SYNOPSIS

Name of Sponsor: Amgen Inc, Thousand Oaks, CA

Name of Finished Product: Not applicable

Name of Active Ingredient: AMG 853

Title of Study: A Randomized, Double-blind, Placebo-controlled, Multiple Dose Phase 2 Study to Determine the Safety and Efficacy of AMG 853 in Subjects With Inadequately Controlled Asthma

Investigators and Study Centers: This study was conducted at 73 sites in the United States, Canada, and Europe. A list of study investigators is provided in Attachment 2.

Publications: No publications

Study Period: 21 December 2009 (first subject enrolled) to 13 December 2010 (last subject visit)

Development Phase: 2

Introduction and Objectives: AMG 853 [redacted] PGD_2 is the major cyclooxygenase product formed by activated mast cells and is known to induce a variety of physiological responses, including vasodilation and bronchoconstriction. [redacted] AMG 853 has been evaluated in 5 completed clinical studies conducted in healthy adult subjects: a phase 1 first-in-human single ascending dose study (20070280), a phase 1 multiple ascending dose study (20070281), a phase 1 food-effect study (20090125), a phase 1 gastrointestinal absorption study (20090218), and a phase 1 pharmacokinetic (PK) study (20090226). Studies 20070280 and 20070281 showed that single (≤ 400 mg) and multiple doses (≤ 100 mg twice daily [BID] and ≤ 200 mg once daily [QD] for 14 days) of AMG 853 were well tolerated in healthy adult subjects. In Studies 20090125, 20090218, and 2009226, AMG 853 had an acceptable safety and tolerability profile when administered as a single oral dose over 4 treatment periods at 10 mg, 100 mg via Enterion™ capsule, and 100 mg as a free-acid tablet and mono-Na salt, respectively. The purpose of this phase 2 study (20080615) was to determine the efficacy and safety of AMG 853 compared with placebo after 12 weeks of treatment in subjects with inadequately controlled asthma.

The primary objective of this study was to determine if AMG 853 is effective compared with placebo as measured by the change in Asthma Control Questionnaire (ACQ) symptom scores from baseline to week 12. The secondary objective was to evaluate the efficacy of AMG 853 as measured by pre- and postbronchodilator forced expiratory volume in 1 second (FEV_1), AM and PM peak expiratory flow rate (PEFR), use of rescue short-acting β-agonist (SABA), daily symptom score (aggregate/night and individual symptoms; and symptom-free days), and asthma quality of life questionnaire (AQLQ). [redacted] The safety objectives were to evaluate the safety of AMG 853

as measured by adverse events, changes in electrocardiograms (ECG), laboratory profiles, and vital signs.

Because interim and final analyses of data from this phase 2 study indicated insufficient effectiveness of AMG 853 in subjects with inadequately controlled asthma, Amgen discontinued the AMG 853 program, [redacted]. No safety concerns were associated with AMG 853.

Methodology: The protocol for this study is provided in Attachment 1. Study 20080615 was a randomized, double-blind, placebo-controlled, multiple-dose phase 2 study to determine the safety and efficacy of AMG 853 in subjects with inadequately controlled asthma.

Subjects were randomized in a 1:1:1:1:1 ratio to receive 5, 25, or 100 mg AMG 853 BID; 200 mg AMG 853 QD; or placebo. All subjects received 2 tablets in the morning and 2 tablets in the evening. Any medication washout was to take place after informed consent and before a 4-week run-in period. Randomization was stratified by atopy status. Subjects were defined as atopic if they were positive to skin prick (wheal diameter ≥ 3 mm and documented negative control) or RadioAllergoSorbent Test™ (RAST) for any allergen at screening or documented within the last 12 months. All subjects must have been receiving a total daily inhaled corticosteroid (ICS) dose of 200 to 1000 µg of fluticasone powder or equivalent, and must have been on a stable dose ≥ 30 days before screening, and remained on the stable dose through the end of the study.

Control Group: Placebo BID

Number of Subjects Planned: 375

Number of Subjects Enrolled: 397 subjects were enrolled; 396 subjects received treatment

Sex: 159 men (40.2%), 237 women (59.8%)

Mean (standard deviation) Age: 44.9 (11.4) years

Ethnicity (Race): 301 White (76.0%), 51 Black (12.9%), 27 Hispanic (6.8%), 10 Asian (2.5%), 1 American Indian or Alaskan Native (0.3%), 5 Pacific Islander (1.3%), 1 unknown (0.3%)

Diagnosis and Main Criteria for Eligibility: AMG 853-naïve, non-smoking, men and women with asthma; 18 to 65 years old; percent-predicted FEV_1 ≥ 50% and ≤ 80% at both screening and baseline; at least 12% reversibility over prebronchodilator FEV_1 with SABA inhalation or nebulized equivalent; ICS 200 to 1000 µg/day of fluticasone powder or equivalent for at least 3 months before screening, and stable for ≥ 30 days before screening; if receiving allergen immunotherapy, stable for > 3 months before screening; ongoing asthma symptoms with ACQ score ≥ 1.5 points at both screening and baseline; physical examination, clinical laboratory test values, and ECGs that were clinically acceptable to the investigator and/or Amgen; and no history of a chronic pulmonary condition other than asthma, aspirin-sensitive asthma, uncontrolled and clinically significant systemic disease, malabsorption syndromes, gastric bypass surgery, or small intestinal bypass surgery requiring resection.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: AMG 853 was supplied as tablets and was administered orally. The manufacturing lot numbers were 5 mg: [redacted]; 25 mg: [redacted]; 100 mg: [redacted]; and 200 mg: [redacted].

Duration of Treatment: 12 weeks

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: Placebo was supplied as tablets and was administered orally. The manufacturing lot numbers were [redacted] and [redacted].

Primary Efficacy Endpoints: Change in ACQ scores from baseline to week 12

Secondary Efficacy Endpoints:

- Change in percent-predicted FEV1 pre- and postbronchodilator treatment from baseline to week 12
- Change in AM and PM PEFR from baseline to week 12
- Change in frequency of rescue SABA use from baseline to week 12
- Change in daily asthma symptoms (aggregate/night and individual) from baseline to week 12
- Change in AQLQ score from baseline to week 12
- Proportion of symptom-free days over the 12-week treatment period

Exploratory Endpoints:

[redacted]

Safety Endpoints: Adverse events, clinical laboratory tests, ECGs, and vital signs

Statistical Methods: The primary endpoint, change in ACQ score from baseline to week 12, was analyzed using an analysis of covariance (ANCOVA) model with the treatment group (AMG 853 dose arms or placebo) as the main factor, and adjusting for baseline ACQ and the stratification factor. A linear trend test of AMG 853 BID treatment arms was performed as the primary analysis to test for a drug effect.

Differences between each of the AMG 853 dose groups and placebo group and their 95% confidence intervals were provided using least squares means in an ANCOVA model. To find the minimum effective dose, the comparison of the AMG 853 dose versus placebo was tested sequentially from 100 mg to 5 mg for differences in the primary endpoint, maintaining the overall significance level of 0.05. The mean change in ACQ was estimated for the 200-mg QD dose group to investigate whether QD dosing provided meaningful clinical efficacy. Similar ANCOVA analyses were performed for the rest of the continuous secondary and exploratory end points, and the stratified Cochran-Mantel-Haenszel test was used to analyze categorical endpoints. The last observation carried forward method was used to impute missing data. All categorical variables were summarized using the number and percent of subjects, and ordinal categorical variables were also summarized using the median. All continuous variables were summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects.

All safety and efficacy analyses were performed on all randomized subjects who received at least 1 dose of investigational product. For some endpoints, baseline and at least 1 postbaseline assessment were required.

[redacted]

Summary of Results:

Subject Disposition: A total of 397 subjects were randomized to 1 of 5 treatment groups (5, 25, and 100 mg AMG 853 BID; 200 mg AMG 853 QD; or placebo), and 396 received investigational product (Table 1). One subject ([redacted]) was enrolled into the 5-mg BID group but did not receive investigational product because the subject did not meet eligibility requirements and was randomized in error; details are presented in the database errata in Attachment 6. Of all subjects randomized, 351 (88.4%) completed the study; 46 subjects prematurely discontinued the study (14 [5 mg BID], 4 [25 mg BID], 9 [100 mg BID], 12 [200 mg QD], and 7 placebo) (Table 14-1.1). Of all subjects randomized, 352 (88.7%) completed 12 weeks of investigational product; 44 subjects prematurely discontinued treatment with investigational product (13 [5 mg BID], 3 [25 mg BID], 9 [100 mg BID], 12 [200 mg QD], and 7 placebo) (Table 14-1.2). Early discontinuation from both the study and from investigational product was most commonly due to adverse events (3.3%), consent withdrawn (2.5%), and protocol deviations (1.5%). Overall, treatment assignments were well balanced across groups. Seventeen subjects (4.3%) had ≥ 1 important protocol deviation during the study (Listing 1).

Table 1. Subject Disposition

		AMG 853					
	Placebo	5 mg BID	25 mg BID	100 mg BID	200 mg QD	All AMG 853	All Subjects
Total number of subjects, n (%)							
Randomized	79	80	79	79	80	318	397
Discontinued study	7 (8.9)	14 (17.5)	4 (5.1)	9 (11.4)	12 (15.0)	39 (12.3)	46 (11.6)
Treated with IP	79 (100.0)	79 (98.8)	79 (100.0)	79 (100.0)	80 (100.0)	317 (99.7)	396 (99.7)
Completed 12 week IP, n (%)							
Yes	72 (91.1)	66 (82.5)	76 (96.2)	70 (88.6)	68 (85.0)	280 (88.1)	352 (88.7)
No	7 (8.9)	13 (16.3)	3 (3.8)	9 (11.4)	12 (15.0)	37 (11.6)	44 (11.1)
Adverse event	3 (3.8)	4 (5.0)	0 (0.0)	4 (5.1)	2 (2.5)	10 (3.1)	13 (3.3)
Full consent withdrawn	1 (1.3)	1 (1.3)	3 (3.8)	0 (0.0)	5 (6.3)	9 (2.8)	10 (2.5)
Protocol deviation	0 (0.0)	3 (3.8)	0 (0.0)	2 (2.5)	1 (1.3)	6 (1.9)	6 (1.5)
Noncompliance	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)	2 (2.5)	3 (0.9)	4 (1.0)
Lost to follow-up	1 (1.3)	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	4 (1.0)
Alternative therapy	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)	1 (0.3)
Administrative decision	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)	1 (0.3)
Ineligible	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial consent withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.3)	0 (0.0)	0 (0.0)	2 (2.5)	1 (1.3)	3 (0.9)	4 (1.0)

BID = twice daily; IP = investigational product; QD = once daily. Percentages are based on the number of subjects randomized.
Source: Table 14-1.1 and Table 14-1.2

Efficacy Results: Because of the abbreviated format of this synopsis report, only the primary endpoint, key secondary endpoints (change in percent-predicted FEV_1 prebronchodilator treatment from baseline to week 12), [redacted]) are presented.

The primary endpoint was the change in ACQ score from baseline to week 12. At week 12, the mean change in ACQ score from baseline was -0.541, -0.555, -0.444, -0.498, and -0.492 for the AMG 853 5-mg BID, 25-mg BID, 100-mg BID, and 200-mg QD groups, and the placebo group, respectively (Table 2 and Table 14-4.1.1). The overall BID treatment effect on the ACQ change from baseline score was not statistically significant (p = 0.77; least square [LS] means = -0.621 [5 mg BID], -0.659 [25 mg BID], and -0.516 [100 mg BID], vs -0.568 [placebo]) (Table 14-4.1.1). Further pairwise comparisons of week-12 ACQ change from baseline scores from each AMG 853 dose group showed no statistically significant difference over placebo (p = 0.67 [5 mg BID], 0.46 [25 mg BID], 0.68 [100 mg BID], and 0.99 [200 mg QD]).

[redacted]

Table 2. ACQ Score Change From Baseline to Week 12 (Full Analysis Set - LOCF Imputation)

	Placebo (N=79)	AMG 853 5 mg BID (N=79)	AMG 853 25 mg BID (N=79)	AMG 853 100 mg BID (N=79)	AMG 853 200 mg QD[c] (N=80)	p-value[a]
Baseline						
n	79	79	79	79	80	
Mean (SE)	2.497 (0.069)	2.470 (0.069)	2.409 (0.061)	2.479 (0.067)	2.530 (0.069)	
SD	0.613	0.614	0.544	0.596	0.616	
LS mean[a]	2.523	2.496	2.434	2.504		
Difference from placebo[b]		-0.027	-0.089	-0.019	0.036	
95% confidence interval[b]		(-0.213, 0.159)	(-0.275, 0.096)	(-0.205, 0.167)	(-0.156, 0.228)	
p-value of pairwise comparison[b]		0.7740	0.3443	0.8416	0.7129	
Week 12 change from baseline						
n	79	76	79	76	80	
Mean (SE)	-0.492 (0.086)	-0.541 (0.100)	-0.555 (0.072)	-0.444 (0.100)	-0.498 (0.076)	
SD	0.764	0.870	0.637	0.875	0.682	
LS mean[a]	-0.568	-0.621	-0.659	-0.516		0.7653
Difference from placebo[b]		-0.053	-0.091	0.051	-0.002	
95% confidence interval[b]		(-0.295, 0.189)	(-0.331, 0.149)	(-0.190, 0.293)	(-0.227, 0.224)	
p-value of pairwise comparison[b]		0.6664	0.4560	0.6763	0.9882	

BID = twice daily; QD = once daily; N = number of subjects who were randomized and received at least 1 dose of investigational product
Treatment groups represent original randomized treatment.

[a] From linear trend test of treatment effect (placebo, 5-mg, 25-mg and 100-mg BID doses) using linear contrast of (-3, -1, 1, 3) in Analysis of Covariance model, adjusted for randomized strata and baseline value of ACQ.

[b] Pairwise comparison of each BID treatment with placebo respectively from the same Analysis of Covariance model above.

[c] The difference from placebo and its 95% confidence interval were estimated using Analysis of Covariance model with placebo and AMG 853 200-mg QD treatments only, adjusted for randomized strata and baseline value of ACQ.

Source: Table 14-4.1.1

A key secondary endpoint was the change in percent-predicted FEV_1 prebronchodilator treatment from baseline to week 12. At week 12, the mean change in prebronchodilator percent-predicted FEV_1 was 1.462, 1.019, -0.518, 1.288, and 0.896 for the AMG 853 5-mg BID, 25-mg BID, 100-mg BID, and 200-mg QD groups, and the placebo group, respectively (Table 3 [redacted]). The overall BID treatment effect on the change from baseline in prebronchodilator percent-predicted FEV_1 at week 12 was not statistically significant (p = 0.34; LS means = 1.808 [5 mg BID], 1.274 [25 mg BID], -0.320 [100 mg BID], and 1.075 [placebo]). Further pairwise comparisons of week-12 prebronchodilator percent-predicted FEV_1 from each AMG 853 dose group showed no statistically significant difference over placebo (p = 0.64 [5 mg BID], 0.90 [25 mg BID], 0.38 [100 mg BID], and 0.79 [200 mg QD].

[redacted].

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Table 3. Prebronchodilator Percent-predicted FEV_1 Change From Baseline to Week 12 (Full Analysis Set - LOCF Imputation)

		AMG 853				
	Placebo (N = 79)	5 mg BID (N = 79)	25 mg BID (N = 79)	100 mg BID (N = 79)	200 mg QD[c] (N = 80)	p-value[a]
Baseline						
n	79	79	79	79	80	
Mean (SE)	66.319 (0.883)	68.190 (0.892)	67.071 (0.892)	66.722 (0.959)	66.141 (1.000)	
SD	7.847	7.931	7.924	8.522	8.942	
LS mean[a]	66.189	68.060	66.945	66.596		
Difference from placebo[b]		1.871	0.756	0.407	-0.177	
95% confidence interval[b]		(-0.657, 4.398)	(-1.772, 3.284)	(-2.120, 2.935)	(-2.822, 2.469)	
p-value of pairwise comparison[b]		0.1463	0.5566	0.7514	0.8953	
Week 12 change from baseline						
n	79	76	79	76	80	
Mean (SE)	0.896 (0.986)	1.462 (1.348)	1.019 (1.135)	-0.518 (0.938)	1.288 (1.204)	
SD	8.765	11.755	10.085	8.174	10.769	
LS mean[a]	1.075	1.808	1.274	-0.320		0.3427
Difference from placebo[b]		0.733	0.199	-1.395	0.423	
95% confidence interval[b]		(-2.365, 3.830)	(-2.864, 3.261)	(-4.487, 1.696)	(-2.665, 3.511)	
p-value of pairwise comparison[b]		0.6419	0.8985	0.3751	0.7872	

BID = twice daily; QD = once daily; N = number of subjects who were randomized and received at least 1 dose of investigational product.

Treatment groups represent original randomized treatment

[a] From linear trend test of treatment effect (placebo, 5-mg, 25-mg, and 100-mg BID doses) using linear contrast of (-3, -1, 1, 3) in Analysis of Covariance model, adjusted for randomized strata and baseline value of percent-predicted FEV_1.

[b] Pairwise comparison of each BID treatment with placebo respectively from the same Analysis of Covariance model above.

[c] The difference from placebo and its 95% confidence interval were estimated using Analysis of Covariance model with placebo and AMG 853 200-mg QD treatments only, adjusted for randomized strata and baseline value of percent-predicted FEV_1.

Source: Table 14-4.2.1

[redacted]

Safety Results: The safety analysis set included 396 subjects who received at least 1 dose of investigational product. AMG 853 had an acceptable safety and tolerability profile at all dose levels administered (Table 4). Nine subjects had serious adverse events, including 1 subject in the 200-mg QD AMG 853 group who died of dilated cardiomyopathy. The death and all other serious adverse events in this study were assessed by the investigator to be unrelated to investigational product, and there were no dose-related trends. Adverse events caused study withdrawal in 11 subjects (9 AMG 853 [2.8%] and 2 placebo [2.5%]), and investigational product withdrawal in 16 subjects (13 AMG 853 [4.1%] and 3 placebo [3.8%]). Overall, adverse events were reported for more subjects in the AMG 853 groups (56.2%) than the placebo group (45.6%). The incidence of adverse events was higher in the AMG 853 groups than in the placebo group largely because of headache. Slightly more subjects in the AMG 853 groups had adverse events with a severity of grade 3, 4, or 5 (based on the Common Terminology Criteria for Adverse Events [CTCAE]) than those in the placebo group (3.8% vs 2.5%, respectively). No trends were observed that suggested an impact of AMG 853 on measured laboratory values, vital signs, physical examinations, or ECGs.

Table 4. Summary of Adverse Events

		AMG 853				
	Placebo (N = 79)	5 mg BID (N = 79)	25 mg BID (N = 79)	100 mg BID (N = 79)	200 mg QD (N = 80)	All AMG 853 (N = 317)
TEAEs, n (%)						
All	36 (45.6)	43 (54.4)	52 (65.8)	42 (53.2)	41 (51.3)	178 (56.2)
Serious	2 (2.5)	1 (1.3)	0 (0.0)	3 (3.8)	3 (3.8)	7 (2.2)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Leading to study withdrawal	2 (2.5)	2 (2.5)	1 (1.3)	4 (5.1)	2 (2.5)	9 (2.8)
Leading to IP withdrawal	3 (3.8)	4 (5.1)	0 (0.0)	5 (6.3)	4 (5.1)	13 (4.1)
CTCAE Grade 3, 4, or 5	2 (2.5)	3 (3.8)	0 (0.0)	6 (7.6)	3 (3.8)	12 (3.8)

BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; QD = once daily; N = number of subjects who were randomized and received at least 1 dose of investigational product; TEAE = treatment-emergent adverse event defined as an adverse event that occurred on or after first dose date and before or on the end of study date.
Subjects were analyzed by the actual treatment received.
Source: Table 14-6.1.1

Adverse Events: A total of 214 (54%) subjects had adverse events during the study (Table 5). The most commonly-reported adverse event preferred terms (approximately ≥ 5% of subjects) were asthma (15.1% in AMG 853 and 15.2% in placebo groups), upper respiratory tract infection (8.5% in AMG 853 and 7.6% in placebo groups), and headache (4.7% in AMG 853 and 0% of placebo groups). The subject incidence of adverse events was higher in the AMG 853 groups overall than in the placebo group (56.2% vs 45.6%, respectively), and was largely due to adverse events of headache. In addition, 37 AMG 853-treated subjects had treatment-related adverse

events; the subject incidence was higher in the AMG 853 groups than in the placebo group (11.7% vs 7.6%, respectively) [redacted].

Table 5. Summary of Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group

		AMG 853				
	Placebo (N = 79)	5 mg BID (N = 79)	25 mg BID (N = 79)	100 mg BID (N = 79)	200 mg QD (N = 80)	All AMG 853 (N = 317)
Number of subjects reporting TEAEs, n (%)	36 (45.6)	43 (54.4)	52 (65.8)	42 (53.2)	41 (51.3)	178 (56.2)
Asthma	12 (15.2)	12 (15.2)	13 (16.5)	12 (15.2)	11 (13.8)	48 (15.1)
Upper respiratory tract infection	6 (7.6)	9 (11.4)	9 (11.4)	5 (6.3)	4 (5.0)	27 (8.5)
Headache	0 (0.0)	4 (5.1)	5 (6.3)	1 (1.3)	5 (6.3)	15 (4.7)
Nasopharyngitis	3 (3.8)	2 (2.5)	3 (3.8)	5 (6.3)	1 (1.3)	11 (3.5)
Sinusitis	1 (1.3)	3 (3.8)	4 (5.1)	1 (1.3)	0 (0.0)	8 (2.5)
Gastroenteritis viral	0 (0.0)	4 (5.1)	2 (2.5)	0 (0.0)	1 (1.3)	7 (2.2)
Back pain	4 (5.1)	0 (0.0)	2 (2.5)	1 (1.3)	0 (0.0)	3 (0.9)

BID = twice daily; QD = once daily; N = number of subjects who were randomized and received at least 1 dose of investigational product
TEAE = treatment-emergent adverse event defined as an adverse event that occurred on or after first dose date and before or on the end of study date.
Subjects were analyzed by the actual treatment received.
TEAEs were coded using MedDRA version 13.1.
Source: Table 14-6.2.3

Nine subjects had serious adverse events during the study: 1 subject in the AMG 853 5-mg BID group, 3 subjects in the AMG 853 100-mg BID group, 3 subjects in the AMG 853 200-mg QD group, and 2 subjects in the placebo group (Table 14-6.3.2). Asthma was the only serious adverse event preferred term reported for > 1 subject, and occurred in 3 subjects (1-5 mg AMG 853 BID and 2-100 mg AMG 853 BID). Except for 1 event of fatal dilated cardiomyopathy in the 200-mg AMG 853 QD group, all serious adverse events were considered severe (CTCAE grade 3) (Listing 9). Of the non-fatal serious adverse events, 6 resulted in investigational product and/or study withdrawal, 1 (acute pancreatitis) in investigational product being altered or withheld, and 1 (asthma) no action taken with investigational product. No serious adverse events were considered by the investigators to be related to investigational product. A subject narrative for the fatal event appears below. Subject narratives for all serious adverse events are provided in Attachment 4.

Subject [redacted] (200-mg QD AMG 853), died during the study due to dilated cardiomyopathy. The subject was a [redacted] who was randomized and received the first dose of investigational product on [redacted]. [redacted] was last seen by the investigator on [redacted], and was reported as lost to follow-up on [redacted]. The subject was subsequently found dead in [redacted] home on [redacted]. An autopsy was performed on [redacted] which stated the cause of death as dilated cardiomyopathy and the manner as natural. The subject's last dose of investigational product prior to [redacted] death was administered on [redacted]; the subject received 65 doses of investigational product. The investigator reported that there was not a reasonable possibility that the event of death and dilated cardiomyopathy was related to investigational product. In the opinion of the sponsor, a causal relationship cannot be excluded considering the event occurred less than 30 days from the last dose of investigational product.

Subject [redacted]'s fatal adverse event is described in this report using the attribution given in the autopsy report, dilated cardiomyopathy, rather than the preferred term, congestive cardiomyopathy. Congestive cardiomyopathy is a clinical diagnosis that describes a clinical syndrome. Dilated cardiomyopathy is a diagnosis based on imaging or autopsy. Since the subject did not have a clinical diagnosis of congestive cardiomyopathy, the autopsy finding of dilated cardiomyopathy is a more appropriate term in describing the diagnosis associated with this fatal event.

There were 14 subjects who had adverse events of CTCAE grade 3 and above, and the incidence of these adverse events was slightly higher in the AMG 853 groups (3.8%) than in the placebo group (2.5%) (Table 14-6.8.1). Thirteen subjects had grade 3 adverse events (8 serious and 7 non-serious events), and 1 subject had a serious grade 5 adverse event; there were no grade 4 adverse events (Listing 6). Asthma was the only adverse event preferred term of grade ≥ 3 reported for > 1 subject, and occurred in 6 subjects in the AMG 853 groups (2 [5 mg BID] and 4 [100 mg BID]) (Table 14-6.8.1).

Sixteen subjects had adverse events leading to withdrawal of investigational product, and the incidence was similar for the AMG 853 groups (4.1%) and the placebo group (3.8%) (Table 14-6.6.1). Asthma and insomnia were the only adverse event preferred terms leading to withdrawal of investigational product reported for > 1 subject; asthma occurred in 7 subjects in the AMG 853 groups (3 [5 mg BID], 3 [100 BID], and 1 [200 mg QD]), and insomnia occurred in 2 subjects in the AMG 853 groups (1 [100 mg BID] and 1 [200 mg QD]) (Table 14-6.6.1).

There were 11 subjects who had adverse events leading to withdrawal from the study, and the incidence was similar for the AMG 853 groups (2.8%) and the placebo group (2.5%) (Table 14-6.1.1). Asthma was the only adverse event preferred term that lead to withdrawal from the study reported for > 1 subject, and occurred in 5 subjects in the AMG 853 groups (2 [5 mg BID],2 [100 mg BID], and 1 [200 mg QD]) (Listing 6). Overall, 6 subjects were withdrawn from the study for adverse events related to investigational product, and 5 subjects were withdrawn from the study for non-related adverse events.

Other Safety Results: There were no clinically significant changes in vital sign measurements (Tables 14-8.1.1 to 14-8.1.5). QTc prolongation was uncommon, not related to dose, and did not appear to be associated with adverse events (Table 14-8.2.1 and Table 14-8.5.2).

Eight subjects (1 [5 mg AMG 853 BID], 2 [25 mg AMG 853 BID], 1 [100 mg AMG 853 BID], 2 [200 mg AMG 853 QD], and 2 [placebo]) had treatment-emergent CTCAE grade 3 laboratory toxicities during the study (increased aspartate aminotransferase, increased glucose, decreased glucose, increased potassium, decreased total neutrophils, and increased urine protein) (Table 6, Listing 10, and Table 14-7.2.1). All laboratory toxicities were transient and there was no apparent dose relationship.

Table 6. All Subjects With Treatment-emergent CTCAE Grade ≥ 3 Laboratory Toxicities (Safety Analysis Set)

Laboratory Test	Subject No.	IP	Visit Day: Laboratory Value[a]	Completed IP/Study
Aspartate aminotransferase increased	[redacted]	5 mg BID	Day 29: 193 U/L	Yes
Glucose increased		200 mg QD	Day 85: 327 mg/dL	Yes
		25 mg BID	Day 57: 396 mg/dL	Yes
Glucose decreased		100 mg BID	Day 6: 33 mg/dL	Yes
Potassium increased		25 mg BID	Day 29: 6.1 mmol/L	Yes
		200 mg QD	Day 29: 6.2 mmol/L	Yes
Total neutrophils decreased		placebo	Day 56: 0.943 10^9/L	Yes
Urine protein		placebo	Day 36: 3+	No; adverse event[b]

BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; QD = once daily

[a] Laboratory values presented are the highest or lowest (depending on the category) for each subject.

[b] Subject [redacted] was withdrawn from investigational product and the study due to a serious adverse event of nephrolithiasis (duration study day 29 to 31). A subject narrative is provided in Attachment 4.

Toxicity grades were based on Common Terminology Criteria for Adverse Events version 4.0

Subjects with CTCAE grade ≥ 3 laboratory toxicities at both baseline and post-treatment are not included in this table.

Source: Listing 5 and Listing 10

Exposure: Compliance was consistently high across all treatment groups (mean duration of exposure ranged from 77.7 to 83.7 days out of the 12-week treatment period; dose compliances were over 98%) (Table 14-5.1). Subjects followed the meal instruction (morning doses [94.9% AMG 853, 95.9% placebo], or evening doses [95.5% AMG 853, 95.6% placebo]) (Table 14-5.2). The average dose of ICS at baseline was similar for all treatment groups (409.5 - 483.8 µg/day) (Table 14-5.3).

[redacted]

[redacted]

Conclusions: The study results indicate that after 12 weeks of treatment, AMG 853 is not effective in improving asthma composite symptom scores (measured by ACQ) in subjects with inadequately controlled asthma. Oral administration of AMG 853 demonstrated an acceptable safety and tolerability profile.