C79102, 2005-001731-30

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

Sponsor:

UCB Celltech

208 Bath Road

Slough, Berkshire, SL1 3WE

England

Official study title:

A Two-Part, Open Label Phase II Trial: Part One, Dose Escalation Safety; Part Two, Randomized/Comparing CDP791 (10 or 20 mg/kg) Plus Carboplatin/Paclitaxel With Carboplatin/Paclitaxel Alone in Subjects With Locally Advanced or Metastatic (Stage IIIb or Stage IV) Non-Squamous, Non-Small-Cell Lung Cancer

2. SYNOPSIS

Name of Sponsor/Company: UCB Celltech, the UK branch of UCB SA	Individual Study Table Referring to Module 5	*(For National Authority Use only)*
Name of Finished Product: Not Applicable	Volume:	
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Title of Study: A Two-Part, Open Label Phase II Trial: Part One, Dose Escalation Safety; Part Two, Randomized/ Comparing CDP791 (10 or 20 mg/kg) Plus Carboplatin/Paclitaxel With Carboplatin/Paclitaxel Alone in Subjects With Locally Advanced or Metastatic (Stage IIIb or Stage IV) Non-Squamous Non-Small-Cell Lung Cancer – Results from the first database lock (ie, 24-Week analysis)		
Principal Investigator: Prof [redacted]		
Study Center(s): This was a multicenter study involving 26 sites in 3 countries: [redacted]		
Publication: None at the time of reporting		
Studied Period (years): September 2005 – ongoing	**Phase of Development:** Phase II	
Objectives: **Part I:** To evaluate safety and tolerability of CDP791 given at 10 and 20 mg/kg in combination with chemotherapy - carboplatin/paclitaxel (CT) in subjects with locally advanced and metastatic (Stage IIIb with malignant pleural effusion or Stage IV) non-squamous non-small-cell lung cancer (NSCLC). **Part II:** To compare the tumor response rate (RR) of CDP791 given at 10 and 20 mg/kg in combination with CT with that of CT alone in subjects with locally advanced, metastatic or recurrent (Stage IIIb or Stage IV) non-squamous NSCLC. **Part I and II treatment extension:** To evaluate the safety of long term CDP791 therapy in subjects who have completed Part I or II without disease progression. To evaluate the efficacy of long term CDP791 therapy. **Methodology:** The study was divided into 2 parts: Part I (dose escalating), and Part II (Open Label randomized). Protocol amendment 3 (07-Jul-2006) added a Treatment Extension Phase enabling those subjects without disease progression at the end of Part I or Part II of the study to continue treatment with CDP791. Part I comprised an initial cohort of 3 subjects dosed with CDP791 10 mg/kg + CT. Dose-limiting toxicity (DLT) was assessed up to completion of 14 days of combination therapy (CDP791+ CT) in Cycle 2. When this dose was assessed as well tolerated, a second cohort of 6 subjects was opened at CDP791 20 mg/kg + CT. Dose-limiting toxicity was assessed, as in Part I and when the CDP791 20 mg/kg dose was assessed as well tolerated, Part II was opened to 156 subjects. In both parts of the study, subjects were initially given 6 cycles (doses) of CDP791 treatment combined with CT, each cycle lasting 21 days. CDP791-treated subjects with stable disease or better at the Cycle 6 tumor assessment were eligible to receive continued 3-weekly cycles of CDP791 monotherapy at the same dose (either 10 mg/kg or 20 mg/kg) to a maximum of 12 additional cycles, or until disease progression. Subjects		

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in the CT alone arm who developed disease progression at any time were eligible to receive CDP791 10 mg/kg monotherapy given in 3-weekly cycles until further disease progression or up to a maximum of 18 cycles of CDP791. Subjects with stable disease or better at the end of Part I/II were eligible for the treatment extension phase and received CDP791 therapy, at the same dose level they had received previously, until disease progression.

Number of Subjects:
Across Parts I and II of the study, recruitment was planned at 165 subjects. The recruitment target was achieved and data from all 165 subjects were analyzed.
With a total number of 156 response-evaluable subjects, Part II of the study was designed to have 80% power to detect an increase in the RR of 25% (ie, from 30% to 55%) in the pooled CT + CDP791 treated arms versus CT alone, using a 2-sided, $\alpha = 0.05$ level, chi-square test.

Diagnosis and Main Criteria for Inclusion:

- Male and female subjects, aged 18 years or above, with histologically or cytologically confirmed Stage IIIb (with malignant pleural effusion, or if no pleural effusion was present subjects who were not candidates for combined modality therapy or who were being treated at centers where combined modality therapy was not standard of care), Stage IV, or recurrent non-squamous, non-small-cell lung carcinoma. Mixed tumors were categorized by the predominant cell type unless small cell elements were present in which case the subject was ineligible.
- Subjects with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and a life expectancy of at least 3 months.
- Subjects with measurable disease defined by the response evaluation criteria in solid tumors (RECIST) as at least 1 lesion that is measurable in 1 dimension
- Subjects able to understand the information provided to them and give written informed consent.

In addition to meeting these inclusion criteria, subjects were to be excluded if they met any of the 17 predefined exclusion criteria, including having had previous chemotherapy or immunotherapy (registered, off label or experimental).

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
CDP791	CDP791 diluted (10 mg/kg or 20 mg/kg) in 0.9% saline given as a 200 mL intravenous (iv) infusion over approximately 60 minutes following administration of standard chemotherapy (see comparator section below).	[redacted]

Duration of Treatment:
Subjects initially received 6, 3-weekly cycles of chemotherapy with or without CDP791. CDP791-treated subjects with stable disease or better at the Cycle 6 tumor assessment were eligible to continue to receive 3-weekly cycles of CDP791 monotherapy at the same dose to a maximum of 12 additional cycles, or until disease progression. Subjects with stable disease or better at the end of Part I or Part II were eligible to enter the treatment extension phase.

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Subjects in the CT alone arm of Part II who developed disease progression at any time were eligible to receive CDP791 10 mg/kg monotherapy given in 3-weekly cycles until further disease progression or up to a maximum of 18 cycles (54 weeks).
Subjects in the treatment extension phase were eligible to continue CDP791 therapy, at the same dose level they had received previously, until disease progression.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
Combined chemotherapy: carboplatin/paclitaxel	Paclitaxel: 200 mg/m^2 (with premedication) given iv over 3 hours, and carboplatin AUC=6.0: given iv over 15 to 30 minutes immediately after paclitaxel.	Commercially available batches

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was tumor RR. Tumor status was assessed using RECIST. Responses were assessed by an independent review facility (BioImaging), blinded to treatment assignment.
Secondary efficacy variables included: progression free survival (PFS); overall survival (OS); time to treatment failure (TTF); time to response and duration of overall response.
Health-related quality of life (HRQOL) was assessed during Part II of the study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core questionnaire, version 3.0 (EORTC QLQ-C30) supplemented with the Lung Cancer specific module (EORTC QLQ-LC13).

Pharmacokinetics and Pharmacodynamics:

Pharmacokinetic (PK) assessments were based on the plasma concentrations of carboplatin, paclitaxel and CDP791. Plasma levels of soluble vascular endothelial growth factor receptor 2 (VEGFR-2) were measured to explore the use of this variable as a marker of biological response.

Safety:

Safety was assessed by AE reporting, physical examination, vital sign measurement, laboratory safety tests, ECOG performance, concomitant medications and body mass. Laboratory tests included: hematology analyses; coagulation tests; serum biochemistry; urinalysis; pregnancy testing in women of childbearing potential; measurement of antibodies to CDP791 in plasma (performed on samples collected for PK analysis).

Statistical Methods:

Three database locks were planned corresponding to: 1) the main analysis at the time all subjects were either discontinued or on study for at least 24 weeks; 2) the analysis of the study at the time when 80% of Part II subjects had died or experienced disease progression as defined by independent radiological review performed by BioImaging; 3) the final updates of safety and efficacy at the time when 75 to 80% of subjects were known to have died. Data from the first database lock are presented in this synopsis.
Summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics were tabulated.
All statistical tests were performed using a 2-sided 5% level of significance unless otherwise specified.
The primary and secondary efficacy analysis was based on assessments made by BioImaging.
Primary efficacy analysis: Primary analysis of RR, was the comparison between the pooled CDP791 10 mg/kg or 20 mg/kg + CT treatment arms and the CT alone treatment arm, using a 2-sided

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Chi-square test. The comparison was also performed using a Cochran-Mantel-Haenszel (CMH) test stratified by country and disease stage.
A logistic regression analysis for response was performed, stratified by country and included treatment and the following prognostic factors: age, histological subtype and disease stage.
The tumor RR, along with its exact 2-sided 95% confidence interval, was computed within each treatment arm. A 2-sided 95% confidence interval for the difference of RR between these 2 treatment arms was computed.
Secondary efficacy analyses: Progression free survival was compared between the pooled CDP791 10 mg/kg or 20 mg/kg + CT treatment arms and the CT alone treatment arm using a 2-sided log-rank test stratified for country and disease stage. The corresponding hazard ratio of CDP791 (10 mg/kg or 20 mg/kg) + CT versus CT alone and associated 2-sided 95% confidence intervals, were estimated using an unadjusted Cox proportional hazards model stratified for country and disease stage.
Further analyses of PFS were performed using adjusted and unadjusted Cox proportional hazards model stratified by country. The adjusted Cox proportional hazards model included treatment and the following prognostic factors: age, histological subtype and disease stage.
Progression free survival functions for each treatment arm were estimated using the Kaplan-Meier product-limit method and 2-sided 95% confidence intervals for the median PFS were computed.
Time to treatment failure and OS were analyzed using the same statistical methodology as for PFS.
Descriptive analyses were performed of time to response and duration of overall response based on the BioImaging assessments. Median and 95% confidence intervals were estimated for the duration of overall response based on Kaplan-Meier estimates.
Exploratory analyses: At an exploratory level, comparisons of CDP791 10 mg/kg + CT versus CT alone, and of CDP791 20 mg/kg + CT versus CT alone, were performed, regarding all endpoints, using the same statistical methodology as described for primary and secondary analyses.
The effects of demographic and Baseline prognostic factors on RR and PFS based on the BioImaging assessment in addition to OS were examined and included : gender, disease stage, Baseline sum of the longest diameters of all target lesions, age, histological subtype, number of metastatic sites, and prior lung surgeries. Descriptive summaries of RR were produced for each level of the Baseline variables for each treatment arm. For PFS and OS, the median time to event were derived for each level of the Baseline variables for each treatment arm. Kaplan-Meier plots of PFS and OS by Baseline variable and treatment arm were produced.
The effect of each of the Baseline variables on RR was assessed using logistic regression models. Cox proportional hazards models were used for PFS and OS. For each variable, a regression model included factors for treatment and the individual variable; an additional model was constructed with the interaction term added. The odds ratio or hazard ratio (depending on the type of regression model) and associated 2-sided 95% confidence interval for the model parameters were presented. All models were stratified by country. A final multivariate model was constructed using a forward selection procedure, as follows:

- The initial model included treatment and most significant prognostic factor (if any). Additional variables were selected in order of significance when added to the updated model.
- The final model was defined when no more significant factors could be added.
- The treatment interaction with the prognostic factors in the final model was investigated.

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The following analyses, specified in the original SAP and SAP Amendment 1, were not performed:

- Tumor status by cycle based on BioImaging data – removed as tumor status by cycle differed by blind reader as only differences in overall response were adjudicated.
- Summary of actual dose administered, dose intensity and cumulative dose administered – removed due to unreliability of data.
- Electrocardiogram measurements listing – removed as measurements were not recorded on Case Report Form.
- AEs occurring within 2 hours and time to onset of selected treatment-emergent adverse events (TEAEs) – removed due to high number of partial onset dates.
- Duration of selected TEAEs – removed as it was not valid to calculate duration of preferred term groupings and interpretation of duration summaries of individual preferred terms was meaningless due to low numbers of each event.

In addition, statistical analysis of selected TEAEs was based on preferred term categories instead of individual preferred terms.

HRQOL analyses: Descriptive statistics (mean scores, standard deviations [SD], median, range) of the change from Baseline were generated for the EORTC QLQ-C30 and the EORTC QLQ-LC13 scales at Cycle 1 (Day 7) and Day 0 on each of Cycles 3, 6, 10, 14, 18 or Withdrawal Visit, for each treatment group (CDP791 10 mg/kg or 20 mg/kg + CT and CT alone).

Pharmacokinetic and Pharmacodynamic analyses: Non-compartmental PK analyses were performed for CT during Cycles 1 and 2 of Part I of the study. For CDP791 a population PK model with NONMEM (non-linear mixed effect model) software is under development and will be reported separately. This population PK analysis was performed at each cycle.

Observed plasma concentrations for each drug were listed and summarized by descriptive statistics (number [N] of non missing observations, geometric mean and its coefficient of variability [CV], mean, SD, minimum, median, maximum) per dose group (10 mg/kg, 20 mg/kg). For paclitaxel and carboplatin plasma concentration, descriptive statistics were also presented over the 2 dose groups.

Individual and average (geometric mean with SD) plasma concentration (µg/mL) versus time (days) profiles were depicted for each product using linear-linear and logarithmic-linear scales.

Further to the population PK analysis for CDP791, exposure/response and exposure/toxicity models are under development and will be reported separately.

Individual plasma concentrations of soluble VEGFR-2 were summarized by descriptive statistics (N, mean, SD, CV, geometric mean, minimum, median, maximum) per study part and group (dose) and in Part II per gender at each time-point.

Safety analyses: Safety parameters were summarized for each of the 3 treatment arms. Toxicity rates of selected AEs, based on preferred term categories and laboratory tests results were compared between the pooled CDP791 (10 mg/kg or 20 mg/kg) + CT treatment arms (also given for 10 mg/kg and 20 mg/kg arms separately) and the CT alone treatment arm. Comparisons were made for any occurrence and severe events only (denoted as worst Common Toxicity Criteria (CTC) grade per subject being 3 or 4 for laboratory parameters and worst CTC grade per subjects being 3 or 4 or classified as severe in intensity for AEs) using Fisher's exact test. Relative risk and 95% confidence intervals were also provided.

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SUBJECT DISPOSITION:

In Part I of the study, 15 subjects were screened and 9 subjects were given either CDP791 10 mg/kg + CT (3 subjects) or CDP791 20 mg/kg + CT (6 subjects). Eight subjects completed Chemotherapy Period of Part I while 1 subject in the CDP791 20 mg/kg + CT group discontinued due to lack of efficacy (Table 14.1.1:5). Seven subjects entered long-term CDP791 monotherapy: 2 subjects from the CDP791 10 mg/kg + CT group and 5 subjects from the CDP791 20 mg/kg + CT group. One subject from the CDP791 20 mg/kg + CT group completed monotherapy. The 6 remaining subjects discontinued due to lack of efficacy (3 subjects), withdrawal of consent (1 subject) and other reasons (2 subjects; decision of study staff and progression of disease). There were no protocol violations (Table 14.1.1:5).

In Part II of the study, 216 subjects were screened and 156 subjects were randomized to treatment with either CT (50 subjects), CDP791 10 mg/kg + CT (53 subjects) or CDP791 20 mg/kg + CT (53 subjects). Eighty-six subjects completed the Chemotherapy Period (Table 14.1.1.1). Seventy subjects discontinued the Chemotherapy Period: 28 subjects in the CT group, 23 subjects in the CDP791 10 mg/kg + CT group and 19 subjects in the CDP791 20 mg/kg + CT group. The main reasons for discontinuing treatment were AEs (19 subjects), loss of efficacy (13 subjects) and death (7 subjects). All other reasons for discontinuing treatment may be found in (Table 14.1.1.1). Treatment discontinuations due to AEs during the Chemotherapy Period were as follows: 9 subjects in the CT group, and 5 subjects in each of the CDP791 10 mg/kg and 20 mg/kg + CT groups. Of the 7 subjects that died, 1 was in the CT group (death due to disease) and 3 subjects were in each of the CDP791 10 mg/kg (2 due to unknown reasons and 1 due to disease) and 20 mg/kg + CT groups (2 due to disease and 1 due to pneumonia). One subject in each of the CT and CDP791 10 mg/kg + CT groups discontinued due to a protocol violation (brain metastases and progressive disease assessed clinically at Cycle 6 as no scans performed beyond Cycle 3, respectively). Sixty-eight subjects from Part II entered the long-term CDP791 Monotherapy Phase. At week 24, 1 subject from the CDP791 10 mg/kg + CT group had completed monotherapy, 30 subjects (5 from the CT group and 12 and 13 from the CDP791 10 mg/kg and 20 mg/kg + CT groups, respectively) were still on monotherapy, and 37 subjects had discontinued from monotherapy (8 subjects from the CT group and 13 and 16 subjects, respectively from the CDP791 10 mg/kg + CT and CDP791 20 mg/kg + CT groups). The main reasons for discontinuing monotherapy were: other (17 subjects – including progression of disease), loss of efficacy (12 subjects), AEs (4 subjects), and death (2 subjects – 1 in each of the CT and CDP791 20 mg/kg + CT groups and both due to disease) (Table 14.1.1.1). There were no discontinuations due to protocol violations. 43 subjects had died at the time of database lock: 39 due to disease progression, 2 for whom cause of death was unknown (but who had AEs leading up to death) and 2 due to other reasons (lung edema and circulatory insufficiency in 1 subject and pneumonia in the other) (Listing 16.2.6:2).

DEMOGRAPHICS:

At Screening, the mean age of all randomized Part II subjects was 60.15 years, range 35.1 to 83.2 years. 67.3% of subjects were less than 65 years old. 55.1% were male and all subjects were Caucasian. Mean weight of the study population was 68.0 (± 13.2) kg, and mean body surface area (BSA) was 1.76 (± 0.19) m^2. All subjects were capable of self care, with 28.8% of subjects having an ECOG PS of 0 and 71.2% having a PS of 1. Of note is the imbalance in the CDP791 20 mg/kg + CT group which had the highest percentage of female subjects (54.7%), subjects aged less than 65 years (75.5%) and ECOG PS of 0

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(32.1%) compared to either the CT group or the CDP791 10 mg/kg + CT group (Table 14.1.2:1). 82.1% of subjects had Stage IV tumors with the lowest percentage being in the CDP791 20 mg/kg + CT group (77.4%) (Table 14.1.2:2).
Overall, 82.1% of subjects had adenocarcinoma with the highest percentage being in the CDP791 20 mg/kg + CT group (92.5%). Mean time, at entry into the study, since cancer diagnosis was 6.45 (± 16.96) months: 6.00 (± 15.28) months in the CT group; 7.25 (± 20.76) months in CDP791 10 mg/kg + CT and 6.10 (± 14.43) months in the CDP791 20 mg/kg + CT group (Table 14.1.2:2).

EFFICACY RESULTS:
Due to the high number of discrepancies between tumor response and tumor measurements recorded by the Investigator, endpoints based on Investigator-assessment were not performed.
Primary Analysis of Efficacy: The primary efficacy endpoint for the study was tumor RR in Part II subjects which was assessed using data from an independent assessor, BioImaging.

Statistical Analysis of Tumor Response Rate – BioImaging Assessment – Frequency Table Analysis – All Randomized Part II Subjects

	CT (N=50) n (%)	**CT + CDP791 (N=106) n (%)**	**CT + CDP791 10 mg/kg (N=53) n (%)**	**CT + CDP791 20 mg/kg (N=53) n (%)**
Response rate	10 (20.0)	28 (26.4)	12 (22.6)	16 (30.2)
Complete responder	0	0	0	0
Partial responder	10 (20.0)	28 (26.4)	12 (22.6)	16 (30.2)
Exact 95% CI for response rate within treatment	[10.0; 33.7]	[18.3; 35.9]	[12.3; 36.2]	[18.3; 44.3]
Difference of response rate vs CT 95% CI for the difference of response rate vs CT		6.4 [-7.7; 20.5]	2.6 [-13.5; 18.8]	10.2 [-6.8; 27.2]
p-value (Chi-square test [a])		0.384	0.744	0.234
p-value (CMH test [b])		0.409	0.782	0.228

[a] Two-sided Chi-square test. Fisher's Exact test presented when number of responders in a treatment group is <5.
[b] CMH test stratified by country and disease stage (3 levels: Stage IIIb without malignant pleural effusion versus Stage IIIb with malignant pleural effusion or Stage IV or recurrent).
Response rate = number of subjects whose best overall response is a complete or a partial response, divided by the number of subjects in this population.
CT: chemotherapy carboplatin/paclitaxel; CI: Confidence interval; vs: versus; CMH: Cochran-Mantel-Haenszel.
Source: Table 14.2.1:1

All Part II subjects with response were partial responders to treatment. There were no complete responders. A 25% increase in RR in the pooled CDP791 + CT groups compared to the CT group, as defined in the protocol, was not achieved. The tumor RR was 22.6% and 30.2% in the CDP791 10 mg/kg and 20 mg/kg + CT groups, respectively, compared to 20.0% for the CT group.

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The effects of demographic and baseline prognostic characteristics on RR based on the BioImaging assessment were examined and included : gender, disease stage, Baseline sum of the longest diameters of all target lesions, age, histological subtype, number of metastatic sites, and prior lung surgeries. The analyses showed that the RR was greater for the pooled CDP791 + CT group for all subsets compared to the CT group, except for subjects with <2 metastatic sites, prior lung surgeries, or aged <65 years. None of demographic and Baseline prognostic characteristics were statistically significant at the 5% level when added to the logistic regression models along with treatment. Further exploratory analyses to investigate potential differences in RR due to demographic imbalances will be explored in the second interim analysis when the data are more mature as further scans are available.

Note: 2 subjects ([redacted] and [redacted]) with protocol deviations (no target lesions at Baseline according to BioImaging assessment) were included in the response-evaluable population in error since their deviations were not appropriately flagged at the time of database lock.

Secondary Analysis of Efficacy:

Note: Date of death for subject [redacted] was incomplete therefore the record was not included in the statistical analysis of secondary endpoints.

Progression free survival: The number of subjects with the event of disease progression or death was 24 (48.0%) in the CT group and 56 (52.8%) in the pooled CDP791 + CT groups. Consequently, the information level for this data cut is too low for definitive analysis, and interpretation of these PFS results must be made with caution. The median PFS in the CT group was 24.14 weeks (95% CI: 20.29; 29.29) and 26.86 weeks (95% CI: 24.43; 30.14) in the pooled CDP791 + CT group. The difference in PFS between the groups was not statistically significant (p=0.461) and the hazard ratio was 0.833 (95% CI: 0.513; 1.354) (Table 14.2.2:2). Subjects treated with CDP791 + CT therefore had a slightly lower risk of experiencing an event of disease progression or death during the study as those treated with CT alone. Median PFS in the 2 CDP791 treatment groups was 26.86 weeks (95% CI: 21.14; 30.71) and 25.43 weeks (95% CI: 24.29; 30.43) for the CDP791 10 mg/kg and 20 mg/kg + CT groups, respectively, and showed no dose relationship.

Due to the low information level, exploratory analysis of PFS was not performed for this data cut.

Time to treatment failure: The Open Label study design means that the results of TTF must be interpreted with caution, although interestingly, the number of subjects being discontinued was greater in the CDP791 + CT groups.

The number of subjects with events leading to treatment failure (discontinuation, disease progression, or death) was 40 (80.0%) in the CT group and 83 (78.3%) in the pooled CDP791 + CT groups.

The median TTF was 13.21 weeks (95% CI: 6.86; 20.29) in the CT group and 21.71 weeks (95% CI: 18.14; 24.71) in the pooled CDP791 + CT groups (Table 14.2.2:4). This increase in TTF in the CDP791 treated groups appeared dose-related in that the median TTF was 18.43 weeks (95% CI: 12.14; 24.71) and, 24.29 weeks (95% CI: 18.14; 27.00) in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively. The difference in TTF between the CDP791 treatment groups and the CT group was statistically significant (p=0.031), as is reflected in the hazard ratio for the pooled CDP791 + CT group, of 0.654 (95% CI: 0.444; 0.963) (Table 14.2.2:4).

Time to response: The median time to response was 8.57 weeks (min, max: 5.9, 31.7) in the CT group and 9.14 weeks (min, max: 5.9, 18.0) in the pooled CDP791 + CT groups (Table 14.2.2:6).

Duration of response: If subjects had not progressed or died, they were censored at the date of their last

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scan. Of the 24% (38/156) of subjects that had a response, only 39.5% (15/38) had an event, hence the median duration of overall response should be interpreted with caution (Table 14.2.2:6). However, 14 of the responders in the CDP791 20 mg/kg + CT group had a duration of response of at least 12 weeks duration compared to 6 of the responders in the CT group, and 7 of the responders in the CDP791 10 mg/kg + CT group (Listing 16.2.6:4).

Overall survival: Survival is defined as the time from date of randomization until the date of death. At the time of database lock, 27.6% (43/156) of subjects had a date of death (Listing 16.2.6:2). Consequently, the information level for this data cut is too low for analysis.

HEALTH-RELATED QUALITY OF LIFE ANALYZES:

The number of evaluable subjects for the calculation of EORTC questionnaire scores decreased over successive cycles. Missing data are usually not missing at random since observations on subjects who are experiencing a negative impact on their lives, as a result of treatment-related toxicity, progressive disease or death, are more likely to be missing. When analyses are based only on observed data of subjects who are doing well, the estimates of HRQOL will be overestimated compared to the entire subject population in the study. Therefore the estimates of EORTC questionnaire scores are likely to be overestimated, particularly in the CT alone group where 60.0% (30/50) of assessments were missing at Cycle 6, compared to 47.2% (25/53) and 52.8% (28/53) in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively (Table 14.4.1:2).

Most scales and item scores of the EORTC QLQ-C30 worsened over time from Baseline to Cycle 6 in at least 1 treatment group. After 6 cycles of study treatment, score changes in global QOL and in all other scales except nausea and vomiting, pain, and insomnia, were numerically better for the pooled CDP791 + CT group compared to the CT alone group (Table 14.4.1:2).

Similarly, at Cycle 6, the EORTC QLQ-LC13 score changes in the hemoptysis, peripheral neuropathy, alopecia and pain in the arm or shoulder were numerically better in the pooled CDP791 + CT group compared to the CT alone group. The remaining symptoms were numerically worse in the pooled CDP791 + CT group compared to the CT alone group (Table 14.4.2:2).

PHARMACOKINETIC RESULTS:

PK samples were taken over Cycle 1 and Cycle 2 for paclitaxel and carboplatin. For both compounds, plasma concentration profiles were similar in both cycles (Figure 14.5.1.1 for paclitaxel and Figure 14.5.1:2 for carboplatin).

The maximum plasma concentration observed at the end of the infusion of the chemotherapeutic drugs (C_{max}) was quite similar for both compounds over the 2 cycles (4.55 µg/mL and 5.38 µg/mL for paclitaxel and 20.0 µg/mL and 18.2 µg/mL for carboplatin, after Cycle 1 and Cycle 2, respectively) (Table 14.5.1:3 and Table 14.5.1:4). No accumulation is expected over the 6-cycles of treatment for both chemotherapeutic drugs. Despite a slight carboplatin residue observed at the end of Cycle 1 (0.131µg/mL), it is unlikely that accumulation occurs (Figure 14.5.1:2). Paclitaxel concentrations were only quantifiable until 24 h post infusion (Figure 14.5.1:1).

For CDP791 plasma concentrations assay, 6 samples per Part I subject were taken during the first 2 cycles. For the subsequent cycles, only peak and trough samples were taken. After the end of the infusion, CDP791

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plasma concentrations showed a time-dependant decrease over the whole cycle (Figure 14.5.1:3). CDP791 was still quantifiable at the end of each cycle, prior to the following cycle (Table 14.5.1:1). The average maximum plasma concentration observed in Part I subjects was 279 µg/mL after infusion of 10 mg/kg of CDP791 and 557 µg/mL after infusion of 20 mg/kg of CDP791 (Table 14.5.1:2). The average minimum plasma concentration was observed to be between 11 µg/mL to 21 µg/mL and between 29 µg/mL to 64 µg/mL after 10 mg/kg and 20 mg/kg CDP791 dose, respectively.
Peak and trough concentration measured during Part II in all subjects (approximately 50 subjects for each dose), indicated that the steady-state was reached as soon as the second cycle was administered (Table 14.5.1:6). There was little difference between males or females in either peak or trough concentrations at steady state (Table 14.5.1:6). The observed peak concentration averaged approximately 222 and 412 µg/mL after 10 and 20 mg/kg infusion (Table 14.5.1:6). The observed trough concentrations averaged approximately 12 µg/mL and 42 µg/mL, after 10 and 20 mg/kg CDP791 infusion and were beyond 10 µg/mL, the minimum concentration predicted preclinically to be required for activity (Table 14.5.1:6).
CDP791 PK analysis was subjected to a population PK analysis, using the NONMEM software (Version VI, Level 1.0, with PsN Version 2.2.4 interface). CDP791, as many macromolecules, was following a target-mediated drug disposition (TMDD) PK (Lammerts JJ *et al.*, 2006 [1]; Levy G., 1994 [2]; Lobo ED *et al.*, 2004 [3]). Thus, a specific TMDD model has been developed to describe the PK behavior of CDP791. This analysis is presented in Appendix 16.1.9.3.

PHARMACODYNAMIC RESULTS:
Geometric mean values (CV%) for soluble VEGFR-2 were seen to increase cycle on cycle after administration of CDP791 10 mg/kg + CT and CDP791 20 mg/kg + CT (Table 14.5.2:1 for Part I subjects and Table 14.5.2:2 for Part II subjects). However, there was no apparent dose dependency in the increase in sVEGFR-2, as both doses of CDP791 produced similar increases.
Unfortunately, interpretation of these data is precluded since it is not possible to distinguish between the contribution of changes in expression of sVEGFR-2, and of the effects that CDP791 may have on the half-life and clearance of sVEGFR-2.

SAFETY RESULTS:
Forty-three subjects died, primarily due to disease progression (Listing 16.2.6:2). No subjects from Part I of the study had died at the time of database lock. Deaths were reported in 7 (4.5%) Part II subjects during the Chemotherapy Period; 2.0% of subjects in the CT group and 5.7% of subjects in each of the CDP791 10mg/kg and 20mg/kg + CT groups, respectively (Table 14.1.1:1). During the Overall Study Period, 14 (9.0%) Part II subjects had AEs leading to death; 6 (12%) in the CT group, 3 (5.7%) in the CDP791 10 mg/kg + CT group and 5 (9.4%) in the CDP791 20 mg/kg + CT group (Listing 14.3.2:1). When the AEs leading to death of disease progression, cardiopulmonary failure or respiratory failure of unlikely relationship to study drug were removed, the incidence of AEs leading to death in the CT group was 0.0% (0 subjects) compared to 5.7 % (3 subjects) in both the CDP791 10mg/kg and 20mg/kg + CT groups.
There was no increase in discontinuations during the Chemotherapy Period due to AEs in CDP791 + CT-treated subjects (10 subjects, 8.7%), with the highest incidence of discontinuations due to AEs seen in the CT group (9 subjects, 18.0%) (Table 14.1.1:1 and Table 14.1.1:5). As this was an Open Label study

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there may have been bias towards discontinuing CT subjects early.
The incidence of Grade 3 to 4 AEs or severe AEs during the Chemotherapy Period of Parts I and II of the study was higher in CDP791 treatment groups (64.3% and 72.9% of subjects in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively) compared to the CT group (56.0%) and appeared to be dose-related (Table 14.3.1:6 and Table 14.3.1:22). The most frequently reported Grade 3 to 4 AEs or severe AEs reported by the Investigators across all treatment groups, combining events from Parts I and II of the study, were neutropenia and anemia (Table 14.3.1:6 and Table 14.3.1:22). However, raw laboratory data give a more accurate representation of these data. Common toxicity criteria Grade 3 to 4 abnormalities (decreases) in neutrophil count were reported by 56.0% of CT subjects, and 69.6% and 66.1% of subjects in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively during the Chemotherapy Period (Table 14.3.5:2 and Table 14.3.5:13). Common toxicity criteria Grade 3 to 4 abnormalities (decreases) in lymphocytes were seen more commonly in the CDP791 + CT-treated subjects than in the CT-treated subjects (10.4% versus 8.0%) but anemia was not enhanced by treatment with CDP791 (Table 14.3.5:2 and Table 14.3.5:13). Indeed, evolution over time of change from Baseline plots for hemoglobin (Figure 14.3.5:28) and red blood cell count (Figure 14.3.5:53) suggested that the decrease seen with chemotherapy treatment in CDP791-treated Part II subjects may be slightly less. Grade 3 to 4 thrombocytopenia was also more commonly reported in the CDP791 treatment groups (14.8%) than in the CT group (2.0%) and had a suggestion of a dose-related effect (Table 14.3.5:2 and Table 14.3.5:13).
There was little difference in the incidence of serious AEs between the 3 treatment groups during the Chemotherapy Period (24.0% in the CT group compared to 28.6% and 18.6% of subjects in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively) (Table 14.3.1:8 and Table 14.3.1:24).
The majority of AEs and other abnormalities were expected in the populations studied, as a result of their underlying disease and the therapies (VEGF inhibitor +/- carboplatin/paclitaxel) received.
Clinically significant differences, defined as a >5 % increased incidence between treatments for non laboratory related events were found between combined CDP791 treatment groups compared with the CT group for events of arthralgia (11.3% versus 6.0%), bone pain (11.3% versus 2.0%), and hypertension (9.6% versus 2.0%) (Table 14.3.1:14 and Table 14.3.1:30). It is noteworthy that fatigue, reported as an AE, did not seem to be a significant problem in subjects treated with CDP791 (14.8% of subjects) compared to subjects in the CT group (18.0% of subjects) (Table 14.3.1:14 and Table 14.3.1:30).
AEs of hypertension (combined with blood pressure increased) were reported by a higher number of Part I and II subjects in the combined CDP791 + CT groups (10.4%) than in the CT group (2.0%) (Table 14.3.1:16 and Table 14.3.1:32). No subjects discontinued the study as a result of hypertension, which is a known side effect of this class of agents.
Proteinuria is a known side-effect of this class of agents and was more commonly reported as an AE in the CDP791 + CT-treated groups of Part I and II subjects (11.3% of subjects) compared to the CT-treated group (2.0% of subjects), although the severity remained low (Grade 1 to 2) (Table 14.3.1:10 and Table 13.3.1:26). This is probably dose-related but not cumulative.
Grade 3 abnormalities in APTT were reported only in CDP791 + CT-treated Part II subjects during this study (1 and 2 subjects in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively) (Table 14.3.5:6). An evolution over time plot of change from Baseline in APTT for Part II subjects showed dose-related increases in APTT for CDP791-treated subjects compared to CT-treated subjects (Figure 14.3.5:32).

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Increases in APTT are thought to be due to interaction of the PEGylated portion of CDP791 with the APTT assay.

Hemorrhage/bleeding is a known toxicity of this class of agent. Therefore, further analysis was done on this parameter to elucidate its incidence. Hemorrhage/bleeding was divided into major and minor categories. Hemorrhage/bleeding (major subcategory) included hemoptysis, hemorrhage, metrorrhagia, vaginal hemorrhage, gastrointestinal hemorrhage, and menstruation irregular. Hemorrhage/bleeding (minor subcategory) included epistaxis, hemoglobinuria, and hematuria. Hemorrhage/bleeding (major subcategory) occurred in Part II subjects only and was reported by 4.0% of CT subjects, and 5.7% of subjects in both the CDP791 10mg/kg and 20mg/kg + CT groups, respectively during the Chemotherapy Period (Table14.3.1:16). An additional 2 subjects (total 9.4%) in the CDP791 20 mg/kg + CT group reported hemorrhage/bleeding (major subcategory) during the Overall Study Period (Table 14.3.1:15). However, it should be noted that data for the Overall Study Period are very limited at this stage of the trial. Of the 8 subjects who experienced hemorrhage/bleeding (major subcategory) in the CDP791 groups only 1 subject was taking a non-steroidal anti-inflammatory drug during the Chemotherapy Period. The risk of major bleeding was increased by 41.5% (relative risk = 1.415 [95% CI: 0.296; 6.765]) for CDP791-treated subjects compared to CT alone subjects during the Chemotherapy Period (Table 14.3.1:16). There was a possible relationship to dose but no apparent link with thrombocytopenia or rises in APTT. Two subjects died due to a major hemorrhage/bleeding event: 1 subject in each CDP791 group (Listing 14.3.2:1).

Hemorrhage/bleeding is a known AE of this class of agent.

Hemorrhage/bleeding (minor subcategory) was reported by 2.0% of CT subjects, and 7.5% and 11.3% of Part II subjects in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively during the Chemotherapy Period (Table 14.3.1:16). One subject in the CDP791 20 mg/kg + CT group of Part I of the study also had a minor bleeding event. In Part II subjects, the risk of minor bleeding was 4.717 times greater (95% CI for relative risk: 0.621; 35.84) for CDP791 + CT-treated subjects compared to CT-treated subjects during the Chemotherapy Period. The event may be dose-related, and was in some cases associated with a low platelet count but not rises in APTT.

Of note is the occurrence of hemangiomata reported by 3 (2.8%) CDP791 + CT-treated Part II subjects during the Overall Study Period, and not reported during the Chemotherapy Period (Table 14.3.1:3). In addition, there were reports of a neoplasm of the skin and a skin nodule which on further review appeared suggestive of hemangiomata giving a possible incidence of 3.8% and 5.7% of Part II subjects in the CDP791 10mg/kg and 20mg/kg + CT groups, respectively (Table 14.3.1:3). Evidence from the Phase I study CDP791-001 suggests that hemangiomata may be caused by the cumulative effect of treatment with CDP791 and resolve on cessation of treatment. Indeed all the cases in this study occurred after the subjects had received 6 or more cycles of CDP791 therapy.

Infections and infestations were more commonly reported in CDP791 + CT-treated subjects of Parts I and II (18.3%) than in the CT-treated subjects (10.0%) during the Chemotherapy Period (Table 14.3.1:4 and Table 14.3.1:20) and also during the Overall Study Period (Table 14.3.1:3 and Table 14.3.1:19), although again it should be noted that data from the Overall Study Period are limited at this stage of the trial. The increased incidence of infections in the CDP791 + CT-treated subjects is probably associated with an increase in leukopenia in this group. The increase in infections and infestations during the Chemotherapy Period appeared dose-related (16.1% and 20.3% of subjects in the CDP791 10mg/kg and 20mg/kg + CT

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groups, respectively) (Table 14.3.1:4 and Table 14.3.1:20).
As expected, the ECOG PS of Part II subjects worsened from Screening during the study for all treatment groups (Table 14.3.6:1).

CONCLUSIONS:

- The primary endpoint of the study was not met. However, a 10.2% increase in RR (although not statistically significant) was seen in the CDP791 20 mg/kg + CT group compared to the CT alone group.
- The hazard of tumor progression or death was reduced by 16.7% for the pooled CDP791 + CT group compared to CT alone group. There was little difference between treatment groups in PFS. However, due to low information level, interpretation of these results must be made with caution.
- The Open Label study design means that the results of TTF must be interpreted with caution, although interestingly, the number of subjects being discontinued was greater in the CDP791 + CT groups. However, median TTF was 13.21 weeks in the CT group and 21.71 weeks in the pooled CDP791 + CT groups. The difference in TTF between the CDP791 and the CT treatment groups was statistically significant (p=0.031), as is reflected in the hazard ratio for the pooled CDP791 + CT group, of 0.654 (95% CI: 0.444; 0.963).
- Duration of response was affected by the high level of censorship. However, 14 of the responders in the CDP791 20 mg/kg + CT group had a duration of response of at least 12 weeks duration compared to 6 of the responders in the CT group.
- At the time of database lock, 27.6% (43/156) of subjects had a date of death. Consequently, the information level for these data was too low for analysis of OS.
- The EORTC QLQ-C30 data suggested a better HRQOL and functioning for subjects in the CDP791 treatment groups compared to the CT group at Cycles 3 and 6. However, missing data may have led to an overestimation of questionnaire scores. In contrast, symptoms assessed by the EORTC-QLQ-C30 and –LC13 seemed worse in the CDP791 treatment groups compared to the CT group, especially at Cycle 3.
- The plasma concentration of CDP791 showed a time-dependant decrease over the whole treatment cycle but was still quantifiable at the end of each cycle prior to the next. Trough concentrations observed following both doses of CDP791 were above 10 µg/mL, the minimum concentration predicted preclinically to be required for activity. There was no difference between males or females in either peak or trough concentrations.
- Measurement of VEGFR-2 was not found to be a useful pharmacodynamic marker for the development of CDP791.

In assessing the safety of combining CDP791 with CT, the following overall conclusions were drawn:

- The majority of AEs and other abnormalities observed following the administration of CDP791 to subjects with non squamous NSCLC at doses of 10 mg/kg and 20 mg/kg in combination with standard dose CT were expected in the populations studied, as a result of their underlying disease and the therapies (VEGF inhibitor +/- CT) received. Indeed, hypertension, hemorrhage/bleeding (major and minor subcategories), and proteinuria were seen more commonly in CDP791-treated subjects.
- There was no increase in discontinuations during the Chemotherapy Period due to AEs in CDP791 +

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CT-treated subjects (8.7%), compared to the CT-treated subjects (18.0%). Although this was an Open Label study and so there may have been bias towards discontinuing CT subjects early.

- The incidence of Grade 3 to 4 AEs or severe AEs was higher in CDP791 treatment groups and appeared to be dose-related.
- Grade 3 to 4 neutropenia and thrombocytopenia occurred with a higher frequency in the CDP791 treatment groups than in the CT group and in the case of thrombocytopenia appeared to be dose-related.
- Infections and infestations were more commonly reported in the CDP791 + CT group compared to the CT group and were probably associated with an increase in neutropenia, predominantly in the clinically important Grade 4 category. They seemed to be dose-related although there was not an obvious dose relationship for neutropenia.
- Hemangiomata may be induced by CDP791 in some subjects, particularly when administered for longer than 6 cycles.
- Dose-related Grade 3 abnormalities in APTT were only reported by CDP791-treated subjects. Increases in APTT are thought to be due to interaction of the PEGylated portion of CDP791 with the APTT assay.

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