1) **Title page**.

Study title:	A randomized multicenter, Phase IIb/IIIa study of Gemcitabine and monoclonal antibody Nimotuzumab (OSAG 101) versus Gemcitabine and placebo for the treatment of chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer
Name of test drug/investigational product:	Gemcitabine and monoclonal antibody nimotuzumab (OSAG 101, Theraloc®)
Study indication:	Locally advanced, unresectable or metastatic pancreatic cancer in chemotherapy naïve patients with measurable disease
Study design:	Phase IIb/IIIa, multicenter, randomized, double-blind, placebo-controlled clinical trial
Name of the sponsor:	Oncoscience AG, [redacted]
Protocol identification:	OSAG 101-PCS-07
EudraCT No.:	2007-000338-38
Development phase of study	Phase IIb/IIIa
Study initiation date	First patient enrolled: 20 September 2007
Study completion date:	Last patient: 30 September 2011, DB lock: 08 November 2012
Name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer	Prof. Dr. D. Strumberg, [redacted]
Name of company/sponsor signatory	[redacted] Oncoscience AG, [redacted]
Statement on GCP compliance	The study was conducted in compliance with Good Clinical Practice, Ethics Committee recommendations, informed consent regulations, the Declaration of Helsinki and with the laws and regulations of the country in which the study was conducted
Date of the amending report	18 July 2016

SIGNATURE PAGE:

Authors	[redacted]
Prof. Dr Dirk Strumberg (Principal Investigator) [redacted]	
Statistician	
[redacted]	
Sponsors	
[redacted]	

2) **Synopsis**.

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Name of active ingredient: nimotuzumab		
Title of study: A randomized multicenter, Phase IIb/IIIa study of gemcitabine and monoclonal antibody nimotuzumab (OSA101) versus gemcitabine and placebo for the treatment of chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer		
Investigators: Principal investigator: Prof. Dr. D. Strumberg, [redacted] Other investigators are listed in appendix 16.1.4.1 of the CSR		
Study centre(s): 13 active centres in Germany, 2 in Turkey and 1 in Switzerland		
Publication (reference):		
Study period: September 2007 – November 2012	Phase of development: Phase IIb/IIIa	
Objectives: To evaluate the antitumor activity of nimotuzumab, as assessed by overall survival (OS) in chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer and to assess the efficacy of nimotuzumab as add on therapy to gemcitabine in comparison with gemcitabine and placebo		
Methodology: Phase IIb/IIIa, multicenter, randomized, double-blind, placebo-controlled clinical trial		
Number of patients (planned and analysed): A total of 192 patients were randomized and enrolled in the clinical study (96 in the gemcitabine plus nimotuzumab arm and 96 in the gemcitabine plus placebo arm)		
Diagnosis and main criteria for inclusion: **Diagnosis**: Chemotherapy-naïve patients with confirmed, measurable locally advanced, unresectable or metastatic pancreatic cancer. **Main inclusion criteria**:		

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1) Written informed consent.
2) Histologically or cytologically confirmed locally advanced or metastatic adenocarcinoma of the pancreas not amenable to curative radiotherapy or surgery.
3) Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (i.e, target lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm using spiral computed tomography (CT) scan).
4) Able to take medications orally.
5) At least 18 years of age or older.
6) Karnofsky Performance Status (KPS) ≥ 70%.
7) Life expectancy of 12 weeks.
8) Adequate organ function as defined by the following criteria
   - Transaminases AST (SGOT) and ALT (SGPT) ≤ 2.5 times the upper limit of normal (ULN).
   - If liver function abnormalities are due to underlying liver metastasis, then AST (SGOT) and ALT (SGPT) may be ≤ 5 times ULN.
   - Total serum bilirubin ≤ 3.0 times ULN (if due to underlying liver metastasis, then total bilirubin may be ≤ 5 times ULN).
   - Absolute granulocyte count ≥ 1,500/mm^3 (i.e., 1.5 x 10^9/L by International Units (IU]).
   - Platelet count ≥ 100,000/mm^3 (IU: 100 x 10^9/L).
   - Hemoglobin value ≥ 9.0 g/dL.
   - Calculated creatinine clearance ≥ 60 mL/min (based on serum creatinine) (Cockcroft-Gault formula)
9) Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
10) Both female and male patients must use adequate methods of contraception

Test product, dose and mode of administration, batch number:

Gemcitabine: 1000 mg/m^2 (administered as a 30-min intravenous infusion) once weekly for 3 weeks, followed by a 1-week rest (d1, 8, 15; q28) and

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Nimotuzumab: Fixed dose of 400 mg (8 vials) once weekly, administered as a 30 min intravenous infusion for 3 weeks, followed by a 1-week rest (d1, 8, 15, q28) until disease progression or unacceptable toxicity

Hereafter referred to as "Experimental Group or gemcitabine plus nimotuzumab arm"

Duration of the treatment:
Patients will receive study treatment until disease progression (PD), death, occurrence of intolerable side effects, or withdrawal of consent, whichever comes first

Reference therapy, dose and mode of administration, batch number:

Gemcitabine: 1000 mg/m^2 (administered as a 30-min intravenous infusion) once weekly for 3 weeks, followed by a 1-week rest (d1, 8, 15; q28) and
Placebo: Fixed dose of 400 mg (8 vials) once weekly, administered as a 30 min intravenous infusion for 3 weeks, followed by a 1-week rest (d1, 8, 15, q28) until disease progression or unacceptable toxicity

Hereafter referred to as "Control Group or gemcitabine plus placebo arm"

Criteria for evaluation:
Efficacy:

1) **Primary endpoint**.

a) Overall survival (OS):
Overall survival was defined as the time from the day of randomization to the day of death from any cause. Follow up assessment for all patients was performed for 12 months or more and in the case of the last patient for at least 12 months.

2) **Secondary endpoints**:

a) Progression-free-survival (PFS)

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Progression-free survival was defined as the time from the day of randomization to the day of progression or death from any cause, whichever came first (the same definition used in the initial clinical study report (1), but in that report was named as TTP).

b) Overall response rate (ORR), clinical benefit rate (CBR), best response (BR) and duration of the response (DR)
Overall response rate was defined as the percentage of subjects with complete response (CR) or partial response (PR) in the best overall response [(CR + PR) / number of patients]. Clinical benefit rate (CBR) was defined as the proportion of patients with CR, PR, or stable disease (SD) as the best overall response [(CR + PR + SD) / number of patients], best response was defined as the best overall response recorded from the start of treatment until disease progression and duration of response (DR) was defined as the duration of time from the day when the best overall response satisfied CR or PR (whichever recorded first) until the first date when recurrent or progressive disease was objectively documented.

c) Safety profile
Defined as all related adverse events and clinical laboratory data according to Common Toxicity Criteria (CTC version 3.0 of the National Cancer Institute)

d) Quality of life (QoL)
QoL questionnaire according to EORTC and to evaluate the effect of Nimotuzumab on Karnofsky Performance Status (KPS) and pain assessments, including pain intensity and analgesic consumption.

Safety:

Safety assessment included monitoring of adverse events (AEs), serious adverse events (SAEs), physical examination, vital signs, ECG and clinical laboratory tests according to Common Toxicity Criteria (CTC version 3.0 of the National Cancer Institute)

Statistical methods:

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Analysis of efficacy:

Efficacy analyses were performed using intent-to-treat (ITT) analysis, modified intent-to-treat (mITT) analysis and per-protocol (PP) analysis. ITT analysis was the secondary analysis performed for the efficacy endpoints.

1) **Primary endpoint**:

Primary analysis:

Analysis of overall survival, the primary efficacy endpoint, was performed after 12 months of the inclusion of the last patient using a stratified log rank test, stratified by the same stratification factors as used for randomization, with treatment group as an independent variable. Kaplan-Meier estimates were displayed, and the median overall survival, the hazard ratio and its two-sided 95% confidence interval (CI) were calculated by treatment group using Cox regression.

Secondary analysis:

In light with current state-of-the-art for the statistical analysis of Phase III clinical studies it was necessary to perform additional post-hoc analysis taken into consideration new statistical method and new knowledge on clinical trial data processing and statistical analysis that was not available at the time of the protocol and Statistical Analysis Plan (SAP) design.

It was implemented a secondary analysis of overall survival, the primary efficacy endpoint, using the Inverse Probability of Censoring Weight (IPCW) model and the median overall survival, hazard ratio and its two-sided 95% confidence interval (CI) were calculated by treatment group using Cox regression.

The IPCW model was frequently used before to adjust for no representative sampling or dropouts. In this method, patients who switch to another treatment are censored, while patients remaining in protocol treatment are weighted to compensate for missing data. The bias introduced by this informative switch is corrected by weighting each patient by the inverse of his or her predicted probability

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of not being censored at a given time. The IPCW model assumes that the probability of switching to another treatment at a given time depends only on observed covariates and must be independent of the outcome and its timing. If these assumptions hold, then censoring can be made non-informative through the IPCW model. In this case the data from current clinical trial contain enough information about the covariates that affect the probability of switching to another treatment.

2) **Secondary endpoints**.

Primary analysis.

Statistical analyses for PFS was performed in the same manner as for OS. In both treatment arms, median PFS, the HR and their 95% CIs were calculated. A log-rank test was performed to evaluate the difference in PFS at a significance level of 5 % (2-sided) using Cox regression.

Analysis of safety:

The number and percentage of subjects with adverse events were summarized for each event classified by system organ class (SOC) and preferred term (PT) of ICH Medical Dictionary for Regulatory Activities terminology (MedDRA) by treatment group: adverse events, adverse events with a suspected relationship with the study drug (adverse drug reactions), serious adverse events, Grade 3 or higher adverse events with a suspected relationship with the study drug (adverse drug reactions), adverse events leading to discontinuation of study drug administration, and adverse events leading to discontinuation of gemcitabine administration.
Adverse events and adverse events with a suspected relationship with the study drug (adverse drug reactions) were tabulated and summarized.

Summary – Conclusions
Disposition of subjects:

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A total of 192 patients were recruited in the study at 13 clinical centers in Germany, 2 in Turkey and 1 in Switzerland. Ninety-six (96) patients (62 male and 34 female) with a median age of 67 years, range (31, 83 years) were randomized to the treatment arm and 96 patients (57 male and 39 female) with a median age of 64 years, range (41, 82 years) were randomized to the control arm.

Efficacy Results:

a) Overall survival, the primary endpoint.

- In the primary analysis there was an increase in the median OS of 2.54 months in the ITT population and 2.60 months on mITT population for gemcitabine plus nimotuzumab arm when compared to gemcitabine plus placebo arm. Although there was a trend toward improvements in the median OS, median overall survival results at the protocol-specified analysis time were not statistically significant. Main reason for the lack of statistical significance can be attributable to the fact that 42.2 % of the patients in the gemcitabine plus nimotuzumab arm and 42.7 % in the gemcitabine plus placebo arm in the ITT population and 43.01 % of the patients in the gemcitabine plus nimotuzumab arm and 44.1% in the gemcitabine plus placebo arm in the mITT population switched to non-specified in the protocol second and third line therapy including best supportive care after disease progression.

- In the secondary analysis the median OS was statistically significant when compared locally advanced or metastatic pancreatic cancer patients that received treatment with gemcitabine plus nimotuzumab with those that received gemcitabine plus placebo in the ITT and mITT populations after using IPCW model and Cox regression. Median OS [95% CI] in the gemcitabine plus nimotuzumab arm was 7.57 months [6.17, 8.73 months] versus 5.93 months [5.37, 7.30 months] in the gemcitabine plus placebo arm and the HR [95% CI] was 0.81 [0.67, 0.98] with a p = 0.030 for the ITT population and 7.63 months [6.97, 9.13 months] in the gemcitabine plus nimotuzumab arm versus 6.17

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months [5.53, 7.57 months] for gemcitabine plus placebo arm and the HR [95% CI] was 0.80 [0.66, 0.98] with a p = 0.028 for the mITT population.

b) Progression free survival, secondary endpoint.

- The median PFS was statistically significant when compared locally advanced or metastatic pancreatic cancer patients that received treatment with gemcitabine plus nimotuzumab with those that received gemcitabine plus placebo for the ITT and mITT populations using Kaplan Meier curves, log-rank test and Cox regression model in the primary analysis. The median PFS [95% CI] in the gemcitabine plus nimotuzumab arm was 4.43 months [3.67, 6.00 months] versus 3.47 months [2.60, 4.03 months] in the gemcitabine plus placebo arm and the HR [95% CI] was 0.68 [0.51, 0.92] with a p = 0.012 for the ITT population and 4.43 months [3.77, 6.93 months] in the gemcitabine plus nimotuzumab arm versus 3.47 months [2.60, 4.03 months] for gemcitabine plus placebo arm and the HR [95% CI] was 0.67 [0.50, 0.91] with a p = 0.010 for the mITT population.

c) Subgroup analysis according to KRAS status.

a) Overall survival. The primary endpoint.

- There was an increase in the median OS of KRAS wild type patients of 5.95 months for the ITT population and 6.70 months for the mITT population for gemcitabine plus nimotuzumab arm when compared to gemcitabine plus placebo arm. Although there was a trend toward improvements in the median OS, median overall survival results at the protocol-specified analysis time were not statistically significant in the primary analysis.
- The median OS for KRAS Wild type population after using IPCW model in the secondary analysis was statistically significant when compared locally advanced or metastatic pancreatic cancer patients that received treatment with gemcitabine plus nimotuzumab with those that received gemcitabine plus placebo. Median OS [95% CI] was 9.03 months [7.43, 12.77 months] in the

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gemcitabine plus nimotuzumab arm versus 7.03 months [5.53, 8.43 months] for gemcitabine plus placebo arm and the HR [95% CI] was 0.58 [0.36, 0.91] with a p = 0.018 for the ITT population and 9.3 months [7.43, 13.10 months] in the gemcitabine plus nimotuzumab arm versus 7.03 months [5.53, 9.03 months] for gemcitabine plus placebo arm and the HR [95% CI] was 0.56 [0.35, 0.90] with a p = 0.015 for the mITT population

- No improvement or statistically significant differences were observed for KRAS mutated population for the ITT and mITT populations in both primary analysis and secondary analysis.

d) Overall response rate (ORR) and Clinical Benefit Rate (CBR). Secondary endpoints.

- In the ITT population, ORR was similar in both treatment arms, while the CBR was higher in the gemcitabine plus nimotuzumab arm 61.5 % compared with 50.0 % for gemcitabine plus placebo arm, p = 0.15 and in the PP population both ORR and CBR were similar. There were not statistically significant differences between both treatment arms.

e) Duration of the response (DR). Secondary endpoints.

- There was statistically significant difference for the median duration of the response (DR) [95% CI] that was 6.5 months [2.1, 8.8] for the gemcitabine plus nimotuzumab arm and 2.1 months [1.9, 3.9] for the gemcitabine plus placebo arm with a p = 0.01.

Safety Results:

In the safety data set of study OSAG 101-PCS-07 there were 186 patients who received treatment (93 patients in the gemcitabine plus nimotuzumab arm and 93 patients in the gemcitabine plus placebo arm). These patients experienced a total of 1641 adverse events (AEs) reported in 180 patients (96.8%). Out of 1641 AEs, 896 AEs in 90 patients (96.8%) occurred in the gemcitabine plus nimotuzumab arm and

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745 AEs in 90 patients (96.8%) occurred in the gemcitabine plus placebo arm. The most frequently reported AEs (> 14 patients, 15.1 %) in the gemcitabine plus nimotuzumab arm regardless of relationship to the study drug, were nausea (34 subjects, 36.6 %), fatigue (28 subjects, 30.1 %), thrombocytopenia (24 subjects, 25.8%), pyrexia (24 subjects, 25.8 %), diarrhoea (22 subjects, 23.7 %), abdominal pain (21 subjects, 22.6 %), leukopenia (20 subjects, 21.5%), vomiting (19 subjects, 20.4 %), chills (17 subjects, 18.3 %), rash (17 subjects, 18.3 %), constipation (16 subjects, 17.2 %) and appetite decreased (15 subjects, 16.1 %).

Of the 896 AEs that occurred in the gemcitabine plus nimotuzumab arm, 378 were not related and 519 AEs in 78 patients (83.9%) were reported to be related to the study drug and of 745 AEs in the gemcitabine plus placebo arm, 338 were not related and 407 AEs in 67 patients (72.0%) were reported to be related to gemcitabine. The most common study-drug related AEs (> 14 patients, 15.1%) were nausea (30 subjects, 32.3%), thrombocytopenia (23 subjects, 24.7%), leukopenia (21 subjects, 22.6%), fatigue (20 subjects, 21.5%), pyrexia (15 subjects, 16.1%) and rash (14 subjects, 15.1%).

Of the 926 AEs reported to be related in the study, there were 519 AEs in the gemcitabine plus nimotuzumab arm, of them 324 AEs in 69 patients (74.2%) were Grade 1, 154 AEs in 51 patients (54.8%) were Grade 2 and 41 AEs in 24 patients (25.8%) were Grade 3 or 4 and 407 AEs in the gemcitabine plus placebo arm, of them 238 AEs in 56 patients (60.2%) were Grade 1, 115 AEs in 44 patients (47.3%) were Grade 2 and 54 AEs in 25 patients (26.9%) were Grade 3 or 4. The most frequently reported Grade 3 or 4 treatment-related adverse events in patients treated with gemcitabine plus nimotuzumab were leukopenia (4.3%), neutropenia (4.3%), nausea (3.2%), vomiting (3.2%), thrombocytopenia (2.2%), rash (2.2%) and general physical deterioration (2.2%).

Serious adverse events were reported in 119 (64.0%) patients, 57 (61.3%) patients in the gemcitabine plus nimotuzumab arm and 62 (66.7 %) patients on gemcitabine plus placebo arm. On these 119 patients a total of 234 SAEs were reported. Of them 117 SAEs in the gemcitabine plus nimotuzumab arm, were reported in 57 patients (61.3%) and 117 SAEs in the gemcitabine plus placebo arm, were reported in 62 patients (66.7%). Of the 117 SAEs, reported in the gemcitabine plus nimotuzumab arm, 16 SAEs in 8 patients (8.6 %) were reported to be related to the

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study drug. Most common SAEs reported to be related to study drug gemcitabine plus nimotuzumab were nausea (2 subjects, 2.2 %), vomiting (2 subjects, 2.2%), and thrombocytopenia (2 subjects, 2.2 %) and of 117 SAEs, reported in the gemcitabine plus placebo arm, 15 SAEs in 12 patients (12.9 %) were reported to be related to gemcitabine. The most common SAE reported to be related to gemcitabine was the haemolytic uraemic syndrome (2 subjects, 2.2 %). No notable difference was found in the incidence of serious adverse events between the treatments arms.

There were 176 patients (94.5%) who died during the course of the study. Fifty-four (54) death were reported as SAEs (22 deaths in the gemcitabine plus nimotuzumab arm and 32 deaths in the gemcitabine plus placebo arm). In no case, did the investigator associate a causal relationship between the death of a patient and the application of the study drug.

Conclusions:

Addition of nimotuzumab to gemcitabine had proven to be efficacious in terms of increasing overall survival, progression-free-survival, survival rate and PFS rate at 1 year when compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer.

The safety profile of nimotuzumab when is added to gemcitabine appears to be better than the safety profile seen in clinical trials of other monoclonal antibodies and the incidence of hematologic toxicities Grade III/IV in locally advanced or metastatic pancreatic cancer patients after receiving the combination treatment of gemcitabine plus nimotuzumab is at least 5 times lower than the incidence of the same adverse events seen with FOLFIRINOX and Nab-paclitaxel

Date of the amendment of the report: 18 July 2016