SYNOPSIS

Title of the study: Randomized Phase 2 study of gemcitabine/cisplatin with or without SAR240550 (BSI-201), a PARP1 inhibitor, in patients with stage IV non-small cell lung cancer (TCD11420)

Investigator(s): [redacted]

Study center(s): France, Italy, Spain, Germany, and the United Kingdom (14 centers)

Publications (reference):

Besse B, Felip E, Barlesi F, Mazieres J, Zalcman G, von Pawel J, et al. Results of a randomized Phase 2 trial of gemcitabine/cisplatin/iniparib (GCI) vs gemcitabine/cisplatin (GC) in patients with stage IV NSCLC. J Thoracic Oncol. 2011;6(6):S469-70. Presented at the International Association of the Study of Lung Cancer 14th World Conference on Lung Cancer, July 3-7, 2011, Amersterdam, The Netherlands [abstract O43.04].

Novello S, Felip E, Barlesi F, Mazieres J, Zalcman G, von Pawel J, et al. Results of a phase 2 study of gemcitabine/cisplatin/iniparib (GCI) versus gemcitabine/cisplatin (GC) in patients with advanced NSCLC. Eur J Cancer. 2011;47(1):S593. Presented at the European Multidisciplinary Cancer Congress, 23-27 September, 2011, Stockholm, Sweden [abstract 9006].

Study period:

Date first patient signed informed consent form: 17 May 2010

Date last patient completed: 12 December 2011

Database lock date: 23 December 2011

Phase of development: 2

Objectives:

The primary objective of the study was to assess the objective response rate (ORR) of SAR240550 (iniparib) administered as a 60-minute intravenous (IV) infusion twice weekly when combined with gemcitabine + cisplatin (GC) chemotherapy regimen in patients with Stage-IV non-small cell lung cancer (NSCLC).

The secondary objectives of the study were to assess the safety profiles of the study combination gemcitabine + cisplatin + iniparib (GCI) and of the standard regimen of GC alone and to assess the progression-free survival (PFS) and overall survival (OS) in both arms in patients with Stage-IV NSCLC.

Additional secondary objectives were as follows:

- To assess the relationship between DNA repair pathway characteristics of tumors at baseline and clinical outcome of disease in patients with Stage-IV NSCLC; and
- To assess the effect of iniparib on poly(ADP-ribose) (PAR) levels in peripheral blood mononuclear cells (PBMCs) in patients with Stage-IV NSCLC

Results for the DNA repair objective will be reported separately when they become available. Data collection for the PAR level objective was permanently discontinued (protocol Amendment 2, dated 08 October 2010), and data will not be presented for this objective.

Methodology:

This was a multicenter, Phase 2, multinational, randomized, open-label study to evaluate iniparib, administered as a 60-minute IV infusion on Days 1, 4, 8, and 11, in combination with GC every 3 weeks (GCI arm) or GC alone.

Eligible patients were randomly assigned to the GCI arm or the GC arm (defined below) via an interactive voice response system (IVRS). Randomization was stratified by disease histological type (squamous versus nonsquamous NSCLC) and smoking status (smoker versus never smoker). Within each of the strata, patients were randomized in a 2:1 ratio in favor of the investigational arm into 1 of the 2 treatment arms as follows:

GCI arm: Gemcitabine (1250 mg/m^2; IV) on Day 1 and Day 8 of each 21-day cycle and cisplatin (75 mg/m^2; IV) on Day 1 of each 21-day cycle; and iniparib (5.6 mg/kg; IV) on Days 1, 4, 8, and 11 of each 21-day cycle.

GC arm: Gemcitabine (1250 mg/m2; IV) on Day 1 and Day 8 of each 21-day cycle and cisplatin (75 mg/m2; IV) on Day 1 of each 21-day cycle.

For both treatment arms, cycles were repeated every 21 days (3 weeks) up to a maximum of 6 cycles as long as the patient had no evidence of disease progression and did not meet any criteria for treatment discontinuation or study withdrawal. Maintenance therapy was not allowed.

Tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, at every other cycle (approximately every 6 weeks) beginning at Cycle 2. The ORR was assessed by each individual investigator without a central review.

Patients were assessed for safety for a minimum of 30 days after the last study treatment administration. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status (PS), electrocardiograms (ECGs), and laboratory safety tests (including complete blood count and serum chemistry) were obtained prior to drug administration and at designated intervals throughout the study. Adverse events (AE) were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0, during the study. All safety assessments were repeated at the end of each cycle (3 weeks), and the final assessments were performed within 30 days following the final dose. Additionally, patients had their overall tumor response assessed via clinical imaging if not done within 30 days prior to the last dose of study treatment.

A steering committee reviewed the safety data on a regular basis, including the data from the first 6 treated and evaluable (for at least 1 cycle) patients in the GCI arm, as well as the overall efficacy and safety data at the end of the study. In the event of unexpected or more frequent Grade 3 to 4 AEs during Cycle 1 of study treatment in the GCI arm, the steering committee was to be consulted for advice on the continuation of the study. Data from the GC arm were provided as information regarding the safety profile of the background therapy.

Number of patients: Planned: 105 patients (35 in GC arm; 70 in GCI arm)

Efficacy:

Intent-to-treat (ITT): 119 patients (39 in GC arm; 80 in GCI arm)

Evaluable patients (EP) population: 116 patients (38 in GC arm; 78 in GCI arm)

Safety: 117 patients (39 in GC arm; 78 in GCI arm)

Pharmacokinetics: Not applicable.

Diagnosis and criteria for inclusion:

- Adult patients with histologically confirmed Stage-IV NSCLC (squamous cell bronchogenic carcinoma OR nonsquamous cell carcinoma) with no prior systemic therapy. Adjuvant therapy was allowed if it had ended more than 1 year before inclusion in the study.
- At least 1 measurable lesion according to RECIST, version 1.1
- ECOG PS score of 0 or 1

Study treatments

Investigational medicinal product(s): Iniparib (SAR240550 or BSI-201)

Formulation: Drug product consisted of iniparib at a concentration of 10 mg/mL formulated in 25% hydroxypropylbetacyclodextrin/10 mM phosphate buffer, pH 7.4. The dosage form was a sterile liquid in 10 mL, single-use, Type 1 USP glass vials, with an extractable volume not less than 10 mL. Each patient received a weight-based dose over a maximum 1-hour IV infusion period.

Route(s) of administration: IV

Dose regimen: Patients in the GCI arm received iniparib at a dose of 5.6 mg/kg as a 60-minute IV infusion twice weekly (Days 1, 4, 8, and 11) every 3 weeks in the absence of disease progression or unacceptable toxicity for a total of up to 6 cycles. Iniparib infusion was initiated after completion of GC regimen administration.

Batch number: [redacted]

Noninvestigational medicinal product(s): Gemcitabine and cisplatin

Formulation: Depending on the country and on local regulatory requirements, GC was provided and labeled by the clinical site via normal procedures at each site, at the charge of the sponsor when agreed upon with the site, or provided directly by the sponsor.

Route(s) of administration: IV

Dose regimen: Patients in both treatment arms (ie, GCI or GC) received gemcitabine and cisplatin. Gemcitabine was administered at 1250 mg/m^2 as a 30-minute IV infusion on Day 1 and Day 8 and cisplatin 75 mg/m^2 as a 1- to 4-hour IV infusion, according to the local practice at the study center, on Day 1 of each 3-week cycle after the end of gemcitabine infusion. Treatment was continued every 3 weeks in the absence of disease progression or unacceptable toxicity for a total of up to 6 cycles.

Batch number(s): Not applicable.

Duration of treatment: Patients were treated until disease progression, unacceptable toxicity, investigator's decision to discontinue treatment, or withdrawal of consent, or up to 6 study treatment cycles.

Duration of observation: End-of-treatment assessments were performed 30 days (±5 days) after the last dose of study treatment. Additionally, patients had their overall tumor response assessed via clinical imaging if not done within 30 days prior to the last dose of study treatment. In the case of study treatment discontinuation without disease progression, efficacy data were collected every 6 weeks until disease progression, death, or end of study, whichever came first. After disease progression, the patients were followed-up every 12 weeks (3 months) for OS until death, consent withdrawal, or end of study, whichever came first.

Criteria for evaluation:

Efficacy:

Primary Endpoint: The primary efficacy endpoint was ORR assessed by the investigator per RECIST, version 1.1, in the GCI and the GC arms. Tumor measurements were assessed at baseline (within 3 weeks before randomization) and then every 2 cycles (6 weeks) until disease progression.

Secondary Endpoints: PFS and OS in the GCI arm and the GC arm (disease progression assessed by the investigator per RECIST, version 1.1).

Safety: Safety endpoints included AEs monitored throughout the study period according to NCI-CTCAE, version 4.0, clinical and laboratory tests (hematology and serum chemistry), vital signs, physical examinations, ECOG PS, and ECGs. For blood pressure, heart rate, and body temperature, only clinically significant abnormalities were reported on the eCRF.

Pharmacokinetics: Not applicable.

Pharmacokinetic/pharmacodynamic sampling times and bioanalytical methods: Not applicable.

Statistical methods:

Sample size determination: Initially, the sample size for the GCI arm was 70 patients, who were to be enrolled in a 2-stage manner (Simon 2-stage optimal design). In protocol Amendment 2, the design was changed to a single-stage fixed design. With the fixed design, a total of 70 patients in the GCI arm were needed to provide approximately 90% statistical power to reject the null hypothesis that the true ORR was ≤20% (upper efficacy boundary, >36%) based on a 1-sided exact binomial test at a significance level of 0.05. For the GC arm, a total of 35 patients were to be treated to check the accuracy of the assumption of an ORR of 28%. Therefore, a total of 105 patients (70 in the GCI arm and 35 in the GC arm) needed to be randomized and treated.

Analysis populations:

ITT population: All randomized patients (ie, the set of all patients who had given their informed consent and for whom there was confirmation of successful allocation of a randomization number through the IVRS). This population was used for the efficacy analyses based on the treatment arm assigned by the IVRS.

Evaluable patient population for tumor response: All treated patients with at least 1 baseline tumor assessment and 1 post-baseline tumor assessment, as well as all treated patients with early disease progression (PD before first planned tumor assessment [ie, within 6 weeks after first infusion]). This population was used for the supportive efficacy analyses.

Safety population: A subset of randomized patients who received at least part of 1 (even incomplete) of the study treatments (iniparib, gemcitabine, and/or cisplatin).

Primary analysis: All efficacy variables were analyzed based on the ITT population. The ORR was analyzed using both the ITT population and the EP population for tumor response.

The primary efficacy analysis of ORR was performed using the cut-off date defined as 30 days after the last dose of study drug across all treated patients in the study. The ORRs and corresponding 95% confidence intervals (CIs) were calculated based on the ITT population. Patients who were not evaluable were considered nonresponders. The null hypothesis that the true ORR was ≤20% was tested using a 1-sided exact binomial test with a significance level of 0.05.

A supportive analysis of the primary endpoint (ORR) consisted of calculating the relative response rate ratio (GCI versus GC) and corresponding 95% CI within each stratum if relevant (squamous-smoker / squamous-never smoker/ nonsquamous-smoker / nonsquamous-never smoker).

Analysis of secondary endpoints: PFS and OS were estimated using the Kaplan-Meier method based on the ITT population. Preliminary analyses of PFS and OS were performed at the time of the primary analysis for ORR. In addition, the analyses were updated at the time of the final analysis using the study cut-off date (ie, end of study), defined as 12 months after the first dose of the last patient treated. As the study was designed in a noncomparative manner, any p values associated with non-protocol-specified comparisons between the study arms were for descriptive purposes.

Safety analyses: All safety analyses were performed on the safety population. Only descriptive statistics were used for the safety analyses. The summary of safety results was presented by treatment group.

All AEs were graded per NCI-CTCAE, version 4.0, and coded using Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. AEs were summarized for the pretreatment, treatment-emergent (TEAE), and post-treatment periods as defined in the statistical analysis plan (SAP). Deaths on-treatment (during the TEAE period, including deaths within 30 days of last study drug dose) and on-study (during the on-study observation period, including deaths after 30 days following last study drug dose) as defined in the SAP were summarized.

Clinical laboratory parameters were graded per NCI-CTCAE, version 4.0, when applicable. Summary statistics (ie, number, mean, median, standard deviation, minimum, and maximum) for weight (measurements and changes from baseline) were calculated for each visit by treatment group. For ECOG PS, the last on-treatment evaluation was tabulated according to the baseline value; a similar table presented the worst on-treatment evaluation. The incidence of clinically significant abnormal ECGs at the end of treatment was summarized by treatment group whatever the baseline level and according to the baseline status categories normal/missing, abnormal but not clinically significant, and abnormal and clinically significant.

Interim analysis: An interim analysis (after the first Simon stage) was included in the original study protocol. As a consequence of the changes in the study design, this section was removed in Amendment 2 (dated 08 October 2010).

Summary: A total of 119 patients were randomized: 39 patients in the GC arm and 80 patients in the GCI arm. There were no substantial differences in the median number of cycles administered in each arm.

Population characteristics: Demographic and baseline characteristics were well balanced between the 2 treatment arms with the exception of ECOG PS, ethnicity, and sex. The proportion of patients with a PS score of 0 in the GCI arm was about 13% higher than in the GC arm. The proportion of male patients in the GCI arm was about 13% higher than in the GC arm.

Efficacy results:

Primary efficacy endpoints: For the ITT population, the ORR (investigator-assessed) was 25.6% (95% CI, 13.0% to 42.1%) in the GC arm compared with 20.0% (95% CI, 11.9% to 30.4%) in the GCI arm. The ORRs for the EP population were as follows: GC 26.3% (95% CI, 13.4% to 43.1%) and GCI 20.5% (95% CI, 12.2% to 31.2%). The test for H_0:ORR ≤20% yielded a p value of 0.5445 for the ITT population and 0.4999 for the EP population for tumor response.

There were 26 responders: 10 patients in the GC arm and 16 patients in the GCI arm. Twenty-four of the 26 responders had nonsquamous cell histology. The ORR analysis by randomization stratum, however, did not allow conclusions to be drawn due to the small patient numbers.

Of note, 43.6% (95%CI, 27.8% to 60.4%) of patients in the GC arm had stable disease (SD) compared with 55.0% (95%CI, 43.5% to 66.2%) in the GCI arm. In the GC and the GCI arms, 20.5% (95% CI, 9.3% to 36.5%) and 13.8% (95% CI, 7.1% to 23.3%) of patients, respectively, had PD.

Secondary efficacy endpoints:

Progression-free survival and overall survival

Thirty-two (82.1%) patients in the GC arm experienced a PFS event; 28 (71.8%) patients had radiological disease progression and 4 (10.3%) patients died on study without documented disease progression. Fifty-two (65.0%) patients in the GCI arm experienced a PFS event; 47 (58.8%) patients had radiological disease progression and 5 (6.3%) patients died on study without documented disease progression. The proportion of patients whose PFS data were censored because of starting new antitumor therapy was higher in the GCI arm (27.5%) than in the GC arm (10.3%).

The median PFS was 4.3 (95% CI, 2.8 to 5.6) months in the GC arm and 5.7 (95% CI, 4.6 to 6.6) months in the GCI arm. The PFS rates at 3 months (GC 64.2% versus GCI 72.9%), 6 months (GC 32.2% versus GCI 44.5%), and 12 months (GC 0% versus GCI 5.6%) showed a slight trend in favor of iniparib treatment. This trend was not observed at 9 months (GC 11.0% versus GCI 8.4%). The hazard ratio for the GCI treatment relative to the GC treatment was 0.885, with a 95% CI of 0.561 to 1.397 (p value [stratified log-rank test] = 0.5978).

The median OS was 12.0 months in the GCI arm compared with 8.5 months in the GC arm (hazard ratio = 0.780; p value [stratified log-rank test] = 0.3174; 95% CI, 0.477 to 1.273). At the time of the final analysis, 41.3% of patients were alive in the GCI arm compared with 35.9% of patients in the GC arm.

OS rates at 3 months (GC 87.2% versus GCI 90%), 6 months (GC 64.1% versus GCI 78.8%), 9 months (GC 46.2% versus GCI 58.8%), 12 months (GC 35.9% versus GCI 48.8%), and 15 months (GC 35.9% versus GCI 42.9%) showed a trend toward improved survival with iniparib treatment.

It should be noted that, although the study design included randomization, the study was not designed for formal statistical comparisons between the 2 treatment arms. Therefore, the CIs and the p values for the PFS and OS analyses are regarded as descriptive rather than inferential statistics.

Safety results:

The median number of cycles administered per patient was 4.5 in the GCI arm and 4.0 in the GC arm. Sixteen (41.0%) patients completed 6 cycles of therapy in the GC arm compared with 35 (44.9%) patients in the GCI arm. The median relative dose intensity for any drug (gemcitabine, cisplatin, and iniparib) was >85%.

There were no notable differences between the 2 treatment arms in the overall frequency of TEAEs (any TEAE, GC 39 [100%] versus GCI 78 [100%] patients), Grade 3 to 4 TEAEs (GC 32 [82.1%] versus GCI 66 [84.6%] patients), TEAEs leading to death within 30 days after the last dose (GC 3 [7.7%] versus GCI 5 [6.4%] patients), or TEAEs leading to permanent treatment discontinuation (GC 7 [17.9%] versus GCI 16 [20.5%] patients). Treatment-emergent serious adverse events (SAEs) were reported in 17 (43.6%) patients in the GC arm and 40 (51.3%) patients in the GCI arm.

The incidence of study treatment-related Grade 3 to 4 TEAEs was comparable between the 2 arms (GC 25 [64.1%] versus GCI 51 [65.4%] patients). Grade 3 to 4 treatment-related hematologic toxicities were reported in approximately half of the patients in both arms (GC 19 [48.7%] versus GCI 39 [50.0%] patients). Grade 3 to 4 treatment-related TEAEs with a difference of at least 5% between the 2 treatment arms were febrile neutropenia (GC 3 [7.7%] versus GCI 0 [0.0%] patients) and asthenia (GC 7 [17.9%] versus GCI 4 [5.1%] patients), which were reported more frequently in the GC arm, and anemia (GC 4 [10.3%] versus GCI 12 [15.4%] patients), hypokalemia

(GC 0 [0.0%] versus GCI 4 [5.1%] patients), and nausea (GC 1 [2.6%] versus GCI 11 [14.1%] patients), which were reported in a higher proportion of patients in the GCI arm. The excess of febrile neutropenia and asthenia in the GC arm could be explained either by the higher proportion of patients with a baseline PS of 1 in this arm or by a true positive effect of the addition of iniparib in improving patients' PS.

A total of 8 patients died within 30 days after the end of study treatment, including 5 patients due to an AE (2 [5.1%] patients in the GC arm and 3 [3.8%] patients in the GCI arm) and 3 due to disease progression (1 [2.6%] patient in the GC arm and 2 [2.6%] patients in the GCI arm). Of the 8 deaths, 3 were due to treatment-related AEs, including septic shock (n=1) and mental status changes (n=1) in the GC arm and cardiac failure (n=1) in the GCI arm. The remaining 5 deaths were attributed to respiratory failure (1 [2.6%] patient) in the GC arm and acute pancreatitis (1 [1.3%] patient), general physical health deterioration (2 [2.6%] patients), and disseminated intravascular coagulation (1 [1.3%] patient) in the GCI arm. During the study period, the proportion of deaths due to disease progression was approximately 8% higher in the GC arm compared with the GCI arm (23 [59.0%] versus 40 [51.3%] patients).

The incidence of treatment-emergent SAEs (all grades) was slightly lower in the GC arm than in the GCI arm (GC 17 [43.6%] versus GCI 40 [51.3%] patients); however, the incidence of treatment-emergent Grade 3 to 4 SAEs was similar in both the arms (GC 15 [38.5%] versus GCI 32 [41.0%] patients). The most frequently reported treatment-emergent Grade 3 to 4 SAEs by primary system organ class in either arm were respiratory, thoracic, and mediastinal disorders (GC 5 [12.8%] versus GCI 5 [6.4 %]); blood and lymphatic system disorders (GC 4 [10.3%] versus GCI 8 [10.3%] patients); gastrointestinal disorders (GC 4 [10.3%] versus GCI 5 [6.4%]); general disorders and administration site conditions (GC 4 [10.3%] versus GCI 6 [7.7%]); and infections and infestations (GC 3 [7.7%] versus GCI 6 [7.7%]

patients). Grade 3 to 4 treatment-emergent SAEs with a difference of at least 5% between the 2 arms were febrile neutropenia (GC 2 [5.1%] versus GCI 0 [0.0%] patients) and asthenia (GC 4 [10.3%] versus GCI 3 [3.8%] patients). Grade 3 to 4 vomiting was reported in 2 (5.1%) patients in the GC arm and 1 (1.3%) patient in the GCI arm. Grade 3 to 4 treatment-emergent SAEs reported in the GCI arm in more than 1 patient were anemia (4 [5.1%] patients), thrombocytopenia (4 [5.1%] patients), sepsis (2 [2.6%] patients), hypertension (2 [2.6%] patients), and pulmonary embolism (2 [2.6%] patients).

Treatment-emergent SAEs considered by the investigator to be related to study treatment were reported in 12 (30.8%) patients in the GC arm and 18 (23.1%) patients in the GCI arm. Treatment-related, treatment-emergent SAEs reported with a difference of at least 5% between the 2 arms were febrile neutropenia (GC 2 [5.1%] versus GCI 0 [0.0%] patient) and asthenia (GC 4 [10.3%] versus GCI 2 [2.6%] patients).

Seven patients (17.9%, all grades) in the GC arm and 16 patients (20.5%; all grades) in the GCI arm had at least 1 TEAE leading to discontinuation of all study drugs. Nine (23.1%) patients in the GC arm and 17 (21.8%) patients in the GCI arm had TEAEs leading to discontinuation of 1 or more study drugs. As expected, most of these withdrawals were a result of a Grade 3 to 4 TEAE (GC 6 [15.4%] versus GCI 13 [16.7%] patients for discontinuation of all study drugs; GC 8 [20.5%] versus GCI 14 [17.9%] patients for discontinuation of 1 or more study drugs). The only TEAE with a difference of at least 5% between 2 treatment arms that led to discontinuation of 1 or more study drugs was Grade 3 to 4 asthenia (GC 3 [7.7%] versus GCI 1 [1.3%] patients). Again, this could be reflective either of a better PS in the GCI arm or a greater ability of the GCI combination to improve the patient's general condition.

More than half of the patients (GC 22 [56.4%] versus GCI 44 [56.4%] patients) had at least 1 TEAE leading to dose reduction of any study drug(s). At least one-third of dose reductions occurred due to a Grade 3 to 4 event (GC 15 [38.5%] versus GCI 26 [33.3%] patients). Hematologic toxicities were the most common TEAEs leading to dose reduction (GC 11 [28.2%] versus GCI 20 [25.6%] patients). TEAEs (all grades and Grade 3 to 4) with a difference of at least 5% between the 2 arms leading to dose reduction were febrile neutropenia (Grade 3 to 4, GC 2 [5.1%] versus GCI 0 [0.0%] patients), vomiting (all grades, GC 4 [10.3%] versus GCI 1 [1.3%] patients), fatigue (Grade 3 to 4, GC 0 [0.0%] versus GCI 4 [5.1%] patients), and asthenia (Grade 3 to 4, GC 3 [7.7%] versus GCI 2 [2.6%] patients).

Approximately one-third of patients (GC 14 [35.9%] and GCI 26 [33.3%] patients) had at least 1 TEAE leading to dose delay of any study drug. An equal proportion of patients had at least 1 Grade 3 to 4 TEAE leading to dose delay of any study drug (GC 9 [23.1%] versus GCI 18 [23.1%] patients). More than 80% of these Grade 3 to 4 events were hematologic in nature (86% in GC and 81% in GCI). TEAEs with a difference of at least 5% between the 2 treatment arms leading to dose delay were thrombocytopenia (all grades, GC 1 [2.6%] versus GCI 6 [7.7%] patients) and febrile neutropenia (Grade 3-4, 2 [5.1%] versus GCI 0 [0.0%] patients).

More patients in the GCI arm than in the GC arm maintained or improved their ECOG PS from baseline to the end of the study. For patients with a baseline PS of 0, 37% treated with GC and 49% treated with GCI maintained a PS of 0 at the last on-treatment evaluation. For patients with a baseline PS of 1, 70% treated with GC maintained a PS of 1 or improved to a PS of 0 whereas 80% of those patients who had a baseline PS of 1 and were treated with GCI either improved or maintained their baseline PS score.

Pharmacokinetic results: Not applicable.

Conclusions: [redacted]

Date of report: 05-Apr-2013