2. SYNOPSIS

Name of Sponsor: Amgen, Inc. One Amgen Center Drive, Thousand Oaks, CA 91320-1799

Name of Finished Product: Not applicable

Name of Active Ingredient: Dulanermin (AMG 951)

Title of Study: A Multicenter, Open Label, Randomized Study of AMG 951 in Subjects with Previously Untreated Stage IIIb/IV Non-Small Cell Lung Cancer (NSCLC) Treated with Chemotherapy with or without Bevacizumab (Primary Analysis Clinical Study Report)

Investigator(s) and Study Center(s): This study was conducted at 38 centers in 12 countries in Europe. A complete list of study investigators may be found in Appendix 4

Publication(s): Soria JC, Smit E, Khayat D, et al. Phase 1b study of dulanermin (recombinant Apo2L/TRAIL) in combination with paclitaxel, carboplatin, and bevacizumab in patients with advanced non-squamous non-small-cell lung cancer. *J Clin Oncol*. 2010;28:1527-1533.

Blackhall FH, Márk Z, Zatloukal P, et al. A randomized phase II study of paclitaxel (P) and carboplatin (C) ± bevacizumab (B) ± dulanermin (D) in non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2010; 28: 7s (suppl; abstr 7534).

Study Period: The first patient was enrolled on 20 June 2006 and, at the time of this report, the study is still ongoing.

Development Phase: 1b/2

Introduction and Objectives:

Lung cancer is the leading cause of cancer death. Globally, standard first-line treatment for subjects with advanced NSCLC is platinum-based combination chemotherapy that yields median survival times of approximately 8 to 10 months. The addition of the vascular endothelial growth factor inhibitor, bevacizumab, to first line therapy of advanced NSCLC in combination with paclitaxel and carboplatin offers approximately 20% improvement in both progression-free survival (PFS) and overall survival (OS). However, patients with squamous cell NSCLC and/or central nervous system metastases are unsuitable for treatment with bevacizumab.

Dulanermin (AMG 951; recombinant human Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand [Apo2L/TRAIL]) has been shown to induce apoptosis in vitro in lung cancer cell lines. In combination with carboplatin and paclitaxel, a significant antitumor response was established in NCI-H460 human lung cancer xenografts in nude mice.

The present study was designed to explore dulanermin's safety and tolerability in subjects with NSCLC in combination with chemotherapy ± bevacizumab. In phase 2 of the study, response rates following varying dose schedules of dulanermin administered in combination with chemotherapy ± bevacizumab were evaluated compared to standard of care in subjects with NSCLC.

Primary Objective:

Phase 1b:

To determine the maximum tolerated dose (MTD) (up to 8 mg/kg/day for 5 days treatment and up to 20 mg/kg/day for 2 days treatment) through safety and tolerability of multiple doses of dulanermin administered by intravenous (IV) infusion to subjects with NSCLC in combination with chemotherapy and bevacizumab.

Phase 2:

To evaluate differences or the absence thereof in the objective response rates (Complete Response [CR] and Partial Response [PR]) as assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) for dulanermin at varying dose schedules in combination with carboplatin/ paclitaxel ± bevacizumab for subjects with NSCLC.

Secondary Objectives:

Phase 1b:

- To characterize the pharmacokinetics (PK) of dulanermin

Phase 2:

- To evaluate overall response rate (CR, PR and Stable Disease [SD]; note this is a protocol-specific term referred herein as the clinical benefit rate [CBR]), PFS, time to response, duration of response, time to progression (TTP), and OS for dulanermin at varying dose schedules
- To evaluate the safety profile of dulanermin at varying dose schedules
- To evaluate the formation of anti-dulanermin antibodies
- To characterize the PK of dulanermin

Methodology: This was a phase 1b/2 multicenter, open-label, randomized study of dulanermin in subjects with previously untreated stage IIIb/IV NSCLC with chemotherapy with or without bevacizumab.

The phase 1b part of the study was designed to evaluate the safety, tolerability and PK of dulanermin in combination with bevacizumab, carboplatin, and paclitaxel. Bevacizumab-ineligible subjects (ie, those with squamous NSCLC and/or central nervous system [CNS] metastases) were not enrolled. Up to 6 subjects were enrolled in each of 4 cohorts. Subjects enrolled in the 4 phase 1b cohorts received chemotherapy plus bevacizumab in combination with various dosing regimens of dulanermin as follows:

Cohort A1: chemotherapy plus bevacizumab plus 4 mg/kg/day dulanermin for 5 days
Cohort A2: chemotherapy plus bevacizumab plus 8 mg/kg/day dulanermin for 5 days
Cohort A4: chemotherapy plus bevacizumab plus 15 mg/kg/day dulanermin for 2 days
Cohort A5: chemotherapy plus bevacizumab plus 20 mg/kg/day dulanermin for 2 days

The phase 2 part of the study was designed to evaluate the objective response rate, clinical benefit rate, PFS, time to response, duration of response, TTP and OS of dulanermin at varying doses and schedules in combination with carboplatin and paclitaxel with and without bevacizumab. Subjects were assigned to one of two treatment groups depending on their eligibility to receive bevacizumab. Cohorts for the phase 2 part of the study were as follows:

Cohort A: chemotherapy alone
Cohort B: chemotherapy plus 8 mg/kg/day dulanermin for 5 days
Cohort C: chemotherapy plus bevacizumab
Cohort D: chemotherapy, bevacizumab, plus 8 mg/kg/day dulanermin for 5 days
Cohort E: chemotherapy, bevacizumab plus 20 mg/kg/day dulanermin for 2 days

Number of Subjects Planned: Approximately 24 subjects were planned for the phase 1b part of the study and approximately 200 subjects (40 subjects per cohort) were planned for the phase 2 part of the study.

Number of Subjects Enrolled:

Phase 1b

Sex: male 52% (n = 13); female 48% (n = 12)

Age: mean (SD) age 55.6 (8.7) years

Ethnicity (Race): White or Caucasian 92% (n = 23); Asian 4% (n = 1); Other 4% (n = 1)

Phase 2

Sex: male 63% (n = 135); female 37% (n = 78)

Age: mean (SD) age 60.1 (8.6) years

Ethnicity (Race): White or Caucasian 99% (n = 210), Black or African American <1% (n = 1), Asian 1% (n = 2)

Diagnosis and Main Criteria for Eligibility: Subjects enrolled were ≥ 18 years old with histologically or cytologically confirmed Stage IIIb or IV NSCLC or with recurrent disease, who planned to receive up to 6 cycles of chemotherapy, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and life expectancy > 3 months. A complete list of study inclusion and exclusion criteria are provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Dulanermin was manufactured by [redacted] and packaged and distributed using Amgen clinical study drug distribution procedures. Dulanermin was supplied as a single use lyophilized formulation containing 100, 110 or 300 mg of dulanermin per 15, 10 or 50 mL glass vial, respectively. Dulanermin was administered as a continuous IV infusion over 60 minutes (±10 minutes). For 100 mg vials, manufacturing lot numbers used were [redacted], and [redacted]. For 300 mg vials, manufacturing lot numbers [redacted], and [redacted] were used. Manufacturing lot numbers for dulanermin 110 mg vials were [redacted] and [redacted] and were only used in the phase 1b part of the study.

Duration of Treatment: Following enrollment, all subjects in the phase 1b and phase 2 parts of the study were treated with up to 6 cycles of chemotherapy per their assigned cohort regimen. Each cycle lasted for 21 days plus additional days for recovery from treatment-emergent adverse events, if needed.

In the phase 2 part of the study, subjects enrolled into Cohort A, who completed up to 6 cycles of chemotherapy, were withdrawn from study treatment. Subjects enrolled into cohorts B, C, D and E who completed up to 6 cycles of chemotherapy ± bevacizumab ± dulanermin or who discontinued chemotherapy early due to chemotherapy-related toxicity continued to receive bevacizumab ± dulanermin, as per their assigned cohort regimen, until disease progression, study drug (bevacizumab ± dulanermin) intolerability, withdrawal of consent or until 24 months from the date the last subject was randomized, whichever occurred first.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Bevacizumab was manufactured by [redacted] and packaged and distributed by Amgen using Amgen clinical study drug procedures. It was supplied as single use only vials that were to be stored refrigerated at 2°C to 8°C and diluted to the appropriate dose just prior to use. The first dose was administered over 90 (+ 10) minutes with adjustment to the duration of infusion based on tolerance. Manufacturing lot numbers of bevacizumab administered were [redacted], and [redacted], and [redacted].

Study Endpoints

Phase 1b

Primary Endpoint: incidence of dose limiting toxicities (DLTs) and incidence and severity of adverse events (AEs)

Secondary Endpoint: PK endpoints included but were not limited to area under the concentration-time curve (AUC), maximum concentration (C_{max}), half-life ($t_{1/2}$), clearance, and volume of distribution

[redacted]

Phase 2

Primary Endpoint: Objective response rate (complete or partial response)

Secondary Efficacy Endpoints: OS, PFS, time to response, duration of response, TTP, and clinical benefit rate

Secondary Safety Endpoints: Incidence and severity of adverse events and clinical laboratory abnormalities, and incidence of anti-dulanermin antibody formation

Secondary PK Endpoints: PK endpoints included but were not limited to AUC, C_{max}, $t_{1/2}$, clearance and volume of distribution

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Statistical Methods: Complete details of the analyses carried out in this study are provided in the Statistical Analysis Plan (Appendix 2).

All analyses were conducted separately for subjects in the phase 1b and phase 2 parts of the study. Appropriate summary statistics were provided for all safety, efficacy, PK, and antibody data. For continuous variables, the mean, standard deviation, median, first and third quartiles, minimum, and maximum were calculated. For categorical variables, the frequency and percentage in each category were displayed.

For each study drug (dulanermin, bevacizumab, carboplatin, and paclitaxel), summary statistics were provided over the duration of the study. To minimize potential bias due to the open-label study design, unless stated otherwise, the efficacy analyses used blinded tumor evaluations conducted by a Central Reader. Due to the small sample size of each cohort and lack of randomization, a detailed analysis of efficacy data collected in phase 1b was not performed, but listings are provided. The Intent to Treat (ITT) Analysis Set included all randomized phase 2 subjects. The primary efficacy analysis used the ITT Analysis Set. Subjects were analyzed as randomized.

The primary endpoint for phase 2 was the objective response rate (CR + PR). The differences in responder rates (at any time point postdose) between cohorts B and A, cohorts D and C, and cohorts E and C and corresponding 95% confidence interval (CI) for the difference, calculated using the Newcombe-Wilson method, was estimated. For each pair-wise comparison specified, a 2-sided p-value indicating the strength of evidence against a null hypothesis of no difference was calculated using Fisher's exact test. Differences in responder rates at any time point post first dose between cohorts was expressed in terms of an odds ratio with corresponding exact 95% CI.

For OS, PFS, time to response, TTP, and duration of response, Cox's proportional hazard model was applied to estimate the hazard ratio and 95% CI for Cohort B to Cohort A, Cohort D to Cohort C, and Cohort E to Cohort C.

For each endpoint and cohort, the Kaplan-Meier method was used to estimate the median time to event, 95% CI for the median, 25th and 75th percentiles. Comparison between the cohorts, as specified for the Cox's proportional hazard model, for each endpoint (with the exception of the duration of response) was tested using a Log-rank test. A sensitivity analysis of PFS was conducted using data recorded by the individual investigators rather than the central reader.

The Safety Analysis Set for the phase 1b part of the study included all subjects who received at least one dose of dulanermin. The DLT Assessment Set included all subjects in phase 1b of the study who received at least one dose of dulanermin and completed the DLT assessment window (21 days following the first dose of dulanermin). The Safety Analysis Set for the phase 2 part of the study included all randomized phase 2 subjects who received at least one dose of any drug administered as protocol therapy. The primary analysis of safety used the Safety Analysis Set.

Pharmacokinetic parameters for each study drug were summarized by cohort and for each cycle using mean, standard deviation, median, quartiles, minimum and maximum. Where data permitted, the PK parameters of dulanermin were calculated for each subject using non-compartmental analysis.

Summary of Results:

The results for the phase 1b part of the study are based on the primary analyses of the study with a data cutoff date of 21 March 2008. A primary analysis of the phase 2 data was carried out on a data set with a cut-off date of 27 May 2009; however, as some of the efficacy data (eg, OS) were immature at that time, an updated analysis of phase 2 efficacy and safety was performed with a data cut-off date of 21 October 2009. Data for the phase 2 part of the study presented herein are derived from the updated analysis.

Subject Disposition:

Phase 1b: A total of 25 subjects were enrolled. One subject was not treated with dulanermin, bevacizumab, or chemotherapy and was excluded from the Safety Analysis Set and the DLT Assessment Set. Seventy-two percent of subjects completed 6 cycles of dulanermin, and 72% completed 6 cycles of bevacizumab. The most common reasons for discontinuing dulanermin or bevacizumab were adverse events (12% and 8%, respectively) and disease progression (12% each). At the last long-term follow-up prior to the primary analysis, 28% of subjects had died.

Phase 2: A total of 213 subjects were randomized in the phase 2 part of the study and were included in the ITT Analysis Set. Dulanermin was discontinued by 8% of subjects: 3% due to adverse events, 3% due to disease progression, 1% due to administrative decision, and 1% due to subject request or other (< 1% each). Bevacizumab was discontinued by 5% of subjects: 4% due to adverse events and 1% due to disease progression. At the time of the data cutoff, 12% of subjects had completed investigational product and chemotherapy and 43% had discontinued investigational product and chemotherapy. The percentage of subjects who discontinued investigational product and chemotherapy was consistent across treatment cohorts. Among subjects who discontinued treatment, 55% had died.

At the time of data cutoff for the updated analysis, 94% of subjects had discontinued the study. Principal reasons for discontinuation were: 45% due to disease progression, 16% due to adverse events, 9% due to protocol specified criteria, and 8% due to death. Among the 66% study subjects who entered long-term follow-up, 51% were alive at the time of the data cut-off for the updated analysis.

Efficacy Results:

Phase 1b: Due to the limited sample size within each cohort and the lack of randomization, efficacy was not formally analyzed.

Phase 2: There were no significant differences noted between the cohorts in any measure of efficacy using the updated analyses as per the Central Reader.

The objective response rate (CR + PR) was 41% (n = 88 subjects with PR) with no complete responses. There were no significant differences identified in the objective response rate between cohorts.

Cohort	Test	Reference	P value
Cohort B vs Cohort A	38.1%; 95% CI: 23.6, 54.4	39.0%; 95% CI: 24.2, 55.5	1.000
Cohort D vs Cohort C	39.5%; 95% CI: 25.0, 55.6	50.0%; 95% CI: 34.6, 65.4	0.391
Cohort E vs Cohort C	39.5%; 95% CI: 25.0, 55.6	50.0%; 95% CI: 34.6, 65.4	0.391
Cohort D + E vs Cohort C	39.5%; 95% CI: 29.2, 50.7	50.0%; 95% CI: 34.6, 65.4	0.268

There were no statistically significant differences identified in the clinical benefit rate (CR + PR + SD) between cohorts. In the bevacizumab-ineligible cohorts (n = 66 subjects), the clinical benefit rate was higher in cohort B (88%) which received dulanermin and chemotherapy than in cohort A (71%) which received chemotherapy alone. In the bevacizumab-eligible cohorts (n = 109 subjects), the clinical benefit rate in the combined dulanermin-treated cohorts (D+E) and the chemotherapy cohort (C) was 84% each.

Cohort	Test	Reference	P value
Cohort B vs Cohort A	71.4%; 95% CI: 55.4, 84.3	87.8%; 95% CI: 73.8, 95.9	0.101
Cohort D vs Cohort C	79.1%; 95% CI: 64.0, 90.0	84.1%; 95% CI: 69.9, 93.4	0.590
Cohort E vs Cohort C	88.4%; 95% CI: 74.9, 96.1	84.1%; 95% CI: 69.9, 93.4	0.757
Cohort D + E vs Cohort C	83.7%; 95% CI: 74.2, 90.8	84.1%; 95% CI: 69.9, 93.4	1.000

At the time of data cutoff, 56% (n = 119) of subjects had died due to any cause and 44% (n = 94) of subjects were censored. The proportion of subjects who died due to any cause was generally similar across treatment cohorts. The median OS was 10.0 months (95% CI: 8.2, 13.4) and 14.3 months (95% CI: 11.9, 16.6) in bevacizumab-ineligible and bevacizumab-eligible subjects, respectively. There were no significant differences in overall survival between treatment cohorts. The adjusted hazard ratios for Cohort A versus Cohort B, Cohort D versus Cohort C, Cohort E versus Cohort C, and combined Cohorts D and E versus Cohort C ranged from 1.040 (95% CI [0.585, 1.849]) (p = 0.886) to 1.127 (95% CI [0.644, 1.971]) (p = 0.636).

The median PFS across all cohorts was 6.8 months (95% CI [6.1, 8.0]). The median PFS was 5.8 months; (95% CI [5.4, 6.7]) and 8.5 months; (95% CI [6.8, 9.9]) in bevacizumab-ineligible and bevacizumab-eligible subjects, respectively. There were no significant differences in PFS observed between treatment cohorts. The adjusted hazard ratios for Cohort B versus Cohort A, Cohort D versus Cohort C, Cohort E versus Cohort C, and combined Cohort D + E versus Cohort C ranged from 0.838 (95% CI [0.493, 1.425]) (p = 0.478) to 0.904 (95% CI [0.548, 1.492]) (p = 0.645).

Pharmacokinetic Results:

Phase 1b and Phase 2: In general, dulanermin exhibited a dose-proportional increase in exposure (AUC_{inf} and C_{max}) in Cycle 1 as the dose increased from 8 to 20 mg/kg, while exposures at 4 mg/kg were lower than dose proportional. Dulanermin pharmacokinetic parameters were similar between Cycles 1 and 3. The steady state volumes of distribution were consistent regardless of dose or cycle. The mean half-life values were between 21 and 41 minutes, which agree with the small volume of distribution and rapid clearance. Dulanermin serum concentration levels from the phase 2 part of this study were similar to the phase 1b data.

Dulanermin did not appear to have an impact on bevacizumab concentration. Due to the small sample size in each cohort, no evaluation of mean peak and trough plasma platinum concentrations (total and unbound) could be made. Paclitaxel peak concentrations during cycles 2 and 4 were generally in the same range among cohorts, although they appeared slightly higher when comparing dulanermin treatment groups to placebo groups.

Antibody Assay Results:

Phase 1b: Anti-dulanermin antibodies were not identified in any subject in this phase of the study.

Phase 2: Ten subjects (8.5%) in the phase 2 part of the study tested positive for anti-dulanermin antibodies. All antibody-positive subjects were in the bevacizumab-eligible cohorts (4 subjects in Cohort D and 6 subjects in Cohort E). In each case, antibodies were detected at cycle 5 or later.

Safety Results:

Phase 1b: The mean average weight-adjusted dose of dulanermin delivered per infusion was consistent with the intended dose of dulanermin assigned to each treatment cohort. The mean relative dose intensity (RDI) was 0.95 overall and was generally consistent across treatment groups.

The Safety Analysis Set consisted of 24 subjects (6 from each cohort). Treatment-emergent adverse events were reported in 100% (n = 24) of subjects. One fatal adverse event of general physical health deterioration, considered by the investigator as not related to investigational product, was reported in Cohort A1.

Adverse events reported by the investigators as related to dulanermin occurred in 96% of subjects (83% - Cohort A1, 100% - Cohort A2, 100% - Cohort A4, and 100% - Cohort A5). The majority of these events were mild to moderate in severity with the exception of constipation which was grade 3. There were no grade 4 or 5 dulanermin-related adverse events. Serious adverse events reported by the investigators as related to dulanermin were reported in 8% (n = 2) of subjects (1 subject in Cohort A2 [relapse of perineal abscess] and 1 subject in Cohort A5 [tachycardia, constipation, intestinal perforation and body temperature increased]).

Adverse events reported by the investigators as related to bevacizumab occurred in 92% of subjects) (67% - Cohort A1, 100% - Cohort A2, 100% - Cohort A4, and 100% -Cohort A5). Most of these events were mild or moderate in severity with the exception of grade 3 constipation, and grade 4 pulmonary embolism. There were no grade 5 bevacizumab-related adverse events. Serious adverse events reported by the investigators as related to bevacizumab occurred in 13% of subjects including 1 subject each in Cohort A2 (relapse of perineal abscess), A4 (pulmonary embolism), and A5 (tachycardia, constipation, intestinal perforation and body temperature increased).

Adverse events leading to withdrawal of investigational product (dulanermin or bevacizumab) or removal from the study occurred in 13% of subjects and were evenly distributed among cohorts. Dulanermin- or bevacizumab-related adverse events resulting in withdrawal from the study occurred in 2 subjects (grade 2 intestinal perforation and grade 1 arthralgia).

There were no DLTs identified and an MTD was not reached.

Phase 2: There were 83 and 130 subjects enrolled in the bevacizumab-ineligible cohorts (A and B) and bevacizumab-eligible cohorts (C, D and E), respectively. Of these, 96% and 95%, respectively, received at least 1 dose of study drug. The 5% of subjects who did not receive study drug were excluded from the Safety Analysis Set. The mean average weight-adjusted dose of dulanermin delivered per infusion was consistent with the intended dose of dulanermin assigned to each treatment cohort. The mean relative dose intensity was 0.94 overall and was generally consistent across treatment groups.

Treatment-emergent adverse events were reported for 95% of subjects and the subject incidence was similar across treatment cohorts. The most commonly reported adverse events (ie, those reported in ≥ 20% subjects) included nausea (35.5%), alopecia (34.5%), neutropenia (27.6%), anemia (26.1%), diarrhea (24.1%), constipation (23.2%), asthenia (22.7%), fatigue (22.2%), decreased appetite (21.7%), and dyspnea (21.2%). Treatment-emergent adverse events considered related to dulanermin by the investigator were reported in 46%, 53% and 54% of subjects in Cohort B, D, E, respectively. Treatment-emergent adverse events considered related to bevacizumab by the investigator were reported in 35% of subjects and were similar across treatment cohorts eligible to receive bevacizumab (Cohort C, D and E).

Treatment-emergent serious adverse events were reported for 43% of subjects. Among bevacizumab-ineligible subjects (Cohorts A and B), serious adverse events and grade 3, 4, or 5 adverse events were reported in a greater proportion of subjects randomized to Cohort B (56% and 77%, respectively) than Cohort A (27% and 41%, respectively). Serious adverse events and grade 3, 4 or 5 adverse events occurred in 45% and 67% of bevacizumab-eligible (Cohorts C, D and E), respectively, and were reported with similar frequency across treatment cohorts. Serious, dulanermin- and buvacizumab-related adverse events occurred in 5% and 6% of subjects, respectively.

Fatal adverse events were reported for 14.8% of subjects in the phase 2 part of the study. Fatal adverse events considered by the investigator to be at least possibly related to dulanermin were grade 5 hemoptysis in 2 subjects (both in Cohort B). A fatal adverse event of intestinal perforation in 1 subject in Cohort C was reported as related to bevacizumab by the investigator. There were 4 cases of fatal hemoptysis in Cohort B, including 1 subject who had discontinued investigational product 6 months prior, and 1 case of fatal pulmonary embolism/infarction in Cohort D. Subsequently, 6 subjects in Cohort B with cavitating lesions or lesions > 8 cm in greatest diameter were withdrawn from the study. Additional details are provided in Section 7.11.

Adverse events leading to discontinuation of investigational product or withdrawal from the study were reported in 15% of subjects and were reported consistently across treatment groups. Dulanermin- and bevacizumab-related adverse events leading to discontinuation of investigational product or withdrawal from the study were reported in 4% and 3% of subjects, respectively.

Conclusions:

This study did not show any evidence of clinical benefit attributable to dulanermin when added to chemotherapy (carboplatin + paclitaxel) or chemotherapy in combination with bevacizumab in subjects with NSCLC, as indicated by a lack of differences in response rates, PFS, or OS. The addition of dulanermin to combination chemotherapy resulted in more frequent adverse events in the bevacizumab ineligible cohorts, but the incidence of adverse events was similar among the cohorts of bevacizumab eligible subjects.