG 151 and placebo, there were no severe hypoglycemic events; 36 subjects (17.9%) in AMG 151 group and 1 subject (2.9%) in placebo group had documented symptomatic hypoglycemic events; 43 subjects (21.4%) in AMG 151 and 4 subjects (11.8%) in placebo had asymptomatic events; and 5 subjects (2.5%) in AMG 151 and none in placebo had probable symptomatic events during the treatment period (Table 14-8.1). Details on hypoglycemic and hyperglycemic events are provided in Table 14-8.2 to Table 14-8.12 and Table 14-9.36 to Table 14-9.40.

Laboratory Assessments:

Triglycerides were raised in all AMG 151 BID groups compared with placebo. The median percent increase from baseline to day 28 ranged from 17.49% to 24.59% in the

BID regimen groups compared with 2.03% in the placebo group. A median increase of 7% was observed in the 400-mg QD dosing group compared with 2.03%, 1.35% and -0.75% in the placebo, 100-mg QD, and 200-mg QD groups, respectively (Table 14-7.36). For the subjects with percent of triglyceride changes ≥ 30% from baseline there was a trend towards an increase in mean and median in all treatment groups including placebo. The increases were numerically greater in the BID treatment groups, and especially in subjects treated at 200 mg BID (Listing 14-7.1.1 and Table 14-7.36). There were no notable changes observed for fasting HDL (Table 14-7.34), LDL (Table 14-7.35), or total cholesterol (Table 14-7.33).

Free fatty acids were reduced from baseline to day 28 in the 100-mg and 200-mg BID groups with a median change of -12.92% and -10.99%, respectively (Table 14-4.149) and for the 200-mg and 400-mg QD groups, which showed a median change of -7.5% and -10.0% compared with the placebo group which showed a median change of 5.26% (Table 14-4.150).

Two subjects in the 50-mg BID group had ≥ 2 grade shifts in alanine aminotransferase (1 subject from grade 0 to grade 2 and 1 subject from grade 1 to grade 3) (Table 14-7.96). Other laboratory values are summarized in Table 14-7.1 to Table 14-7.93 and in shift tables in Table 14-7.94 to Table 14-7.116.

There were no notable changes in vital signs (Table 14-8.13 to Table 14-8.25) or ECG (Table 14-8.26 to Table 14-8.35) in any of the groups.

Pharmacokinetics (PK) Result

After oral administration of AMG 151 to adult subjects with type 2 diabetes mellitus, AMG 151 exposure increased less than dose-proportionally with increasing dose. A detailed account of PK results including the bioanalytical report is provided in Section 16.1.13.1.

Conclusions:

- In subjects with type 2 diabetes treated with metformin, a statistically significant linear trend was observed for dose level in the AMG 151 BID dosing regimen for change in fasting plasma glucose from baseline to day 28: subjects receiving AMG 151 200 mg BID had a statistically significant decrease in mean fasting plasma glucose compared with placebo.
- A statistically significant linear trend was observed in both AMG 151 BID and QD regimen in $AUC_{0\text{-}4hrs}$ and incremental $AUC_{0\text{-}4hrs}$ glucose after a meal tolerance test from baseline to day 28. All QD dose groups and the 200-mg BID dosing regimen showed statistically significant treatment effect compared with placebo.
- The overall safety and tolerability profile of AMG 151 in subjects with type 2 diabetes was found to be acceptable for all dosing regimens.
- No severe hypoglycemia was reported during treatment with AMG 151, however the incidence of hypoglycemia was increased compared with placebo.